IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 7,488,827

Patentee: Laine et al.

Issued: February 10, 2009

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Dear Sir:

Pursuant to 35 U.S.C. §156, the Applicant, Glaxo Group Limited (d/b/a GlaxoSmithKline) (hereinafter "GGL") hereby requests an extension of the patent term of U.S. Patent No. 7,488,827 (the '827 Patent), under 35 USC §156 by providing the following information pursuant to 37 C.F.R. §1.740.

U.S. Patent No. 7,488,827 is granted to Dramane I. Laine, Michael R. Palovich, Brent W. McCleland, Christopher E. Neipp and Sonia N. Thomas.

GGL is the assignee of the entire right, title and interest in the above-captioned patent by virtue of an assignment of the parent application 11/568,330 filed May 3, 2007 (now U.S. Patent No. 7,498,440, and published as US 2007/0186155), which is the §371 national stage entry of PCT/US2005/014386, filed 27 April 2005 to GGL as recorded on January 15, 2008 at Reel 020365, Frame 0661 (**Exhibit A1**). All of the named inventors assigned their rights in the PCT application, PCT/US2005/014386 (**Exhibit A2**) of which USSN 11/568330 was the national stage entry, and by which USSN 11/774,867 (now U.S. Patent No. 7,488,827), filed July 9, 2007, is a continuation application of.

By the Power of Attorney and Statement under 37 C.F.R. § 3.73(b) (**Exhibit B**), Applicant has appointed individual attorneys, including Dara L. Dinner, with regard to this application

for extension of term of the '827 Patent and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Applicant further represents, pursuant to 37 C.F.R. § 1.785(d), that Applicant is the holder of the regulatory approval granted by the Food and Drug Administration ("FDA") for ANORO™ ELLIPTA™. A copy of the Food and Drug Administration (FDA) Approval Letter for ANORO™ ELLIPTA™ is attached as **EXHIBIT C**.

For convenience, the information contained in this application will be presented according to the format set forth in 37 CFR § 1.740(a).

1. Identification of the Approved Product [§ 1.740(a)(1)]:

The approved product, ANORO™ ELLIPTA™, is an inhalation powder with two active ingredients, umeclidinium 62.5mcg and vilanterol 25mcg for use in the long-term, once daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. This is the first approval for marketing in the US of the two active agents together as a single inhalation product. This is the first approval for the active agent, Umeclidinium. Umeclidinium is present in the approved drug product as the bromide quaternary salt.

Vilanterol, as the triphenyl acetate salt ("vilanterol trifenatate") has been previously approved for use as an inhalation powder in combination with another active ingredient, Fluticasone Furoate as BREO™ ELLIPTA™.

A copy of the package insert for the ANORO™ ELLIPTA™, approved by the FDA as part of the New Drug Application (NDA) 203,975 is attached as **Exhibit D**.

I. Identification of umeclidinium is provided as follows:

Chemical names for umeclidinium are:

a) 1-Azoniabicyclo[2.2.2]octane, 4-(hydroxydiphenylmethyl)-1-[2-(phenylmethoxy)ethyl]; or

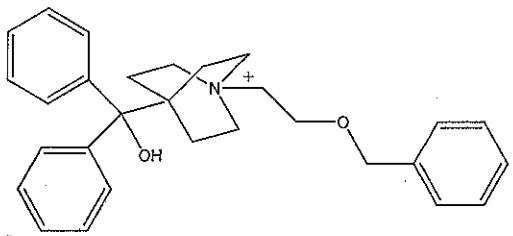
b) 1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane; or

c) 4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane

The molecular weight of umeclidinium is 428.6

The molecular formula of umeclidinium is $C_{29}H_{34}NO_2^+$

The structural formula of umeclidinium is:



As noted above, umeclidinium is present in the approved product as the bromide quaternary salt.

Chemical names for umeclidinium bromide are:

a) 1-Azoniabicyclo[2.2.2]octane,-4-(hydroxydiphenylmethyl)-1-[2-(phenylmethoxy)ethyl] bromide (1:2); or

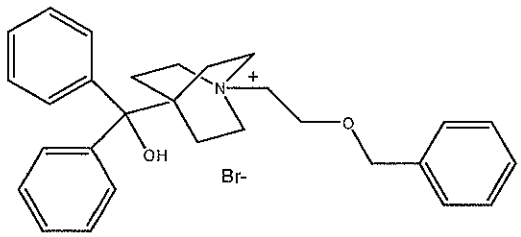
b) 1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide; or

c) 4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

The molecular weight of umeclidinium bromide is 508.5

The molecular formula of umeclidinium bromide is $C_{29}H_{34}BrNO_2$

The structural formula of umeclidinium bromide is



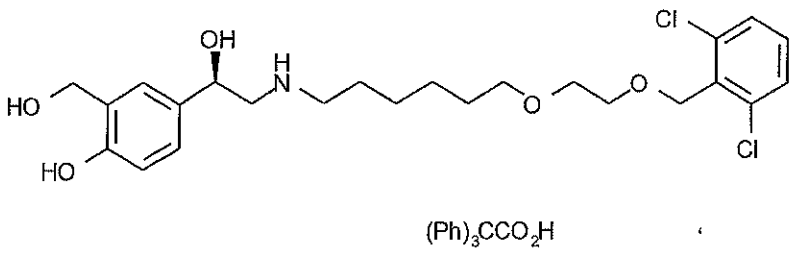
II. Identification of vilanterol (present as the triphenyl acetate salt) is provided as follows:

Chemical name: triphenyl acetic acid-4-{(1*R*)-2-[(6-{2-[(2,6-dichloro benzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol

Molecular formula: $C_{24}H_{33}Cl_2NO_5$. $C_{20}H_{16}O_2$

Molecular weight: 774.8 (triphenyl acetate salt)
486.43 (free base)

Structural Formula:



The approved product is presented in the form of an inhalation dry powder in a delivery device (i.e., ELLIPTA™). ANORO™ ELLIPTA™ contains two double-foil blister strips of powder formulation. Each blister on one strip contains a white powder mix of umeclidinium bromide (62.5 mcg), magnesium stearate (75 mcg) and lactose monohydrate (up to 12.5 mg), and each blister on the other strip contains a

white powder mix of micronized vilanterol trifenatate (25 mcg), magnesium stearate (125 mcg) and lactose monohydrate (up to 12.5 mg).

2. Federal Statute Governing Regulatory Approval of the Approved Product [§ 1.740(a)(2)]:

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section §505 (21 U.S.C. § 355 *et seq.*). See **Exhibit C**.

3. Date of Approval for Commercial Marketing [§ 1.740(a)(3)]:

The drug product, ANORO™ ELLIPTA™ received approval for commercial marketing and use under §505 of the Federal Food, Drug and Cosmetic Act on December 18, 2013. See **Exhibit C**.

4. Identification of Active Ingredient and Certifications Related to Commercial Marketing of Approved Product [§ 1.740(a)(4)]:

The drug product ANORO™ ELLIPTA™ contains two active ingredients in combination, umeclidinium 62.5mg and vilanterol 25mcg. The active ingredient umeclidinium has not been previously approved for commercial marketing or use either alone or in combination under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval granted on December 18, 2013 to the present Applicant. *See* **Exhibit D**, a copy of the package insert describing the drug product ANORO™ ELLIPTA™ and the two active agents in combination approved by the FDA as part of the New Drug Application (NDA) 203,975.

As noted above, and in the Summary Review of the FDA for the NDA approval of the ANORO™ ELLIPTA™, (*see* **Exhibit E**, attached hereto), vilanterol trifenatate is not a new molecular entity having been recently previously approved for first commercial marketing or use in combination with fluticasone furoate in the approved

drug product BREO™ ELLIPTA™ under NDA 204,275. A copy of the approved label for the drug product BREO™ ELLIPTA™ is attached as **Exhibit F**.

5. Statement Regarding Timeliness of Submission of Patent Term Extension Request [§ 1.740(a)(5)]:

This application for extension of patent term under 35 U.S.C. §156 is being submitted within the permitted sixty (60) day period pursuant to 37 C.F.R. §1.720(f). The last day on which this application may be submitted is February 16, 2014.

6. Complete Identification of the Patent for Which Extension is Being Sought [§ 1.740(a)(6)]:

Patent No.: 7,488,827

Inventors: Dramane I. Laine, Michael R. Palovich, Brent W. McCleland, Christopher E. Neipp and Sonia N. Thomas

Issue Date: February 10, 2009

Expiration Date: April 27, 2025 (without extension under 35 U.S.C. §156)

7. Copy of the Patent for Which an Extension is Being Sought [§ 1.740(a)(7)]:

A complete copy of U.S. Patent 7,488,827 is attached hereto as **Exhibit G**.

8. Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate [§ 1.740(a)(8)]:

a) No certificate of correction or reexamination certificate has been issued on this patent.

b) A copy of the terminal disclaimer over U.S. Patent No. 7,498,440 (parent of the '827 Patent) filed on April 27, 2003 is attached hereto as **Exhibit H**.

c) The first Maintenance Fee for U.S. 7,488,827 was paid on July 25, 2012 (copy attached as **Exhibit I**).

9. Statement Regarding Patent Claims Relative to Approved Product [§ 1.740(a)(9)]:

The statements below are made solely to comply with the requirements of 37 C.F.R. § 1.740(a)(9). Applicant notes that, as the M.P.E.P. acknowledges, § 1.740(a)(9) does not require an applicant to show whether or how the listed claims would be infringed, and that this question cannot be answered without specific knowledge concerning acts performed by third parties. As such, these comments are not an assertion or an admission of Applicant as to the scope of the listed claims, or whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale or the importation of any product.

Claims 1-5, 7-9, 11-18 of U.S. Patent 7,488,827 claim the approved active ingredient umeclidinium bromide, present as one of the two active ingredients in the drug product, ANORO™ ELLIPTA™.

Claim 1 reads as follows:
The compound which is 4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide.

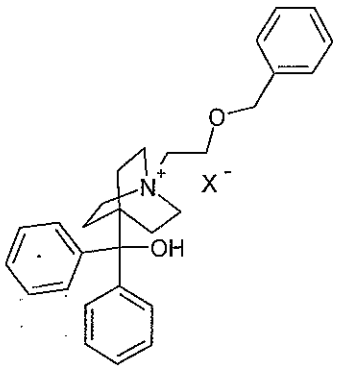
Claim 1 reads on one of the approved active ingredients, umeclidinium bromide, in the approved combination drug product, ANORO™ ELLIPTA™. *See* package insert ANORO™ ELLIPTA™, Section 11, Description, **Exhibit D**.

Claim 2 reads as follows:
A pharmaceutical composition comprising 4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide and a pharmaceutically acceptable carrier thereof.

Claim 2 reads on one of the approved active ingredients, umeclidinium bromide in a pharmaceutical composition. The approved combination drug product, ANORO™ ELLIPTA™, contains the active ingredient umeclidinium bromide in a blister strip as a pharmaceutical composition with lactose monohydrate, a pharmaceutically acceptable carrier, and magnesium stearate a pharmaceutically acceptable excipient. *See* package insert ANORO™ ELLIPTA™, Section 2, Dosage and Administration; and Section 11, Description, **Exhibit D**.

Claim 3 reads as follows:

The compound



wherein

X^- is a pharmaceutically acceptable anion.

Claim 4 reads as follows:

The compound according to Claim 3 wherein the pharmaceutically acceptable anion is chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate or p-toluenesulfonate.

Claim 5 reads as follows:

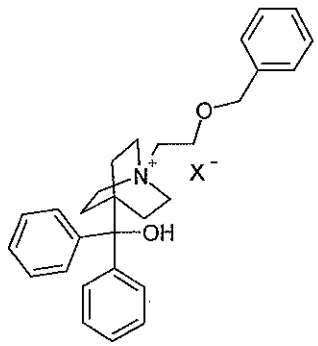
The compound according to Claim 3 wherein the pharmaceutically acceptable anion is bromide.

Claims 3 -5 read on one of the approved active ingredients, umeclidinium and a pharmaceutically acceptable anion. Bromine is a pharmaceutically acceptable anion,

and bromine is specifically covered by claims 4 and 5. The approved active ingredient in the combination drug product, ANORO™ ELLIPTA™ is umeclidinium bromide. *See* package insert ANORO™ ELLIPTA™, Section 11, Description, **Exhibit D**.

Claim 7 reads as follows:

A pharmaceutical composition comprising the compound



wherein

X^- is a pharmaceutically acceptable anion,

and a pharmaceutically acceptable carrier thereof.

Claim 8 reads as follows:

The composition according to Claim 7 wherein the pharmaceutically acceptable anion is chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate or p-toluenesulfonate.

Claim 9 reads as follows:

The composition according to Claim 7 wherein the pharmaceutically acceptable anion is bromide.

Claims 7-9 read on umeclidinium and a pharmaceutically acceptable anion in a pharmaceutical composition in the approved combination drug product, ANORO™ ELLIPTA™. Bromine is a pharmaceutically acceptable anion, and bromine is specifically covered by claims 8 and 9. The approved active ingredient in the drug

product, ANORO™ ELLIPTA™ is umeclidinium bromide. The approved drug product contains the active ingredient umeclidinium bromide in a pharmaceutical composition with lactose monohydrate, a pharmaceutically acceptable carrier, and with magnesium stearate, a pharmaceutically acceptable excipient. *See* package insert ANORO™ ELLIPTA™, Section 11, Description, **Exhibit D**.

Claim 11 reads as follows:

A pharmaceutical composition according to Claim 2 in a form suitable for administration by oral or nasal inhalation.

Claim 11 (dependent upon claim 2) reads on the approved drug product which is administered by oral inhalation. The approved drug product contains the active ingredient umeclidinium bromide in a pharmaceutical composition with lactose monohydrate, a pharmaceutically acceptable carrier, and with magnesium stearate, a pharmaceutically acceptable excipient. *See* package insert ANORO™ ELLIPTA™, Section 2, Dosage and Administration; Section 11, Description; and the Medication Guide Figures, **Exhibit D**.

Claim 12 reads as follows:

A pharmaceutical composition according to Claim 11 wherein the form is suitable for administration by inhalation via a medicament dispenser selected from a reservoir dry powder inhaler, multi-dose dry powder inhaler, or a metered dose inhaler.

Claim 12 reads on the approved drug product which is an inhalation powder contained in a dispenser which is a multi-dosage dry powder inhaler. The blister strips contain 30 blisters and the product is dosed once daily. *See* package insert ANORO™ ELLIPTA™, Section 2, Dosage and Administration; Section 3, Dosage Forms and Strengths; and Section 11, Description, **Exhibit D**.

Claim 13 reads as follows:

A pharmaceutical composition according to Claim 2 which is a dry powder composition.

Claim 14 reads as follows:

A pharmaceutical composition according to Claim 2 wherein the pharmaceutically acceptable carrier is lactose.

Claims 13 and 14 (dependent upon claim 2) read on the approved drug product which contains the active ingredient umeclidinium bromide in a pharmaceutical composition, a powder, with lactose monohydrate, a pharmaceutically acceptable carrier. *See* package insert ANORO™ ELLIPTA™, Section 11, Description, **Exhibit D**.

Claim 15 reads as follows:

A pharmaceutical composition according to Claim 7 in a form suitable for administration by oral or nasal inhalation.

Claim 15 (dependent upon claim 7) reads on the approved drug product which is administered by oral inhalation. The approved drug product contains the active ingredient umeclidinium and a pharmaceutically acceptable anion in a pharmaceutical composition with lactose monohydrate, a pharmaceutically acceptable carrier, and with magnesium stearate, a pharmaceutically acceptable excipient. Bromine is a pharmaceutically acceptable anion. The approved active ingredient in the drug product, ANORO™ ELLIPTA™, is umeclidinium bromide. *See* package insert ANORO™ ELLIPTA™, Section 2, Dosage and Administration; Section 3, Dosage Forms and Strengths; and the Medication Guide Figures, **Exhibit D**.

Claim 16 reads as follows:

A pharmaceutical composition according to Claim 15 wherein the form is suitable for administration by inhalation via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler, or a metered dose inhaler.

Claim 16 reads on the approved drug product which is an inhalation powder contained in a dispenser which is a multi-dosage dry powder inhaler. The blister strips contain 30 blisters and the product is dosed once daily. The approved drug product contains the active ingredient umeclidinium and a pharmaceutically acceptable anion. Bromine is a pharmaceutically acceptable anion. The approved active ingredient in the drug

product, ANORO™ ELLIPTA™, is umeclidinium bromide. The approved drug product also contains the active ingredient umeclidinium bromide with lactose monohydrate, a pharmaceutically acceptable carrier. *See* package insert ANORO™ ELLIPTA™, Section 2, Dosage and Administration; Section 3 Dosage and Administration; Section 11, Description; and the Medication Guide Figures **Exhibit D.**

Claim 17 reads as follows:

A pharmaceutical composition according to Claim 7 which is a dry powder composition.

Claim 18 reads as follows:

A pharmaceutical composition according to Claim 7 wherein the pharmaceutically acceptable carrier is lactose.

Claims 17 and 18 (dependent upon claim 7) read on the approved drug product which contains the active ingredient umeclidinium and a pharmaceutically acceptable anion in a pharmaceutical composition with lactose monohydrate, a pharmaceutically acceptable carrier. Bromine is a pharmaceutically acceptable anion. The approved active ingredient in the drug product, ANORO™ ELLIPTA™, is umeclidinium bromide. *See* package insert ANORO™ ELLIPTA™, Section 3 Dosage Forms and Strengths, and Section 11, Description, **Exhibit D**.

10. Relevant Dates Under 35 U.S.C. § 156 for Determination of Applicable Regulatory Review Period [37 C.F.R. § 1.740(a)(10)]:

The relevant dates and information pursuant to 35 U.S.C. § 156(g) are as follows:

The first Investigational New Drug Application (IND) for umeclidinium was submitted on July 14, 2009 and assigned IND No. 104,479 as a monotherapy inhalation product. Pursuant to 21 CFR 312.40(b)(2) the IND became effective on 13 August 2009. *See* IND Diligence Log, a copy attached hereto as **Exhibit J**.

U.S. Patent No. 7,488,827 issued on February 10, 2009. A copy of the '827 Patent is provided as **Exhibit G.**

The New Drug Application (NDA) for umeclidinium in combination with vilanterol was submitted on December 18, 2012 and assigned NDA No. 203,975. *See* NDA Approval letter, **Exhibit C**.

NDA No. 203,975 for umeclidinium in combination with vilanterol was approved December 18, 2013. *See* NDA Approval letter, **Exhibit C**.

11. Summary of Significant Events During Regulatory Review Period [§ 1.740(a)(11)]:

A summary of the significant activities undertaken by Applicant during the regulatory review period with respect to the approved product is seen in the IND No. 104,479 Diligence Log, **Exhibit J**.

(a) The IND Diligence Log reflects significant communications with FDA during regulatory periods. Such communications include, but are not limited to: submission of preclinical reports; registration of clinical protocols and amendments thereof; registration of clinical investigators and amendments thereof; submission of adverse event reports; submission of IND Annual Reports, etc.

(b) Periods between such communications enumerated in the IND Diligence Log reflect Applicant's diligent undertaking of the necessary clinical studies and other activities required by the FDA in order to obtain approval for Applicant's product.

Applicant has filed multiple IND's for this active ingredient. The drug's dosage form and strength during the IND phase of the mono-therapy product is identical to that of the drug's dosage form and strength in the approved combination drug product. The information from the studies of IND No. 104,479 are believed to be material to the approval of the approved ANORO™ ELLIPTA™ drug product, and are reflected in the NDA filing of the approved drug product.

IND No. 104,479 was filed on July 14, 2009. The effective date of IND No. 104,479 was August 13, 2009, as noted in the diligence log (**Exhibit J**), and is the date used for the calculations of the "Testing Phase" herein.

Applicant reserves their right to supplement the this extension with additional data and to supplement the chronology with materials from which it was derived or other evidence related to Applicant's conduct in obtaining the approval of ANORO™ ELLIPTA™, as provided by 21 C.F.R. § 60.32.

12. Statement Concerning Eligibility for and Duration of Extension Sought Under 35 U.S.C. § 156 [37 C.F.R. § 1.740(a)(1)]:

I. Applicant is of the opinion that U.S. Patent No. 7,488,827 is eligible for extension based upon meeting the requirements under 35 U.S.C. § 156 as follows:

(a) 35 U.S.C. § 156(a): U.S. Patent No. 7,488,827 claims a compound, and a composition of the active ingredient in the drug product

(b) 35 U.S.C. § 156(a)(1): U.S. Patent No. 7,488,827 has not expired before the submission of this application.

(c) 35 U.S.C. § 156(a)(2): The term of U.S. Patent No. 7,488,827 has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3): The application for patent term extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4): The active ingredient umeclidinium, as umeclidinium bromine, in the drug product ANORO™ ELLIPTA™, has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A): The commercial marketing or use of the active ingredient umeclidinium in the drug product ANORO™ ELLIPTA™, after the regulatory review period is the first permitted commercial marketing or use of umeclidinium under the provisions of §355 of the Federal Food Drugs and Cosmetics Act.

(g) 35 U.S.C. § 156(c)(4): No other patent has been extended for the same regulatory review period for active ingredient, umeclidinium bromide in the drug product ANORO™ ELLIPTA™ .

II. Applicant respectfully submits that the term of U.S. Patent No. 7,488,827 should be extended from April 27, 2025 up to and including December 18, 2027, or 966 days.

This extension was calculated as follows:

Patent Term Extension Calculation for U.S. Patent 7,488,827

Patent Issue Date:	February 10, 2009
IND Submission Date	July 14, 2009
IND Effective Date:	**August 13, 2009**
NDA Submission Date:	**December 18, 2012**
NDA Approval Date:	**December 18, 2013**

IND 104,479 Regulatory Review Period Occurring After Date of Patent Issuance
7/14/2009 – 12/17/2012

8/13/2009 – 12/17/2012 1228 days

Testing Phase

IND phase/2 = 1228/2 614

NDA 203,975 Regulatory Review Period
12/18/2012 – 12/18/2013

12/18/2012 – 12/18/2013 365 days

IND phase/2 + NDA phase = 614 + 365 = 979

Total Patent Term Extension: 979 days

5 Year Patent Term Extension Cap (35 USC §156 (g)(6)(A)) does not apply

14 years from NDA approval date
12/18/2013 + 14 years = 12/18/2027

Expiry without Patent Term Extension: 4/27/2025

Expiry with Extension: 4/27/2025 + 979 days = 1/1/2028

PTE of 1/1/2028 is > 12/18/2027 so PTE expiry will be 12/18/2027

Total PTE time is therefore 966 days, subject to the 14 year cap.

In a more formalized manner:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on August 13, 2009 and ended on December 17, 2013, which is a total of 979 days, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period," began on August 13, 2009 and ended on December 17, 2012, which is calculated at 614 days; and

(2) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii), the "Approval Period," began on December 18, 2012 and ended on December 18, 2013, which is 365 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in (a), less the sum of (1) and (2) below which is zero:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (February 10, 2009), which is zero days; and

(2) The number of days during which applicant did not act with due diligence, which is zero days; and

(c) The number of days as determined in (a) minus (b) above (979 days) when added to the original term of the patent (April 27, 2025) would result in the date of January 1, 2028.

(d) Fourteen years when added to the date of Approval of the NDA under 35 USC §156(C) (3), (December 14, 2013) would result in the date of December 18, 2027.

(e) The earlier date as determined in (c) and (d) above is December 18, 2027.

(f) The five year patent term extension cap (35 USC §156 (g)(6)(A) does not apply. Since U.S. Patent No. 7,488,827 issued after September 24, 1984, the period of extension may not exceed five years from the original expiration date of April 27, 2025. Five years added to April 27, 2025 would result in a date of April 27, 2030.

(g) The earlier date as determined in (e) and (f) above is December 18, 2027, which would apply.

As a supplement to items (10) and (11), Applicant provides additional information relating to regulatory filings and activities regarding:

(1) an Investigational New Drug Application (IND) for umeclidinium combination therapy with vilanterol was submitted on November 13, 2009 and assigned IND No. 106,616. Pursuant to 21 CFR 312.40(b)(2) this IND became effective on December 16, 2009.

(2) the approved product, BREO™ ELLIPTA™ contains two double-foil blister strips of powder formulation. Each blister on one strip contains a white powder mix of micronized fluticasone furoate and lactose monohydrate, and each blister on the other strip contains a white powder mix of micronized vilanterol trifenatate (40 mcg equivalent to 25 mcg of vilanterol), magnesium stearate and lactose monohydrate. The IND for BREO™ ELLIPTA™ was submitted on May 23, 2008 as IND No. 77,855. BREO™ ELLIPTA™ was approved on May 10, 2013 under NDA No. 204,275.

(3) The NDA for umeclidinium mono-therapy as ESPANDA™ ELLIPTA™ (now "INCRUSE ELLIPTA") was submitted to the FDA on April 30, 2013 and assigned NDA No. 205,382.

Should the Commissioner require Due Diligence logs for any of the INDs referenced above, please contact the undersigned for submission accordingly.

13. Statement Pursuant to 37 C.F.R. § 1.740(a)(13):

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

14. Applicable Fee [§ 1.740(a)(14)]:

The transmittal document filed herewith authorizes the U.S. Patent and Trademark Office to charge the prescribed fee pursuant to 37 C.F.R. §1.20(j) for receiving and acting upon the application for extension to the deposit account associated with the undersigned attorney. Applicants also authorize the Commissioner to charge any necessary fees for the filing of the enclosed documents, or credit any over-payment, to Deposit Account No. 19-2570.

15. Name and Address for Correspondence [§ 1.740(a)(15)]:

Please address all correspondence to:

Dara L. Dinner
Assistant Patent Counsel, Patents
GlaxoSmithKline
Global Patents (UW 2220)
709 Swedeland Road
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone: 610-270-5017
Fax: 610-270-5090
Email: Dara.l.Dinner@gsk.com

The correspondence address for U.S. Patent No. 7,488,827 is unchanged for all other purposes.

Two additional copies of this application are enclosed, in compliance with 37 C.F.R. § 1.740(b).

Respectfully submitted,

/ Dara L Dinner/
Dara L. Dinner
Attorney for Applicants
Registration No. 33,680

Date: February 6, 2014

Index of Exhibits

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PU60851
Docket Number

Assignment COPY Not for Recordation

WHEREAS, I/we **Dramane I. Laine a citizen of France, Michael R. Palovich a citizen of the United States of America, Brent W. McCleland a citizen of the United States of America; Chistopher E. Neipp a citizen of the United States of America; and Sonia M. Thomas a citizen of the United States of America,** and residing at King of Prussia, Pennsylvania, USA, respectively has/have invented or discovered certain improvements in **MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS** hereinafter referred to as said invention and improvements for which a priority application **60/565623** was filed on **27 April 2004** in the United States Patent and Trademark Office and for which a PCT international application is now being filed designating the United States of America and naming assignor as inventor, and in the United States only applicant/inventor. I/We hereby authorize and request that the filing date and application number of said PCT application, when known be inserted in parentheses below.

(PCT/US05/14386 filed 27 April 2005)

WHEREAS, **GLAXO GROUP LIMITED.**, a company incorporated in England, whose registered office is at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, England, is desirous of acquiring the whole right, title and interest in and to said invention and improvements, and in and to any applications for said invention and improvements and any Letters Patent to be obtained therefor, in all countries, including the United States, its territories and possessions;

NOW, THEREFORE, to all whom it may concern, be it known that I/we, **Dramane I. Laine, Michael R. Palovich, Brent W. McCleland, Christopher E. Neipp, and Sonia M. Thomas** for good and valuable consideration unto me/us moving, the receipt whereof is hereby acknowledged, have sold, assigned and transferred, and by these presents do sell, assign and transfer my/our whole right, title and interest in and to said invention and improvements to said **GLAXO GROUP LIMITED**, throughout the United States of America, its territories and possessions, and in and to said application and any extensions, reissues, continuations, continuations-in-part, and any divisions thereof, and in and to any and all Letters Patent of the United States of America;

AND, my/our whole right, title and interest in and to said invention and improvements to **GLAXO GROUP LIMITED**, in all other countries throughout the world, and in and to any applications in said other countries, and continuations-in-part, patents of addition, revalidation patents, patents of importation,

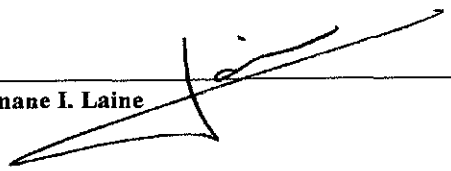
registrations, and any renewals, extensions and divisions thereof, and in and to any and all Letters Patent of said all other countries which may be granted on said invention and improvements including any priority rights under the International Convention.

AND, I/we do hereby authorize and request the issue of any Letters Patent in the respective areas referred to, to said **GLAXO GROUP LIMITED**, as assignees of my/our whole right, title and interest in and to the same for the sole use and behalf of the said assignees, their successors and assigns as their interests appear herein;

AND, I/we warrant that I/we have not knowingly conveyed to others any right in said invention, improvements, applications or patents or any license to use the same or to make, use or sell anything embodying or utilizing said invention and improvements and that I/we have good right to assign the same to **GLAXO GROUP LIMITED**;

AND, I/we the undersigned **Dramane I. Laine, Michael R. Palovich, Brent W. McCleland, Christopher E. Neipp, and Sonia M. Thomas** for the consideration aforesaid, do hereby agree that I/we or my/our executors or legal representatives, will provide information and make, execute and deliver any and all other instruments in writing, and any and all further acts, application papers, affidavits, assignments and other documents which may be necessary or desirable to more effectually secure to and vest in said **GLAXO GROUP LIMITED**, their successors and assigns, the whole right, title and interest in and to the said invention and improvements, applications, Letters Patent, rights, title and interest hereby sold, assigned and conveyed, or intended so to be. *This assignment should be deemed effective as of **27 April 2004***

IN WITNESS WHEREOF, I/we have hereunto set my/our hand(s) and affixed my/our seal(s) on the date(s) indicated below.



Inventor: **Dramane I. Laine** 04/26/05
Date

PU60851
Docket Number

IN WITNESS WHEREOF, I/we have hereunto set my/our hand(s) and affixed my/our seal(s) on the date(s) indicated below.

04/26/05
Inventor: **Michael R. Palovich** Date

IN WITNESS WHEREOF, I/we have hereunto set my/our hand(s) and affixed my/our seal(s) on the date(s) indicated below.

04/27/05
Inventor: **Brent W. McCleland** Date

IN WITNESS WHEREOF, I/we have hereunto set my/our hand(s) and affixed my/our seal(s) on the date(s) indicated below.

Christopher E. Neipp 06-28-05
Inventor: **Christopher E. Neipp** Date

IN WITNESS WHEREOF, I/we have hereunto set my/our hand(s) and affixed my/our seal(s) on the date(s) indicated below.

Sonia M. Thomas 06/28/05
Inventor: **Sonia M. Thomas** Date

PTO/SB/81 (06-04)
Approved for use through 12/31/2008. OMB 0651-0035
U.S. Patent and Trademark Office: US DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM		
	Patent Number	7,488,827
	Grant Date	10 February 2009
	First Named Inventor	Dramane Ibrahim LAINE
	Title	MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS
	Art Unit	
	Examiner Name	
	Attorney Docket Number	PU60851

I hereby appoint:

☒ **Practitioners associated with the Customer Numbers.** **20462**

Or

☐ Practitioner(s) named below:

Name	Registration Number

As my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

☐ The address associated with the above-mentioned Customer Number:

Or

☒ **The address associated with Customer Number 20462**

Or

☐ Firm or Individual Name:		
Address:		
Address:		
City:	State:	Zip:
Country:		
Telephone:	Fax:	

I am the:

☐ Applicant/Inventor:

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature: Theodore R. Furman	Date: 27 January 2014
Name: **Theodore R. Furman**	Telephone: 610-270-6857

Title and Company: Attorney and Authorised Official, **Glaxo Group Limited**

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of: _____ forms are submitted.

This collection of information is required by 37 CFR 1.31 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CRF 1.14. This collection is essential to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commission for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/SB/96 (06-08)
Approved for use through 2/29/2008. OMB 0651-0035
U.S. Patent and Trademark Office: US DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Glaxo Group Limited
Patent No 7,488,827 Issue Date: 10 February 2009
Entitled: MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

Glaxo Group Limited, a corporation, states that it is:

1. ☒ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____% in the patent application/patent identified above by virtue of either;

A. [x] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel **020365**, Frame **0661**, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[X] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being submitted for recordation pursuant to 37CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CRF Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Theodore R. Furman — Signature

27 January 2014 — Date

Theodore R. Furman — Printed or Typed Name

610-270-6857 — Telephone Number

Attorney and Authorised Official — Title

This collection of information is required by 37 CFR 1.31 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CRF 1.14. This collection is essential to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commission for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Power of Attorney

BY THIS POWER OF ATTORNEY given this Nineteenth day of June ,Two Thousand and Thirteen, **Glaxo Group Limited**, a company incorporated in **England** (Registration No. **00305979**) and having its registered office at **980 Great West Road, Brentford, Middlesex TW8 9GS, England** (hereinafter called "the Company"), **HEREBY** appoints all and any of its Directors, Secretary and Assistant Secretary for the time being, and **CARL W. BATTLE, KAREN A. CRAWLEY, MARCUS J. W. DALTON, RICHARD L. EASEMAN, THEODORE R. FURMAN, EDWARD R. GIMMI, CHARLES M. KINZIG, JOHN L. LEMANOWICZ, LORRAINE B. LING, WILLIAM R. MAJARIAN, HELEN K. QUILLIN, ALAN SCRIVNER and RACHEL M. THORNLEY** jointly and severally to be its true and lawful agents and attorneys (hereinafter called "the Attorneys," and each an "Attorney") on behalf and in the name of the Company or otherwise to do, perform, exercise or execute or concur with any other person or persons in doing, performing or exercising in or for any country or countries or jurisdiction in any part of the world all or any of the following powers, acts, deeds and things in connection with: letters patent, including extensions thereto (including supplementary protection certificates and the like); utility models; design rights; designs and all rights analogous thereto and all applications therefor, all of which are hereinafter called "Intellectual Property Rights", that is to say:

1. In any country or countries or jurisdiction in any part of the world to make application or cause application to be made for the grant or issue or transfer to the Company or registration in its name of Intellectual Property Rights and to take all steps necessary for the same to be prosecuted, maintained, withdrawn, renewed, enforced, defended or extended.

2. As the act and deed of the Company to sign, seal, deliver and execute all or any assignments or assurances, licences to the Company of or under any Intellectual Property Rights or the right to and interest in any inventions to be the subject of Intellectual Property Rights for the purpose of fully and effectually vesting and transferring the same in and to the Company.

3. As the act and deed of the Company to sign, seal, deliver and execute all or any assignments and acceptances of the transfer or assignment of such rights, and also any licences, sub-licences and consents from the Company of or under any Intellectual Property Rights or the right to and interest in any invention to be the subject of Intellectual Property Rights, for the purpose of fully and effectually vesting transferring or granting the same in and to any entity, whether in any country or countries or jurisdiction in any part of the world, in so far as such documents can be executed without the Company's seal being affixed thereto. For purposes of this Power of Attorney, the term "entity" means, and includes, any person, firm or company or group of persons or unincorporated body.

4. To commence, prosecute and defend any proceedings or applications whether judicial or extra judicial relating to Intellectual Property Rights and to maintain, withdraw or settle the same.

5. To act in regard to all official communications which may now or hereafter be addressed to the Attorneys relating to Intellectual Property Rights or the renewal thereof in such manner that the Attorneys may be recognised as the authorised agent(s) of the Company in all proceedings in relation thereto.

6. For and in connection with any Intellectual Property Rights to sign, seal, deliver and execute any Power of Attorney or other deed or document authorising any agent, including patent agents and attorneys, to act on behalf of the Company to the extent provided for in this Power of Attorney.

7. For all or any of the purposes contained herein as the act and deed of the Company to sign, seal, deliver, execute and do all such documents, deeds, agreements, instruments and to do such acts as shall be requisite or may be deemed proper for or in relation to the said purposes.

It is hereby agreed that:

(a) this Power of Attorney shall remain in force until **30 June 2015**, or (in respect of any Attorney) until his or her employment by the GlaxoSmithKline group of companies ceases, or until revocation by the Company, whichever first occurs; and

(b) in respect of any Attorney this Power of Attorney shall supersede and revoke with effect from the day and year first before written any Power of Attorney granted by the Company in favour of that Attorney covering all or some of the authorities herein contained.

(c) nothing in this Power of Attorney shall grant the Attorneys any power to conclude any contract on behalf of the Company or otherwise to bind the Company, save to the extent expressly provided herein.

(d) this Power of Attorney shall be construed, interpreted and governed by the laws of England. Any matter, claim or dispute arising out of or in connection with this Power of Attorney, whether contractual or non-contractual, is to be governed by and determined in accordance with English law.

AND THE COMPANY HEREBY RATIFIES and confirms and agrees to ratify and confirm all and whatsoever the Attorneys or any person, persons, firm or company appointed by them shall lawfully do or have done by virtue of the authorities herein contained.

AND THE COMPANY HEREBY INDEMNIFIES the Attorneys or any person, persons, firm or company appointed by them for all and whatsoever that they shall lawfully do or have done by virtue of the authorities herein contained.

AND THE COMPANY HEREBY DECLARES that all instruments executed under and by virtue of this Power shall be as valid and effectual as if executed as a deed by the Company or sealed by the Common Seal of the Company.

IN WITNESS whereof **Glaxo Group Limited** has caused its Common Seal to be hereunto affixed the day and year first before written.

The **COMMON SEAL** of)
Glaxo Group Limited
was hereto affixed in the presence of:)

Director

Paul Williamson
Authorised Signatory
For and on behalf of
The Wellcome Foundation Limited
Corporate Director

Director

Balbir Kelly-Bhila
Authorised Signatory
For and on behalf of
Edinburgh Pharmaceutical Industries Limited
Corporate Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203975

NDA APPROVAL

GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Mary V. Sides
Director, Global Regulatory Affairs

Dear Ms. Sides:

Please refer to your New Drug Application (NDA) dated and received December 18, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Anoro Ellipta (umeclidinium /vilanterol powder for inhalation), 62.5 mcg/ 25 mcg.

We acknowledge receipt of your amendments dated December 19, 2012, and February 1, 8 (2), 15, and 22, March 19 and 25 (3), April 12 and 26, May 8, 16, 20, and 31(2), June 7 and 11, August 1, 14 (2), and 16, September 6 and 25, October 3, 4, 18, and 28, November 15 and 18 (2), and December 10, 11, 12, and 13, 2013.

This new drug application provides for the use of Anoro Ellipta (umeclidinium /vilanterol powder for inhalation) for the long-term, once daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on December 10, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 203975.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because studies would be impossible or highly impracticable since the disease does not exist in pediatric patients.

EXPIRATION DATING PERIOD

A 24-month expiration dating period is granted for Anoro Ellipta when stored at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59° to 86°F (15° to 30°C).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Leila P. Hann, Regulatory Project Manager, at (301) 796-3367.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use the ANORO ELLIPTA inhaler safely and effectively. See full prescribing information for ANORO ELLIPTA.

ANORO ELLIPTA (umeclidinium and vilanterol inhalation powder)
FOR ORAL INHALATION USE
Initial U.S. Approval: 2013

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol. (5.1)**
- **The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma. (5.1)**

----------INDICATIONS AND USAGE----------

ANORO ELLIPTA is a combination of umeclidinium, an anticholinergic, and vilanterol, a long-acting beta$_2$-adrenergic agonist (LABA), indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). (1)

Important limitations: Not indicated for the relief of acute bronchospasm or for the treatment of asthma. (1, 5.2)

---------- DOSAGE AND ADMINISTRATION ----------

- For oral inhalation only. (2)
- Maintenance treatment of COPD: 1 inhalation of ANORO ELLIPTA once daily. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Inhalation Powder. Inhaler containing 2 double-foil blister strips of powder formulation for oral inhalation. One strip contains umeclidinium 62.5 mcg per blister and the other contains vilanterol 25 mcg per blister. (3)

----------CONTRAINDICATIONS----------

- Severe hypersensitivity to milk proteins or any ingredients. (4)

---------- WARNINGS AND PRECAUTIONS----------

- LABA increase the risk of asthma-related death. (5.1)
- Do not initiate in acutely deteriorating COPD or to treat acute symptoms. (5.2)
- Do not use in combination with an additional medicine containing LABA because of risk of overdose. (5.3)
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy. (5.5)
- Use with caution in patients with cardiovascular disorders. (5.7)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.8)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to contact a physician immediately if symptoms occur. (5.9)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur. (5.10)
- Be alert to hypokalemia and hyperglycemia. (5.11)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥1% and more common than placebo) include pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain, and chest pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole): Use with caution. May cause cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of vilanterol on cardiovascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)
- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of ANORO ELLIPTA with other anticholinergic-containing drugs. (7.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in ANORO™ ELLIPTA™ ***[see Warnings and Precautions (5.1)]*****.**

The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

1 INDICATIONS AND USAGE

ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

2 DOSAGE AND ADMINISTRATION

ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg) should be administered as 1 inhalation once daily by the orally inhaled route only.

ANORO ELLIPTA should be taken at the same time every day. Do not use ANORO ELLIPTA more than 1 time every 24 hours.

No dosage adjustment is required for geriatric patients, patients with renal impairment, or patients with moderate hepatic impairment *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Powder. Disposable light grey and red plastic inhaler containing 2 double-foil blister strips, each with 30 blisters containing powder intended for oral inhalation only. One strip contains umeclidinium (62.5 mcg per blister), and the other strip contains vilanterol (25 mcg per blister). An institutional pack containing 7 blisters per strip is also available.

4 CONTRAINDICATIONS

The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

- Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
- A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.
- No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes

ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.

ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists

ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose

may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

5.5 Paradoxical Bronchospasm

As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.

5.6 Hypersensitivity Reactions

Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.

5.7 Cardiovascular Effects

Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2)]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.8 Coexisting Conditions

ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.9 Worsening of Narrow-Angle Glaucoma

ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.10 Worsening of Urinary Retention

ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.11 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*

The following adverse reactions are described in greater detail in other sections:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%).

Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

Table 1. Adverse Reactions With ANORO ELLIPTA With ≥1% Incidence and More Common Than With Placebo in Subjects With Chronic Obstructive Pulmonary Disease

Adverse Reaction	Placebo (n = 555) %	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %
Infections and infestations				
Pharyngitis	<1	2	1	2
Sinusitis	<1	1	<1	1
Lower respiratory tract infection	<1	1	<1	<1
Gastrointestinal disorders				
Constipation	<1	1	<1	<1
Diarrhea	1	2	<1	2
Musculoskeletal and connective tissue disorders				
Pain in extremity	1	2	<1	2
Muscle spasms	<1	1	<1	<1
Neck pain	<1	1	<1	<1
General disorders and administration site conditions				
Chest pain	<1	1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than with placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest

pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.

12-Month Trial: In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)].*

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical

significance of these effects is not known, caution is advised in the coadministration of ANORO ELLIPTA with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.9, 5.10), Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking ANORO ELLIPTA.

Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

Nonteratogenic Effects: *Umeclidinium:* There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

ANORO ELLIPTA: It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

Umeclidinium: It is not known whether umeclidinium is excreted in human breast milk. However, administration to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

Vilanterol: It is not known whether vilanterol is excreted in human breast milk. However, other $beta_2$-agonists have been detected in human milk.

8.4 Pediatric Use

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of ANORO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 and older and, of those, 478 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment (CrCl<30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together

with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

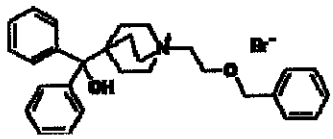
10.2 Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

11 DESCRIPTION

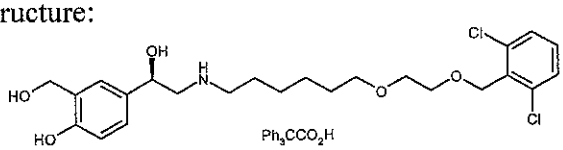
ANORO ELLIPTA is an inhalation powder drug product for delivery of a combination of umeclidinium (an anticholinergic) and vilanterol (a LABA) to patients by oral inhalation.

Umeclidinium bromide has the chemical name 1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide and the following chemical structure:



Umeclidinium bromide is a white powder with a molecular weight of 508.5, and the empirical formula is $C_{29}H_{34}NO_2$•Br (as a quaternary ammonium bromide compound). It is slightly soluble in water.

Vilanterol trifenatate has the chemical name triphenylacetic acid-4-{(1*R*)-2-[(6-{2-[(2,6-dicholorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1) and the following chemical structure:



Vilanterol trifenatate is a white powder with a molecular weight of 774.8, and the empirical formula is $C_{24}H_{33}Cl_2NO_5$•$C_{20}H_{16}O_2$. It is practically insoluble in water.

ANORO ELLIPTA is a light grey and red plastic inhaler containing 2 double-foil blister strips. Each blister on one strip contains a white powder mix of micronized umeclidinium bromide (74.2 mcg equivalent to 62.5 mcg of umeclidinium), magnesium stearate (75 mcg), and

lactose monohydrate (to 12.5 mg), and each blister on the other strip contains a white powder mix of micronized vilanterol trifenatate (40 mcg equivalent to 25 mcg of vilanterol), magnesium stearate (125 mcg), and lactose monohydrate (to 12.5 mg). The lactose monohydrate contains milk proteins. After the inhaler is activated, the powder within both blisters is exposed and ready for dispersion into the airstream created by the patient inhaling through the mouthpiece.

Under standardized *in vitro* test conditions, ANORO ELLIPTA delivers 55 mcg of umeclidinium and 22 mcg of vilanterol per dose when tested at a flow rate of 60 L/min for 4 seconds.

In adult subjects with obstructive lung disease and severely compromised lung function (COPD with FEV_1/FVC less than 70% and FEV_1 less than 30% predicted or FEV_1 less than 50% predicted plus chronic respiratory failure), mean peak inspiratory flow through the ELLIPTA inhaler was 66.5 L/min (range: 43.5 to 81.0 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ANORO ELLIPTA: ANORO ELLIPTA contains both umeclidinium and vilanterol. The mechanisms of action described below for the individual components apply to ANORO ELLIPTA. These drugs represent 2 different classes of medications (an anticholinergic and a LABA) that have different effects on clinical and physiological indices.

Umeclidinium: Umeclidinium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of umeclidinium is predominantly a site-specific effect.

Vilanterol: Vilanterol is a LABA. *In vitro* tests have shown the functional selectivity of vilanterol was similar to salmeterol. The clinical relevance of this *in vitro* finding is unknown.

Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenergic agonist drugs, including vilanterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic

AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

12.2 Pharmacodynamics

Cardiovascular Effects: *Healthy Subjects:* QTc interval prolongation was studied in a double-blind, multiple dose, placebo- and positive-controlled crossover trial in 86 healthy subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 4.6 (7.1) ms and 8.2 (10.7) ms for umeclidinium/vilanterol 125 mcg/25 mcg and umeclidinium/vilanterol 500 mcg/100 mcg (8/4 times the recommended dosage), respectively.

A dose-dependent increase in heart rate was also observed. The maximum mean (95% upper confidence bound) difference in heart rate from placebo after baseline correction was 8.8 (10.5) beats/min and 20.5 (22.3) beats/min seen 10 minutes after dosing for umeclidinium/vilanterol 125 mcg/25 mcg and umeclidinium/vilanterol 500 mcg/100 mcg, respectively.

Chronic Obstructive Pulmonary Disease: The effect of ANORO ELLIPTA on cardiac rhythm in subjects diagnosed with COPD was assessed using 24-hour Holter monitoring in 6- and 12-month trials: 53 subjects received ANORO ELLIPTA, 281 subjects received umeclidinium/vilanterol 125 mcg/25 mcg, and 182 subjects received placebo. No clinically meaningful effects on cardiac rhythm were observed.

12.3 Pharmacokinetics

Linear pharmacokinetics was observed for umeclidinium (62.5 to 500 mcg) and vilanterol (25 to 100 mcg).

Absorption: *Umeclidinium:* Umeclidinium plasma levels may not predict therapeutic effect. Following inhaled administration of umeclidinium in healthy subjects, C_{max} occurred at 5 to 15 minutes. Umeclidinium is mostly absorbed from the lung after inhaled doses with minimum contribution from oral absorption. Following repeat dosing of inhaled ANORO ELLIPTA, steady state was achieved within 14 days with up to 1.8-fold accumulation.

Vilanterol: Vilanterol plasma levels may not predict therapeutic effect. Following inhaled administration of vilanterol in healthy subjects, C_{max} occurred at 5 to 15 minutes. Vilanterol is mostly absorbed from the lung after inhaled doses with negligible contribution from oral absorption. Following repeat dosing of inhaled ANORO ELLIPTA, steady state was achieved within 14 days with up to 1.7-fold accumulation.

Distribution: *Umeclidinium:* Following intravenous administration to healthy subjects, the mean volume of distribution was 86 L. *In vitro* plasma protein binding in human plasma was on average 89%.

Vilanterol: Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 165 L. *In vitro* plasma protein binding in human plasma was on average 94%.

Metabolism: *Umeclidinium: In vitro* data showed that umeclidinium is primarily metabolized by the enzyme cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-

glycoprotein (P-gp) transporter. The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O-dealkylation) followed by conjugation (e.g., glucuronidation), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low.

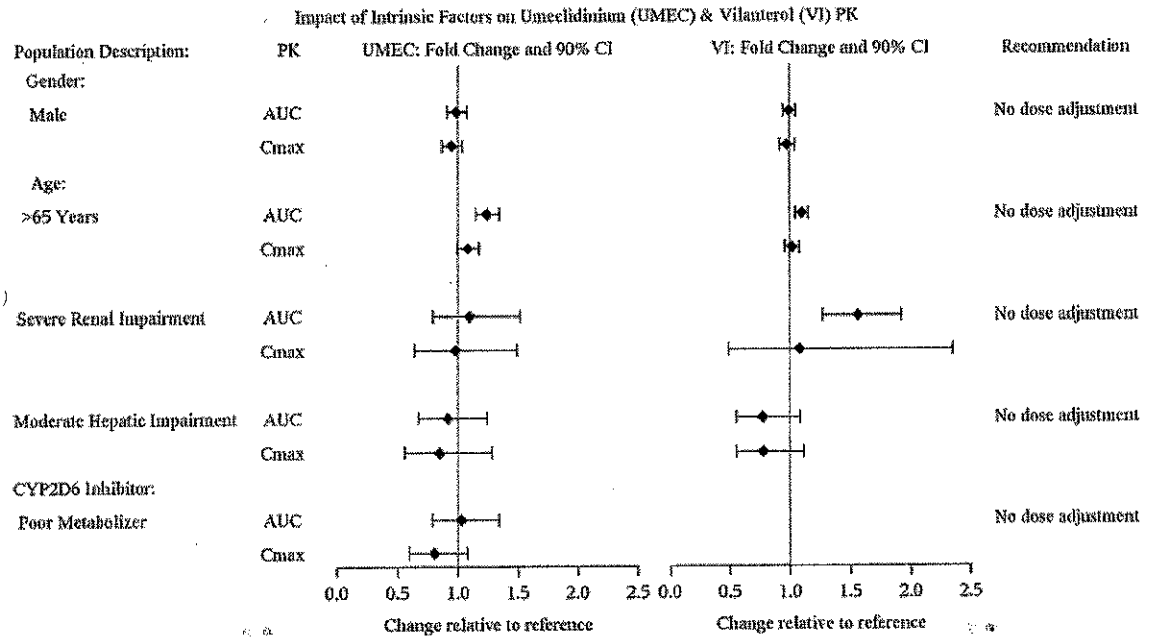
Vilanterol: In vitro data showed that vilanterol is metabolized principally by CYP3A4 and is a substrate for the P-gp transporter. Vilanterol is metabolized to a range of metabolites with significantly reduced β_1- and β_2-agonist activity.

Elimination: *Umeclidinium:* Following intravenous dosing with radio-labeled umeclidinium, mass balance showed 58% of the radio-label in the feces and 22% in the urine. The excretion of the drug-related material in the feces following intravenous dosing indicated elimination in the bile. Following oral dosing to healthy male subjects, radio-label recovered in feces was 92% of the total dose and that in urine was less than 1% of the total dose, suggesting negligible oral absorption. The effective half-life after once daily dosing is 11 hours.

Vilanterol: Following oral administration of radio-labeled vilanterol, mass balance showed 70% of the radio-label in the urine and 30% in the feces. The effective half-life for vilanterol, as determined from inhalation administration of multiple doses, is 11 hours.

Special Populations: The effects of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics of umeclidinium and vilanterol are shown in Figure 1. Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age (40 to 93 years) (see Figure 1), gender (69% male) (see Figure 1), inhaled corticosteroid use (48%), or weight (34 to 161 kg) on systemic exposure of either umeclidinium or vilanterol. In addition, there was no evidence of a clinically significant effect of race.

Figure 1. Impact of Intrinsic Factors on the Pharmacokinetics (PK) of Umeclidinium and Vilanterol



Hepatic Impairment: The impact of hepatic impairment on the pharmacokinetics of ANORO ELLIPTA has been evaluated in subjects with moderate hepatic impairment (Child-Pugh score of 7-9). There was no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC) (see Figure 1). There was no evidence of altered protein binding in subjects with moderate hepatic impairment compared with healthy subjects. ANORO ELLIPTA has not been evaluated in subjects with severe hepatic impairment.

Renal Impairment: The pharmacokinetics of ANORO ELLIPTA has been evaluated in subjects with severe renal impairment (creatinine clearance <30 mL/min). Umeclidinium systemic exposure was not increased and vilanterol systemic exposure ($AUC_{(0-24)}$) was 56% higher in subjects with severe renal impairment compared with healthy subjects (see Figure 1). There was no evidence of altered protein binding in subjects with severe renal impairment compared with healthy subjects.

Drug Interactions: When umeclidinium and vilanterol were administered in combination by the inhaled route, the pharmacokinetic parameters for each component were similar to those observed when each active substance was administered separately.

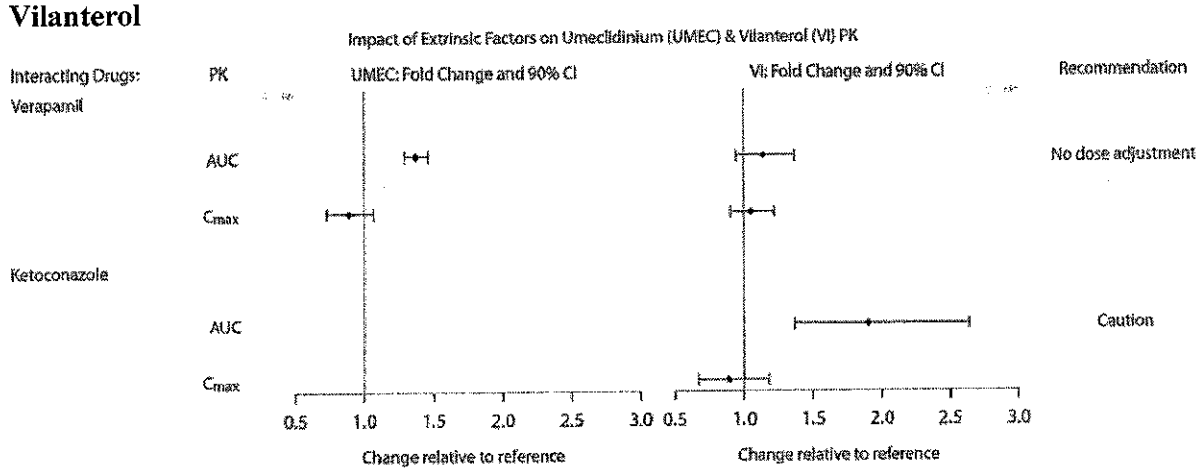
Inhibitors of Cytochrome P450 3A4: Vilanterol is a substrate of CYP3A4. A double-blind, repeat-dose, 2-way crossover drug interaction trial was conducted in healthy subjects to investigate the pharmacokinetic and pharmacodynamic effects of vilanterol 25 mcg as an inhalation powder with ketoconazole 400 mg. The plasma concentrations of vilanterol were higher after single and repeated doses when coadministered with ketoconazole than with placebo

(see Figure 2). The increase in vilanterol exposure was not associated with an increase in beta-agonist–related systemic effects on heart rate or blood potassium.

Inhibitors of P-glycoprotein Transporter: Umeclidinium and vilanterol are both substrates of P-gp. The effect of the moderate P-gp transporter inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium and vilanterol was assessed in healthy subjects. No effect on umeclidinium or vilanterol C_{max} was observed; however, an approximately 1.4-fold increase in umeclidinium AUC was observed with no effect on vilanterol AUC (see Figure 2).

Inhibitors of Cytochrome P450 2D6: In vitro metabolism of umeclidinium is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to umeclidinium (500 mcg) (8 times the approved dose) was observed following repeat daily inhaled dosing in CYP2D6 normal (ultrarapid, extensive, and intermediate metabolizers) and poor metabolizer subjects (see Figure 1).

Figure 2. Impact of Extrinsic Factors on the Pharmacokinetics (PK) of Umeclidinium and Vilanterol



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for individual components, umeclidinium and vilanterol, as described below.

Umeclidinium: Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 mcg/kg/day and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vivo* rat bone marrow micronucleus assay, *in vivo* rat unscheduled DNA synthesis (UDS) assay, and *in vitro* Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the *in vitro* mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

14 CLINICAL STUDIES

The safety and efficacy of ANORO ELLIPTA were evaluated in a clinical development program that included 6 dose-ranging trials, 4 lung function trials of 6 months' duration (2 placebo-controlled and 2 active-controlled), two 12-week crossover trials, and a 12-month long-term safety trial. The efficacy of ANORO ELLIPTA is based primarily on the dose-ranging trials in 1,908 subjects with COPD or asthma and the 2 placebo-controlled confirmatory trials with additional support from the 2 active-controlled and 2 crossover trials in 5,388 subjects with COPD.

14.1 Dose-Ranging Trials

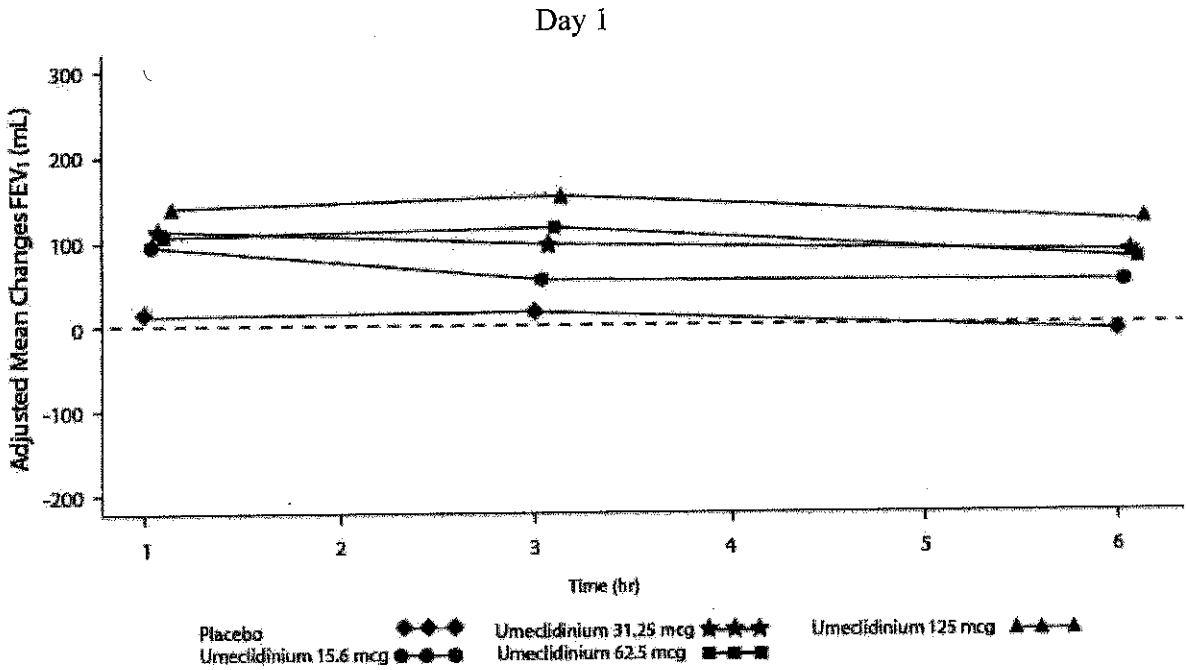
Dose selection for ANORO ELLIPTA for COPD was based on dose-ranging trials for the individual components, vilanterol and umeclidinium. Based on the findings from these studies, once-daily doses of umeclidinium/vilanterol 62.5 mcg/25 mcg and umeclidinium/vilanterol 125 mcg/25 mcg were evaluated in the confirmatory COPD trials. **ANORO ELLIPTA is not indicated for asthma.**

Umeclidinium: Dose selection for umeclidinium in COPD was supported by a 7-day, randomized, double-blind, placebo-controlled, crossover trial evaluating 4 doses of umeclidinium (15.6 to 125 mcg) or placebo dosed once daily in the morning in 163 subjects with COPD. A dose ordering was observed, with the 62.5- and 125-mcg doses demonstrating larger improvements in FEV_1 over 24 hours compared with the lower doses of 15.6 and 31.25 mcg (Figure 3).

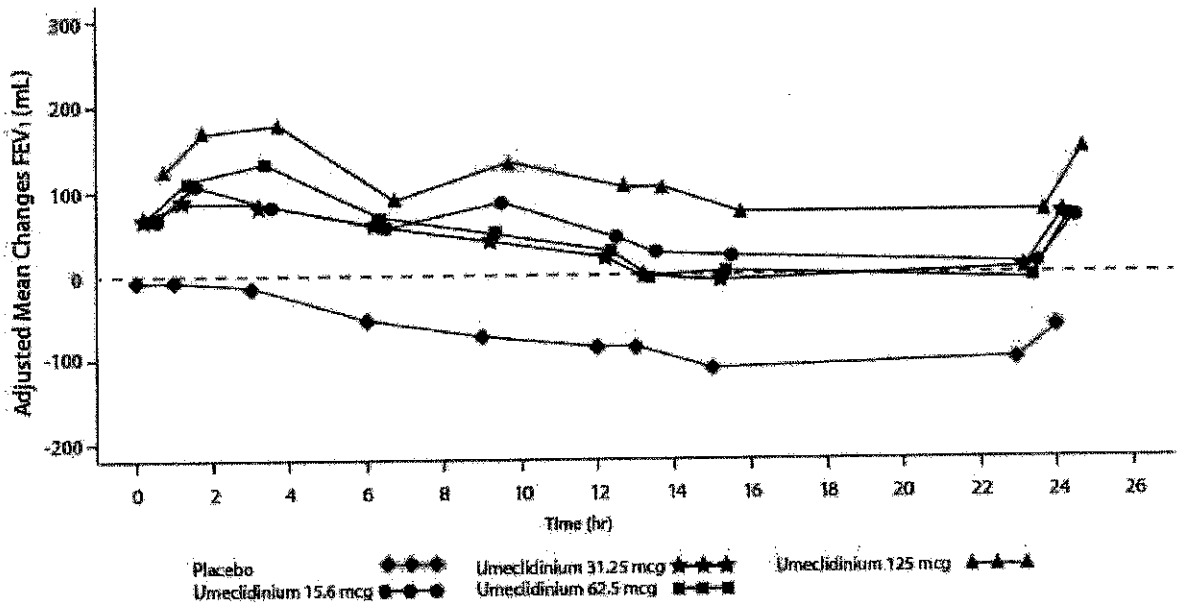
The differences in trough FEV_1 from baseline after 7 days for placebo and the 15.6-, 31.25-, 62.5-, and 125-mcg doses were -74 mL (95% CI: -118, -31), 38 mL (95% CI: -6, 83), 27 mL (95% CI: -18, 72), 49 mL (95% CI: 6, 93), and 109 mL (95% CI: 65, 152), respectively. Two additional dose-ranging trials in subjects with COPD demonstrated minimal additional benefit at doses above 125 mcg. The dose-ranging results supported the evaluation of 2 doses of umeclidinium, 62.5 and 125 mcg, in the confirmatory COPD trials to further assess dose response.

Evaluations of dosing interval by comparing once- and twice-daily dosing supported selection of a once-daily dosing interval for further evaluation in the confirmatory COPD trials.

Figure 3. Adjusted Mean Change From Baseline in Post-Dose Serial FEV_1 (mL) on Days 1 and 7



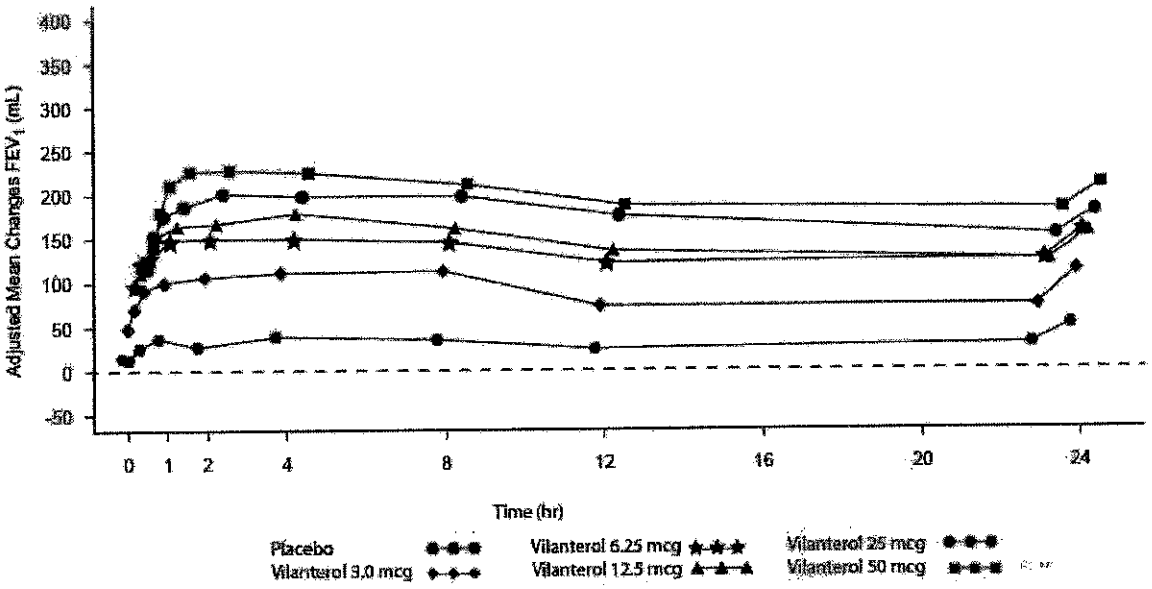
Day 7



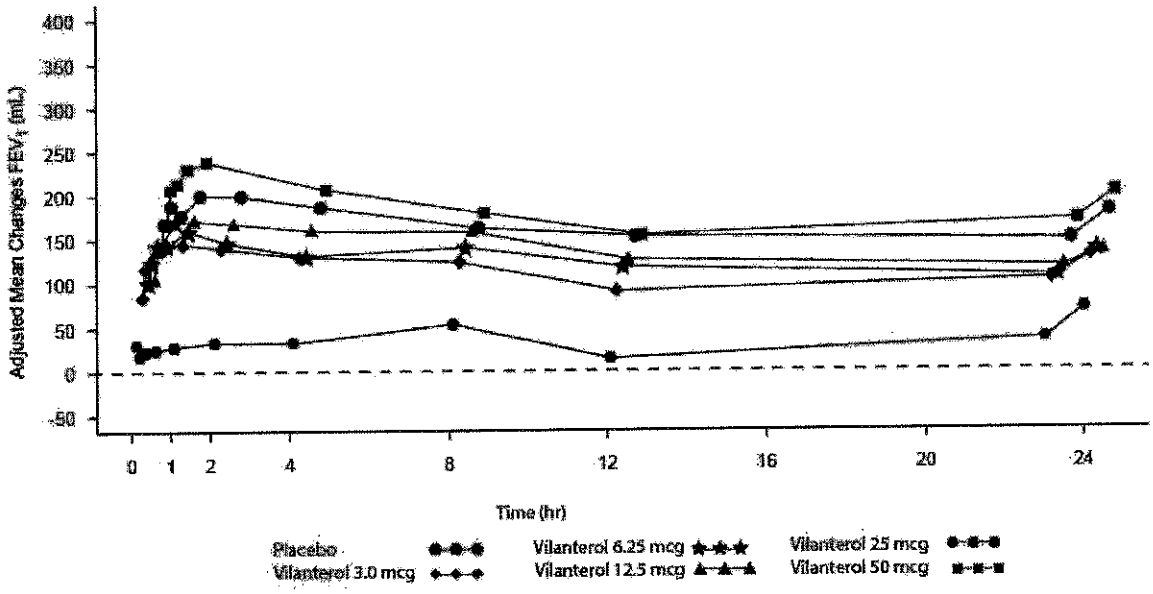
Vilanterol: Dose selection for vilanterol in COPD was supported by a 28-day, randomized, double-blind, placebo-controlled, parallel-group trial evaluating 5 doses of vilanterol (3 to 50 mcg) or placebo dosed in the morning in 602 subjects with COPD. Results demonstrated dose-related increases in FEV_1 compared with placebo at Day 1 and Day 28 (Figure 4).

Figure 4. Adjusted Mean Change From Baseline in Post-Dose Serial FEV_1 (0-24 hr, mL) on Days 1 and 28

Day 1



Day 28



The differences in trough FEV_1 after Day 28 from baseline for placebo and the 3-, 6.25-, 12.5-, 25-, and 50-mcg doses were 29 mL (95% CI: -8, 66), 120 mL (95% CI: 83, 158), 127 mL (95% CI: 90, 164), 138 mL (95% CI: 101, 176), 166 mL (95% CI: 129, 203), and 194 mL (95%

CI: 156, 231), respectively. These results supported the evaluation of vilanterol 25 mcg in the confirmatory COPD trials.

Dose-ranging trials in subjects with asthma evaluated doses from 3 to 50 mcg and 12.5 mcg once-daily versus 6.25 mcg twice-daily dosing frequency. The results supported the selection of the vilanterol 25 mcg once-daily dose for further evaluation in the confirmatory COPD trials.

14.2 Confirmatory Trials

The clinical development program for ANORO ELLIPTA included two 6-month, randomized, double-blinded, placebo-controlled, parallel-group trials; two 6-month active-controlled trials; and two 12-week crossover trials in subjects with COPD designed to evaluate the efficacy of ANORO ELLIPTA on lung function. The 6-month trials treated 4,733 subjects that had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a post-albuterol FEV_1 less than or equal to 70% of predicted normal values, had a ratio of FEV_1/FVC of less than 0.7, and had a Modified Medical Research Council (mMRC) score greater than or equal to 2. Of the 4,713 subjects included in the efficacy analysis, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted FEV_1 was 48% (range: 13% to 76%), the mean post-bronchodilator FEV_1/FVC ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -36% to 109%).

Trial 1 evaluated ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), umeclidinium 62.5 mcg, vilanterol 25 mcg, and placebo. The primary endpoint was change from baseline in trough (predose) FEV_1 at Day 169 (defined as the mean of the FEV_1 values obtained at 23 and 24 hours after the previous dose on Day 168) compared with placebo, umeclidinium 62.5 mcg, and vilanterol 25 mcg. The comparison of ANORO ELLIPTA with umeclidnium 62.5 mcg and vilanterol 25 mcg was assessed to evaluate the contribution of the individual comparators to ANORO ELLIPTA. ANORO ELLIPTA demonstrated a larger increase in mean change from baseline in trough (predose) FEV_1 relative to placebo, umeclidinium 62.5 mcg, and vilanterol 25 mcg (Table 2).

Table 2. Least Squares (LS) Mean Change From Baseline in Trough FEV_1 (mL) at Day 169 in the Intent-to-Treat Population (Trial 1)

		Trough FEV_1 (mL) at Day 169		
		Difference From		
Treatment	n	Placebo (95% CI) n = 280	Umeclidinium 62.5 mcg[a] (95% CI) n = 418	Vilanterol 25 mcg[a] (95% CI) n = 421
ANORO ELLIPTA	413	167 (128, 207)	52 (17, 87)	95 (60, 130)

n = Number in intent-to-treat population.

[a] The umeclidinium and vilanterol comparators used the same inhaler and excipients as ANORO ELLIPTA.

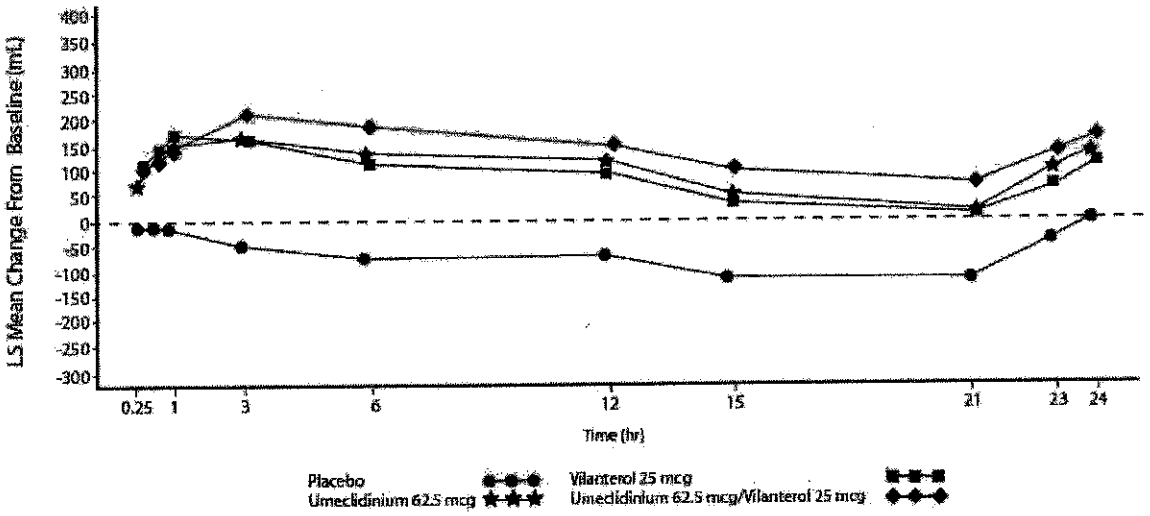
Trial 2 had a similar study design as Trial 1 but evaluated umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, and placebo. Results for umeclidinium/vilanterol 125 mcg/25 mcg in Trial 2 were similar to those observed for ANORO ELLIPTA in Trial 1.

Results from the two active-controlled trials and the two 12-week trials provided additional support for the efficacy of ANORO ELLIPTA in terms of change from baseline in trough FEV_1 compared with the single-ingredient comparators and placebo.

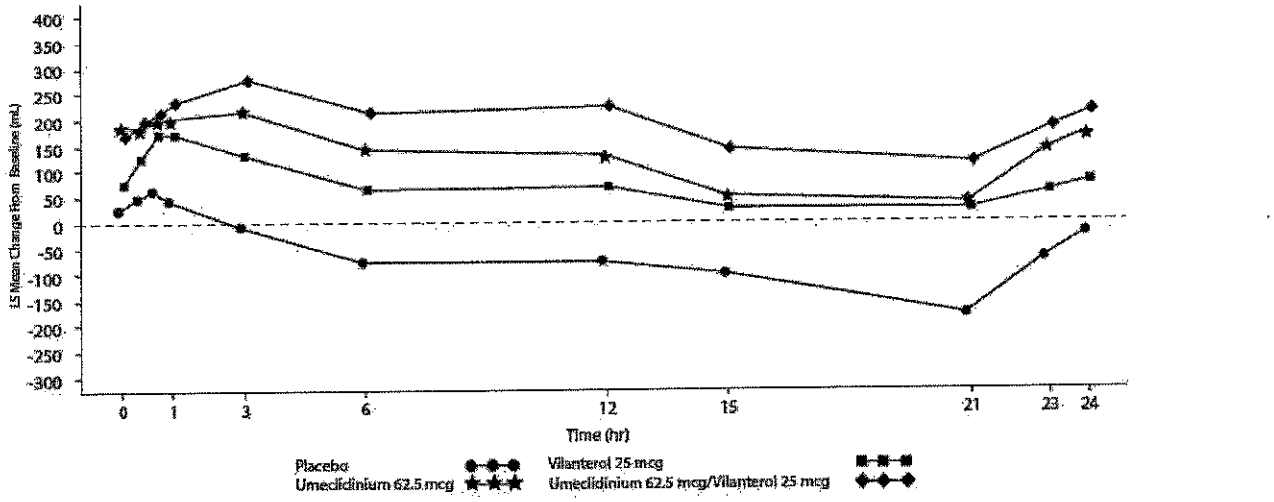
Serial spirometric evaluations throughout the 24-hour dosing interval were performed in a subset of subjects (n = 197) at Days 1, 84, and 168 in Trial 1. Results from Trial 1 at Day 1 and Day 168 are shown in Figure 5.

Figure 5. Least Squares (LS) Mean Change From Baseline in FEV_1 (mL) Over Time (0-24 h) on Days 1 and 168 (Trial 1 Subset Population)

Day 1



Day 168



The peak FEV_1 was defined as the maximum FEV_1 recorded within 6 hours after the dose of trial medicine on Days 1, 28, 84, and 168 (measurements recorded at 15 and 30 minutes and 1, 3, and 6 hours). The mean peak FEV_1 improvement from baseline for ANORO ELLIPTA compared with placebo at Day 1 and at Day 168 was 167 and 224 mL, respectively. The median time to onset on Day 1, defined as a 100-mL increase from baseline in FEV_1, was 27 minutes in subjects receiving ANORO ELLIPTA.

16 HOW SUPPLIED/STORAGE AND HANDLING

ANORO ELLIPTA is supplied as a disposable light grey and red plastic inhaler containing 2 double-foil blister strips with 30 blisters each. The inhaler is packaged in a moisture-protective foil tray with a desiccant and a peelable lid (NDC 0173-0869-10).

ANORO ELLIPTA is also supplied in an institutional pack of a disposable light grey and red plastic inhaler containing 2 double-foil blister strips with 7 blisters each. The inhaler is packaged in a moisture protective foil tray with a desiccant and a peelable lid (NDC 0173-0869-06).

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. Keep out of reach of children.

ANORO ELLIPTA should be stored inside the unopened moisture-protective foil tray and only removed from the tray immediately before initial use. Discard ANORO ELLIPTA 6 weeks after opening the foil tray or when the counter reads "0" (after all blisters have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Asthma-Related Death: Inform patients that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma.

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Symptoms get worse
- Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with ANORO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists: Instruct patients to not use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA.

Risks Associated With Beta-Agonist Therapy: Inform patients of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Narrow-Angle Glaucoma: Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Urinary Retention: Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

ANORO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
GlaxoSmithKline
Research Triangle Park, NC 27709

ANR:1PI

MEDICATION GUIDE

ANORO™ [*a-nor'oh*] ELLIPTA™
(umeclidinium and vilanterol inhalation powder)

Read the Medication Guide that comes with ANORO ELLIPTA before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ANORO ELLIPTA?

ANORO ELLIPTA is only approved for use in chronic obstructive pulmonary disease (COPD). ANORO ELLIPTA is NOT approved for use in asthma.

ANORO ELLIPTA can cause serious side effects, including:

- **People with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines, such as vilanterol (one of the medicines in ANORO ELLIPTA), have an increased risk of death from asthma problems.**
- **It is not known if LABA medicines, such as vilanterol (one of the medicines in ANORO ELLIPTA), increase the risk of death in people with COPD.**
- **Call your healthcare provider if breathing problems worsen over time while using ANORO ELLIPTA.** You may need different treatment.
- **Get emergency medical care if:**
  - your breathing problems worsen quickly
  - you use your rescue inhaler, but it does not relieve your breathing problems.

What is ANORO ELLIPTA?

ANORO ELLIPTA combines an anticholinergic, umeclidinium, and a LABA medicine, vilanterol.

Anticholinergic and LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.

ANORO ELLIPTA is a prescription medicine used to treat COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. ANORO ELLIPTA is used long term as 1 inhalation, 1 time each day, to improve symptoms of COPD for better breathing.

- **ANORO ELLIPTA is not for use to treat sudden symptoms of COPD.** Always have a rescue inhaler (an inhaled, short-acting bronchodilator) with you to treat sudden symptoms. If you do not have a rescue inhaler, contact your healthcare provider to have one prescribed for you.
- **ANORO ELLIPTA is not for the treatment of asthma. It is not known if ANORO ELLIPTA is safe and effective in people with asthma.**
- ANORO ELLIPTA should not be used in children. It is not known if ANORO ELLIPTA is safe and effective in children.

Who should not use ANORO ELLIPTA?

Do not use ANORO ELLIPTA if you:

- have a severe allergy to milk proteins. Ask your healthcare provider if you are not sure.
- are allergic to umeclidinium, vilanterol, or any of the ingredients in ANORO ELLIPTA. See "What are the ingredients in ANORO ELLIPTA?" below for a complete list of ingredients.

What should I tell my healthcare provider before using ANORO ELLIPTA?

Tell your healthcare provider about all of your health conditions, including if you:

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems
- have diabetes
- have liver problems
- have eye problems such as glaucoma. ANORO ELLIPTA may make your glaucoma worse.
- have prostate or bladder problems, or problems passing urine. ANORO ELLIPTA may make these problems worse.
- are allergic to any of the ingredients in ANORO ELLIPTA, any other medicines, or food products. See "What are the ingredients in ANORO ELLIPTA?" below for a complete list of ingredients.
- have any other medical conditions
- are pregnant or planning to become pregnant. It is not known if ANORO ELLIPTA may harm your unborn baby.
- are breastfeeding. It is not known if the medicines in ANORO ELLIPTA pass into your milk and if they can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ANORO ELLIPTA and certain other medicines may interact with each other. This may cause serious side effects.

Especially tell your healthcare provider if you take:

- anticholinergics (including tiotropium, ipratropium, aclidinium)
- atropine

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use ANORO ELLIPTA?

Read the step-by-step instructions for using ANORO ELLIPTA at the end of this Medication Guide.

- **Do not** use ANORO ELLIPTA unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- Use ANORO ELLIPTA exactly as your healthcare provider tells you to use it. **Do not** use ANORO ELLIPTA more often than prescribed.
- Use 1 inhalation of ANORO ELLIPTA 1 time each day. Use ANORO ELLIPTA at the same time each day.
- If you miss a dose of ANORO ELLIPTA, take it as soon as you remember. Do not take more than 1 inhalation each day. Take your next dose at your usual time. Do not take 2 doses at one time.
- If you take too much ANORO ELLIPTA, call your healthcare provider or go to the nearest hospital emergency room right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- **Do not use other medicines that contain a LABA or an anticholinergic for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are LABA or anticholinergic medicines.
- Do not stop using ANORO ELLIPTA unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **ANORO ELLIPTA does not relieve sudden symptoms.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems get worse
  - you need to use your rescue inhaler more often than usual
  - your rescue inhaler does not work as well to relieve your symptoms

What are the possible side effects with ANORO ELLIPTA?

ANORO ELLIPTA can cause serious side effects, including:

- **See "What is the most important information I should know about ANORO ELLIPTA?"**
- **sudden breathing problems immediately after inhaling your medicine**

- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of the face, mouth, and tongue
  - breathing problems
- **effects on your heart**
  - increased blood pressure
  - a fast and/or irregular heartbeat
  - chest pain
- **effects on your nervous system**
  - tremor
  - nervousness
- **new or worsened eye problems including acute narrow-angle glaucoma.** Acute narrow-angle glaucoma can cause permanent loss of vision if not treated. Symptoms of acute narrow-angle glaucoma may include:
  - eye pain or discomfort
  - nausea or vomiting
  - blurred vision
  - seeing halos or bright colors around lights
  - red eyes

  If you have these symptoms, call your doctor right away before taking another dose.
- **urinary retention.** People who take ANORO ELLIPTA may develop new or worse urinary retention. Symptoms of urinary retention may include:
  - difficulty urinating
  - painful urination
  - urinating frequently
  - urination in a weak stream or drips

  If you have these symptoms of urinary retention, stop taking ANORO ELLIPTA and call your doctor right away before taking another dose.
- **changes in laboratory blood levels**, including high levels of blood sugar (hyperglycemia) and low levels of potassium (hypokalemia)

Common side effects of ANORO ELLIPTA include:

- sore throat
- sinus infection

- lower respiratory infection
- common cold symptoms
- constipation
- diarrhea
- pain in your arms or legs
- muscle spasms
- neck pain
- chest pain

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with ANORO ELLIPTA. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store ANORO ELLIPTA?

- Store ANORO ELLIPTA at room temperature between 68°F and 77°F (20°C and 25°C). Keep in a dry place away from heat and sunlight.
- Store ANORO ELLIPTA in the unopened foil tray and only open when ready for use.
- Safely throw away ANORO ELLIPTA in the trash 6 weeks after you open the foil tray or when the counter reads "0", whichever comes first. Write the date you open the tray on the label on the inhaler.
- **Keep ANORO ELLIPTA and all medicines out of the reach of children.**

General information about ANORO ELLIPTA

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use ANORO ELLIPTA for a condition for which it was not prescribed. Do not give your ANORO ELLIPTA to other people, even if they have the same condition that you have. It may harm them.

This Medication Guide summarizes the most important information about ANORO ELLIPTA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ANORO ELLIPTA that was written for healthcare professionals.

For more information about ANORO ELLIPTA, call 1-888-825-5249 or visit our website at www.myANORO.com.

What are the ingredients in ANORO ELLIPTA?

Active ingredients: umeclidinium, vilanterol
Inactive ingredients: lactose monohydrate (contains milk proteins), magnesium stearate

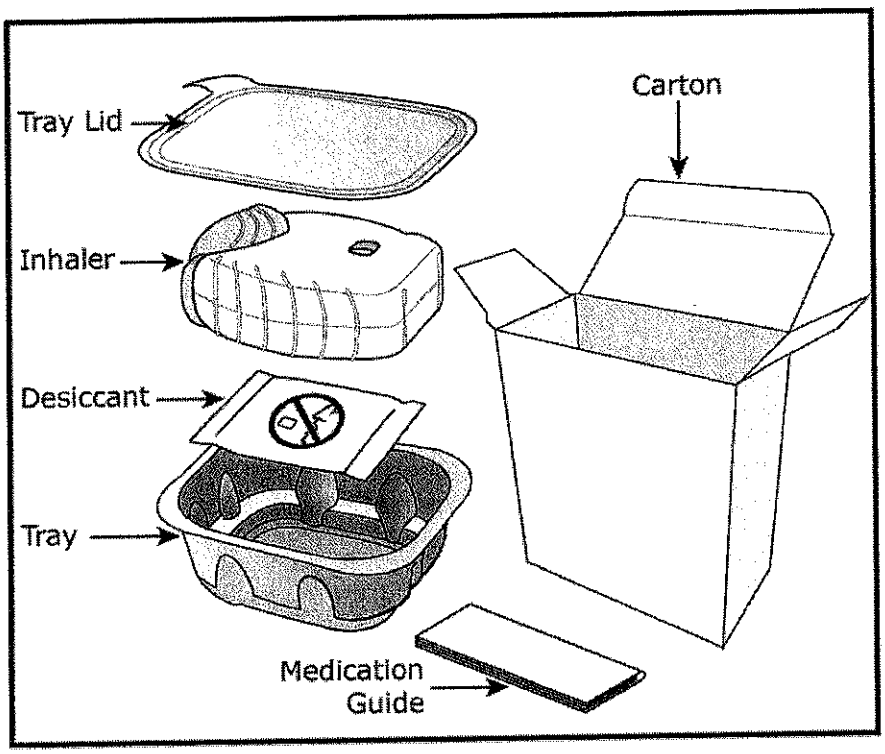
Instructions for Use

For Oral Inhalation Only.

Read this before you start:

- **If you open and close the cover without inhaling the medicine, you will lose the dose.**
- **The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled.**
- **It is not possible to accidentally take a double dose or an extra dose in one inhalation.**

Your ANORO ELLIPTA inhaler



How to use your inhaler

- ANORO ELLIPTA comes in a foil tray.
- Peel back the lid to open the tray. See Figure A.
- The tray contains a desiccant to reduce moisture. Do not eat or inhale. Throw it away in the household trash out of reach of children and pets. See Figure B.

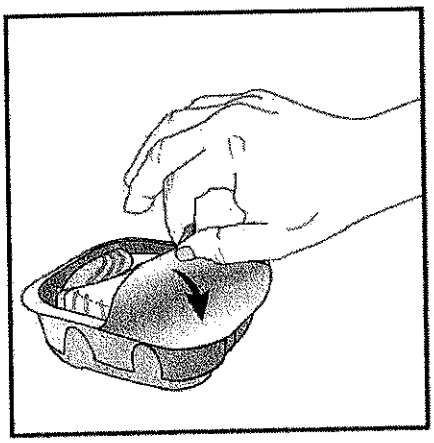


Figure A

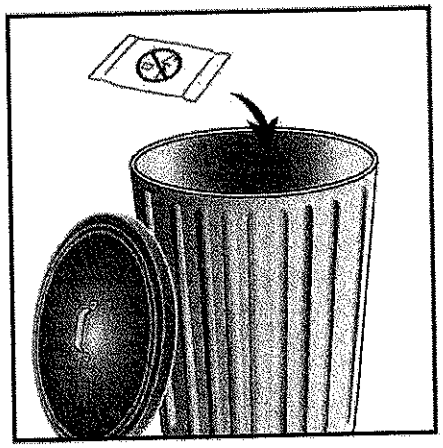


Figure B

Important Notes:

- Your inhaler contains 30 doses (7 doses if you have a sample or institutional pack).
- Each time you open the cover of the inhaler fully (you will hear a clicking sound), a dose is ready to be inhaled. This is shown by a decrease in the number on the counter.
- If you open and close the cover without inhaling the medicine, you will lose the dose. The lost dose will be held in the inhaler, but it will no longer be available to be inhaled. It is not possible to accidentally take a double dose or an extra dose in one inhalation.
- **Do not** open the cover of the inhaler until you are ready to use it. To avoid wasting doses after the inhaler is ready, **do not** close the cover until after you have inhaled the medicine.
- Write the "Tray opened" and "Discard" dates on the inhaler label. The "Discard" date is 6 weeks from the date you open the tray.

Check the counter. See Figure C.

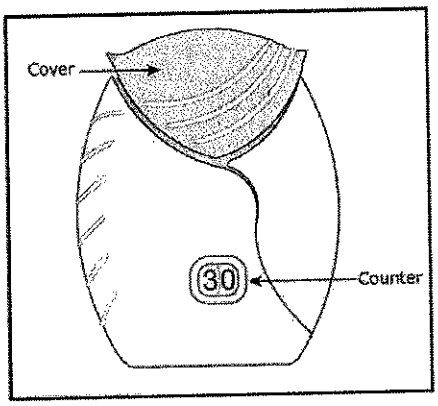


Figure C

- Before the inhaler is used for the first time, the counter should show the number 30 (7 if you have a sample or institutional pack). This is the number of doses in the inhaler.
- Each time you open the cover, you prepare 1 dose of medicine.
- The counter counts down by 1 each time you open the cover.

Prepare your dose:
Wait to open the cover until you are ready to take your dose.

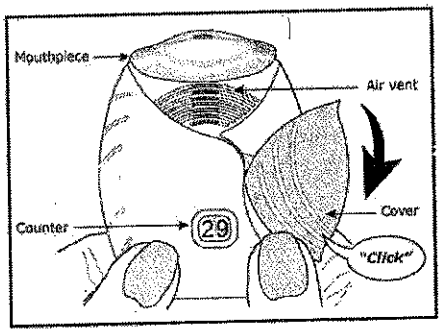


Figure D

Step 1. Open the cover of the inhaler. See Figure D.

- Slide the cover down to expose the mouthpiece. You should hear a "click." The counter will count down by 1 number. You do not need to shake this kind of inhaler. **Your inhaler is now ready to use.**
- If the counter does not count down as you hear the click, the inhaler will not deliver the medicine. Call your healthcare provider or pharmacist if this happens.

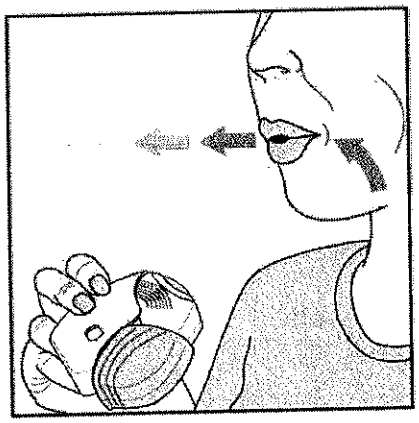


Figure E

Step 2. Breathe out. See Figure E.

- While holding the inhaler away from your mouth, breathe out (exhale) fully. Do not breathe out into the mouthpiece.

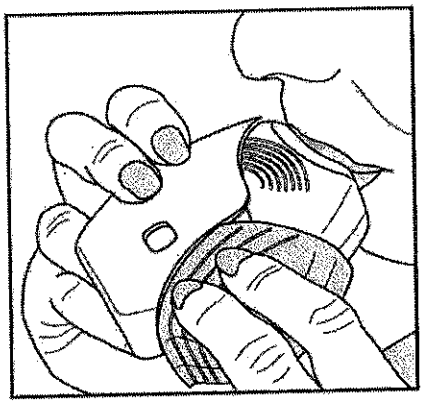


Figure F

Step 3. Inhale your medicine. See Figure F.

- Put the mouthpiece between your lips, and close your lips firmly around it. Your lips should fit over the curved shape of the mouthpiece.
- Take one long, steady, deep breath in through your mouth. **Do not** breathe in through your nose.

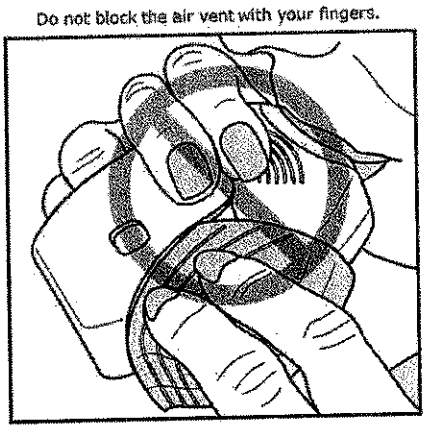


Figure G

- Do not block the air vent with your fingers. **See Figure G.**

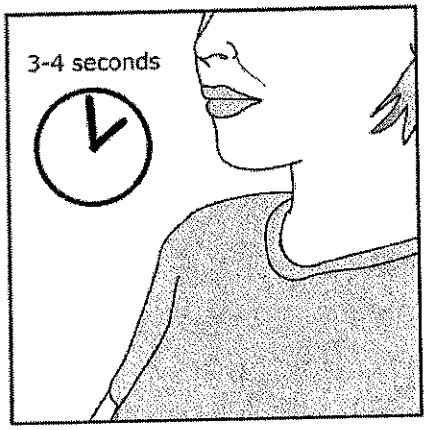


Figure H

- **Remove the inhaler from your mouth and hold your breath for about 3 to 4 seconds** (or as long as comfortable for you). **See Figure H.**

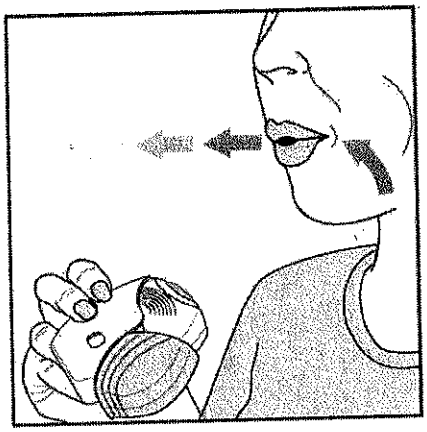


Figure I

Step 4. Breathe out slowly and gently. See Figure I.

- You may not taste or feel the medicine, even when you are using the inhaler correctly.
- **Do not** take another dose from the inhaler even if you do not feel or taste the medicine.

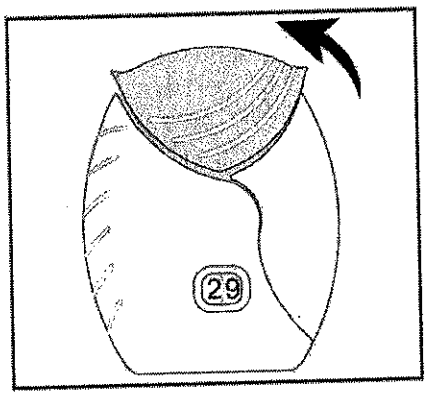


Figure J

Step 5. Close the inhaler. See Figure J.

- You can clean the mouthpiece if needed, using a dry tissue, before you close the cover. Routine cleaning is not required.
- Slide the cover up and over the mouthpiece as far as it will go.

Important Note: When should you get a refill?

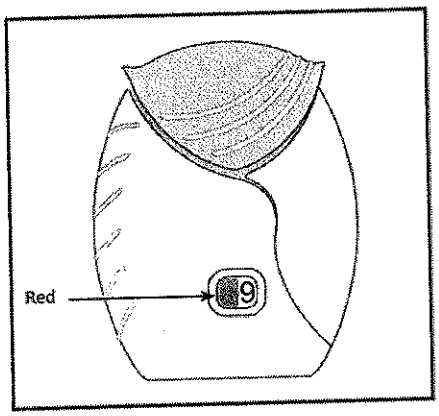


Figure K

- **When you have less than 10 doses remaining** in your inhaler, the left half of the counter shows red as a reminder to get a refill. **See Figure K.**
- After you have inhaled the last dose, the counter will show "0" and will be empty.
- Throw the empty inhaler away in your household trash out of reach of children and pets.

If you have questions about ANORO ELLIPTA or how to use your inhaler, call GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www.myANORO.com.

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

ANORO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
GlaxoSmithKline
Research Triangle Park, NC 27709

December 2013
ANR:1MG

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
12/18/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203975s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	November 26, 2013
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	20-3975
Applicant Name:	GlaxoSmithKline
Date of Submission:	December 18, 2012
PDUFA Goal Date:	December 18, 2013
Proprietary Name:	Anoro Ellipta
Established Name:	Umeclidinium and vilanterol
Dosage form:	Inhalation Powder (inhaler contains 2 double-foil blister strips, each with 30 blisters containing powder for oral inhalation)
Strength:	Umeclidinium 62.5 mcg per blister and vilanterol 25 mcg per blister
Proposed Indications:	Maintenance treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD)
Action:	Approval

1. Introduction

GlaxoSmithKline (GSK) submitted this 505(b)(1) new drug application for use of Anoro Ellipta (umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder) for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The proposed dose is one inhalation (umeclidinium 62.5 mcg and vilanterol 25 mcg) once daily. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include short- and long-acting beta-2 adrenergic agonists, short- and long-acting anticholinergics, combination products containing beta-2 adrenergic agonists and anticholinergics, combination of long-acting beta-2 adrenergic agonists and corticosteroids, methylxanthines, and phosphodiesterase-4 (PDE4) inhibitors. There are a smaller number of drug classes available for reducing exacerbations in COPD. These include long-acting anticholinergics, combination products containing long-acting beta-2 adrenergic agonists (LABA) and inhaled corticosteroids (ICS), and PDE inhibitors. With the exception of methylxanthines and PDE-4 inhibitors, all others are inhalation products.

Anoro Ellipta is a new inhalation product comprised of a long-acting anticholinergic umeclidinium and a long-acting beta-2 adrenergic agonist (LABA) vilanterol. Neither

component is currently approved for marketing in the US as a single-ingredient inhalation product. Vilanterol is approved as one of the two active ingredients in Breo Ellipta. Breo Ellipta is an inhalation product containing the ICS fluticasone furoate and the LABA vilanterol, which was approved in the US in May 2013 for use in COPD patients. Umeclidinium is a new molecular entity and not marketed for any indication in the US.

The Anoro Ellipta development program is distinctive in terms of the nature of the combination and the data available with the single active ingredients. While short-acting anticholinergics and short-acting beta-2 adrenergic agonists have been previously combined in inhalation dosage forms (such as ipratropium and albuterol in Combivent and in DuoNeb), Anoro Ellipta is comprised of the novel anticholinergic umeclidinium and the LABA vilanterol. The data available for the single ingredient umeclidinium and vilanterol were limited at the start of the Anoro Ellipta program. This was a departure from the historical development programs for inhalation combination products in the United States where the single ingredient products were developed first, followed by development of the combination product. The Anoro Ellipta development program was therefore large with dose ranging and dose frequency regimen studies for the single ingredient products and the pivotal COPD studies for the combination product folded into one development program.

In the subsequent sections of this review, the anticholinergic component umeclidinium and the LABA component vilanterol are discussed, followed by a discussion of regulatory interaction between the Agency and GSK related to this application.

Umeclidinium:

Umeclidinium is a new molecular entity that belongs to the anticholinergic class. Inhaled anticholinergics are widely available in the US and worldwide for the treatment of COPD. In the US, one short-acting anticholinergic, ipratropium bromide, and two long-acting anticholinergics, tiotropium bromide (Spiriva HandiHaler) and aclidinium bromide (Tudorza Pressair), are currently available. All of these products have anticholinergic adverse effects, such as dry mouth, constipation, and urinary retention. A meta-analysis of various studies suggested a concern regarding increased risk of stroke, cardiovascular death, and myocardial infarction associated with the use of short-acting and long-acting anticholinergics .[1] A pooled analysis of 29 studies conducted by Boehringer Ingelheim in 2007 (25 studies with Spiriva HandiHaler, and 4 studies with Spiriva Respimat) suggested an increased risk of stroke with tiotropium bromide.[2] In contrast, a 6,000 patient, 4-year study with Spiriva HandiHaler conducted by Boehringer Ingelheim in COPD patients (The UPLIFT Study – Understanding Potential Long-term Impacts on Function with Tiotropium) did not show increased mortality or cardiovascular safety risk

[1] Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008; 300:1439-50.
[2] FDA Early Communication about an Ongoing Safety Review of Tiotropium. Http://ww.fda.gov/cder/drug/early_comm/tiotropium.htm

with Spiriva HandiHaler.[3, 4] A more recent study conducted by Boehringer Ingelheim involving 17,135 COPD patients followed for 2.3 years (The TIOSPIR study – Tiotropium Safety and Performance in Respimat) showed comparable all-cause mortality between Spiriva Respimat and Spiriva HandiHaler.[5] These two large controlled studies, pending review of TIOSPIR study by the FDA, largely alleviate the concerns regarding excess mortality and cardiovascular safety risks with long-acting anticholinergic tiotropium. Nevertheless, it is important to select an appropriate dose and dose regimen for any anticholinergic in COPD program to limit high systemic exposure and potential safety concerns. Dose ranging and dose regimen studies with inhaled anticholinergics are done in patients with COPD and not asthma because patients with asthma are usually not responsive to bronchodilation with anticholinergics.

Vilanterol:

Vilanterol is not a new molecular entity. It belongs to the class called long-acting beta-2 adrenergic agonists (LABAs). Inhaled LABAs are widely used in the United States and worldwide to treat bronchospasm in patients with asthma and COPD. LABAs currently marketed in the United States include salmeterol, formoterol, arformoterol, indacaterol, and vilanterol. Some of these are marketed as single ingredient products and others as combination products with inhaled corticosteroids. Salmeterol, formoterol, and arformoterol are dosed twice-daily, and indacaterol and vilanterol are dosed once-daily.

Inhaled beta-2 adrenergic agonists, particularly inhaled LABAs, have a safety concern of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Severe asthma exacerbations and asthma-related deaths have been described with short-acting inhaled beta-2 adrenergic agonists over the last 50 years.[6, 7, 8, 9] More recently, inhaled LABAs have also been linked to severe asthma exacerbations and asthma-related deaths.[10] This has been discussed at various FDA Advisory Committee meetings,[11] which has led to publications expressing concerns on safety,[12, 13, 14] and the establishment of a safe use strategy outlined by the FDA.[15] To

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[3] Tashkin DP, Celli B, Senn S. et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Eng J Med 2008; 359: 1543-54.
[4] Michele TM, Pinheiro S. Iyasu S. The safety of tiotropium – The FDA conclusions. N Eng J Med 2010; 363: 1097-99.
[5] Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Eng J Med 2013; 369:1491-501.
[6] Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. J Allergy 1948; 19:129-140.
[7] Lowell FC, Curry JJ, Schiller IW. A clinical and experimental study of isoproteronol in spontaneous and induced asthma. N Eng J Med 1949; 240:45-51.
[8] Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. Thorax 1991; 46:105-111.
[9] Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al., The use of beta-agonist and the risk of death and near death from asthma. N Eng J Med 1992; 326:501-506.
[10] US Product Labels of salmeterol and formoterol containing products.
[11] Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.
[12] Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. New Eng J Med 2005; 353:2637-2639.

further assess the safety of LABAs in asthma, the FDA has asked all manufacturers of LABAs that are marketed in the United States for asthma to conduct controlled clinical trials to assess the safety of a regimen of LABAs plus inhaled corticosteroids as compared with inhaled corticosteroids alone.[16] The mechanisms by which inhaled beta-adrenergic agonists cause severe asthma exacerbations and asthma-related deaths are not known. Controlled studies and epidemiological studies suggest that higher doses of inhaled beta-adrenergic agonists are a contributing factor. In the United States, a higher dose of inhaled formoterol was not approved because the higher dose caused more severe asthma exacerbation compared to the approved lower dose.[17] Unlike patients with asthma, patients with COPD do not appear to carry a similar signal of worsening disease. Nevertheless, the selection of an appropriate and safe dose is an important consideration for development of all LABAs, including vilanterol. Most of the U.S.-marketed beta-adrenergic agonists carry both asthma and COPD indications. The dose and dosing frequency in both indications are the same. Dose ranging and dose regimen studies for beta-adrenergic agonists are usually done first in patients with asthma and then in COPD patients. Patients with asthma are generally more responsive and allow for larger separation of doses. Patients with COPD with some degree of fixed obstruction are likely to have a smaller response range to a bronchodilator. The regulatory precedence of performing dose ranging and dose regimen studies in patients with asthma was followed in the development of indacaterol, a LABA that was approved for marketing in the United States in 2011 as a bronchodilator in patients with COPD. [18]

Regulatory interaction between the Agency and GSK:

The Division and GSK had typical milestone meetings on Anoro Ellipta for its COPD program, in addition to meetings on the development of individual components. The following timeline highlights some major discussion that occurred during clinical development of these products.

- Pre-IND meeting for vilanterol, January 31, 2007: The Division recommended that GSK characterize the vilanterol fully prior to development of Anoro.
- Pre-IND meeting for umeclidinium, June 4, 2009: The Division recommended evaluation of dose and dosing frequency for umeclidinium, and recommended that efficacy and safety of the individual component be demonstrated.

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[13] Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists—the influence of values. New Eng J Med 2009; 360:1952-1955.
[14] Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. New Eng J Med 2009; 360:1671-1672.
[15] Chowdhury BA, DalPan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. New Eng J Med 2010; 362:1169-1171.
[16] Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. New Eng J Med 2011; 364:2473-2475.
[17] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. Chest 2003; 124:70-74.
[18] Chowdhury BA, Seymour SM, Michelle TM, Durmowicz AG, Diu D, Rosebrough CJ. The risks and benefits of indacaterol – The FDA review. N Eng J Med 2011; 365:2247-2249.

- Type C teleconference meeting for asthma and COPD program, March 24, 2010: The Division stated that the proposed vilanterol 25 mcg once daily dose appeared reasonable for further evaluation in confirmatory studies.
- End-of-Phase 2 meeting for Anoro Ellipta, October 29, 2010: The Division did not confirm the proposed umeclidinium 125 mcg dose. The Division stated that demonstration of a dose response would be useful, particularly in light of ongoing safety concerns with inhaled anticholinergics in COPD.
- Pre-NDA meeting for Anoro Ellipta, January 18, 2012: The Division stated the need for replicate evidence of efficacy for the single ingredient products as well as the Anoro Ellipta combination product.
- Breo Ellipta for COPD approved on May 10, 2013.

3. Chemistry, Manufacturing, and Controls

The product Anoro Ellipta (umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder) includes a dry powder inhaler device, the Ellipta inhaler, which contains 2 separate double-foil blister strips inside. Each blister on one strip contains micronized umeclidinium bromide (74.2 mcg equivalent to 62.5 mcg umeclidinium), magnesium stearate, and lactose monohydrate; and each blister on the other strip contains micronized vilanterol trifenatate (40 mcg equivalent to 25 mcg of vilanterol), magnesium stearate, and lactose monohydrate. The lactose monohydrate may contain trace amounts of milk proteins. The proposed commercial presentation of Anoro Ellipta has 30 blisters each of umeclidinium and vilanterol, which will be a one-month supply with a once daily dosing regimen. The device has a dose counter. The steps needed to use the product are simple and similar to some other dry powder inhaler devices. To deliver a dose, the patient will open the cover of the device. This action makes the powder from one blister containing umeclidinium and one blister containing vilanterol ready for inhalation at the airflow path inside the device. The patient will then inhale through the mouthpiece of the device. If a patient opens and closes the cover of the device without inhaling, the formulation powder will be held inside the device and will no longer be available to be inhaled. The Anoro Ellipta device has been tested for usability, reliability, and ruggedness through in vitro testing, human factor studies, and testing of devices used in the clinical program.

Anoro Ellipta is packaged within a moisture-protecting foil tray with a desiccant packet. GSK submitted adequate stability data to support an expiry of 24 months for the product stored at room temperature inside the protective foil tray. Anoro Ellipta should be discarded after all doses are used or 6 weeks after removal from the protective package, whichever comes first.

The drug substances are manufactured at a GSK facility in Jurong, Singapore and drug product including the Anoro Ellipta device is assembled at a GSK facility in Ware, United Kingdom. The device components are fabricated by [redacted] (b)(4). All manufacturing and testing facilities associated with this drug product have acceptable establishment evaluation status. All DMFs associated with this application were also found to be acceptable.

The single ingredient products containing umeclidinium and vilanterol in the Ellipta device were used in clinical studies (described in section 7 below). The formulations of the single ingredient products were the same as the combination product except the absence of one of the active ingredient. The single ingredient products (with placebo formulations in companion strips) were assessed for key attributes, such as delivered dose content uniformity, and aerodynamic particle size distribution to assure that these were sufficiently similar to the combination product and that there were no pharmaceutical differences that would hinder the interpretability of the clinical studies.

4. Nonclinical Pharmacology and Toxicology

GSK submitted results from a full preclinical program to the Agency. The program included studies in which animals were dosed with umeclidinium and vilanterol individually and in combination via inhalation. The studies assessed the general toxicity, genetic toxicity, carcinogenicity, and reproductive toxicity of each compound and potential interactions between the compounds. In general, these studies showed that umeclidinium and vilanterol each possessed toxicity profiles typical of their respective pharmacological classes, and studies of the combination did not suggest any major interactions or synergistic effects between the two components.

The general toxicity of umeclidinium was evaluated after the inhalation route of administration of the drug for up to 13, 26, and 39-weeks in mice, rates, and dogs, respectively. These studies identified the lungs, tracheal bifurcation, larynx, nasal turbinates, and heart as target organ of toxicity. There were adequate margins of safety between these findings in animals and human doses. In terms of genetic testing, umeclidinium tested negative in the Ames assay, rat bone marrow micronucleus assay in vivo, and the mouse lymphoma assay in vitro. Two-year carcinogenicity studies in rodents showed no evidence of tumorigenicity. Reproductive and developmental studies showed that umeclidinium had no effects on fertility or reproductive performance in rats and was not teratogenic in rats or rabbits. Umeclidinium caused a skeletal variation in rats in a dose-dependent manner. Umeclidinium did not have any effects on pre- or post-natal development in rats.

The general toxicity of vilanterol was evaluated after the inhalation route of administration of the drug for up to 13, 26, and 39-weeks in mice, rats and dogs, respectively. These studies identified the upper airways, lung, heart, liver and testes as target organs of toxicity, and findings were typical of beta agonists. In terms of genetic testing, vilanterol tested negative in the Ames assay, UDS assay in vitro, and SHE cell assay in vitro, and rat bone marrow micronucleus assay in vivo, and equivocal in the mouse lymphoma assay. Two-year carcinogenicity studies in rodents showed a dose-related shortening of latency for pituitary neoplasms in both genders of the rat and increases in the incidence of leiomyomas in female rats. Female mice showed increases in the incidence of tubulostromal carcinomas in the ovaries. These findings were typical of beta agonists in rodents. A battery of reproductive and developmental studies evaluated the effects of vilanterol on male and female fertility in rats, the teratogenicity of vilanterol in rats and rabbits, and peri- and post-natal development of vilanterol in rats.

Results showed that vilanterol was not teratogenic in rats or rabbits, but caused increases in the incidence of skeletal variations at high doses in rabbit fetuses. Vilanterol had no effects on fertility in rats.

5. Clinical Pharmacology and Biopharmaceutics

GSK submitted results from a comprehensive clinical pharmacology program that included studies to assess protein binding and metabolism and the pharmacokinetics after single and multiple inhaled doses of umeclidinium and vilanterol individually and in combination. The majority of studies were conducted in healthy volunteers, but several studies were done specifically to assess pharmacokinetics in COPD patients and the effect of renal and hepatic impairment. Umeclidinium and vilanterol have low oral bioavailability and systemic exposure for both components is primarily due to absorption of the inhaled portion. Following inhaled administration, Cmax of both umeclidinium and vilanterol occurred at 5 to 15 minutes. The primary metabolic pathway for umeclidinium is CYP2D6 and that of vilanterol is CYP3A4. No clinically meaningful difference in systemic exposure to umeclidinium was observed following repeat daily inhaled dosing in CYP2D6 normal and poor metabolizer subjects. The inhibition potential for both metabolic pathways is low when administered by the inhaled route and no specific dose adjustments are recommended when the combination is administered with other drugs. No significant effects due to age, hepatic or renal impairment on pharmacokinetic parameters were observed, so no dose adjustment for age, hepatic or renal function is recommended. A study to assess QTc effects did not indicate any clinically relevant prolongation of the QTc interval at the therapeutic dose.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1 and Table 2. As discussed in section 2 above, GSK conducted a program for umeclidinium and vilanterol that was largely concurrent for the individual components and the combination product. As a result the clinical program submitted with this application is large. Table 1 summarizes the main studies conducted in both COPD and asthma to support dose selection and dosing frequency for the individual umeclidinium and vilanterol components with the to-be-marketed device. Table 2 summarizes the main studies conducted in COPD to support the combination product. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8. For brevity, the studies are referenced later in this review by the last four digits of the study number.

Table 1. Relevant dose selection studies for umeclidinium, and vilanterol

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Primary efficacy variables ¶	Regions and Countries //
Umeclidinium -- Dose-ranging and dose-regimen studies -- COPD patients					
113073 [Oct 2009 – Mar 2010]	- ≥ 40 yr - COPD - XO, active controlled - 14 days	Umec 1000 mcg QD Umec 500 mcg QD Umec 250 mcg QD Umec 125 mcg QD Umec 62.5 mcg QD Umec 250 mcg BID Umec 125 mcg BID Umec 62.5 mcg BID Tiotropium 18 mcg QD Placebo	32 38 38 34 35 38 37 34 35 158	FEV_1 trough at day 15	US (55%), Germany
113589 [Dec 2009 - Jul 2010]	- ≥ 40 yr - COPD - PG, placebo controlled - 28 days	Umec 500 mcg QD Umec 250 mcg QD Umec 125 mcg QD Placebo	71 72 71 71	FEV_1 trough at day 29	US (42%), W Europe, E Europe
115321 [July 2011 - Oct 2011]	- ≥ 40 yr - COPD - XO, active controlled - 7 days	Umec 125 mcg QD Umec 62.5 mcg QD Umec 31.25 mcg QD Umec 15.6 mcg QD Umec 31.25 mcg BID Umec 15.6 mcg BID Tiotropium 18 mcg QD Placebo	60 59 58 57 56 60 56 60	FEV_1 trough at day 8	US (100%)
115408 [July 2011 - Feb 2012]	- ≥ 40 yr - COPD - PG, placebo controlled - 12 weeks	Umec 125 mcg QD Umec 62.5 mcg QD Placebo	69 69 68	FEV_1 trough at day 85	US (23%), Germany, Japan
Vilanterol -- Dose-ranging and dose-regimen studies -- asthma patients					
109575 [Dec 2007-Sep 2008]	- 12 to 80 yr - Asthma - PG, placebo controlled - 28 days	VI 3 mcg QD VI 6.25 mcg QD VI 12.5 mcg QD VI 25 mcg QD VI 50 mcg QD Placebo	101 101 100 101 102 102	FEV_1 trough at day 28	US (36%), E Europe, W Europe, Canada, S Africa, Other
113310 [Sep 2009 - Jan 2010]	- 18 to 71 yr - Asthma - XO, placebo controlled - 7 days	VI 6.25 mcg QD VI 6.25 mcg BID VI 12.5 mcg QD VI 25 mcg QD Placebo	75	FEV_1 trough at the end of 7-day treatment period	US (100%)
112060 [Sep 2010 – Aug 2011]	- 12 to 79 yr - Asthma - PG, placebo controlled - 28 days	VI 25 mcg QD Sal 50 mcg BID Placebo	115 116 116	FEV_1 (0-24h) at end of 12 week treatment period	US (20%), E Europe, W Europe, Other
Vilanterol -- Dose-ranging study -- COPD patients					
111045 [Feb 2008 – Oct 2009]	- ≥ 40 yr - COPD - PG, placebo controlled - 28 days	VI 3 mcg QD VI 6.25 mcg QD VI 12.5 mcg QD VI 25 mcg QD VI 50 mcg QD Placebo	99 101 101 101 99 101	FEV_1 trough at day 29	US (50%), E Europe, W Europe, Canada, Other

* Study ID shown (top to bottom) as GSK's study number, and [month year study started-completed]
† XO=cross over, PG=parallel group
‡ Umec=umeclidinium in Ellipta device; VI=vilanterol in Ellipta device; Sal=salmeterol xinafoate;

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Primary efficacy variables ¶	Regions and Countries //

§ Intent to treat
¶ Primary efficacy variables and selected secondary efficacy variables are shown. The efficacy analysis for the pivotal studies were performed using analysis of covariance (ANCOVA).
// Europe and other included: Argentina, Belgium, Chile, Denmark, Estonia, France, Mexico, Netherlands, Peru, Philippines, Poland, Romania, Russian Federation, S Korea, Slovakia, Sweden, Thailand, Ukraine

Table 2. Relevant clinical studies with Anoro Ellipta (umeclidinium and vilanterol inhalation powder) in patients with COPD

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Primary efficacy variable ¶	Regions and Countries //
Pivotal bronchodilator (or lung function) efficacy and safety studies -- COPD patients					
113373 Trial 1 [Mar 2011 - Apr 2012]	- ≥ 40 yr - COPD by ATS criteria - PG, placebo controlled - 24 weeks	Umec/VI 62.5/25 QD Umec 62.5 QD VI 25 QD Placebo	413 418 421 280	ΔFEV_1 trough baseline to wk 24	US (28%), E Europe, W Europe, Other
113361 Trial 2 [Mar 2011 - Sep 2012]	- ≥ 40 yr - COPD by ATS criteria - PG, placebo controlled - 24 weeks	Umec/VI 125/25 QD Umec 125 QD VI 25 QD Placebo	403 407 404 275	ΔFEV_1 trough baseline to wk 24	US (21%) E Europe, W Europe, Other
113360 Trial 3 [Mar 2011 - Apr 2012]	- ≥ 40 yr - COPD by ATS criteria - PG, active comparator - 24 weeks	Umec/VI 125/25 QD Umec/VI 62.5/25 QD VI 25 QD Tiotropiium 18 QD	214 212 209 208	ΔFEV_1 trough baseline to wk 24	US (27%), E Europe, W Europe, Other
113374 Trial 4 [2009-2011]	- ≥ 40 yr - COPD by ATS criteria - PG, active comparator - 24 weeks	Umec/VI 125/25 QD Umec/VI 62.5/25 QD Umec 125 QD Tiotropium 18 QD	215 217 222 215	ΔFEV_1 trough baseline to wk 24	US (26%), E Europe, W Europe, Other
Exercise endurance efficacy and safety studies -- COPD patients					
114417 [Mar 2011 - Jun 2012]	- ≥ 40 yr - COPD by ATS criteria - XO, placebo controlled - 12 weeks	Umec/VI 125/25 QD Umec/VI 62.5/25 QD Umec 125 QD Umec 62.5 QD VI 25 QD Placebo	144 152 50 49 76 170	ΔETT baseline to week 12 ΔFEV_1 trough baseline to wk 12	US (56%), E Europe, W Europe
114418 [Mar 2011 - July 2012]	- ≥ 40 yr - COPD by ATS criteria - XO, placebo controlled - 12 weeks	Umec/VI 125/25 QD Umec/VI 62.5/25 QD Umec 125 QD Umec 62.5 QD VI 25 QD Placebo	128 130 41 40 64 151	ΔETT baseline to week 12 FEV_1 trough at week 12	US (45%), E Europe, W Europe, S Africa, Canada
Safety study -- COPD patients					
113359 [Jan 2011 - July 2012]	- ≥ 40 yr - COPD by ATS criteria - PG, placebo controlled - 52 weeks	Umec/VI 125/25 QD Umec 125 QD Placebo	226 227 109		US (28%), E Europe, Chile, S Africa

* Study ID shown (top to bottom) as GSK's study number, as referenced in the proposed Anoro Ellipta product label, and [month and year study started-completed]
† XO=cross over, PG=parallel group
‡ Umec=umeclidinium in Ellipta device; VI=vilanterol in Ellipta device

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Primary efficacy variable ¶	Regions and Countries //
§ Intent to treat (ITT) ¶ FEV1 trough is mean values 23 and 24 hours after dosing on day 168. Primary efficacy variables for the four bronchodilator studies were analyzed using mixed model for repeated measure (MMRM) in the ITT population. // Europe and other included: Argentina, Australia, Belgium, Bulgaria, Chile, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Netherlands, Norway, Peru, Philippines, Poland, Romania, Russia, Slovakia, Spain, South Korea, Sweden, Thailand, UK, Ukraine.					

b. Design and conduct of the studies

Umeclidinium dose ranging (3073, 3589, 5321, 5408) and dose regimen (3073, 5321) studies in COPD:

These studies were conducted in patients with COPD. The study treatment arms and primary efficacy variable are shown in Table 1. The primary analysis was the linear trend in dose response in trough FEV1 at day 8. Safety assessments included adverse event recording, vital signs, physical examination, and clinical laboratory and hematology measures.

Vilanterol dose ranging (9575), dose regimen (3310), and comparative (2060) studies in asthma:

These studies were conducted in patients with persistent asthma. The study treatment arms and primary efficacy variable are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, and ECGs.

Vilanterol dose ranging (1045) study in COPD:

This study was conducted in patients with COPD. The study treatment arms and primary efficacy variable are shown in Table 1. The primary analysis for study 9575 was the linear trend in dose response in trough FEV1 at day 28. Safety assessments included adverse event recording, vital signs, physical examination, ECGs, and incidence of asthma exacerbation.

Pivotal bronchodilator (or lung function) studies (placebo-controlled studies 3373 and 3361; active-controlled studies 3360 and 3373) in COPD:

These studies were identical in design except for the doses of study treatments and comparators (Table 2). Patients eligible for the studies were required to have a diagnosis of moderate-to-severe COPD as defined by ATS/ERS criteria, [19] with post-

[19] Celli BR, MacNee W. Standards of the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J 2004; 23:932-946.

bronchodilator FEV1 of ≤70% predicted, a post-bronchodilator FEV1/FVC ratio of ≤0.70, and a score of ≥2 on the Modified Medical Research Council Dyspnea Scale (mMRC). Eligible patients entered a 1-2 week single-blind placebo run-in period, and the patients who remained eligible entered the 24-week double-blind treatment period. These studies allowed inhaled corticosteroids at a constant dose, mucolytics, oxygen therapy ≤12 hours/day, and albuterol for rescue use. Prohibited medications included systemic corticosteroids, LABAs, other combination products containing ICS+LABA, short- and long-acting anticholinergics, combination product containing ipratropium+albuterol, and theophylline. The use of a placebo control for up to 24 weeks was considered ethically acceptable given the availability of rescue SABA and other medications in conjunction with close clinical monitoring for exacerbation symptoms. Study treatment arms and primary efficacy variables are shown in Table 2. To account for multiplicity across treatment comparisons, a step-down procedure was used with testing for high dose combination to placebo first, followed by low dose combination to placebo, and then combination to single ingredient products. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, ECGs, and 24-hour Holter monitoring in a subset of patients.

Exercise endurance studies (4417, 4418) in COPD:

These studies were identical in design (Table 2). Eligibility criteria were similar to pivotal bronchodilator studies with a demonstrated ability to perform exercise shuttle walk test. Eligible patients entered a 12-21 day run in period, followed by 12-week treatment periods separated by 14-day washout period. The crossover study treatment arms and the primary efficacy variables are shown in Table 2. Safety assessments were similar to the pivotal bronchodilator studies.

Long-term safety study (3359) in COPD:

This study enrolled more stable COPD patients than those enrolled in the pivotal bronchodilator studies (there were no mMRC criteria, and the FEV1 criteria was ≥35% to ≤70%). A wide range of concomitant medications was allowed that justifies using a placebo arm. Safety assessments were similar to the pivotal bronchodilator studies.

c. Efficacy findings and conclusions

The clinical program is adequate to support the efficacy of Anoro Ellipta 62.5/25 mcg (umeclidinium 62.5 mcg and vilanterol 25 mcg) for bronchodilation in patients with COPD. The efficacy demonstration of Anoro Ellipta builds on the selection of an appropriate dose and dosing regimen for umeclidinium and vilanterol, and then demonstrates the benefit for Anoro Ellipta for the claimed benefits of bronchodilation over the single ingredients umeclidinium and vilanterol.

Umeclidinium dose ranging and dose regimen in COPD:

As discussed in section 2 above, selection of an appropriate dose and dosing regimen is important for the development of an anticholinergic for COPD. GSK conducted adequate exploration of dose ranges and dose regimen in patients with COPD (Table 1).

Dose ranging data are available from studies 3073, 3589, 5321, and 5408. Studies 3073 and 3589 showed no bronchodilation benefit for doses over the 125 mcg once-daily dose, and the difference between the 125 mcg and the 62.5 mcg once daily doses (lowest two doses explored) was not consistent (data not shown in this review). To explore lower doses, study 5321 evaluated doses ranging from 15.6 mcg to 125 mcg once daily. Time profile FEV1 over 6 hours on day 1 (Figure 1) and over 24 hours on day 7 (Figure 2) from study 5321 showed a dose response, with the lowest umeclidinium 15.6 mcg once daily dose falling off in bronchodilation efficacy compared to the higher doses, and the 125 mcg once daily umeclidinium dose showing higher bronchodilation efficacy compared to other lower doses and to the benchmark tiotropium. Dose separation between umeclidinium 62.5 mcg once daily and 125 mcg once daily was supported by data from study 5408 (Table 3). These data suggest 62.5 mcg as a reasonable optimum dose for umeclidinium, and also supports GSK's decision to carry forward the 62.5 mcg and the 125 mcg umeclidinium doses to phase 3 studies.

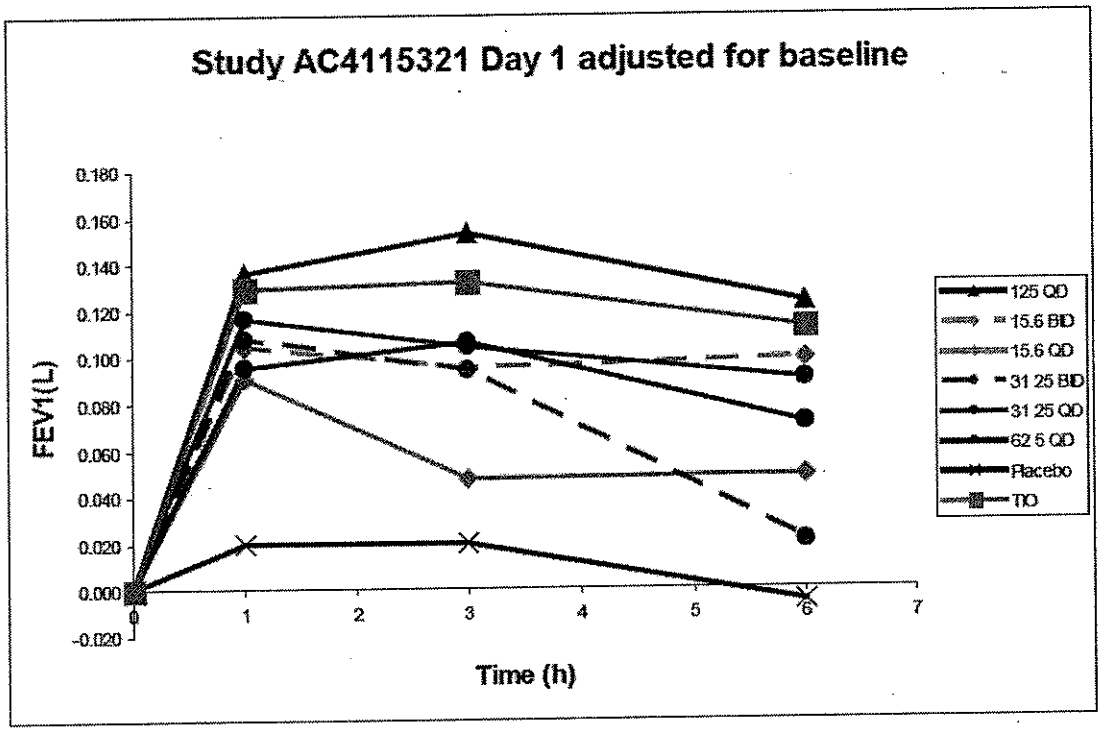


Figure 1. Adjusted mean change from baseline in FEV1 over time on day 1, study 115321

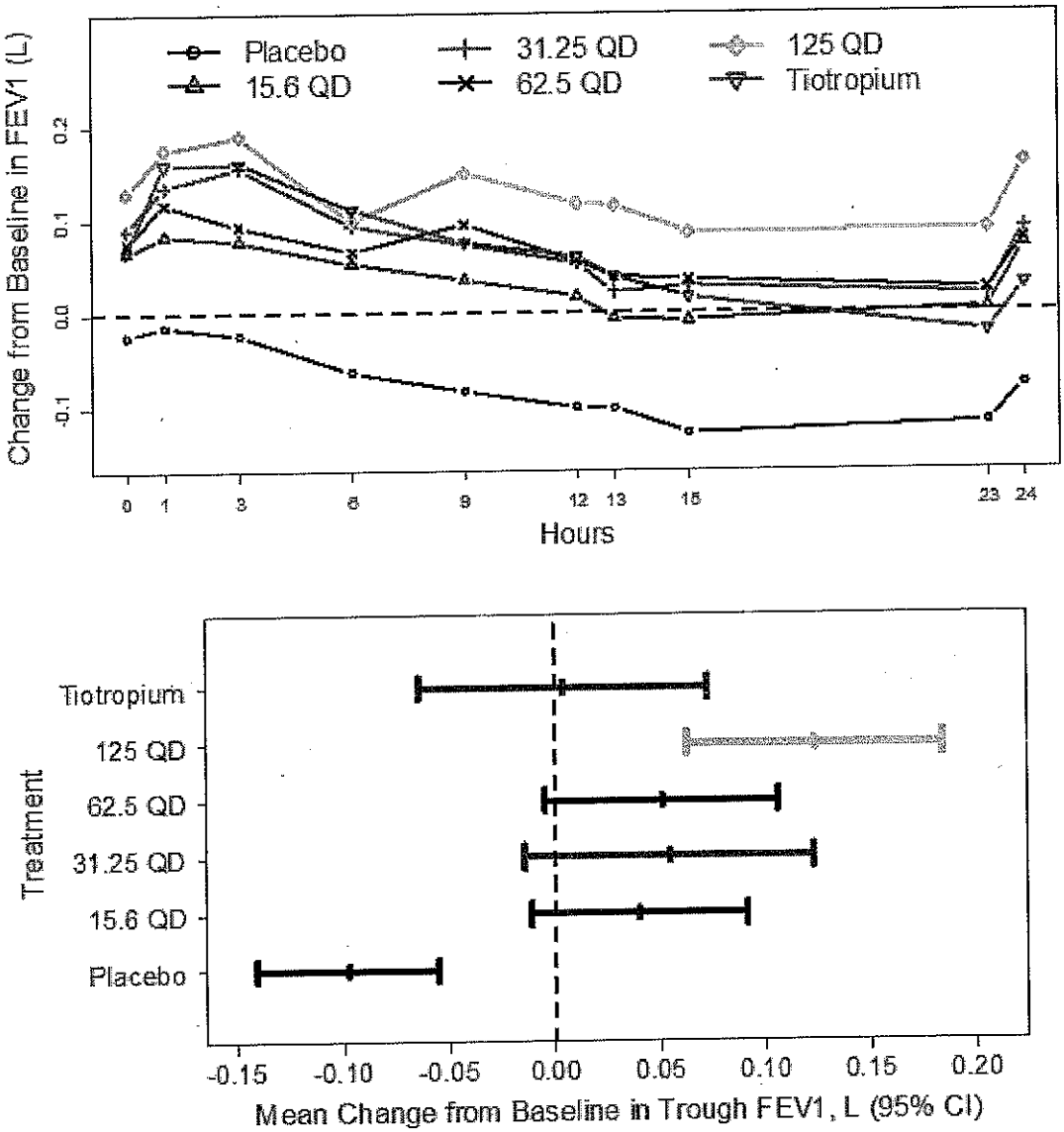


Figure 2. Post-dose 24-hour serial mean change from baseline in FEV1 on day 7 (top panel) and mean change from baseline in trough FEV1 on day 8 (bottom panel) for once-daily umeclidinium (125 mcg, 62.5 mcg, 31.25 mcg, 15.6 mcg), tiotropium (18 mcg), and placebo, Study 115321.

Table 3. Mean change from baseline in trough FEV1 at day 85

Treatment	n	LS mean change from baseline	Difference from placebo (95% CI)	P value
Umec 62.5 mcg	69	0.12	0.13 (0.05, 0.20)	<0.001
Umec 125 mcg	69	0.15	0.15 (0.08, 0.23)	<0.001
Placebo	68	-0.01		

Dose regimen (dose frequency) of umeclidinium was evaluated in studies 3073 and 5321. Study 5321 is relevant because it explored doses identified as optimum in dose ranging studies (discussed above). The time profile FEV1 over 24 hours on day 7 did not show differences between the 62.5 mcg once-daily dose and 31.25 mcg or 15.6 mcg twice-daily dose (Figure 4), which did not suggest that twice-daily was preferable to once-daily dosing. These data support 62.5 mcg twice-daily as a reasonable optimum dose and dose regimen for umeclidinium, and also supports GSK's decision to carry forward the 62.5 mcg and the 125 mcg umeclidinium once-daily doses to phase 3 studies.

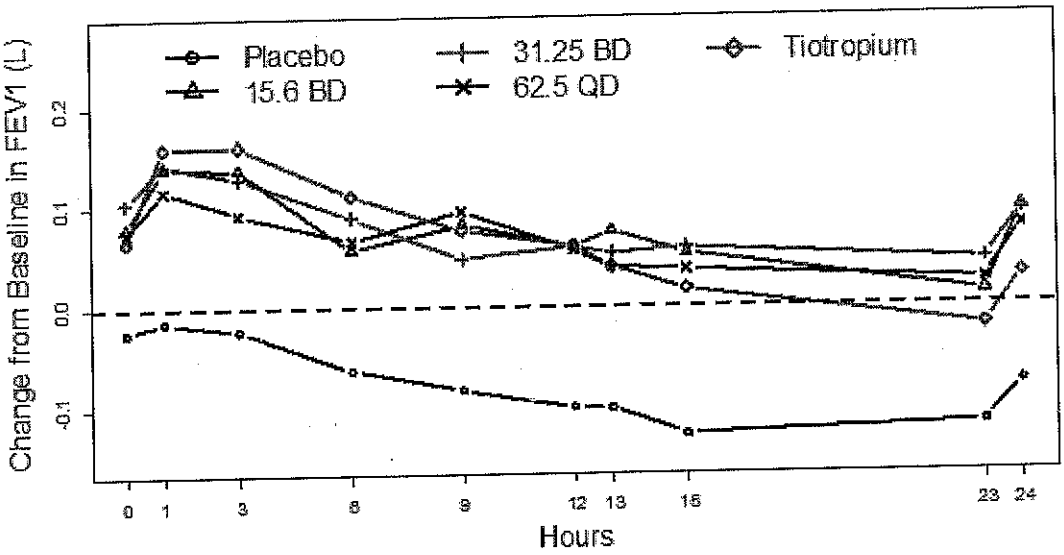


Figure 3. Post-dose 24-hour serial mean change from baseline in FEV1 on day 7 for once-daily and twice daily umeclidinium (62.5 mcg once-daily, 31.25 mcg twice-daily, and 15.6 mcg twice-daily), and tiotropium (18 mcg once-daily), Study 115321.

Vilanterol dose ranging and dose regimen in asthma and COPD:

As discussed in section 2 above, the selection of an appropriate dose and dosing regimen is important for development of LABAs, and these studies need to be conducted in patients with asthma in addition to COPD because the bronchodilator response is greater in bronchoresponsive patients, such as patients with asthma who can show larger separation between doses. GSK conducted adequate exploration of the dose ranges and dose regimens in patients with asthma and COPD (Table 1). These and other studies were reviewed for the Breo Ellipta (fluticasone furoate and vilanterol) NDA and it was determined that vilanterol 25 mcg once daily is the optimum dose for COPD. Data supporting that conclusion are briefly summarized below.

In the asthma dose ranging study (9575), vilanterol 3 mcg and 6.25 mcg once daily were not statistically significantly different from placebo for the primary endpoint of trough FEV1; vilanterol 12.5 mcg, 25 mcg, and 50 mcg once daily resulted in similar level of

improvement in the primary endpoint of trough FEV1 that were all statistically significantly greater than that observed with placebo (Figure 5). In the COPD dose ranging study (1045), all doses of vilanterol were statistically significantly different from placebo for the primary endpoint of trough FEV1 with a numerical increasing trend with increasing dose (Figure 5). Based on the results of these two studies, GSK selected the vilanterol 25 mcg nominal dose in combination with umeclidinium for confirmatory COPD studies for the Anoro Ellipta program. This was reasonable and acceptable to the Agency.

Lack of an active comparator was a limitation in these dose-ranging studies. GSK has conducted a study (2060) that compared vilanterol 25 mcg once daily to salmeterol 50 mg twice daily (approved dose of salmeterol) in patients with asthma. The study showed a larger increase in trough FEV1 with vilanterol compared to salmeterol (359 mL vs 283 mL), but neither of the treatment groups were statistically significantly different from placebo, because placebo unexpectedly also increased trough FEV1 (289 mL). This study was therefore not helpful. Comparative efficacy studies conducted later with combination product (studies 3107, 3109, 2352, and 3091) showed comparable FEV1 time response curves after the first dose and also at later time points (Figure 6 shows two representative curves after the first done). The first dose bronchodilator response allowed comparison between vilanterol 25 mcg and salmeterol 50 mcg that was relatively unaffected by the ICS component. These results further supported the vilanterol 25 mcg dose.

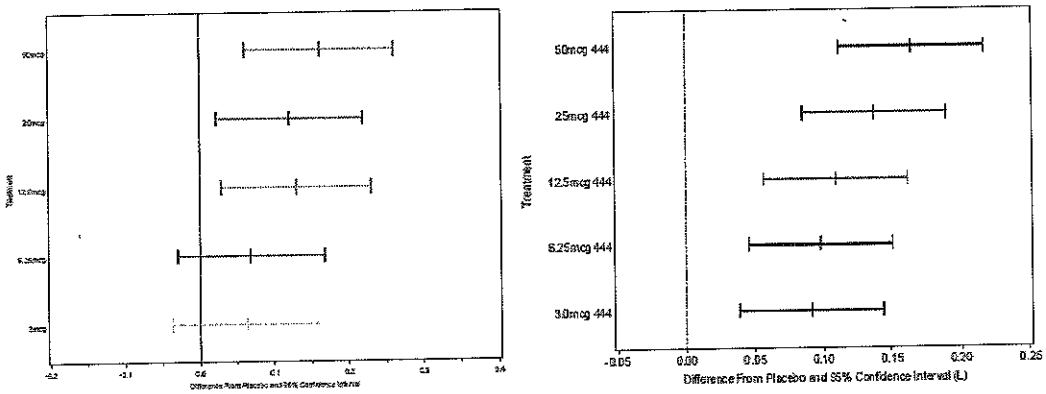


Figure 4. Adjusted treatment difference from placebo change from baseline in trough FEV1 and 95% confidence interval in liters at day 29 in patients with asthma (study 9575, left panel) and COPD (study 1045, right panel).

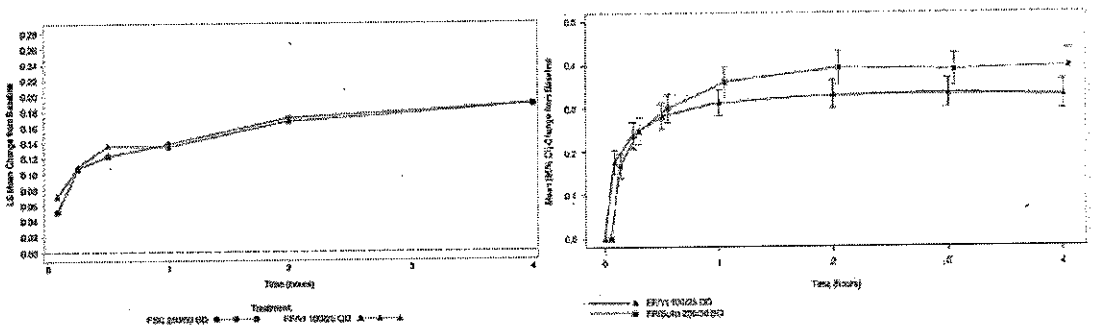


Figure 5. Mean change in FEV1 over time after the first done from COPD study 2352 (left panel) and asthma study 3091 (right panel).

The vilanterol dose regimen was investigated in study 3310 that compared once- and twice-daily dosing in patients with asthma (Table 1). The dose selected for comparison was 12.5 mcg (12.5 mcg once daily compared to 6.25 mcg twice daily), which is expected to be at the steep part of the dose-response curve, where differences between dose regimens would be easier to detect. Mean change in trough FEV1 on day 7 is shown on Figure 7. The trough FEV1 measure at day 7 suggests that vilanterol twice-daily provides a numerically better response than once-daily. The trough FEV1 with vilanterol 6.25 mcg twice daily was numerically comparable to vilanterol 25 mg once daily (Figure 7 left panel). GSK contended that the weighted mean FEV1 time response curve (measures efficacy over 24 hours rather than at trough) is a better way to compare the doses. Using the weighted mean FEV1 time response, vilanterol 6.25 mcg twice daily and vilanterol 12.5 mcg once daily was similar with LS mean differences from placebo of 166 mL and 168 mL, respectively (time response curve shown in Figure 7 right panel). As an additional analysis, the Agency's Clinical Pharmacology team generated the FEV1 time response curve for day 7 using raw FEV1 (Figure 8). The FEV1 time response curves (using either repeated measures or raw FEV1) show higher FEV1 response with higher nominal doses in the first 12 hours of dosing interval, and the curve for the 6.25 mcg twice-daily shifts upwards with the evening dose and is comparable to the 25 mcg and 12.5 mcg once-daily doses for the second 12 hours of the 24-hour interval. These results support a once-daily dosing frequency for vilanterol.

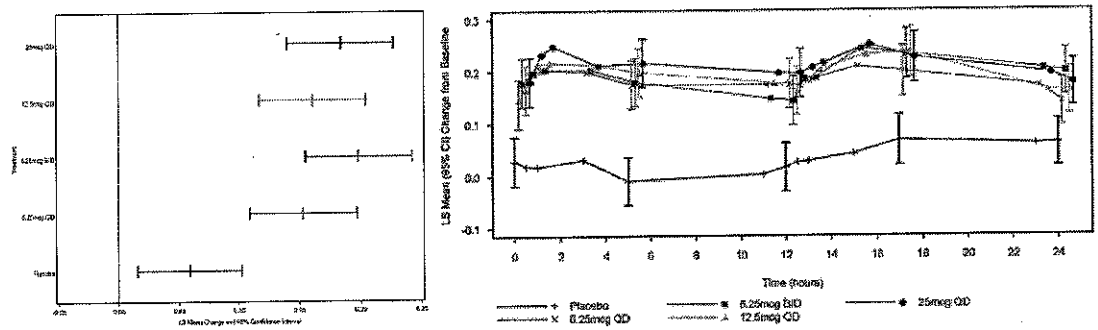


Figure 6. LS mean change in trough FEV1 on day 7 (left panel) and repeated measure adjusted mean change without placebo correction (right panel) on day 7 in patients with asthma, (vilatererol dose regimen study 3310 in asthma).

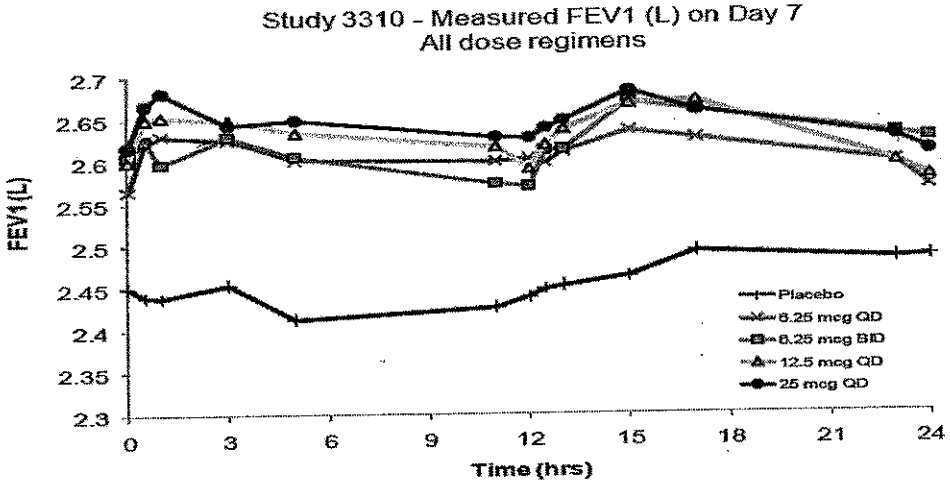


Figure 7. FEV1 time profile for 24 hours on day 7 using raw FEV1 values (vilanterol dose regimen study 3310 in asthma).

Anoro Ellipta, bronchodilator effects:

Studies 3373, 3361, 3360, and 3374 were the primary studies designed to support the bronchodilator claim for Anoro Ellipta. In all these studies there were missing data due to patient dropouts ranging from 15% to 33%. Despite the dropouts, the pre-specified primary analysis remains valid because various sensitivity analyses (that applied different missing data assumptions) were consistent in the magnitude and direction of the results with the primary analysis (applying mixed-model repeated measures method that GSK proposed, and other methods applied by GSK and FDA).

Studies conducted to support combination products compare the combination to each active component to show the contribution of each component, and also to show that the combination provides clinically meaningful benefit over each single ingredient present in the combination to justify the use of the combination product by patients. Studies 3373, 3361, 3360, and 3374 compared Anoro to umeclidinium and to vilanterol and also compared multiple doses of Anoro (Table 2). For a combination product such as Anoro, the bronchodilation benefit will be from both umeclidinium and vilanterol.

The primary efficacy variable of trough FEV1 at day 169 is intended to show the benefit of Anoro over both single ingredients. Anoro was compared to vilanterol alone to show the contribution of umeclidinium, and Anoro was compared to umeclidinium to show the contribution of vilanterol. Results from the analysis of this primary efficacy variable showed a statistically significant difference between Anoro at both the 125/25 mcg and 62.5/25 mcg doses over each of the respective single ingredients (Table 4). The single ingredients were also statistically significantly different from placebo (Table 4). The differences between Anoro and the single ingredients and placebo were maintained over

various time points (data from one representative study for the Anoro 62.5/25 mcg dose is shown in Figure 9). Direct comparison between Anoro 125/25 mcg and 62.5/25 mcg doses are available from the two active comparator studies 3360 and 3374. These studies do not show higher bronchodilator efficacy with the higher dose of Anoro (Table 4). Trough FEV1 results from the exercise endurance studies also allowed for direct comparison between Anoro 125/25 mcg and 62.5/25 mcg doses, which also did not show higher bronchodilator efficacy with the higher dose of Anoro (Table 5). The higher Anoro 125/25 mcg dose was not consistently statistically superior to the corresponding umeclidinium 125 mcg dose (study 1337 in Table 4, and studies 4417 and 4418 in Table 5) suggesting that the addition of vilanterol 25 mcg did not provide substantial benefit over the higher 125 mcg umeclidinium dose. Replicate evidence of the contribution of each component for the Anoro 62.5/25 mcg doses are available from various sources, such as studies 3373, 3360, 3374, 4417, and 4418, which show statistically significant differences for Anoro 62.5/25 mcg over umeclidinium 62.5 mcg and vilanterol 25 mcg (Table 4, Table 5). The submitted data are adequate to support the bronchodilation claim of Anoro Ellipta.

Table 4. Bronchodilator studies; Mean change from baseline in trough FEV1 at day 169 (ITT population)

Treatment *	N	Change (L)	Diff vs comp † (95% CI)	P value	Diff vs treatment ‡ (95% CI)	P value
Study 13373 (Trial 1)						
Umec/VI 62.5/25	413	0.20	0.17 (0.13, 0.21)	<0.001	-	-
Umec 62.5	418	0.17	0.12 (0.08, 0.16)	<0.001	0.05 (0.02, 0.09)	<0.001
VI 25	421	0.08	0.07 (0.03, 0.11)	<0.001	0.10 (0.06, 0.13)	<0.001
Placebo	280	0.00	-	-	0.17 (0.13, 0.21)	<0.001
Study 13361 (Trial 2)						
Umec/VI 125/25	403	0.20	0.24 (0.20, 0.28)	<0.001	-	-
Umec 125	407	0.13	0.16 (0.12, 0.20)	<0.001	0.08 (0.05, 0.11)	<0.001
VI 25	404	0.09	0.12 (0.09, 0.16)	<0.001	0.11 (0.08, 0.15)	<0.001
Placebo	275	-0.03	-	-	0.24 (0.20, 0.28)	<0.001
Study 13360 (Trial 3)						
Umec/VI 125/25	208	0.21	0.09 (0.04, 0.14)	0.004	0.09 (0.04, 0.14)	<0.001
Umec/VI 62.5/25	207	0.21	0.09 (0.04, 0.14)	0.006	0.09 (0.04, 0.14)	<0.001
VI 25	209	0.12	0.00 (-0.05, 0.05)	0.995	-	-
Tiotropium 18	203	0.12	-	-	-	-
Study 13374 (Trial 4)						
Umec/VI 125/25	215	0.22	0.07 (0.03, 0.12)	0.003	0.04 (-0.01, 0.09)	0.142
Umec/VI 62.5/25	217	0.21	0.06 (0.01, 0.11)	0.018 §	-	-
Umec 125	222	0.19	0.04 (-0.01, 0.09)	0.138	-	-
Tiotropium 18	215	0.15	-	-	-	-

* Umec/VI = Umeclidinium and vilanterol in Ellipta; Umec = Umeclidinium in Ellipta; VI=vilanterol in Ellipta

† Diff vs comp (difference versus comparator) for studies 13373 and 13361 is from placebo, and for studies 13360 and 13374 is from tiotropium

‡ Diff (difference) for study13360 is from VI, and for study 13374 is from Umec

§ Nominal p-value. The p-values reported here do not take into account the testing hierarchy pre-specified in the statistical analysis plan. Statistical significance for this difference cannot be claimed as a result of failure of predefined testing hierarchy in the clinical trial design.

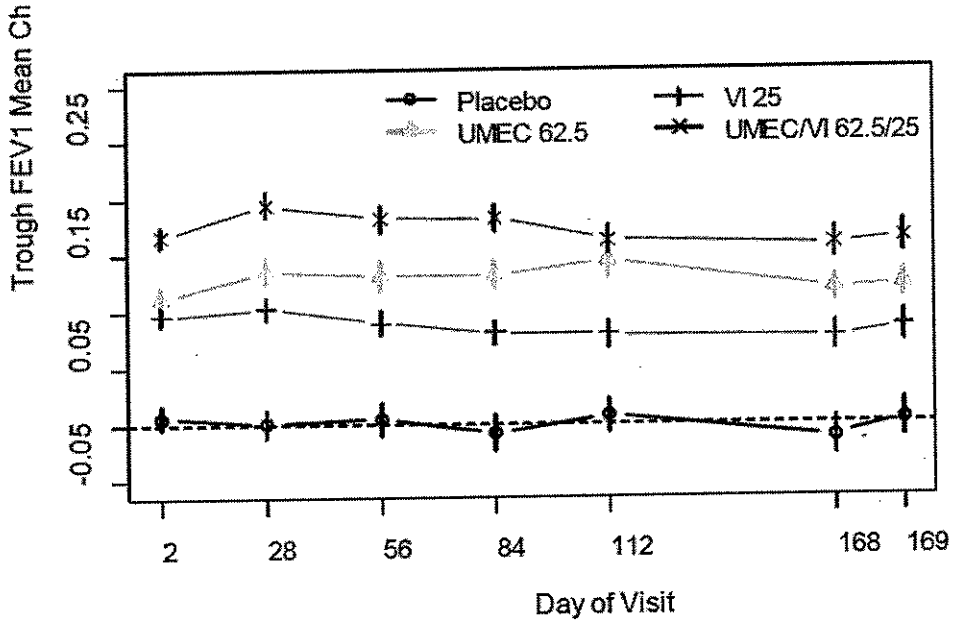


Figure 8. LS Mean change from baseline in trough FEV1 over time in study 13373 (ITT)

Table 5. Exercise endurance studies; Mean change from baseline in trough FEV1 at week 12 (ITT population)

Treatment *	N	Change (L)	Diff vs Umec † (95% CI)	P value	Diff vs VI ‡ (95% CI)	P value
Study 4417						
Umec/VI 125/25	144	0.14	0.03 (-0.03, 0.09)	0.320	0.07 (0.02, 0.12)	0.007
Umec/VI 62.5/25	152	0.18	0.12 (0.07, 0.18)	<0.001	0.11 (0.06, 0.17)	<0.001
Umec 125	50	0.11	-	-	-	-
Umec 62.5	49	0.05	-	-	-	-
VI 25	76	0.07	-	-	-	-
Placebo	170	-0.03	-	-	-	-
Study 4418						
Umec/VI 125/25	128	0.22	0.01 (-0.06, 0.07)	0.849	0.15 (0.10, 0.20)	<0.001
Umec 62.5/25	130	0.20	0.10 (0.04, 0.18)	<0.001	0.13 (0.08, 0.18)	<0.001
Umec 125	41	0.21	-	-	-	-
Umec 62.5	40	0.10	-	-	-	-
VI 25	64	0.07	-	-	-	-
Placebo	151	-0.04	-	-	-	-

* Umec/VI = Umeclidinium and vilanterol in Ellipta; Umec = Umeclidinium in Ellipta; VI=vilanterol in Ellipta
† Umec/VI 125/25 vs Umec 125, Umec/VI 62.5/25 vs Umec 62.5
‡ Umec/VI 125/25 vs VI 25, Umec/VI 62.5/25 vs VI 25

Anoro Ellipta, COPD exacerbation:

GSK is not seeking an exacerbation claim for Anoro Ellipta. While the four pivotal bronchodilator studies (Table 2) were not designed to assess COPD exacerbation, data on exacerbation were collected as an additional support of efficacy. Anoro Ellipta 62.5/25 mcg showed some numerical benefit over umeclidinium and vilanterol in some studies, but none of these findings were statistically significant.

Anoro Ellipta, shortness of breath:

(b) (4)

The SOBDA is based on daily patient recording of shortness of breath on 13 activities related to daily living. The SOBDA assessment has problems and is not fully validated. Nevertheless, the results based on SOBDA were not persuasive. Although Anoro Ellipta showed statistically significant difference from placebo in the pivotal placebo-controlled bronchodilator studies, the differences between Anoro Ellipta and umeclidinium and vilanterol were not consistent (data not shown).

Anoro Ellipta, St. George's Respiratory Questionnaire (SGRQ)

SGRQ is an important health status assessment instrument commonly used in COPD studies. All pivotal bronchodilator studies assessed SGRQ scores. There was a statistically significant difference in change in SGRQ score from baseline to assessment day 168 for both doses of Anoro Ellipta over placebo, but the threshold of 4 units (clinically meaningful improvement) was met only for Anoro 62.5/25 mcg dose with no replication from other studies. The data are not adequate to support a labeling claim for SGRQ because of lack of replication of the SGRQ results.

Anoro Ellipta, exercise endurance

GSK is not seeking an exercise endurance claims for Anoro Ellipta. Results of the two studies conducted to assess exercise endurance showed a statistically significant difference for the two primary endpoints (Table 2) between the two doses of Anoro Ellipta and placebo in study 4418, but not in study 4417 (data not shown in this review). Even in the study that showed separation between Anoro Ellipta and placebo, the effect size is questionable and did not reach the threshold originally defined by GSK. Furthermore, exercise endurance is an entity that is multi-factorial and influenced by many factors, and it is difficult to confirm that any changes noted in these studies is solely attributable to the beneficial effect of Anoro Ellipta.

8. Safety

a. Safety database

The safety assessment of Anoro Ellipta is based on studies shown in Table 1 and Table 2, and some other studies. The primary COPD safety database for Anoro is comprised of four pivotal 6-month primary efficacy COPD studies 3373, 3361, 3360, 3374, and the one-year safety study 3359 (Table 2). The safety database for Anoro was large and adequate.

b. Safety findings and conclusion

The submitted data support the safety of Anoro Ellipta for use as maintenance treatment of airflow obstruction in patients with COPD.

GSK conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events (SAEs[20]), common adverse events (AEs), and assessment for areas of interest such as cardiovascular safety, anticholinergic and adrenergic effects, and pneumonia.

A total of 48 deaths were reported in the COPD program. These were balanced among the treatment groups. Common causes of deaths included COPD exacerbation, respiratory failure, myocardial infarction, and cancers, which are expected causes of death in older COPD patients. Reporting of SAEs was fairly common across treatment arms, as was discontinuation from the studies. These were also balanced among the treatment causes, and the events were typical and expected in COPD patients. Common adverse events included pharyngitis, gastrointestinal disorder, anticholinergic effects, effects related to adrenergic stimulation, and lower respiratory tract infections. The patterns of SAEs and adverse events did not indicate a specific safety concern.

One safety finding of interest identified in the program because of experience with other inhaled drugs of the class (as discussed in section 2 above) was cardiovascular safety.

GSK included several prespecified evaluations to assess cardiovascular safety that included adjudication of deaths and SAEs, analysis of Major Adverse Cardiac Events (MACE), and a separate analysis of cardiovascular adverse events of special interest (AESI) that encompassed a broader set of adverse events terms.

GSK conducted two MACE analyses based on two sets of criteria. The broader criteria included all MedDRA preferred terms falling under the category of Myocardial Infarction SMQ and Other Ischemic Disease SMQ, whereas the narrow criteria specified the preferred terms of "Acute Myocardial Infarction" and "Myocardial Ischemia." The analyses were performed on a pooled ITT population from all COPD studies with treatment duration of at least 12 weeks, with rates adjusted based on duration of

[20] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

exposure. As shown in Table 9, the numbers of patients with MACE events were relatively low across treatment arms, and the exposure-adjusted rates did not suggest an increased risk of MACE events in the active treatment arms compared to placebo. One difference of note was for non-fatal MI between placebo and Anoro 62.5/25 mcg, which was due to 1 versus 3 events in the two treatment groups. Analysis of AESI (included terms used in MACE, and other terms such as long QT, cardiac arrhythmia, cardiac failure, and hypertension) also did not suggest an increased risk of events in the active treatment arms compared to placebo (data not shown in this review). Analysis of cardiovascular SAEs showed an imbalance that favored placebo over active treatments in the primary efficacy studies, but not in all studies (Table 10).

Table 6. MACE analysis, Studies included are: 12-week dose ranging study (115408), 24-week bronchodilator efficacy and safety studies (113373, 113361, 113360, 113374), 12 week exercise endurance efficacy and safety studies (114417, 114418), and 52 week safety study (113359)

	Placebo	Umec/Vl 62.5/25	Umec/Vl 125/25	Umec 62.5	Umec 125	Vl 25	Tio * 18
	N=1053 SY=369	N=1124 SY=408	N=1330 SY=573	N=576 SY=202	N=1016 SY=449	N=1174 SY=441	N=173 SY=173
Total MACE events				Number of events			
Broad-definition MACE †	22	16	22	11	15	18	6
Narrow-definition MACE †	8	5	6	2	7	8	1
Incidence Rate				Number of Subjects with Events per 1000 Subject-Years (SY)			
Broad-definition MACE	54.3	36.8	38.4	44.5	31.2	38.5	34.7
Narrow-definition MACE	19.0	12.3	10.5	9.9	15.6	18.1	5.8
Adjudicated CV death	5.4	4.9	0	0	2.2	4.5	0
Non-fatal cardiac ischemia	38.0	31.9	33.2	39.5	24.5	27.2	28.9
Non-fatal MI	2.7	7.4	5.2	4.9	8.9	4.5	0
Non-fatal stroke	10.9	0	5.2	4.9	4.5	9.1	5.8

* Umec/VI = Umeclidinium and vilanterol in Ellipta; Umec = Umeclidinium in Ellipta; VI = vilanterol in Ellipta; Tio=Tiotropium in Spiriva HandiHaler
† Broad definition used the larger "cardiac ischemia special interest" adverse events, whereas the narrow definition used the preferred terms "myocardial infarction" and "myocardial ischemia"

Table 7. Adjudicated cardiovascular SAEs, number of events (incidence rate per 1000 patient-years)

	Placebo	Umec/VI *	Umec	VI	Tio
All efficacy and safety studies †	9 (27)	23 (25)	20 (32)	15 (35)	2 (12)
Primary efficacy and safety studies ‡	3 (14)	18 (26)	15 (36)	15 (37)	2 (12)

* Umec/VI = includes both 62.5/25 and 125/25 umeclidinium and vilanterol groups; Umec = includes both 62.5 and 125 umeclidinium groups; VI = vilanterol in Ellipta; Tio=Tiotropium in Spiriva HandiHaler
† Studies included are: 12-week dose ranging study (115408), 24-week bronchodilator efficacy and safety studies (113373, 113361, 113360, 113374), 12 week exercise endurance efficacy and safety studies (114417, 114418), and 52 week safety study (113359)
‡ Studies included are: 24-week bronchodilator efficacy and safety studies (113373, 113361, 113360, 113374)

While there were some imbalances seen in these analyses, as noted above, several features of the data decrease concern. In the MACE analyses, the imbalance in the narrow category of non-fatal myocardial infarction was not borne out in broader category

of non-fatal cardiac ischemia. In the cardiovascular SAE analyses, the imbalance noted in the primary efficacy studies was not borne out in the larger analysis set of all studies. The imbalances identified were not seen in the long-term safety study. It would be reasonable to expect that a signal of increased cardiac ischemia, if it represents a true risk, would be observed not just in the primary efficacy studies, but also in the pooled analyses of all studies, or in the long-term safety study. However, limitations of this reasoning are that the total number of events across all studies was small, and a large number of patients were withdrawn from the long-term safety study due to abnormalities on ECGs and on 24-hour Holter monitoring. The outcome of these patients after withdrawal in terms of safety is unknown. Nevertheless, the overall cardiovascular safety profile for Anoro, vilanterol, and umeclidinium as assessed from the safety analyses are reassuring and do not rise to a level that would preclude approval. In general, cardiovascular safety analyses based on the integrated COPD study database and the long-term safety trial were mostly unremarkable, including evaluations for death and MACE-related events, and the total number of cardiovascular-related events in the program was fairly low. Inhaled LABAs have known cardiovascular effects and all product labels of this class of drugs have language in the Warnings and Precautions sections of these labels. The Anoro label will also carry similar labeling language. The findings seen in the studies will be described in the label.

A dedicated post-marketing controlled randomized safety trial (under the provision of the Federal Food, Drug, and Cosmetic Act, Section 505(o)(3)) is not necessary to further explore the cardiovascular safety of Anoro Ellipta. The safety database for Anoro Ellipta is sufficient and there is no consistent pattern for the few imbalances in cardiovascular events. Also UPLIFT (described in section 2 above) was reassuring for another inhaled anticholinergic, tiotropium. The product label will include information on the imbalances identified in the clinical development program.

Asthma exacerbation and asthma-related deaths with LABA are safety concerns for patients with asthma. While a similar safety concern has not been seen in COPD, the clinical experience with vilanterol in asthma is of interest as secondary safety information and as selection of the appropriate dose. GSK provided a summary of safety data from the asthma development program for Breo Ellipta (fluticasone furoate and vilanterol). The summary included an analysis of a composite safety endpoint for asthma-related hospitalizations, intubations, and deaths, which did not suggest an increased risk of severe asthma-related adverse events associated with vilanterol alone or in combination with fluticasone furoate. The asthma safety data related to vilanterol from the Breo Ellipta program also applies to Anoro Ellipta.

c. REMS/RiskMAP

GSK submitted a Risk Management Plan for Anoro Ellipta, which consists of routine pharmacovigilance practices. A REMS is not necessary for Anoro Ellipta. The product will have a Medication Guide to inform patients about the risk of asthma related deaths with LABAs.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on September 10, 2013, to discuss this application. The major issues for discussion were the adequacy of the efficacy data to support the proposed indications of airflow obstruction, the adequacy of the safety database for making an informed benefit-risk assessment, and the benefit-risk assessment for Anoro Ellipta 62.5/25 mcg once daily for the proposed indications. In general, the panel members concluded that there were sufficient data to support the efficacy of Anoro for the proposed indication of airflow obstruction. On voting questions, the Committee voted favorably regarding whether there was substantial evidence of efficacy for airflow obstruction in COPD (13 yes, 0 no, 0 abstain), and whether the safety of Anoro had been adequately demonstrated (10 yes, 3 no, and 0 abstain). Regarding the approvability question, which is essentially the sum of the demonstration of efficacy and safety, the results were in favor of approval for airflow obstruction in COPD (11 yes, 2 no, 0 abstain). The Committee expressed some concerns with safety assessment in the program, noting the small number of cardiovascular safety events in the program, the limited number of patients with cardiovascular risks factors from the studies, and withdrawal of patients from the studies due to abnormalities on ECGs and on 24-hour Holter monitoring. Some Committee members expressed interest in obtaining more safety data, particularly in sicker COPD patients with cardiovascular risks, but did not express a consensus view of what type of safety study would be desirable and what would be the comparative arms in such a study.

10. Pediatric

GSK is requesting a claim for Anoro for COPD only. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required related to this action specific to COPD. PeRC had previously agreed that for such COPD applications a full waiver should be granted because studies would be impossible or highly impracticable since the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two clinic representative sites in the pivotal COPD studies 3373 and 3361. The clinical and statistical review teams recommended the sites because these sites enrolled larger number of patients compared to other sites, had a large percentage of patient dropouts, and had a large efficacy trend. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. There were deviations from GCP for one investigator site, but FDA review determined that this did not impact the overall findings. With the exception, of this single site, all studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. One investigator had significant financial interest in GSK. The number of subjects enrolled in the investigator

site was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

GSK submitted Anoro Ellipta as the proposed proprietary name, which was accepted by DMEPA.

b. Physician Labeling

GSK submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Division of Medical Policy Programs (DMPP), DRISK, DMEPA, SEALD, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. Asthma-related safety warnings are described in the label, including in a Boxed Warning, which are present in all LABAs. The Division and GSK have agreed on the final label language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Anoro Ellipta will carry an asthma-related safety warning that will be part of the Medication Guide.

13. Action and Risk Benefit Assessment

a. Regulatory Action

GSK has submitted adequate data to support approval of Anoro Ellipta (umeclidinium 62.5 mcg mcg and vilanterol 25 mg inhalation powder) for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), at the dose of one inhalation (umeclidinium 62.5 mcg and vilanterol 25 mcg) once daily. The recommended regulatory action on this application is Approval.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of Anoro Ellipta inhalation powder at a dose of one inhalation (umeclidinium 62.5 mcg and vilanterol 25 mcg) once daily for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD.

A major safety concern with vilanterol is linked to the selection of an appropriate dose, because beta-2 adrenergic bronchodilators, particularly at high doses, have the safety concern of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select an appropriate and safe dose for all bronchodilators. GSK conducted a comprehensive program, including dose ranging through pivotal confirmatory studies, to select the 25 mcg once daily dose for the Breo combination product. The same dose is appropriate for the Breo Ellipta and Anoro Ellipta combination products. The safety concerns with umeclidinium, similar to other anticholinergics, are the risk of cardiovascular adverse events, and systemic anticholinergic adverse events at high doses. GSK conducted adequate dose ranging studies for umeclidinium and selected 125 mcg and 62.5 mcg doses for the pivotal studies. Based on the overall data, GSK proposed 62.5 mcg umeclidinium for the Anoro Ellipta combination product. The final proposed doses of 25 mcg for vilanterol and 62.5 mcg for umeclidinium are reasonable and supported by the submitted data. The safety profile of Anoro 62.5/25 mcg was acceptable. The major safety findings were related to cardiovascular safety, anticholinergic effects, and effects related to adrenergic stimulation. These are known safety risks of these classes of drugs, and seemed to occur at frequencies comparable to other products of the class approved for COPD. The efficacy data submitted were adequate to support the indications of maintenance of airflow obstruction in COPD patients. Anoro showed benefit over umeclidinium alone and over vilanterol alone in bronchodilation that was supported by other efficacy measures. The efficacy data showed contribution of each component present in Anoro, and also showed that Anoro provides a clinically meaningful benefit over each single ingredient present in the combination.

c. Post-marketing Risk Management Activities

Anoro will carry an asthma-related safety warning that will be part of the Medication Guide. No other post-marketing risk management activities are required.

d. Post-marketing Study Commitments

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
11/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204275

NDA APPROVAL

GlaxoSmithKline
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Patrick Wire, Pharm.D.
Product Director, Respiratory Group

Dear Dr. Wire:

Please refer to your New Drug Application (NDA) dated July 11, 2012, received July 12, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Breo Ellipta (fluticasone furoate and vilanterol trifenatate inhalation powder).

We acknowledge receipt of your amendments dated July 12 (2), August 13, 16, 27, and 29, September 7 and 27, October 12, 15, 17, and 19, November 1 (2), 5, and 9, and December 3, 6, and 14, 2012, and January 10, February 7 (2) and 28, March 12 (2), 14, 22 (2), and 28 (2), April 2, 9, and 26, and May 6, 8, and 10, 2013.

This new drug application provides for the use of Breo Ellipta (fluticasone furoate 100 mcg and vilanterol trifenatate 25 mcg) for long-term, once daily, maintenance treatment airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) and for the reduction of COPD exacerbations.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

Revise device labels to include strengths of fluticasone furoate and vilanterol trifenatate.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204275.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because the proposed indication, chronic obstructive pulmonary disease (COPD), is an adult-related condition that does not occur in pediatrics. COPD is found on the list of adult-related conditions that qualify for a waiver because studies would be impossible or highly impractical.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your submission dated July 11, 2012, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Breo Ellipta to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

EXPIRATION DATING PERIOD

A 24-month expiration dating period is granted for Breo Ellipta when stored at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59° to 86°F (15° to 30°C).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Angela Ramsey, Senior Program Management Officer, at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
05/10/2013

US007488827B2

(12) **United States Patent**
Laine et al.

(10) **Patent No.: US 7,488,827 B2**
(45) **Date of Patent: *Feb. 10, 2009**

(54) **MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS**

(75) Inventors: **Damane I. Laine**, King of Prussia, PA (US); **Michael R. Palovich**, King of Prussia, PA (US); **Brent W. McCleland**, King of Prussia, PA (US); **Christopher E. Neipp**, King of Prussia, PA (US); **Sonia M. Thomas**, King of Prussia, PA (US)

(73) Assignee: **Glaxo Group Limited**, Greenford, Middlesex (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/774,867**

(22) Filed: **Jul. 9, 2007**

(65) **Prior Publication Data**

US 2007/0249664 A1 Oct. 25, 2007

Related U.S. Application Data

(63) Continuation of application No. 11/568,330, filed as application No. PCT/US2005/014386 on Apr. 27, 2005.

(60) Provisional application No. 60/565,623, filed on Apr. 27, 2004.

(51) **Int. Cl.**
C07D 453/02 (2006.01)
A61K 31/44 (2006.01)

(52) **U.S. Cl.** **546/133**; 514/305

(58) **Field of Classification Search** 546/133; 514/305

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,800,478	A	7/1957	Zirkle et al.	
2,800,481	A	7/1957	Zirkle et al.	
3,634,852	A	1/1972	Hartley et al.	
5,590,645	A	1/1997	Davies et al.	
5,780,466	A	7/1998	Emonds-Alt et al.	
5,860,419	A	1/1999	Davies et al.	
5,873,360	A	2/1999	Davies et al.	
6,248,752	B1	6/2001	Smith	
6,262,066	B1	7/2001	Tulshian et al.	
6,350,758	B1	2/2002	Kozikowski et al.	
6,455,527	B2	9/2002	Tulshian et al.	
6,696,462	B2	2/2004	Eickmeier et al.	
6,750,226	B2	6/2004	Forner et al.	
6,951,868	B2 *	10/2005	Walker et al.	514/305
7,232,841	B2	6/2007	Busch-Petersen et al.	
7,276,521	B2	10/2007	Busch-Petersen et al.	
2005/0020660	A1	1/2005	Guyaux et al.	
2005/0113417	A1	5/2005	Mammen et al.	
2005/0209272	A1	9/2005	Fernandez et al.	
2005/0277676	A1	12/2005	Laine et al.	
2006/0160844	A1	7/2006	Belmonte et al.	
2006/0178395	A1	8/2006	Belmonte et al.	
2006/0178396	A1	8/2006	Belmonte et al.	
2007/0129396	A1	6/2007	Wan et al.	
2007/0135478	A1	6/2007	Palovich et al.	
2007/0149598	A1	6/2007	Busch-Petersen et al.	
2007/0173646	A1	7/2007	Laine et al.	
2007/0179180	A1	8/2007	Busch-Petersen et al.	
2007/0179184	A1	8/2007	Busch-Petersen et al.	
2007/0185088	A1	8/2007	Busch-Petersen et al.	
2007/0185090	A1	8/2007	Busch-Petersen et al.	
2007/0185148	A1	8/2007	Busch-Petersen et al.	
2007/0185155	A1 *	8/2007	Laine et al.	514/304
2007/0232599	A1	10/2007	Palovich et al.	

FOREIGN PATENT DOCUMENTS

EP	0069715	6/1982
GB	2064336	6/1981
GB	2129691	5/1984
GB	2169265	7/1986
GB	2178965	2/1987
GB	2242134	9/1991
WO	87/05213	9/1987
WO	2004/012684	2/2004
WO	2006/050239	5/2006
WO	2006/055503	5/2006
WO	2006/055553	5/2006
WO	2006/062883	6/2006
WO	2006/062931	6/2006
WO	2006/065755	6/2006
WO	2006/065788	6/2006
WO	2007/016639	2/2007

(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 10/585,830, filed Jul. 12, 2006, Laine, et al.

(Continued)

Primary Examiner—Rita J Desai
Assistant Examiner—John Mabry
(74) *Attorney, Agent, or Firm*—Dara L. Dinner; Theodore R. Furman; Charles M. Kinzig

(57) **ABSTRACT**

Muscarinic Acetylcholine Receptor Antagonists and methods of using them are provided.

18 Claims, No Drawings

FOREIGN PATENT DOCUMENTS

WO	2007/016650	2/2007
WO	2007/018508	2/2007
WO	2007/018514	2/2007
WO	2007/022351	2/2007

OTHER PUBLICATIONS

U.S. Appl. No. 10/598,743, filed Sep. 11, 2006, Budzik, et al.
U.S. Appl. No. 10/598,750, filed Sep. 11, 2006, Jin, et al.
U.S. Appl. No. 10/599,717, filed Oct. 6, 2006, Laine, et al.
U.S. Appl. No. 11/570,981, filed Dec. 20, 2006, Cooper, et al.
U.S. Appl. No. 11/573,097, filed Feb. 2, 2007, Busch-Petersen, et al.
U.S. Appl. No. 11/573,099, filed Feb. 2, 2007, Busch-Petersen, et al.
U.S. Appl. No. 11/766,318, filed Jun. 21, 2007, Busch-Petersen, et al.
U.S. Appl. No. 11/766,371, filed Jun. 21, 2007, Busch-Petersen, et al.
U.S. Appl. No. 11/774,885, filed May 1, 2006, Wan, et al.
Brown, *History and Basic Properties*, Humana Press, USA pp. 7-9 (1989).
Caulfield, *Pharmac. Ther.*, vol. 58 pp. 319-379 (1993).
Costello, et al., *American Journal of Physiology*, vol. 276 (5) pp. L709-L714 (1999).
Fryer and Jacoby, *Am J Respir Crit Care Med*, vol. 158 (5, pt 3) pp. 154-160 (1998).
Fryer et al., *Life Sci*, vol. 64 (6-7) pp. 449-455 (1999).
Hedge, et al., *Life Sciences*, vol. 64 (6/7) pp. 419-428 (1999).
Ikeda, et al., *Naunyn-Schmiedeberg's Arch Pharmacol.*, vol. 366, pp. 97-103, (2002).
Minette, et al., *Journal of Applied Physiology*, vol. 67(6) pp. 2461-2465 (1989).
Oprins, et al., *Annals of the New York Academy of Sciences*, vol. 915 pp. 102-106 (2000).
Pauwels et al., *Am. J. Respir. Crit. Care Med.*, vol. 163 pp. 1256-1276 (2001).
Ran, et al., *Yaoxue Xuebao*, vol. 19 (5) pp. 361-366 (1984) Abstract only.
Sarau, *Mol. Pharmacol.*, vol. 56 (3) p. 657-663 (1999).
Van Rossum, et al., *Arch. Int. Pharmacodyn.*, vol. 143 p. 299 (1963) Best Available Copy.
Wu, et al., *Zhongguo Yaowu Huazue Zazhi*, vol. 3 (1) pp. 23-26 (1993)Abstract only.
Zirkle, et al., *J Med Chem*, vol. 27 pp. 1269-1279 (1962).
Zirkle, et al., *J Med Chem*, vol. 27 pp. 1279-1285 (1962).
Zirkle, et al., *J Med Chem*, vol. 5 pp. 341-356 (1962).
Zhang, et al., *J Med Chem*, vol. 44 pp. 3937-3945 (2001).
Ran, et al., *Yaoxue Xuebao*, vol. 19 (5) pp. 361-366 (1984), with translation.
Wu, et al., *Zhongguo Yaowu Huaxue Zazhi*, vol. 3(1) pp. 23-26 (1993), with translation.
Yu, et al., *Yaoxue Xuebao*, vol. 18(10) pp. 766-774 (1983), with translation.
Zhang, et al., *Yaoxue Xuebao*, vol. 20(10) pp. 752-758 (1985), with translation.

* cited by examiner

MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

This application is a continuation application of U.S. Ser. No. 11/568,330, filed 3 May 2007, which is the §371 national stage entry of PCT/US2005/014386, filed 27 Apr. 2005 and which claims the benefit of priority from U.S. Ser. No. 60/565,623, filed 27 Apr. 2004.

FIELD OF THE INVENTION

This invention relates to novel quinuclidines derivatives, pharmaceutical compositions, and use thereof in treating muscarinic acetylcholine receptor mediated diseases of the respiratory tract.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors—the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M_1-M_5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs where they mediate many of the vital functions. Muscarinic receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, M_3 mAChRs mediate contractile responses. For review, please see Caulfield (1993 *Pharmac. Ther.* 58:319-79).

In the lungs, mAChRs have been localized to smooth muscle in the trachea and bronchi, the submucosal glands, and the parasympathetic ganglia. Muscarinic receptor density is greatest in parasympathetic ganglia and then decreases in density from the submucosal glands to tracheal and then bronchial smooth muscle. Muscarinic receptors are nearly absent from the alveoli. For review of mAChR expression and function in the lungs, please see Fryer and Jacoby (1998 *Am J Respir Crit Care Med* 158(5, pt 3) S 154-60).

Three subtypes of mAChRs have been identified as important in the lungs, M_1, M_2 and M_3 mAChRs. The M_3 mAChRs, located on airway smooth muscle, mediate muscle contraction. Stimulation of M_3 mAChRs activates the enzyme phospholipase C via binding of the stimulatory G protein Gq/11 (Gs), leading to liberation of phosphatidyl inositol-4,5-bisphosphate, resulting in phosphorylation of contractile proteins. M_3 mAChRs are also found on pulmonary submucosal glands. Stimulation of this population of M_3 mAChRs results in mucus secretion.

M_2 mAChRs make up approximately 50-80% of the cholinergic receptor population on airway smooth muscles. Although the precise function is still unknown, they inhibit catecholaminergic relaxation of airway smooth muscle via inhibition of cAMP generation. Neuronal M_2 mAChRs are located on postganglionic parasympathetic nerves. Under normal physiologic conditions, neuronal M_2 mAChRs provide tight control of acetylcholine release from parasympathetic nerves. Inhibitory M_2 mAChRs have also been demonstrated on sympathetic nerves in the lungs of some species. These receptors inhibit release of noradrenaline, thus decreasing sympathetic input to the lungs.

M_1 mAChRs are found in the pulmonary parasympathetic ganglia where they function to enhance neurotransmission. These receptors have also been localized to the peripheral lung parenchyma, however their function in the parenchyma is unknown.

Muscarinic acetylcholine receptor dysfunction in the lungs has been noted in a variety of different pathophysiological states. In particular, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation (Fryer et al. 1999 *Life Sci* 64 (6-7) 449-55). This mAChR dysfunction results in airway hyperreactivity and hyperresponsiveness mediated by increased stimulation of M_3 mAChRs. Thus the identification of potent mAChR antagonists would be useful as therapeutics in these mAChR-mediated disease states.

COPD is an imprecise term that encompasses a variety of progressive health problems including chronic bronchitis, chronic bronchiolitis and emphysema, and it is a major cause of mortality and morbidity in the world. Smoking is the major risk factor for the development of COPD; nearly 50 million people in the U.S. alone smoke cigarettes, and an estimated 3,000 people take up the habit daily. As a result, COPD is expected to rank among the top five as a world-wide health burden by the year 2020. Inhaled anti-cholinergic therapy is currently considered the "gold standard" as first line therapy for COPD (Pauwels et al. 2001 *Am. J. Respir. Crit. Care Med.* 163:1256-1276).

Despite the large body of evidence supporting the use of anti-cholinergic therapy for the treatment of airway hyperreactive diseases, relatively few anti-cholinergic compounds are available for use in the clinic for pulmonary indications. More specifically, in United States, Ipratropium Bromide (Atrovent©; and Combivent©, in combination with albuterol) is currently the only inhaled anti-cholinergic marketed for the treatment of airway hyperreactive diseases. While this compound is a potent anti-muscarinic agent, it is short acting, and thus must be administered as many as four times daily in order to provide relief for the COPD patient. In Europe and Asia, the long-acting anti-cholinergic Tiotropium Bromide (Spiriva©) was recently approved, however this product is currently not available in the United States. Thus, there remains a need for novel compounds that are capable of causing blockade at mAChRs which are long acting and can be administered once-daily for the treatment of airway hyperreactive diseases such as asthma and COPD.

Since mAChRs are widely distributed throughout the body, the ability to apply anti-cholinergics locally and/or topically to the respiratory tract is particularly advantageous, as it would allow for lower doses of the drug to be utilized. Furthermore, the ability to design topically active drugs that have long duration of action, and in particular, are retained either at the receptor or by the lung, would allow the avoidance of unwanted side effects that may be seen with systemic anti-cholinergic use.

SUMMARY OF THE INVENTION

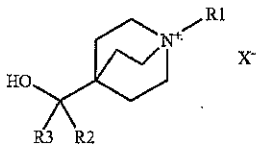
This invention provides for a method of treating a muscarinic acetylcholine receptor (mAChR) mediated disease, wherein acetylcholine binds to an mAChR and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of inhibiting the binding of acetylcholine to its receptors in a mammal in need

thereof which comprises administering to aforementioned mammal an effective amount of a compound of Formula (I).

The present invention also provides for the novel compounds of Formula (I), and pharmaceutical compositions comprising a compound of Formula (I), and a pharmaceutical carrier or diluent.

Compounds of Formula (I) useful in the present invention are represented by the structure:

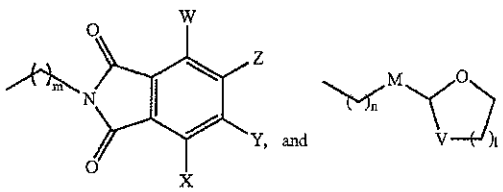


(I)

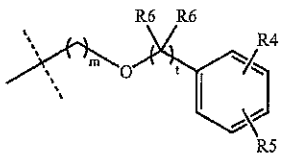
wherein:

R1 is selected from the group consisting of C1-15 alkyl, halosubstituted C1-15 alkyl, C1-15 alkyl cycloalkyl, cycloalkyl, C2-15 alkenyl, hydroxy substituted C1-15 alkyl, C1-15 alkyl aryl, C1-15 alkyl heteroaryl, (CR7R7)qNRaRa, (CR7R7)qNC(O)Ra, (CR7R7)qC(O)NRaRa, (CR7R7)qC(O)Ra, (CR7R7)qOC(O)Ra, (CR7R7)qNRaC(O)NRaRa, (CR7R7)qORc and (CR7R7)qNS(O)$_2$Ra

R1 is selected from the group consisting of:



R1 is selected from the group consisting of:



R2 and R3 are independently selected from the group consisting of aryl, C1-4 alkyl aryl, heteroaryl, C1-4 alkyl heteroaryl, heterocyclic and a C1-4 alkyl heterocyclic moiety, all of which moieties may be optionally substituted;

Ra is selected from the group consisting of hydrogen, C1-15 alkyl, C1-15 alkoxy, aryl, C1-15 alkyl aryl, heteroaryl, C1-15 alkyl heteroaryl, heterocyclic and a C1-15 alkyl heterocyclic moiety, all of which moieties may be optionally substituted;

Rc is selected from the group consisting of hydrogen, C1-15 alkyl, C1-15 alkoxy, heterocyclic and a C1-15 alkyl heterocyclic moiety, all of which moieties may be optionally substituted;

R4 and R5 are independently selected from the group consisting of hydrogen, halogen, C1-4 alkyl, aryl, C1-4 alkyl aryl, cyano, nitro, (CR7R7)pORb, (CR7R7)pNRbRb, or R4 and R5 together may form a 5 to 6 membered saturated or unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroalkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;

R6 is selected from the group consisting of hydrogen, C1-4 alkyl;

q is 0 or an integer having a value of 1 to 15;

n is an integer having a value of 1 to 14;

m is an integer having a value of 1 to 15;

l is an integer having a value of 1 to 4;

t is 0 or an integer having a value of 1 to 5;

p is 0 or an integer having a value of 1 to 4;

X, Y, Z and W are independently selected from the group consisting of hydrogen, C1-4 alkyl;

V is selected from the group consisting of CH_2, O, S, and NRb;

M is O or CH_2;

Rb is selected from the group consisting of hydrogen, C1-4 alkyl, aryl and C1-4 alkyl aryl;

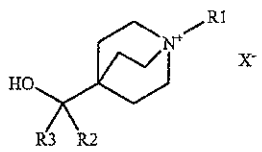
R7 is selected from the group consisting of hydrogen, C1-4 alkyl, halosubstituted C1-4 alkyl, and hydroxysubstituted C1-4 alkyl;

X— is a physiologically acceptable anion, such as chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate and p-toluenesulfonate.

DETAILED DESCRIPTION OF THE INVENTION

This invention related to novel bi-aryl 8-azoniabicyclo [3.2.1]octane compounds, pharmaceutical compositions, processes for their preparation, and use thereof in treating mAChR mediated diseases.

In a preferred embodiment of the present invention the compound is of formula (I) herein below:

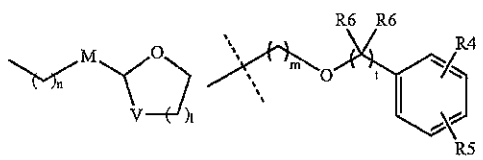


(I)

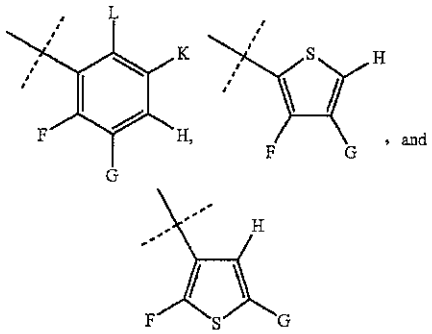
wherein:

R1 is selected from the group consisting of C1-10 alkyl, halosubstituted C1-10 alkyl, C1-10 alkyl aryl, C1-10 alkyl cycloalkyl, cycloalkyl, hydroxy substituted C1-10 alkyl, C2-10 alkenyl, (CR7R7)qORc; (CR7R7)qOC(O)Ra and (CR7R7)qNS(O)$_2$Ra;

or R1 is selected from the group consisting of:



R2 and R3 are, independently, selected from the group consisting of:



, and

F, G, H, K and L are independently selected from the group consisting of hydrogen, halogen, C1-4 alkyl, halosubstituted C1-4 alkyl, hydroxysubstituted C1-4 alkyl, and C1-4 alkoxy;

Ra is selected from the group consisting of hydrogen, C1-10 alkyl, C1-10 alkoxy, aryl and heteroaryl, all of which moieties may be optionally substituted;

Rc is selected from the group consisting of hydrogen, C1-5 alkyl, C1-5 alkoxy, all of which moieties may be optionally substituted;

R4 and R5 are independently selected from the group consisting of hydrogen, halogen, C1-4 alkyl, aryl, C1-4 alkyl aryl, cyano, nitro, (CR7R7)pORb, (CR7R7)pNRbRb, or R4 and R5 together may form a 5 to 6 membered saturated or unsaturated ring;

q is 0 or an integer having a value of 1 to 5;

n is an integer having a value of 1 to 4;

m is an integer having a value of 1 to 5;

l is 1 or 2;

t is 0, 1 or 2;

p is 0, 1 or 2;

V is O, or CH_2;

R6 is selected from the group consisting of hydrogen, C1-4 alkyl;

M is O or CH_2;

Rb is selected from the group consisting of hydrogen, C1-4 alkyl, and aryl C1-4 alkyl R7 is selected from the group consisting of hydrogen, and C1-4 alkyl;

X— is a physiologically acceptable anion, such as chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate and p-toluenesulfonate.

All of the aryl, heteroaryl, and heterocyclic containing moieties may be optionally substituted as defined herein below.

For use herein the term "the aryl, heteroaryl, and heterocyclic containing moieties" refers to both the ring and the alkyl, or if included, the alkenyl rings, such as aryl, arylalkyl, and aryl alkenyl rings. The term "moieties" and "rings" may be interchangeably used throughout.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted $C_{1\text{-}10}$alkyl; $C_{1\text{-}10}$ alkoxy, such as methoxy or ethoxy; $S(O)_m C_{1\text{-}10}$ alkyl, wherein m' is 0, 1 or 2, such as methyl thio, methyl sulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the $NR_{10}R_{11}$ group; $NHC(O)R_9$; $C(O)NR_{10}R_{11}$; C(O)OH; $S(O)_2NR_{10}R_{11}$; $NHS(O)_2R_9$, $C_{1\text{-}10}$ alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted $C_{1\text{-}10}$ alkyl, such CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl, heteroaryl, or heterocyclic moieties may be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; $C_{1\text{-}10}$ alkoxy; $S(O)_m C_{1\text{-}10}$ alkyl; amino, mono & di-substituted alkyl amino, such as in the $NR_{10}R_{11}$ group; $C_{1\text{-}10}$ alkyl, or halosubstituted $C_{1\text{-}10}$ alkyl, such as CF_3.

The following terms, as used herein, refer to:

"halo"—all halogens, that is chloro, fluoro, bromo and iodo.

"$C_{1\text{-}10}$alkyl" or "alkyl"—both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl and the like.

"cycloalkyl" is used herein to mean cyclic moiety, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.

"alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

"aryl"—phenyl and naphthyl;

"heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl")—a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, indole or benzimidazole.

"heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl")—a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, thiomorpholine, or imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.

"arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean $C_{1\text{-}10}$ alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

"sulfinyl"—the oxide S(O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized $S(O)_2$ moiety.

"wherein two R_1 moieties (or two Y moieties) may together form a 5 or 6 membered saturated or unsaturated ring" is used herein to mean the formation of an aromatic ring system, such as naphthalene, or is a phenyl moiety having attached a 6 membered partially saturated or unsaturated ring such as a C_6 cycloalkenyl, i.e. hexene, or a C_5 cycloalkenyl moiety, such as cyclopentene.

Illustrative compounds of Formula (I) include:

1-(2-{[(3-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy] ethyl}-1-azoniabicyclo[2.2.2]octane bromide

1-(2-{[(4-bromophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-chlorophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(4-fluorophenyl)(hydroxy)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(3-methylphenyl)]methyl}-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylcarbonyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(3-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(4-methylphenyl)]methyl}-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{3-[(methylsulfonyl)amino]propyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(3-fluorophenyl)(hydroxy)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(3-chlorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-2-thienyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-cyanophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(4-bromophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(4-fluorophenyl)(hydroxy)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(4-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(1-methyl-1-phenylethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(2-naphthalenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-3-thienyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(3-methylphenyl)]methyl}-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(4-methylphenyl)]methyl}-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(3-{[4-(methyloxy)phenyl]oxy}propyl)-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[3-(2-naphthalenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[2-({[3-(methyloxy)phenyl]methyl}oxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(2-naphthalenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(3-fluorophenyl)(hydroxy)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-2-thienyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{3-[(4-nitrophenyl)oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(2-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{3-[(3-nitrophenyl)oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-({3-[(trifluoromethyl)oxy]phenyl}methyl)-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[(5-nitro-2-furanyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[2-(1H-indol-3-yl)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[3-(4-biphenylyloxy)propyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{3-[(2-methylphenyl)oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(phenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(2-{[2-(methyloxy)ethyl]oxy}ethyl)-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{3-[(phenylmethyl)oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[4-(phenyloxy)butyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(1,3-dioxolan-2-ylmethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{3-[(2-hydroxyphenyl)oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide
1-hexyl-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-3-thienyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[3-({4-[(phenylmethyl)oxy]phenyl}oxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[(3-bromophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-2-naphthalenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[2-(methyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-(hydroxy{bis[4-(methyloxy)phenyl]}methyl)-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(4-cyanophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[2-(1-benzofuran-2-yl)-2-oxoethyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[2-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy)ethyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{[3-(methyloxy)phenyl]methyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-({4-[(trifluoromethyl)oxy]phenyl}methyl)-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-nonyl-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-2-naphthalenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[(4-fluorophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[(4-bromophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{[3-(trifluoromethyl)phenyl]methyl}-1-azoniabicyclo[2.2.2]octane bromide
1-[(2-fluorophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{[4-(trifluoromethyl)phenyl]methyl}-1-azoniabicyclo[2.2.2]octane bromide
1-(5-hexen-1-yl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

1-(3-cyclohexylpropyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(2-phenylethyl)-1-azoniabicyclo[2.2.2]octane bromide
1-ethyl-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo [2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[(4-methylphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-butyl-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo [2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[2-(3-methyl-1H-pyrazol-1-yl)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-(hydroxy{bis[4-(methyloxy)phenyl]}methyl)-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[3-(3-biphenylyloxy)propyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[(1S)-1-methyl-2-oxo-2-(phenylamino)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-propyl-1-azoniabicyclo [2.2.2]octane bromide
1-{3-[(2-bromophenyl)oxy]propyl}-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[(3-fluorophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[(3,4-dichlorophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[(2-fluoro-3-methylphenyl)methyl]-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{4-[(phenylmethyl)oxy]butyl}-1-azoniabicyclo[2.2.2]octane bromide
1-[(4-cyanophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(3-{[3-(diethylamino)phenyl]oxy}propyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(2-propen-1-yl)-1-azoniabicyclo[2.2.2]octane bromide
1-{[4-(1,1-dimethylethyl)phenyl]methyl}-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide
1-[(2,6-difluorophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-({[2-(phenyloxy)-3-pyridinyl]carbonyl}amino)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-2-thienyl)methyl]-1-(2-phenylethyl)-1-azoniabicyclo[2.2.2]octane bromide
1-(3-bromopropyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(2-hydroxyethyl)-1-azoniabicyclo[2.2.2]octane bromide
1-[(3-cyanophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[2-({[(2,4-dichlorophenyl)amino]carbonyl}amino)ethyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(4-penten-1-yl)-1-azoniabicyclo[2.2.2]octane bromide
1-{2-[(2,4-dibromophenyl)oxy]ethyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[(2,4-difluorophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[3-(methyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[3-({2-[(phenylmethyl) oxy]phenyl}oxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[(2-aminoethyl)-1-azoniabicyclo[2.2.2]oct-4-yl] (diphenyl)methanolate trifluoroacetate
4-[hydroxy(di-2-thienyl)methyl]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-methyl-1-azoniabicyclo [2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(tetrahydro-2H-pyran-2-ylmethyl)-1-azoniabicyclo[2.2.2]octane bromide
1-[(2,3-difluorophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-[2-(4-biphenylyl)-2-oxoethyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[2-oxo-2-(4-pentylphenyl) ethyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(2,4-dichlorophenyl)carbonyl]amino}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(3-{[2-(methyloxy)phenyl] oxy}propyl)-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[(1-{[(phenylmethyl)oxy] carbonyl}-4-piperidinyl)methyl]-1-azoniabicyclo[2.2.2] octane bromide
4-[hydroxy(diphenyl)methyl]-1-[2-(2-naphthalenyl)-2-oxoethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[(4-nitrophenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-butyl-4-[hydroxy(di-3-thienyl)methyl]-1-azoniabicyclo [2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane bromide
1-[(3,4-difluorophenyl)methyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(cyclopropylmethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

The preferred compounds useful in the present invention include:

1-(2-{[(3-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy] ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-bromophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-chlorophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(4-fluorophenyl)(hydroxy)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(3-methylphenyl)]methyl}-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylcarbonyl)oxy] ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(3-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(4-methylphenyl)]methyl}-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

4-[hydroxy(diphenyl)methyl]-1-{3-[(methylsulfonyl) amino]propyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(3-fluorophenyl)(hydroxy)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(3-chlorophenyl)oxy]propyl}-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-2-thienyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-cyanophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(4-bromophenyl)oxy]propyl}-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(4-fluorophenyl)(hydroxy)methyl]-1-[3-(phenyloxy) propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(4-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(1-methyl-1-phenylethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(2-naphthalenylmethyl) oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-3-thienyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(3-methylphenyl)]methyl}-1-[3-(phenyloxy) propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(4-methylphenyl)]methyl}-1-[3-(phenyloxy) propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(3-{[4-(methyloxy)phenyl] oxy}propyl)-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[3-(2-naphthalenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-({[3-(methyloxy)phenyl]methyl}oxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-(2-naphthalenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(3-fluorophenyl)(hydroxy)methyl]-1-[3-(phenyloxy) propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-2-thienyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{3-[(4-nitrophenyl)oxy] propyl}-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(2-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide

The more preferred compounds useful in the present invention include:

1-(2-{[(3-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy] ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-bromophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-chlorophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(4-fluorophenyl)(hydroxy)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(3-methylphenyl)]methyl}-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylcarbonyl)oxy] ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(3-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(4-methylphenyl)]methyl}-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{3-[(methylsulfonyl) amino]propyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(3-fluorophenyl)(hydroxy)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(3-chlorophenyl)oxy]propyl}-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-2-thienyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-cyanophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(4-bromophenyl)oxy]propyl}-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(4-fluorophenyl)(hydroxy)methyl]-1-[3-(phenyloxy) propyl]-1-azoniabicyclo[2.2.2]octane bromide
1-{3-[(4-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(1-methyl-1-phenylethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(2-naphthalenylmethyl) oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(di-3-thienyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(3-methylphenyl)]methyl}-1-[3-(phenyloxy) propyl]-1-azoniabicyclo[2.2.2]octane bromide

The most preferred compounds useful in the present invention include:

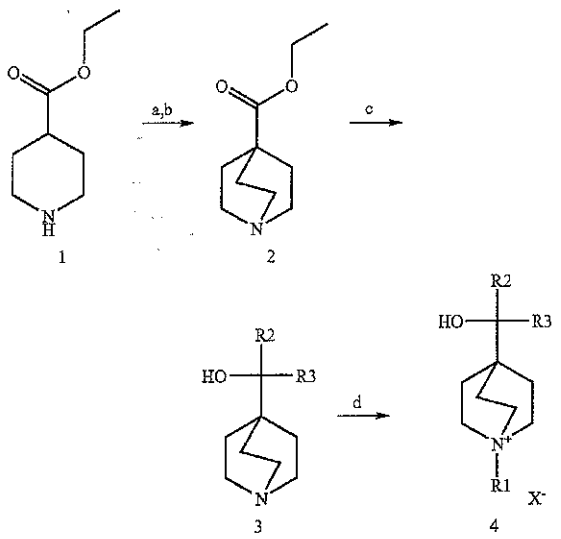
1-(2-{[(3-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy] ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-bromophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-chlorophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[bis(4-fluorophenyl)(hydroxy)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
4-{hydroxy[bis(3-methylphenyl)]methyl}-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide
1-(2-{[(4-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide
4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylcarbonyl)oxy] ethyl}-1-azoniabicyclo[2.2.2]octane bromide

Methods of Preparation

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided in this Scheme is applicable for producing compounds of Formula (I) having a variety of different R1, R2 and R3 groups which are reacted, employing substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While the Schemes are shown with compounds only of Formula (I), this is merely for illustration purpose only.

As shown in Scheme 1, the desired compounds of Formula (I) can be prepared in four synthetic steps from the commercially available ethyl 4-piperidinecarboxylate precursor 1. Compound 1 is reacted with 1-bromo-2-chloroethane following standard alkylation procedures well known in the art such as potassium carbonate in acetone followed by reaction of the intermediate with lithium diisopropylamide in an aprotic solvent such as tetrahydrofurann to give the quinuclidine intermediate 2. Condensation of compound 2 with organometallic reagents such as a Grignard reagent or an organolithium derivative in an aprotic solvent such as tetrahydrofuran, results in the formation of the tertiary alcohol 3 of Formula (I) (R1=nothing). Further N-alkylation of compound 3 with a suitable alkyl halide in a organic solvent such as chloroform or acetonitrile gives compound 4 of Formula (I) (R1 not nothing).

Scheme 1



1 2 3 4

Reagents and conditions: a) 1-bromo-2-chloroethane, K_2CO_3, acetone; b) LDA, THF; c) R_2M then R_3M, THF; d) R1X, ACN, $CHCl_3$.

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following Examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in ° C. Thin layer chromatography (t.l.c.) was carried out on silica and column chromatography on silica (Flash column chromatography using Merck 9385 unless stated otherwise). The following are the experimental conditions for the LC-MS.

LC-MS Experimental Conditions:

Liquid Chromatograph:	
System:	Shimadzu LC system with SCL-10A Controller and dual UV detector
Autosampler:	Leap CTC with a Valco six port injector
Column:	Aquasil/Aquasil (C18 40 x 1 mm)

-continued

Inj. Volume (µL):	2.0
Solvent A:	H_2O, 0.02% TFA
Solvent B:	MeCN, 0.018% TFA
Gradient:	linear
Channel A:	UV 214 nm
Channel B:	ELS

Step	Time (min)	Dura. (min)	Flow (µL/min)	Sol. A	Sol. B
0	0.00	0.00	300.00	95.00	5.00
1	0.00	0.01	300.00	95.00	5.00
2	0.01	3.20	300.00	10.00	90.00
3	3.21	1.00	300.00	10.00	90.00
4	4.21	0.10	300.00	95.00	5.00
5	4.31	0.40	300.00	95.00	5.00

Mass Spectrometer:	PE Sciex Single Quadrupole LC/MS API-150
Polarity:	Positive
Acquisition mode:	Profile

The preparatory HPLC was conducted using a Gilson HPLC system under the following conditions:

Column: 75x33 mm I. D., S-5 um, 12 nm
Flow rate: 30 mL/min
Injection Volume: 0.800 mL
Room temperature
Solvent A: water
Solvent B: acetonitrile

All solvents used herein are of the highest available purity and all reactions are run under anhydrous conditions under an air atmosphere unless otherwise indicated.

Example 1

Preparation of 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol

Ethyl 1-(2-chloroethyl)-4-piperidinecarboxylate

To a solution of ethyl nipecotate (20.0 mL, 130 mmol) in acetone (180 mL) was added 1-bromo-2-chloroethane (21.6 mL, 260 mmol) followed by anhydrous K_2CO_3 (27.12 g, 196 mmol). The reaction mixture was stirred for 24 h and then concentrated under vacuum. The resulting residue was treated with H_2O (75 mL) and extracted with Et_2O. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum. Purification of the crude residue by flash chromatography (50% Et_2O/50% hexane) on silica gel gave the title compound (10.99 g, 38.6%). EI-MS m/z 220($M+H^+$) Rt (1.20 min).

Ethyl 1-azabicyclo[2.2.2]octane-4-carboxylate

A solution of ethyl 1-(2-chloroethyl)-4-piperidinecarboxylate (20.42 g, 92.9 mmol) in THF (600 mL) was cooled to −50° C. under Ar. LDA (2.0 M in heptane/THF/ethyl benzene, 70 mL, 140 mmol) was slowly added to the solution at −50° C. over 25 min. The reaction was allowed to warm up to room temperature over 16 h. The reaction was quenched with K_2CO_3 (saturated aqueous) (500 mL) and extracted with Et_2O (3x500 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting orange oil was co-evaporated three times with DCM to remove excess ethyl benzene, resulting in the title compound (16.29 g, 95.7%). EI-MS m/z 184($M+H^+$) Rt (1.08 min).

1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol

A solution of phenyllithium (1.5-1.7 M in 70 cyclohexane/30 ether, 20.0 mL, 32 mmol) was chilled down to −30° C. under Ar. Ethyl 1-azabicyclo[2.2.2]octane-4-carboxylate (1.51 g, 8.23 mmol) in THF (20 mL) was slowly added to the reaction mixture at −30° C. over 25 min. The reaction was allowed to warm up to room temperature over 16 h. The reaction was quenched with H_2O and then evaporated to dryness under vacuum. H_2O and EtOAc were added, causing a white solid to crash out. This solid was filtered off, to give the title compound (0.79 g). The aqueous phase was further extracted with EtOAc, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was treated with EtOAc and hexane and filtered to yield more of the title compound (0.67 g). Total yield (1.46 g, 60.7%). EI-MS m/z 294($M+H^+$) Rt (1.37 min).

Example 2

Preparation of 4-[hydroxy(diphenyl)methyl]-1-(2-phenylethyl)-1-azoniabicyclo[2.2.2]octane bromide

To a solution of 1-azabicyclo[2.2.2]oct-4-yl(diphenyl) methanol (0.0775 g, 0.264 mmol) in CH_3CN/DCM/MeOH (2 mL/2 mL/1 mL) was added (2-bromoethyl)benzene (0.38 mL, 2.78 mmol). The solution was allowed to stir at room temperature for 4 days and then concentrated under vacuum to give a white solid. This residue was dissolved in DMSO and purified by preparatory HPLC to give the title compound (0.0612 g, 48.6%). EI-MS m/z 398(M^+) Rt (2.06 min).

Example 3

Preparation of 4-[hydroxy(diphenyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide

General Procedure for Salt Formation without HPLC Purification.

To a solution of 1-azabicyclo[2.2.2]oct-4-yl(diphenyl) methanol (0.055 0 g, 0.187 mmol) in 2 CH_3CN/3 $CHCl_3$ (2.5 mL) was added 2-bromoethyl phenyl ether (0.06 0 g, 0.29 mmol). The solution was stirred at 60° C. for 16 h. The reaction was cooled down to room temperature and then diluted with ethyl acetate and hexane causing a solid to crash out of solution. This solid was filtered off, and washed with hexane to give the title compound (0.063 g, 67.6%). EI-MS m/z 414(M^+) Rt (1.94 min).

Example 4

Preparation of 1-(cyclopropylmethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

General Procedure for Salt Formation with HPLC Purification.

To a solution of 1-azabicyclo[2.2.2]oct-4-yl(diphenyl) methanol (0.0552 g, 0.188 mmol) in 2 CH_3CN/3 $CHCl_3$ (2.5 mL) was added (bromomethyl)cyclopropane (0.025 mL, 0.257 mmol). The solution was heated at 60° C. for 16 h, cooled down to room temperature and the solvents evaporated under vacuum. The residue was taken up in 2.5 mL of DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.031 9 g, 39.9%). EI-MS m/z 348(M^+) Rt (1.69 min).

Example 5

Preparation of 4-[hydroxy(diphenyl)methyl]-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0567 g, 0.193 mmol) and 2-bromo-1-phenylethanone (0.0487 g, 0.245 mmol) in 2 CH_3CN/3 $CHCl_3$ (2.5 mL) were reacted to give the desired product (0.0410 g, 43.0%). EI-MS m/z 412 (M^+) Rt (1.90 min).

Example 6

Preparation of 4-[hydroxy(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.045 g, 0.153 mmol) and 3-bromopropyl phenyl ether (0.035 mL, 0.222 mmol) in 2 CH_3CN/3 $CHCl_3$ (3.0 mL) were reacted to give the desired product (0.0662 g, 86.0%). EI-MS m/z 428 (M^+) Rt (1.97 min).

Example 7

Preparation of 4-[hydroxy(diphenyl)methyl]-1-[4-(phenyloxy)butyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0604 g, 0.206 mmol) and 4-bromobutyl phenyl ether (0.106 g, 0.463 mmol) in 2 CH_3CN/3 $CHCl_3$ (5.0 mL) were reacted to give the desired product (0.0649 g, 64.9%). EI-MS m/z 442(M^+) Rt (2.13 min).

Example 8

Preparation of 4-[hydroxy(diphenyl)methyl]-1-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0696 g, 0.237 mmol) and 2-[(2-bromoethyl)oxy]tetrahydro-2H-pyran (0.080 mL, 0.529 mmol) in 2 CH_3CN/3 $CHCl_3$ (5.0 mL) were reacted to give the desired product (0.0348 g, 31.6%). EI-MS m/z 422(M^+) Rt (1.85 min).

Example 9

Preparation of 4-[hydroxy(diphenyl)methyl]-1-{4-[(phenylmethyl)oxy]butyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0646 g, 0.220 mmol) and 4-bromobutyl phenylmethyl ether (0.090 mL, 0.472 mmol) in 2 CH_3CN/3 $CHCl_3$ (5.0 mL) were reacted to give the desired product (0.0531 g, 48.3%). EI-MS m/z 456(M^+) Rt (2.09 min).

Example 10

Preparation of 4-[hydroxy(diphenyl)methyl]-1-{3-[(phenylmethyl)oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0677 g, 0.231 mmol) and 3-bromopropyl phenylmethyl ether (0.070 mL, 0.396 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0663 g, 55.2%). EI-MS m/z 442(M^+) Rt (2.23 min).

Example 11

Preparation of 1-{2-[(2,4-dibromophenyl)oxy]ethyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0557 g, 0.190 mmol) and 2-bromoethyl 2,4-dibromophenyl ether (0.110 g, 0.306 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0525 g, 43.8%). EI-MS m/z 572(M^+) Rt (2.26 min).

Example 12

Preparation of 1-(3-bromopropyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0979 g, 0.334 mmol) and 1,3-dibromopropane (0.35 mL, 3.448 mmol) in 2 CH_3CN/3 $CHCl_3$ (15.0 mL) were reacted to give the desired product (0.0712 g, 43.1%). EI-MS m/z 415(M^+) Rt (1.79 min).

Example 13

Preparation of 4-[hydroxy(diphenyl)methyl]-1-(tetrahydro-2H-pyran-2-ylmethyl)-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0677 g, 0.231 mmol) and 3-(bromomethyl)tetrahydro-2H-pyran (0.050 mL, 0.390 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0508 g, 50.8%). EI-MS m/z 392(M^+) Rt (1.84 min).

Example 14

Preparation of 1-(1,3-dioxolan-2-ylmethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0574 g, 0.196 mmol) and 2-(bromomethyl)-1,3-dioxolane (0.040 mL, 0.386 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0112 g, 12.4%). EI-MS m/z 380(M^+) Rt (1.64 min).

Example 15

Preparation of 1-ethyl-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0581 g, 0.198 mmol) and bromoethane (0.030 mL, 0.402 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0434 g, 54.9%). EI-MS m/z 322(M^+) Rt (1.56 min).

Example 16

Preparation of 4-[hydroxy(diphenyl)methyl]-1-nonyl-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0561 g, 0.191 mmol) and 1-bromononane (0.055 mL, 0.288 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0435 g, 45.8%). EI-MS m/z 420(M^+) Rt (2.34 min).

Example 17

Preparation of 4-[hydroxy(diphenyl)methyl]-1-(4-penten-1-yl)-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0608 g, 0.207 mmol) and 5-bromo-1-pentene (0.045 mL, 0.380 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0806 g, 88.6%). EI-MS m/z 362(M^+) Rt (1.88 min).

Example 18

Preparation of 4-[hydroxy(diphenyl)methyl]-1-(2-hydroxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0638 g, 0.217 mmol) and 2-bromoethanol (0.035 mL, 0.494 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0541 g, 60.1%). EI-MS m/z 338(M^+) Rt (1.42 min).

Example 19

Preparation of 1-(5-hexen-1-yl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0637 g, 0.217 mmol) and 6-bromo-1-hexene (0.050 mL, 0.373 mmol) in 2 CH_3CN/3 $CHCl_3$ (5.0 mL) were reacted to give the desired product (0.0664 g, 67.1%). EI-MS m/z 376(M^+) Rt (1.90 min).

Example 20

Preparation of 4-[hydroxy(diphenyl)methyl]-1-methyl-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0638 g,

0.217 mmol) and bromomethane (2.0 M in t-Butylmethyl ether, 0.250 mL, 0.500 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0739 g, 88.0%). EI-MS m/z 308(M^+) Rt (1.58 min).

Example 21

Preparation of 4-[hydroxy(diphenyl)methyl]-1-[2-(methyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0597 g, 0.203 mmol) and 2-bromoethyl methyl ether (0.030 mL, 0.319 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0372 g, 42.8%). EI-MS m/z 352 (M^+) Rt (1.69 min).

Example 22

Preparation of 1-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0916 g, 0.312 mmol) and 2-(2-bromoethyl)-1H-isoindole-1,3(2H)-dione (0.130 g, 0.512 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0881 g, 51.8%). EI-MS m/z 467(M^+) Rt (1.91 min).

Example 23

Preparation of 1-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0861 g, 0.293 mmol) and 2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione (0.118 g, 0.440 mmol) in 2 CH_3CN/3 $CHCl_3$ (5.0 mL) were reacted to give the desired product (0.1319 g, 82.4%). E-MS m/z 481(M^+) Rt (1.90 min).

Example 24

Preparation of 4-[hydroxy(diphenyl)methyl]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0625 g, 0.213 mmol) and (3-bromopropyl)benzene (0.050 mL, 0.329 mmol) in 2 CH_3CN/3 $CHCl_3$ (5.0 mL) were reacted to give the desired product (0.0722 g, 72.2%). EI-MS m/z 412(M^+) Rt (2.01 min).

Example 25

Preparation of 4-[hydroxy(diphenyl)methyl]-1-(2-{[2-(methyloxy)ethyl]oxy}ethyl)-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0665 g, 0.227 mmol) and 1-bromo-2-{[2-(methyloxy)ethyl]oxy}ethane (0.05 5 mL, 0.405 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0843 g, 78.8%). EI-MS m/z 396(M^+) Rt (1.64 min).

Example 26

Preparation of 1-[4-(ethyloxy)-4-oxobutyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0679 g, 0.231 mmol) and ethyl 4-bromobutanoate (0.055 mL, 0.524 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0637 g, 57.9%). EI-MS m/z 408(M^+) Rt (1.80 min).

Example 27

Preparation of 1-azabicyclo[2.2.2]oct-4-yl(di-2-thienyl)methanol

A solution of 2-thienyllithium (1.0M in THF, 9.10 mL, 9.10 mmol) was chilled down to −30° C. under Ar. Ethyl 1-azabicyclo[2.2.2]octane-4-carboxylate (0.4196 g, 2.289 mmol) in THF (8 mL) was slowly added to the reaction mixture over 20 min. The reaction was allowed to warm up to room temperature over 16 h. The reaction was quenched with water and then evaporated to dryness. H_2O and DCM were added, causing a light brown solid to crash out. This solid was filtered off to give the title compound (0.4161 g, 59.5%). EI-MS m/z 306($M+H^+$) Rt (1.35 min).

Example 28

Preparation of 4-[hydroxy(di-2-thienyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(di-2-thienyl)methanol (0.0693 g, 0.227 mmol) and 2-bromoethyl phenyl ether (0.056 g, 0.279 mmol) in 1 MeOH/1 $CHCl_3$ (3.0 mL) were reacted to give the desired product (0.0822 g, 74.7%). EI-MS m/z 426 (M^+) Rt (2.00 min).

Example 29

Preparation of 4-[hydroxy(di-2-thienyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(di-2-thienyl)methanol (0.0578 g, 0.189 mmol) and 3-bromopropyl phenyl ether (0.033 mL, 0.209 mmol) in 1 MeOH/1 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0448 g, 45.4%). EI-MS m/z 440 (M^+) Rt (1.94 min).

Example 30

Preparation of 4-[hydroxy(di-2-thienyl)methyl]-1-(2-phenylethyl)-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(di-2-thienyl)methanol (0.0658 g, 0.215 mmol) and (2-bromoethyl)benzene (0.050 mL,

0.366 mmol) in 1 MeOH/1 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.051 4 g, 48.9%). EI-MS m/z 410(M^+) Rt (1.83 min).

Example 31

Preparation of 4-[hydroxy(di-2-thienyl)methyl]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(di-2-thienyl)methanol (0.0688 g, 0.225 mmol) and (3-bromopropyl)benzene (0.070 mL, 0.460 mmol) in 1 MeOH/1 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0685 g, 62.3%). EI-MS m/z 424 (M^+) Rt (1.97 min).

Example 32

Preparation of 1-butyl-4-[hydroxy(di-3-thienyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

A solution of n-Butyl lithium (2.5M in hexanes, 5.0 mL, 12.5 mmol) was chilled to −78° C. under Ar. 3-Bromothiophene (1.15 mL, 12.3 mmol) dissolved in ethyl ether (4.0 mL) was slowly added to the reaction mixture. The reaction was stirred for 30 min and then ethyl 1-azabicyclo [2.2.2]octane-4-carboxylate (0.7640 g, 4.16 mmol) in THF/Et_2O (4 mL/4 mL) was added. The reaction was allowed to warm up from −78° C. to room temperature over 16 h then slowly quenched with water. The reaction was concentrated and the resulting brown solid was taken up in water and DCM. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated under vacuum to give a brown solid. The solid was dissolved in DMSO and purified by preparatory HPLC to give the title compound (0.1736 g, 9.4%). EI-MS m/z 362(M^+) Rt (1.73 min).

Example 33

Preparation of 1-azabicyclo[2.2.2]oct-4-yl(di-3-thienyl)methanol.

A solution of t-Butyl lithium (1.7M in pentanes, 5.8 mL, 9.86 mmol) was chilled to −78° C. under Ar. 3-Bromothiophene (0.46 mL, 4.90 mmol) dissolved in THF (4.0 mL) was slowly added to the reaction mixture over 6 min. The reaction was stirred for 30 min and then ethyl 1-azabicyclo [2.2.2]octane-4-carboxylate (0.3132 g, 1.71 mmol) in THF (4 mL) was added. The reaction was allowed to warm up from −78° C. to room temperature over 16 h. After 14 hours, the reaction was slowly quenched with water. EtOAc was added, causing a grey solid to crash out. The solid was filtered off to give the title compound (0.3375 g, 64.6%). EI-MS m/z 306 $(M+H)^+$ Rt (1.27 min).

Example 34

Preparation of 4-[hydroxy(di-3-thienyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(di-3-thienyl)methanol (0.0787 g, 0.258 mmol) and 2-bromoethyl phenyl ether (0.0839 g, 0.417 mmol) in 2MeOH/3 $CHCl_3$/2 CH_3CN (5.0 mL) were reacted to give the desired product (0.0709 g, 54.5%). EI-MS m/z 426(M^+) Rt (1.85 min).

Example 35

Preparation of 4-[hydroxy(di-3-thienyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl(di-3-thienyl)methanol (0.0808 g, 0.264 mmol) and 3-bromopropyl phenyl ether (0.070 mL, 0.444 mmol) in 2MeOH/3 $CHCl_3$/2 CH_3CN (5.0 mL) were reacted to give the desired product (0.0613 g, 44.7%). EI-MS m/z 440(M^+) Rt (2.05 min).

Example 36

Preparation of 1-butyl-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0496 g, 0.169 mmol) and 1-bromobutane (0.030 mL, 0.279 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0509 g, 70.7%). EI-MS m/z 350(M^+) Rt (1.83 min).

Example 37

Preparation of 1-hexyl-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0498 g, 0.170 mmol) and 1-bromohexane (0.040 mL, 0.285 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0562 g, 73.0%). EI-MS m/z 378(M^+) Rt (2.09 min).

Example 38

Preparation of 4-[hydroxy(diphenyl)methyl]-1-propyl-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0518 g, 0.176 mmol) and 1-bromopropane (0.030 mL, 0.330 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0548 g, 75.1%). EI-MS m/z 336(M^+) Rt (1.97 min).

Example 39

Preparation of 4-[hydroxy(diphenyl)methyl]-1-(3-{[2-(methyloxy)phenyl]oxy}propyl)-1-azoniabicyclo [2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0467 g, 0.159 mmol) and 1-[(3-bromopropyl)oxy]-2-(methyloxy) benzene (0.0541 g, 0.221 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0625 g, 73.5%). EI-MS m/z 458(M^+) Rt (1.96 min).

Example 40

Preparation of 4-[hydroxy(diphenyl)methyl]-1-{3-[(2-hydroxyphenyl)oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0505 g, 0.172 mmol) and 2-[(3-bromopropyl)oxy]phenol (0.0547 g, 0.236 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0675 g, 75.0%). EI-MS m/z 444 (M^+) Rt (1.91 min).

Example 41

Preparation of 4-[hydroxy(diphenyl)methyl]-1-[3-(2-naphthalenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0472 g, 0.160 mmol) and 3-bromopropyl 2-naphthalenyl ether (0.0618 g, 0.233 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0567 g, 63.7%). EI-MS m/z 478(M^+) Rt (2.22 min).

Example 42

Preparation of 1-{3-[(3-chlorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0479 g, 0.163 mmol) and 3-bromopropyl 3-chlorophenyl ether (0.0552 g, 0.221 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0655 g, 74.4%). EI-MS m/z 462(M^+) Rt (2.17 min).

Example 43

Preparation of 1-{3-[(4-bromophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0486 g, 0.165 mmol) and 4-bromophenyl 3-bromopropyl ether (0.0630 g, 0.214 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0731 g, 75.4%). EI-MS m/z 506(M^+) Rt (2.18 min).

Example 44

Preparation of 4-[hydroxy(diphenyl)methyl]-1-{3-[(4-nitrophenyl)oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0468 g, 0.159 mmol) and 3-bromopropyl 4-nitrophenyl ether (0.0550 g, 0.211 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0590 g, 67.0%). EI-MS m/z 473(M^+) Rt (2.06 min).

Example 45

Preparation of 4-[hydroxy(diphenyl)methyl]-1-[3-({2-[(phenylmethyl)oxy]phenyl}oxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0492 g, 0.168 mmol) and 1-[(3-bromopropyl)oxy]-2-[(phenylmethyl)oxy]benzene (0.0706 g, 0.220 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0735 g, 71.4%). EI-MS m/z 533(M^+) Rt (2.25 min).

Example 46

Preparation of 1-{3-[(2-bromophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0472 g, 0.161 mmol) and 2-bromophenyl 3-bromopropyl ether (0.0648 g, 0.220 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0703 g, 74.8%). EI-MS m/z 507(M^+) Rt (2.18 min).

Example 47

Preparation of 4-[hydroxy(diphenyl)methyl]-1-[3-({4-[(phenylmethyl)oxy]phenyl}oxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0479 g, 0.163 mmol) and 1-[(3-bromopropyl)oxy]-4-[(phenylmethyl)oxy]benzene (0.0730 g, 0.227 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0833 g, 83.3%). EI-MS m/z 534(M^+) Rt (2.31 min).

Example 48

Preparation of 4-[hydroxy(diphenyl)methyl]-1-[3-(methyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0632 g, 0.215 mmol) and 3-bromopropyl methyl ether (0.0461 g, 0.301 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0826 g, 86.0%). EI-MS m/z 366 (M^+) Rt (1.55 min).

Example 49

Preparation of 4-[hydroxy(diphenyl)methyl]-1-(2-propen-1-yl)-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0577 g, 0.197 mmol) and 3-bromo-1-propene (0.025 mL, 0.289 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0646 g, 79.8%). EI-MS m/z 334(M^+) Rt (1.54 min).

Example 50

Preparation of 4-[hydroxy(diphenyl)methyl]-1-(3-{[4-(methyloxy)phenyl]oxy}propyl)-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0483 g, 0.164 mmol) and 1-[(3-bromopropyl)oxy]-4-(methyloxy) benzene (0.052 g, 0.21 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0687 g, 77.5%). EI-MS m/z 458(M^+) Rt (2.03 min).

Example 51

Preparation of [1-(2-aminoethyl)-1-azoniabicyclo[2.2.2]oct-4-yl](diphenyl)methanolate trifluoroacetate

To a solution of 1-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide (0.078 g, 0.142 mmol) in EtOH (4.0 mL) was added hydrazine (0.25 mL, 7.96 mmol). The solution was stirred at room temperature for 16 h and then filtered. The filtrate was concentrated and taken up in 2.5 mL of DMSO and purified by preparatory HPLC (with TFA) to give the title compound (0.0200 g, 31.2%). EI-MS m/z 338(M^+) Rt (1.28 min).

Example 52

Preparation of 4-[bis(4-fluorophenyl)(hydroxy)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

1-azabicyclo[2.2.2]oct-4-yl[bis(4-fluorophenyl)]methanol

A solution of 4-fluorophenylmagnesiumbromide (1.0 M in THF, 4.4 mL, 4.4 mmol) was chilled down to 0° C. under Ar. Ethyl 1-azabicyclo[2.2.2]octane-4-carboxylate (0.1973 g, 1.08 mmol) in THF (4 mL) was slowly added to the reaction mixture at 0° C. over 20 min. The reaction was allowed to warm up to room temperature and then heated at 60° C. for 16 h. The reaction was chilled in an ice bath, quenched with saturated NH_4Cl, and concentrated under vacuum. The resulting residue was treated with H_2O and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum to yield the desired product (0.3152 g, 88.9%). EI-MS m/z 330($M+H^+$) Rt (1.65 min).

4-[bis(4-fluorophenyl)(hydroxy)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl[bis(4-fluorophenyl)]methanol (0.0538 g, 0.163 mmol) and 3-bromopropyl phenyl ether (0.0386 mL, 0.245 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.058 g, 65.2%). EI-MS m/z 464(M^+) Rt (2.16 min).

Example 53

Preparation of 4-[bis(4-fluorophenyl)(hydroxy)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl[bis(4-fluorophenyl)]methanol (0.0489 g, 0.148 mmol) and 2-bromoethyl phenylmethyl ether (0.0352 mL, 0.222 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0534 g, 66.1%). EI-MS m/z 464(M^+) Rt (1.99 min).

Example 54

Preparation of 4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

1-azabicyclo[2.2.2]oct-4-yl{bis[3-(methyloxy)phenyl]}methanol

A solution of 3-(methyloxy)phenylmagnesiumbromide (1.0 M in THF, 3.3 mL, 3.3 mmol) was chilled down to 0° C. under Ar. Ethyl 1-azabicyclo[2.2.2]octane-4-carboxylate (0.1608 g, 0.877 mmol) in THF (4 mL) was slowly added to the reaction mixture at 0° C. over 20 min. The reaction was allowed to warm up to room temperature and then heated at 60° C. for 16 h. The reaction was chilled in an ice bath, quenched with saturated NH_4Cl, and concentrated under vacuum. The resulting residue was treated with H_2O and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum to yield the desired product (0.2881 g, 92.9%). EI-MS m/z 354($M+H^+$) Rt (1.46 min).

4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl{bis[3-(methyloxy)phenyl]}methanol (0.0506 g, 0.143 mmol) and 3-bromopropyl phenyl ether (0.0338 mL, 0.214 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.027 g, 33.2%). EI-MS m/z 488(M^+) Rt (2.02 min).

Example 55

Preparation of 4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl{bis[3-(methyloxy)phenyl]}methanol (0.0538 g, 0.152 mmol) and 2-bromoethyl phenylmethyl ether (0.0361 mL, 0.228 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0292 g, 33.8%). EI-MS m/z 488(M^+) Rt (2.03 min).

Example 56

Preparation of 4-(hydroxy{bis[4-(methyloxy)phenyl]}methyl)-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

1-azabicyclo[2.2.2]oct-4-yl{bis[4-(methyloxy)phenyl]}methanol

A solution of 4-(methyloxy)phenylmagnesiumbromide (0.5 M in THF, 6.5 mL, 3.25 mmol) was chilled down to 0° C. under Ar. Ethyl 1-azabicyclo[2.2.2]octane-4-carboxylate (0.1587 g, 0.866 mmol) in THF (4 mL) was slowly added to the reaction mixture at 0° C. over 20 min. The reaction was allowed to warm up to room temperature and then heated at

60° C. for 16 h. The reaction was chilled in an ice bath, quenched with saturated NH_4Cl, and concentrated under vacuum. The resulting residue was treated with H_2O and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum to yield the desired product (0.273 g, 89.0%). EI-MS m/z 354($M+H^+$) Rt (1.74 min).

4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl{bis[4-(methyloxy)phenyl]} methanol (0.0525 g, 0.148 mmol) and 3-bromopropyl phenyl ether (0.0351 mL, 0.222 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0515 g, 61.0%). EI-MS m/z 488(M^+) Rt (2.04 min).

Example 57

Preparation of 4-(hydroxy{bis[4-(methyloxy)phenyl]} methyl)-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl{bis[4-(methyloxy)phenyl]} methanol (0.0498 g, 0.141 mmol) and 2-bromoethyl phenylmethyl ether (0.0334 mL, 0.211 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0374 g, 46.7%). EI-MS m/z 488(M^+) Rt (1.94 min).

Example 58

Preparation of 4-[bis(3-fluorophenyl)(hydroxy)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo [2.2.2]octane bromide

1-azabicyclo[2.2.2]oct-4-yl[bis(3-fluorophenyl)] methanol

A solution of 3-fluorophenylmagnesiumbromide (1.0 M in THF, 3.3 mL, 3.3 mmol) was chilled down to 0° C. under Ar. Ethyl 1-azabicyclo[2.2.2]octane-4-carboxylate (0.1756 g, 0.958 mmol) in THF (4 mL) was slowly added to the reaction mixture at 0° C. over 20 min. The reaction was allowed to warm up to room temperature and then heated at 60° C. for 16 h. The reaction was chilled in an ice bath, quenched with saturated NH_4Cl, and concentrated under vacuum. The resulting residue was treated with H_2O and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum to yield the desired product (0.242 g, 76.7%). EI-MS m/z 330($M+H^+$) Rt (1.45 min).

4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl[bis(3-fluorophenyl)]methanol (0.0515 g, 0.156 mmol) and 3-bromopropyl phenyl ether (0.0370 mL, 0.234 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0381 g, 44.8%). EI-MS m/z 464(M^+) Rt (2.01 min).

Example 59

Preparation of 4-[bis(3-fluorophenyl)(hydroxy)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl[bis(3-fluorophenyl)]methanol (0.0507 g, 0.154 mmol) and 2-bromoethyl phenylmethyl ether (0.0365 mL, 0.230 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0362 g, 43.2%). EI-MS m/z 464(M^+) Rt (2.02 min).

Example 60

Preparation of 4-{hydroxy[bis(3-methylphenyl)] methyl}-1-[3-(phenyloxy)propyl]-1-azoniabicyclo [2.2.2]octane bromide

1-azabicyclo[2.2.2]oct-4-yl[bis(3-methylphenyl)] methanol

A solution of 3-methylphenylmagnesiumbromide (1.0 M in THF, 3.3 mL, 3.3 mmol) was chilled down to 0° C. under Ar. Ethyl 1-azabicyclo[2.2.2]octane-4-carboxylate (0.1484 g, 0.810 mmol) in THF (4 mL) was slowly added to the reaction mixture at 0° C. over 20 min. The reaction was allowed to warm up to room temperature and then heated at 60° C. for 16 h. The reaction was chilled in an ice bath, quenched with saturated NH_4Cl, and concentrated under vacuum. The resulting residue was treated with H_2O and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum to yield the desired product (0.1806 g, 69.4%). EI-MS m/z 322($M+H^+$) Rt (1.54 min).

4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl[bis(3-methylphenyl)]methanol (0.0487 g, 0.151 mmol) and 3-bromopropyl phenyl ether (0.0358 mL, 0.227 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0284 g, 34.9%). EI-MS m/z 456(M^+) Rt (2.14 min).

Example 61

Preparation of 4-{hydroxy[bis(3-methylphenyl)] methyl}-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 4, 1-azabicyclo[2.2.2]oct-4-yl[bis(3-methylphenyl)]methanol (0.0496 g, 0.154 mmol) and 2-bromoethyl phenylmethyl ether (0.0364 mL, 0.230 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0091 g, 11.0%). EI-MS m/z 456(M^+) Rt (2.20 min).

Example 62

Preparation of 4-{hydroxy[bis(4-methylphenyl)] methyl}-1-[3-(phenyloxy)propyl]-1-azoniabicyclo [2.2.2]octane bromide

1-azabicyclo[2.2.2]oct-4-yl[bis(4-methylphenyl)] methanol

A solution of 4-methylphenylmagnesiumbromide (1.0 M in THF, 3.3 mL, 3.3 mmol) was chilled down to 0° C. under Ar. Ethyl 1-azabicyclo[2.2.2]octane-4-carboxylate (0.1509 g, 0.823 mmol) in THF (4 mL) was slowly added to the reaction mixture at 0° C. over 20 min. The reaction was allowed to warm up to room temperature and then heated at 60° C. for 16 h. The reaction was chilled in an ice bath, quenched with saturated NH_4Cl, and concentrated under vacuum. The resulting residue was treated with H_2O and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum to yield the desired product (0.2291 g, 86.6%). EI-MS m/z 322($M+H^+$) Rt (1.57 min).

4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl[bis(4-methylphenyl)]methanol (0.0618 g, 0.192 mmol) and 3-bromopropyl phenyl ether (0.0454 mL, 0.288 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0427 g, 41.5%). EI-MS m/z 456(M^+) Rt (1.99 min).

Example 63

Preparation of 4-{hydroxy[bis(4-methylphenyl)] methyl}-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl[bis(4-methylphenyl)]methanol (0.0525 g, 0.163 mmol) and 2-bromoethyl phenylmethyl ether (0.0387 mL, 0.245 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0465 g, 53.1%). EI-MS m/z 456(M^+) Rt (2.09 min).

Example 64

Preparation of 4-[hydroxy(di-2-naphthalenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo [2.2.2]octane bromide

1-azabicyclo[2.2.2]oct-4-yl(di-2-naphthalenyl) methanol

A solution of (2-naphthalenyl)magnesiumbromide (0.5 M in THF, 6.5 mL, 3.25 mmol) was chilled down to 0° C. under Ar. Ethyl 1-azabicyclo[2.2.2]octane-4-carboxylate (0.1597 g, 0.871 mmol) in THF (4 mL) was slowly added to the reaction mixture at 0° C. over 20 min. The reaction was allowed to warm up to room temperature and then heated at 60° C. for 16 h. The reaction was chilled in an ice bath, quenched with saturated NH_4Cl, and concentrated under vacuum. The resulting residue was treated with H_2O and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum to yield the desired product (0.265 g, 77.3%). EI-MS m/z 394($M+H^+$) Rt (1.90 min).

4-(hydroxy{bis[3-(methyloxy)phenyl]}methyl)-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(di-2-naphthalenyl)methanol (0.0547 g, 0.139 mmol) and 3-bromopropyl phenyl ether (0.0329 mL, 0.209 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0268 g, 31.7%). EI-MS m/z 528(M^+) Rt (2.88 min).

Example 65

Preparation of 4-[hydroxy(di-2-naphthalenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(di-2-naphthalenyl)methanol (0.063.7 g, 0.162 mmol) and 2-bromoethyl phenylmethyl ether (0.0384 mL, 0.243 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0246 g, 25.0%). EI-MS m/z 528(M^+) Rt (2.36 min).

Example 66

Preparation of 1-{3-[(2-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2] octane bromide

3-bromopropyl 2-fluorophenyl ether

To a solution of 2-fluorophenol (0.040 mL, 0.448 mmol) in acetonitrile (4 mL) was added 1,3-dibromopropane (0.450 mL, 4.43 mmol) followed by Cs_2CO_3 (0.232 g, 0.713 mmol). The reaction mixture was stirred for 24 h and then concentrated under vacuum. The resulting residue was treated with H_2O (4 mL) and extracted with DCM (8 mL). The organic layer was dried through a phase separator and concentrated under vacuum. The residue was taken up in DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.0274 g, 26.2%). EI-MS Rt (2.24 min).

1-{3-[(2-fluorophenyl)oxy]propyl}-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0282 g, 0.0960 mmol) and 3-bromopropyl 2-fluorophenyl ether (0.0274 g, 0.118 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0345 g, 68.3%). EI-MS m/z 446(M^+) Rt (1.96 min).

Example 67

Preparation of 1-{3-[(3-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2] octane bromide

3-bromopropyl 3-fluorophenyl ether

To a solution of 3-fluorophenol (0.040 mL, 0.448 mmol) in acetonitrile (4 mL) was added 1,3-dibromopropane (0.450

mL, 4.43 mmol) followed by Cs_2CO_3 (0.246 g, 0.756 mmol). The reaction mixture was stirred for 24 h and then concentrated under vacuum. The resulting residue was treated with H_2O (4 mL) and extracted with DCM (8 mL). The organic layer was dried through a phase separator and concentrated under vacuum. The residue was taken up in DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.0137 g, 13.2%). EI-MS Rt (2.28 min).

1-{3-[(3-fluorophenyl)oxy]propyl}-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0137 g, 0.0467 mmol) and 3-bromopropyl 3-fluorophenyl ether (0.0137 g, 0.0588 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0130 g, 53.1%). EI-MS m/z 446(M^+) Rt (2.03 min).

Example 68

Preparation of 1-{3-[(4-fluorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2] octane bromide

3-bromopropyl 4-fluorophenyl ether

To a solution of 4-fluorophenol (0.0567 g, 0.506 mmol) in acetonitrile (4 mL) was added 1,3-dibromopropane (0.520 mL, 5.12 mmol) followed by Cs_2CO_3 (0.252 g, 0.774 mmol). The reaction mixture was stirred for 24 h and then concentrated under vacuum. The resulting residue was treated with H_2O (4 mL) and extracted with DCM (8 mL). The organic layer was dried through a phase separator and concentrated under vacuum. The residue was taken up in DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.0173 g, 14.7%). EI-MS Rt (2.25 min).

1-{3-[(4-fluorophenyl)oxy]propyl}-4-[hydroxy (diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0182 g, 0.0621 mmol) and 3-bromopropyl 4-fluorophenyl ether (0.0173 g, 0.0742 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0143 g, 43.7%). EI-MS m/z 446(M^+) Rt (1.96 min).

Example 69

Preparation of 1-[3-(3-biphenylyloxy)propyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

3-biphenylyl 3-bromopropyl ether

To a solution of 3-biphenylol (0.0574 g, 0.337 mmol) in acetonitrile (4 mL) was added 1,3-dibromopropane (0.340 mL, 3.35 mmol) followed by Cs_2CO_3 (0.172 g, 0.529 mmol). The reaction mixture was stirred for 24 h and then concentrated under vacuum. The resulting residue was treated with H_2O (4 mL) and extracted with DCM (8 mL). The organic layer was dried through a phase separator and concentrated under vacuum. The residue was taken up in DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.0568 g, 57.8%). EI-MS Rt (2.59 min).

1-[3-(3-biphenylyloxy)propyl]-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0433 g, 0.148 mmol) and 3-biphenylyl 3-bromopropyl ether (0.0568 g, 0.196 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0610 g, 70.6%). EI-MS m/z 504(M^+) Rt (2.37 min).

Example 70

Preparation of 1-[3-(4-biphenylyloxy)propyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

4-biphenylyl 3-bromopropyl ether

To a solution of 4-biphenylol (0.0514 g, 0.302 mmol) in acetonitrile (4 mL) was added 1,3-dibromopropane (0.310 mL, 3.05 mmol) followed by Cs_2CO_3 (0.154 g, 0.472 mmol). The reaction mixture was stirred for 24 h and then concentrated under vacuum. The resulting residue was treated with H_2O (4 mL) and extracted with DCM (8 mL). The organic layer was dried through a phase separator and concentrated under vacuum. The residue was taken up in DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.0562 g, 64.0%). EI-MS Rt (2.62 min).

1-[3-(4-biphenylyloxy)propyl]-4-[hydroxy(diphenyl) methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0437 g, 0.144 mmol) and 4-biphenylyl 3-bromopropyl ether (0.0562 g, 0.194 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0655 g, 75.2%). EI-MS m/z 504(M^+) Rt (2.24 min).

Example 71

Preparation of 4-[hydroxy(diphenyl)methyl]-1-{3-[(3-nitrophenyl)oxy]propyl}-1-azoniabicyclo[2.2.2] octane bromide

3-bromopropyl 3-nitrophenyl ether

To a solution of 3-nitrophenol (0.0689 g, 0.495 mmol) in acetonitrile (4 mL) was added 1,3-dibromopropane (0.500 mL, 3.05 mmol) followed by Cs_2CO_3 (0.244 g, 0.748 mmol). The reaction mixture was stirred for 24 h and then concentrated under vacuum. The resulting residue was treated with H_2O (4 mL) and extracted with DCM (8 mL). The organic layer was dried through a phase separator and concentrated under vacuum. The residue was taken up in DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.0730 g, 56.6%). EI-MS Rt (2.20 min).

4-[hydroxy(diphenyl)methyl]-1-{3-[(3-nitrophenyl) oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0608 g, 0.207 mmol) and 3-bromopropyl 3-nitrophenyl ether (0.0730

g, 0.281 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0942 g, 82.2%). EI-MS m/z 474(M^+) Rt (2.04 min).

Example 72

Preparation of 4-[hydroxy(diphenyl)methyl]-1-{3-[(2-methylphenyl)oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide

3-bromopropyl 2-methylphenyl ether

To a solution of 2-methylphenol (0.0954 g, 0.924 mmol) in acetonitrile (4 mL) was added 1,3-dibromopropane (1.00 mL, 9.85 mmol) followed by Cs_2CO_3 (0.469 g, 1.44 mmol). The reaction mixture was stirred for 24 h and then concentrated under vacuum. The resulting residue was treated with H_2O (4 mL) and extracted with DCM (8 mL). The organic layer was dried through a phase separator and concentrated under vacuum. The residue was taken up in DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.0934 g, 44.1%). EI-MS Rt (2.45 min).

4-[hydroxy(diphenyl)methyl]-1-{3-[(2-methylphenyl)oxy]propyl}-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0447 g, 0.152 mmol) and 3-bromopropyl 2-methylphenyl ether (0.0934 g, 0.407 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0586 g, 76.5%). EI-MS m/z 442(M^+) Rt (2.17 min).

Example 73

Preparation of 1-(3-{[3-(diethylamino)phenyl]oxy}propyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

3-[(3-bromopropyl)oxy]-N,N-diethylaniline

To a solution of 3-(diethylamino)phenol (0.0104 g, 0.631 mmol) in acetonitrile (4 mL) was added 1,3-dibromopropane (0.640 mL, 6.30 mmol) followed by Cs_2CO_3 (0.313 g, 0.961 mmol). The reaction mixture was stirred for 24 h and then concentrated under vacuum. The resulting residue was treated with H_2O (4 mL) and extracted with DCM (8 mL). The organic layer was dried through a phase separator and concentrated under vacuum. The residue was taken up in DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.0314 g, 17.4%). EI-MS m/z 286 ($M+H^+$) Rt (1.59 min).

1-(3-{[3-(diethylamino)phenyl]oxy}propyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0257 g, 0.0876 mmol) and 3-[(3-bromopropyl)oxy]-N,N-diethylaniline (0.0314 g, 0.110 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.032.0 g, 63.0%). EI-MS m/z 500(M^+) Rt (1.58 min).

Example 74

Preparation of 1-{3-[(4-cyanophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

4-[(3-bromopropyl)oxy]benzonitrile

To a solution of 4-hydroxybenzonitrile (0.109 g, 0.913 mmol) in acetonitrile (4 mL) was added 1,3-dibromopropane (0.930 mL, 9.16 mmol) followed by Cs_2CO_3 (0.439 g, 1.35 mmol). The reaction mixture was stirred for 24 h and then concentrated under vacuum. The resulting residue was treated with H_2O (4 mL) and extracted with DCM (8 mL). The organic layer was dried through a phase separator and concentrated under vacuum. The residue was taken up in DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.156 g, 71.4%). EI-MS Rt (2.10 min).

1-{3-[(4-cyanophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

Following the general procedure outlined in Example 3, 1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.0520 g, 0.177 mmol) and 4-[(3-bromopropyl)oxy]benzonitrile (0.156 g, 0.652 mmol) in 2 CH_3CN/3 $CHCl_3$ (4.0 mL) were reacted to give the desired product (0.0726 g, 76.8%). EI-MS m/z 453(M^+) Rt (1.86 min).

Example 75

Preparation of 4-[hydroxy(diphenyl)methyl]-1-[2-({[3-(methyloxy)phenyl]methyl}oxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide

2-({[3-(methyloxy)phenyl]methyl}oxy)ethanol

Ethylene glycol (0.084 mL, 1.5 mmol) was added to NaH (38 mg, 1.52 mmol, 95% in oil) in THF (3 mL) (caution: exotherm). m-Methoxybenzyl chloride (0.21 mL, 1.5 mmol) was added to the reaction, and the residual m-methoxybenzyl chloride was transferred to the reaction tube with additional THF (1 mL). $(Bu)_4NI$ (55 mg, 0.15 mmol) was then added, and the reaction was heated at 60° C. for 18 h and then cooled to room temperature for 4 h. H_2O (2 mL) and EtOAc (2 mL) were added, and the layers were separated via pipette. The aqueous layer was extracted with EtOAc (1×1 mL), and the combined organic layers were concentrated. The crude product was purified on a Biotage 12+M cartridge (8 g silica) eluting with 30% EtOAc/hexanes at 5 mL/min to give the title compound (114 mg, 42%). The product was characterized by ^1H NMR (400 MHz) in $CDCl_3$.

1-{[(2-bromoethyl)oxy]methyl}-3-(methyloxy)benzene

A solution of N-bromosuccinimide (272 mg, 1.53 mmol) in DCM (2.5 mL) was added resin-bound triphenylphosphine (510 mg, 1.53 mEquiv, Fluka) in DCM (2.5 mL). The reaction was stirred at room temperature for 10 min. A solution of 2-({[3-(methyloxy)phenyl]methyl}oxy)ethanol (114 mg, 0.626 mmol) in DCM (1.5 mL) was added to the reaction, and the residual alcohol was transferred with additional DCM (1.5 mL). The reaction vessel was wrapped in aluminum foil and stirred at rt for 20 h. The reaction was filtered through a

SPE cartridge (5 g silica) eluting with the following 10 mL fractions: DCM (fraction 1), 30% EtOAc/hexanes (fraction 2), and 50% EtOAc/hexanes (fraction 3) to give the title compound (160 mg). The product was characterized by ^{1}H NMR (400 MHz) in $CDCl_3$.

4-[hydroxy(diphenyl)methyl]-1-[2-({[3-(methyloxy)phenyl]methyl}oxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide

1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (30 mg, 0.102 mmol) was added to a solution of 1-{[(2-bromoethyl)oxy]methyl}-3-(methyloxy)benzene (35 mg, 0.143 mmol) in 2 CH_3CN/3 $CHCl_3$ (3 mL). The reaction was heated at 60° C. for 96 h. The reaction was concentrated, and the crude product washed with EtOAc (3×1 mL) and then MeOH (1×1 mL). The product was dried under high vacuum to give the title compound (7.7 mg, 14%). LC/MS ESI R_T 1.97 min M^+458

Example 76

Preparation of 1-[2-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy)ethyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

2-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy)ethanol

Ethylene glycol (0.084 mL, 1.5 mmol) was added to NaH (38 mg, 1.52 mmol, 95% in oil) in THF (3 mL). 1-(Bromomethyl)-4-(1,1-dimethylethyl)benzene (0.28 mL, 1.5 mmol) was added to the reaction, and the residual 1-(bromomethyl)-4-(1,1-dimethylethyl)benzene was transferred to the reaction tube with additional THF (1 mL). $(Bu)_4NI$ (55 mg, 0.15 mmol) was then added, and the reaction was heated at 60° C. for 18 h and then rt for 4 h. H_2O (2 mL) and EtOAc (2 mL) were added, and the layers were separated via pipette. The aqueous layer was extracted with EtOAc (1×1 mL), and the combined organic layers were concentrated. The crude product was purified on a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: 10% EtOAc/hexanes (fractions 1,2), 30% EtOAc/hexanes (fractions 3,4), and 50% EtOAc/hexanes (fractions 5,6) to give the title compound (312 mg, 51%). The product was characterized by ^{1}H NMR (400 MHz) in $CDCl_3$.

1-{[(2-bromoethyl)oxy]methyl}-4-(1,1-dimethylethyl)benzene

A solution of N-bromosuccinimide (272 mg, 1.53 mmol) in DCM (2.5 mL) was added to resin-bound triphenylphosphine (510 mg, 1.53 mEquiv, Fluka) in DCM (2.5 mL), and the reaction was stirred at rt for 10 min. A solution of 2-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy)ethanol (160 mg, 0.768 mmol) in DCM (1.5 mL) was added to the reaction, and the residual alcohol was transferred with additional DCM (1.5 mL). The reaction vial was capped, wrapped in aluminum foil, and stirred at rt for 20 h. The reaction was filtered through a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: DCM (fraction 1), 30% EtOAc/hexanes (fraction 2), and 50% EtOAc/hexanes (fraction 3) to give the title compound (25 mg, 12%). The product was characterized by ^{1}H NMR (400 MHz) in $CDCl_3$.

1-[2-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy)ethyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (30 mg, 0.102 mmol) was added to a solution of 1-{[(2-bromoethyl)oxy]methyl}-4-(1,1-dimethylethyl)benzene (25 mg, 0.143 mmol) in 2:3 $CH_3CN/CHCl_3$ (3 mL), and the reaction was heated at 60° C. for 96 h. The reaction was concentrated, and the crude product washed with EtOAc (3×1 mL). The product was dried under high vacuum to give the title compound (9 mg, 16%). LC/MS ESI R_T 2.28 min M^+484

Example 77

Preparation of 1-(2-{[(4-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

2-{[(4-fluorophenyl)methyl]oxy}ethanol

Ethylene glycol (0.084 mL, 1.5 mmol) was added to NaH (38 mg, 1.52 mmol, 95% in oil) in THF (3 mL). 1-(Bromomethyl)-4-fluorobenzene (0.19 mL, 1.5 mmol) was added to the reaction, and the residual 1-(bromomethyl)-4-fluorobenzene was transferred to the reaction tube with additional THF (1 mL). $(Bu)_4NI$ (55 mg, 0.15 mmol) was added, and the reaction was heated at 60° C. for 18 h and then rt for 4 h. H_2O (2 mL) and EtOAc (2 mL) were added, and the layers were separated via pipette. The aqueous layer was extracted with EtOAc (1×1 mL), and the combined organic layers were concentrated. The crude product was purified on a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: 30% EtOAc/hexanes (fractions 1,2), 50% EtOAc/hexanes (fraction 3), and 75% EtOAc/hexanes (fraction 4) to give the title compound (122 mg, 48%). The product was characterized by ^{1}H NMR (400 MHz) in $CDCl_3$.

1-{[(2-bromoethyl)oxy]methyl}-4-fluorobenzene

A solution of N-bromosuccinimide (272 mg, 1.53 mmol) in DCM (2.5 mL) was added to resin-bound triphenylphosphine (510 mg, 1.53 mEquiv, Fluka) in DCM (2.5 mL), and the reaction was stirred at rt for 10 min. A solution of 2-{[(4-fluorophenyl)methyl]oxy}ethanol (122 mg, 0.717 mmol) in DCM (1.5 mL) was added to the reaction, and the residual alcohol was transferred with additional DCM (1.5 mL). The reaction vial was capped, wrapped in aluminum foil, and stirred at rt for 20 h. The reaction was filtered through a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: DCM (fraction 1), 30% EtOAc/hexanes (fraction 2), and 50% EtOAc/hexanes (fraction 3) to give the title compound (80 mg, 48%). The product was characterized by ^{1}H NMR (400 MHz) in $CDCl_3$.

1-(2-{[(4-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (30 mg, 0.102 mmol) was added to a solution of 1-{[(2-bromoethyl)oxy]methyl}-4-fluorobenzene (33 mg, 0.143 mmol) in 2:3 $CH_3CN/CHCl_3$ (3 mL), and the reaction was heated at 60° C. for 96 h. The reaction was concentrated, and the crude product washed with EtOAc (3×1 mL). The product was dried under high vacuum to give the title compound (9 mg, 16%). LC/MS ESI R_T 1.89 min M^+446

Example 78

Preparation of 1-(2-{[(4-chlorophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

2-{[(4-chlorophenyl)methyl]oxy}ethanol

Ethylene glycol (0.084 mL, 1.5 mmol) was added to NaH (38 mg, 1.52 mmol, 95% in oil) in THF (3 mL). 1-(Bromomethyl)-4-chlorobenzene (310 mg, 1.5 mmol) was added to the reaction, and the residual 1-(bromomethyl)-4-chlorobenzene was transferred to the reaction tube with additional THF (1 mL). $(Bu)_4NI$ (55 mg, 0.15 mmol) was then added, and the reaction was heated at 60° C. for 18 h and then rt for 4 h. H_2O (2 mL) and EtOAc (2 mL) were added, and the layers were separated via pipette. The aqueous layer was extracted with EtOAc (1×1 mL), and the combined organic layers were concentrated. The crude product was purified on a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: 30% EtOAc/hexanes (fractions 1,2), 50% EtOAc/hexanes (fraction 3), and 75% EtOAc/hexanes (fraction 4) to give the title compound (129 mg, 46%). The product was characterized by ^1H NMR (400 MHz) in $CDCl_3$.

1-{[(2-bromoethyl)oxy]methyl}-4-chlorobenzene

A solution of N-bromosuccinimide (272 mg, 1.53 mmol) in DCM (2.5 mL) was added to resin-bound triphenylphosphine (510 mg, 1.53 mEquiv, Fluka) in DCM (2.5 mL), and the reaction was stirred at rt for 10 min. A solution of 2-{[(4-chlorophenyl)methyl]oxy}ethanol (129 mg, 0.691 mmol) in DCM (1.5 mL) was added to the reaction, and the residual alcohol was transferred with additional DCM (1.5 mL). The reaction vial was capped, wrapped in aluminum foil, and stirred at rt for 20 h. The reaction was filtered through a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: DCM (fraction 1), 30% EtOAc/hexanes (fraction 2), and 50% EtOAc/hexanes (fraction 3) to give the title compound (98 mg, 57%). The product was characterized by ^1H NMR (400 MHz) in $CDCl_3$.

1-(2-{[(4-chlorophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (30 mg, 0.102 mmol) was added to a solution of 1-{[(2-bromoethyl)oxy]methyl}-4-chlorobenzene (36 mg, 0.143 mmol) in 2:3 $CH_3CN/CHCl_3$ (3 mL), and the reaction was heated at 60° C. for 96 h. The reaction was concentrated, and the crude product washed with EtOAc (3×1 mL). The product was dried under high vacuum to give the title compound (17.4 mg, 32%). LC/MS ESI R_T 2.09 min M^+462

Example 79

Preparation of 1-(2-{[(4-bromophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

2-{[(4-bromophenyl)methyl]oxy}ethanol

Ethylene glycol (0.084 mL, 1.5 mmol) was added to NaH (38 mg, 1.52 mmol, 95% in oil) in THF (3 mL). 1-Bromo-4-(bromomethyl)benzene (370 mg, 1.5 mmol) was added to the reaction, and the residual 1-bromo-4-(bromomethyl)benzene was transferred to the reaction tube with additional THF (1 mL). $(Bu)_4NI$ (55 mg, 0.15 mmol) was then added, and the reaction was heated at 60° C. for 18 h and then rt for 4 h. H_2O (2 mL) and EtOAc (2 mL) were added, and the layers were separated via pipette. The aqueous layer was extracted with EtOAc (1×1 mL), and the combined organic layers were concentrated. The crude product was purified on a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: 30% EtOAc/hexanes (fractions 1,2), 50% EtOAc/hexanes (fraction 3), and 75% EtOAc/hexanes (fraction 4) to give the title compound (139 mg, 40%). The product was characterized by ^1H NMR (400 MHz) in $CDCl_3$.

1-bromo-4-{[(2-bromoethyl)oxy]methyl}benzene

A solution of N-bromosuccinimide (272 mg, 1.53 mmol) in DCM (2.5 mL) was added to resin-bound triphenylphosphine (510 mg, 1.53 mEquiv, Fluka) in DCM (2.5 mL), and the reaction was stirred at rt for 10 min. A solution of 2-{[(4-bromophenyl)methyl]oxy}ethanol (139 mg, 0.601 mmol) in DCM (1.5 mL) was added to the reaction, and the residual alcohol was transferred with additional DCM (1.5 mL). The reaction vial was capped, wrapped in aluminum foil, and stirred at rt for 20 h. The reaction was filtered through a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: DCM (fraction 1), 30% EtOAc/hexanes (fraction 2), and 50% EtOAc/hexanes (fraction 3) to give the title compound (87 mg, 49%). The product was characterized by ^1H NMR (400 MHz) in $CDCl_3$.

1-(2-{[(4-bromophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (30 mg, 0.102 mmol) was added to a solution of 1-bromo-4-{[(2-bromoethyl)oxy]methyl}benzene (42 mg, 0.143 mmol) in 2:3 $CH_3CN/CHCl_3$ (3 mL), and the reaction was heated at 60° C. for 96 h. The reaction was concentrated, and the crude product washed with EtOAc (3×1 mL). The product was dried under high vacuum to give the title compound (19.4 mg, 32%). LC/MS ESI R_T 2.07 min M^+506

Example 80

Preparation of 1-(2-{[(4-cyanophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

4-{[(2-hydroxyethyl)oxy]methyl}benzonitrile

Ethylene glycol (0.084 mL, 1.5 mmol) was added to NaH (38 mg, 1.52 mmol, 95% in oil) in THF (3 mL). 4-(Bromomethyl)benzonitrile (290 mg, 1.5 mmol) was added to the reaction, and the residual 4-(bromomethyl)benzonitrile was transferred to the reaction tube with additional THF (1 mL). $(Bu)_4NI$ (55 mg, 0.15 mmol) was then added, and the reaction was heated at 60° C. for 18 h and then rt for 4 h. H_2O (2 mL) and EtOAc (2 mL) were added, and the layers were separated via pipette. The aqueous layer was extracted with EtOAc (1×1 mL), and the combined organic layers were concentrated. The crude product was purified on a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: 10% EtOAc/hexanes (fractions 1,2), 30% EtOAc/hexanes (fractions 3,4), 50% EtOAc/hexanes (fractions 5-7), and 75% EtOAc/hexanes (fraction 8) to give the title compound (95 mg, 36%). The product was characterized by ^1H NMR (400 MHz) in $CDCl_3$.

4-{[(2-bromoethyl)oxy]methyl}benzonitrile

A solution of N-bromosuccinimide (272 mg, 1.53 mmol) in DCM (2.5 mL) was added to resin-bound triphenylphosphine (510 mg, 1.53 mEquiv, Fluka) in DCM (2.5 mL), and the reaction was stirred at rt for 10 min. A solution of 4-{[(2-hydroxyethyl)oxy]methyl}benzonitrile (95 mg, 0.536 mmol) in DCM (1.5 mL) was added to the reaction, and the residual alcohol was transferred with additional DCM (1.5 mL). The reaction vial was capped, wrapped in aluminum foil, and stirred at rt for 20 h. The reaction was filtered through a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: DCM (fraction 1), 30% EtOAc/hexanes (fraction 2), and 50% EtOAc/hexanes (fraction 3) to give the title compound (60 mg, 47%). The product was characterized by ^{1}H NMR (400 MHz) in $CDCl_3$.

1-(2-{[(4-cyanophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (30 mg, 0.102 mmol) was added to a solution of 4-{[(2-bromoethyl)oxy]methyl}benzonitrile (34 mg, 0.143 mmol) in 2:3 $CH_3CN/CHCl_3$ (3 mL), and the reaction was heated at 60° C. for 96 h. The reaction was concentrated, and the crude product washed with EtOAc (3×1 mL). The product was dried under high vacuum to give the title compound (40 mg, 74%). LC/MS ESI R_T 1.82 min M^+453

Example 81

Preparation of 4-[hydroxy(diphenyl)methyl]-1-{2-[(2-naphthalenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

2-[(2-naphthalenylmethyl)oxy]ethanol

Ethylene glycol (0.084 mL, 1.5 mmol) was added to NaH (38 mg, 1.52 mmol, 95% in oil) in THF (3 mL). 2-(Bromomethyl)naphthalene (330 mg, 1.5 mmol) was added to the reaction, and the residual 2-(bromomethyl)naphthalene was transferred to the reaction tube with additional THF (1 mL). $(Bu)_4NI$ (55 mg, 0.15 mmol) was then added, and the reaction was heated at 60° C. for 18 h and then rt for 4 h. H_2O (2 mL) and EtOAc (2 mL) were added, and the layers were separated via pipette. The aqueous layer was extracted with EtOAc (1×1 mL), and the combined organic layers were concentrated. The crude product was purified on a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: 30% EtOAc/hexanes (fractions 1,2), 50% EtOAc/hexanes (fraction 3), and 75% EtOAc/hexanes (fraction 4) to give the title compound (101 mg, 33%). The product was characterized by ^{1}H NMR (400 MHz) in $CDCl_3$.

2-{[(2-bromoethyl)oxy]methyl}naphthalene

A solution of N-bromosuccinimide (272 mg, 1.53 mmol) in DCM (2.5 mL) was added to resin-bound triphenylphosphine (510 mg, 1.53 mEquiv, Fluka) in DCM (2.5 mL), and the reaction was stirred at rt for 10 min. A solution 2-[(2-naphthalenylmethyl)oxy]ethanol (101 mg, 0.499 mmol) in DCM (1.5 mL) was added to the reaction, and the residual alcohol was transferred with additional DCM (1.5 mL). The reaction vial was capped, wrapped in aluminum foil, and stirred at rt for 20 h. The reaction was filtered through a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: DCM (fraction 1), 30% EtOAc/hexanes (fraction 2), and 50% EtOAc/hexanes (fraction 3) to give the title compound (57 mg, 43%). The product was characterized by ^{1}H NMR (400 MHz) in $CDCl_3$.

4-[hydroxy(diphenyl)methyl]-1-{2-[(2-naphthalenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (30 mg, 0.102 mmol) was added to a solution of 2-{[(2-bromoethyl)oxy]methyl}naphthalene (38 mg, 0.143 mmol) in 2:3 $CH_3CN/CHCl_3$ (3 mL), and the reaction was heated at 60° C. for 96 h. The reaction was concentrated, and the crude product washed with EtOAc (3×1 mL). The product was dried under high vacuum to give the title compound (48.1 mg, 84%). LC/MS ESI R_T 2.04 min M^+478

Example 82

Preparation of 1-(2-{[(3-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

2-{[(3-fluorophenyl)methyl]oxy}ethanol

Ethylene glycol (0.1 mL, 1.79 mmol) was added to NaH (46 mg, 1.81 mmol, 95% in oil) in THF (5 mL). 1-(Bromomethyl)-3-fluorobenzene (0.22 mL, 1.79 mmol) was added to the reaction, and the reaction was heated at 60° C. for 5 days. H_2O (2 mL) and EtOAc (2 mL) were added, and the layers were separated via pipette. The aqueous layer was extracted with EtOAc (3×1 mL), and the combined organic layers were washed with saturated NaCl (1×2 mL), dried (Na_2SO_4), and concentrated. The crude product was purified on a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: 30% EtOAc/hexanes (fractions 1,2), 50% EtOAc/hexanes (fraction 3), and 75% EtOAc/hexanes (fraction 4) to give the title compound (76.2 mg, 25%). The product was characterized by ^{1}H NMR (400 MHz) in $CDCl_3$.

1-{[(2-bromoethyl)oxy]methyl}-3-fluorobenzene

N-bromosuccinimide (146 mg, 0.820 mmol) was added to resin-bound triphenylphosphine (274 mg, 0.822 mEquiv, Fluka) and 2-{[(3-fluorophenyl)methyl]oxy}ethanol (70 mg, 0.411 mmol) in DCM (4 mL). The reaction vial was sealed with a Teflon-lined cap, wrapped in aluminum foil, and shaken at rt for 17 h. The reaction was filtered through a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: DCM (fraction 1), 30% EtOAc/hexanes (fraction 2), and 50% EtOAc/hexanes (fraction 3) to give the title compound (75 mg, 78%). The product was characterized by ^{1}H NMR (400 MHz) in $CDCl_3$.

1-(2-{[(3-fluorophenyl)methyl]oxy}ethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (94 mg, 0.321 mmol) was added to a solution of 1-{[(2-bromoethyl)oxy]methyl}-3-fluorobenzene (75 mg, 0.321 mmol) in 2:3 $CH_3CN/CHCl_3$ (4 mL), and the reaction was heated at 60° C. for 3 days. The reaction was concentrated under reduced pressure, and the crude product washed with EtOAc (3×2 mL). The product was dried under high vacuum to give the title compound (50 mg, 30%). LC/MS ESI R_T 1.95 min M^+446

Example 83

Preparation of 4-[hydroxy(diphenyl)methyl]-1-{2-[(1-methyl-1-phenylethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

2-[(1-methyl-1-phenylethyl)oxy]ethanol

A catalytic amount of either p-toluene sulfonic acid•H_2O or Bio-Rad SCX resin (analytical grade, 5.1 meq/g, AG 50W-X8) was added to □-methylstyrene (0.5 mL, 3.85 mmol) and ethylene glycol (0.21 mL, 3.85 mmol), and the reaction was stirred at rt for 5 days. The reaction mixture was loaded directly onto a SPE cartridge (10 g silica) and eluted with the following 10 mL fractions: 10% EtOAc/hexanes (fractions 1,2), 30% EtOAc/hexanes (fractions 3,4), and 50% EtOAc/hexanes (fractions 5,6) to give the title compound (30.5 mg, 4%) for both conditions. The product was characterized by ^1H NMR (400 MHz) in $CDCl_3$.

{1-[(2-bromoethyl)oxy]-1-methylethyl}benzene

N-bromosuccinimide (119 mg, 0.666 mmol) was added to resin-bound triphenylphosphine (222 mg, 0.666 mEquiv, Fluka) and 2-[(1-methyl-1-phenylethyl)oxy]ethanol (60 mg, 0.333 mmol) in DCM (4 mL). The reaction vial was sealed with a Teflon-lined cap, wrapped in aluminum foil, and shaken at rt for 17 h. The reaction was filtered through a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: DCM (fraction 1), 30% EtOAc/hexanes (fraction 2), and 50% EtOAc/hexanes (fraction 3) to give the title compound (34 mg, 42%). The product was characterized by ^1H NMR (400 MHz) in $CDCl_3$.

4-[hydroxy(diphenyl)methyl]-1-{2-[(1-methyl-1-phenylethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (41 mg, 0.14 mmol) was added to a solution of {1-[(2-bromoethyl) oxy]-1-methylethyl}benzene (34 mg, 0.14 mmol) in 2:3 $CH_3CN/CHCl_3$ (3 mL), and the reaction was heated at 60° C. for 3 days. The reaction was concentrated under reduced pressure, and the crude product washed with EtOAc (3×1 mL). The residue was taken up in 2.5 mL of DMSO and purified by preparatory HPLC (without TFA) to give the title compound (18 mg, 24%). LC/MS ESI R_T 2.09 min M^+456

Example 84

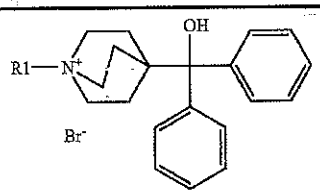
Preparation of 4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide

Method A: 1-Azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.020 g, 0.068 mmol) was diluted in $CHCl_3$ (1.8 mL) and dispensed directly into a 1 dram vial containing 2-bromoethyl phenylmethyl ether (0.022 g, 0.102 mmol). CH_3CN (1.2 mL) was added; the vial was fitted with a stirring bar and capped. The reaction was stirred and heated at 60° C. for 24 h. The contents of the vial were transferred (after removal of stirring bar) into a polypropylene tube and concentrated under Nitrogen. The crude product was collected on a polypropylene tube frit. Excess bromide was removed by washing the crude product with EtOAc (5×2 mL) and Hexane (5×2 mL). The product was then dried under vacuum to give the title compound (0.008 g, 23.8%).

Method B: To a solution of 1-azabicyclo[2.2.2]oct-4-yl (diphenyl)methanol (3.30 g, 11.2 mmol) in 2 $CH_3CN/3$ $CHCl_3$ (200 mL) was added 2-bromoethyl phenylmethyl ether (2.31 mL, 14.6 mmol). The solution was stirred at 60° C. for 16 h. The reaction was cooled down to room temperature and concentrated. EtOAc (200 mL) was added to the solid, and the mixture was allowed to stir for 1 hour then filtered. The resulting solid was taken up in MeOH (125 mL) and heated to 60° C. The solution was filtered hot, and then cooled back to room temperature. The reaction was concentrated to a low volume of MeOH (~20 mL) and filtered. Water (75 mL) was then added and the resulting mixture was heated at 55° C. with brisk stirring for 40 min. After cooling to room temperature, the solid was filtered off, washed with water (20 mL) and dried in a vacuum oven at 45° C. for 16 hours to give the title compound (2.47 g, 43.3%). El-MS m/z 428(M^+) Rt (1.90 min) ^1H NMR (DMSO-d_6) δ 7.56 (d, 4H, J=1.2), 7.28 (m, 11H), 5.95 (s, 1H), 4.50 (s, 2H), 3.81 (d, 2H, J=4.0), 3.48 (t, 6H, J=7.2), 3.38 (d, 2H, J=4.0), 2.01 (t, 6H, J=7.2); Elemental analysis ($C_{29}H_{34}NO_2Br$) C, H, N: calculated, 68.50, 6.74, 2.75; found, 68.28, 6.68, 2.73.

The following examples in Table 1 were prepared according to the procedure outlined in Example 84 method A.

TABLE 1



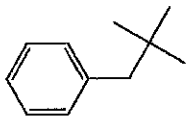
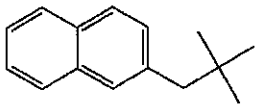
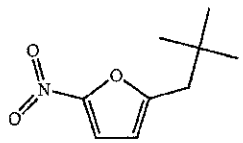
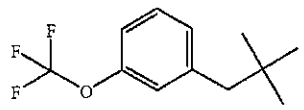
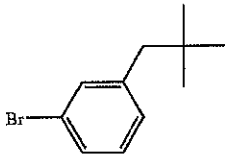
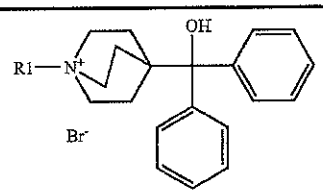
Example	R1	MS [M+]	R_t (min)
85		384	1.64
86		434	1.97
87		419	1.51
88		468	2.02
89		463	1.77

TABLE 1-continued



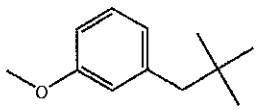
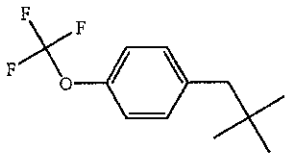
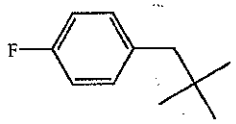
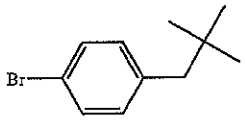
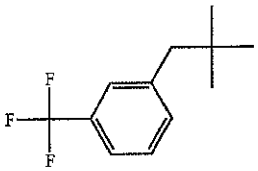
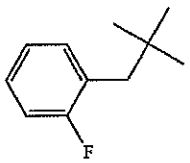
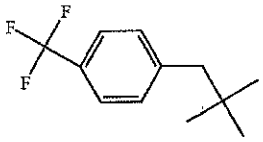
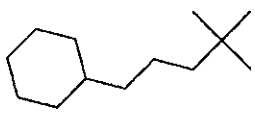
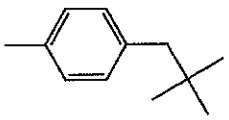
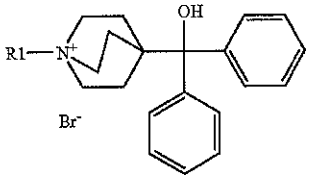
Example	R1	MS [M+]	R_t (min)
90		414	1.84
91		468	1.96
92		402	1.68
93		463	1.82
94		452	1.93
95		402	1.55
96		452	1.97
97		418	2.00
98		398	1.72

TABLE 1-continued



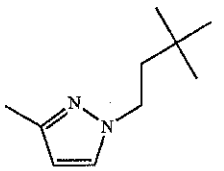
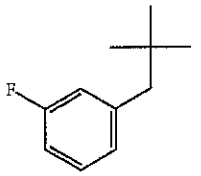
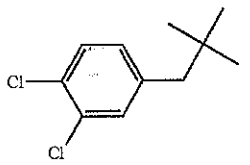
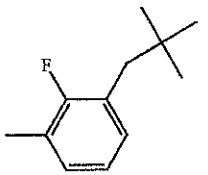
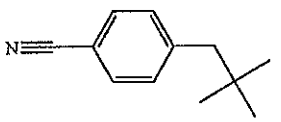
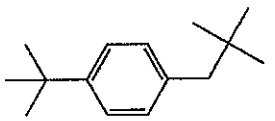
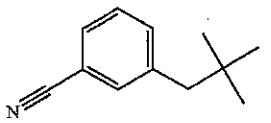
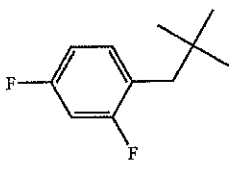
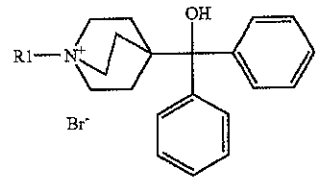
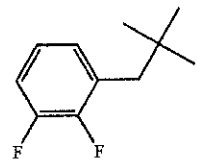
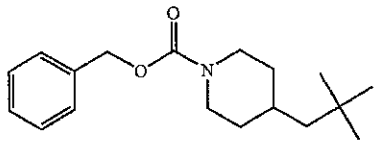
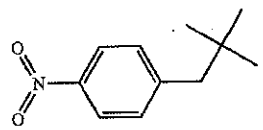
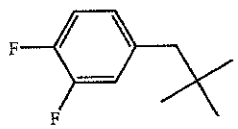
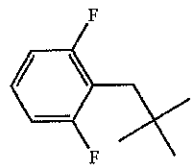
Example	R1	MS [M+]	R_t (min)
99		402	1.60
100		402	1.63
101		453	1.92
102		416	1.87
103		409	1.60
104		440	2.07
105		409	1.55
106		420	1.90

TABLE 1-continued



Example	R1	MS [M+]	R_t (min)
107		420	1.78
108		525	1.67
109		429	1.57
110		420	1.64
111		420	1.67

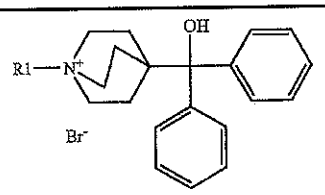
Example 112

Preparation of 1-[2-(1-benzofuran-2-yl)-2-oxoethyl]-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.2]octane bromide

1-azabicyclo[2.2.2]oct-4-yl(diphenyl)methanol (0.022 g, 0.075 mmol) was diluted in $CHCl_3$ (1.8 mL) and dispensed directly into a 1 dram vial containing 1-(1-benzofuran-2-yl)-2-bromoethanone (0.027 g, 0.112 mmol). Added CH_3CN (1.2 mL), the vial was fitted with stirring bar and capped. The reaction was stirred and heated at 60° C. for 24 h and then concentrated under vacuum to give a white solid. This residue was dissolved in DMSO and purified by preparatory HPLC (without TFA) to give the title compound (0.022 g, 57.4%). LC/MS ESI R_T 1.98 min, M^+452

The following examples in Table 2 were prepared according to the procedure outlined in Example 112.

TABLE 2



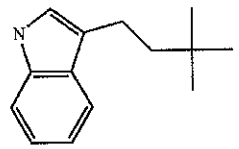
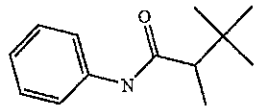
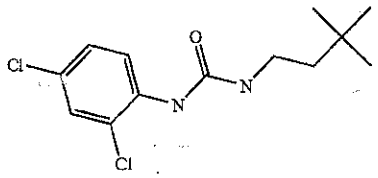
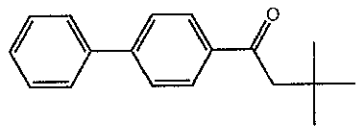
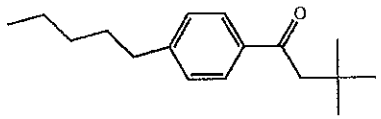
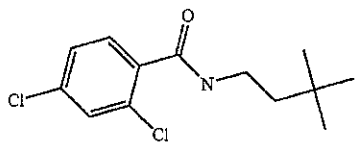
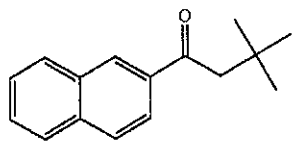
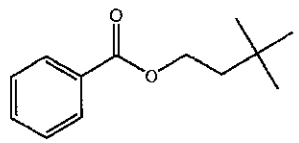
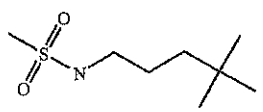
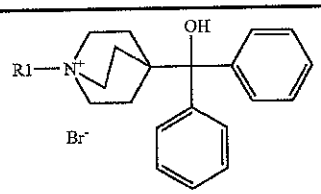
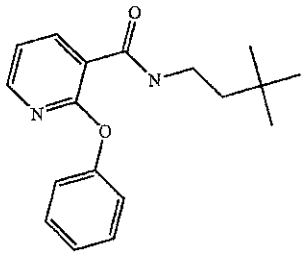
Example	R1	MS [M+]	R_t (min)
113		437	1.96
114		441	1.92
115		525	2.11
116		488	2.31
117		482	2.46
118		510	1.95
119		462	2.03
120		442	1.95
121		429	1.33

TABLE 2-continued



Example	R1	MS [M+]	R_t (min)
122		534	1.92

Abbreviations
Ar Argon
DCM Dichloromethane
DMF Dimethylformamide
DMSO Dimethylsulfoxide
EI/ESI Electrospray ionization
HPLC High pressure liquid chromatography
LC Liquid chromatography
LDA Lithium Diisopropyl Amide
MS Mass spectrometry
NMR Nuclear magnetic resonance
R_t Retention time
rt room temperature
SPE Solid phase extraction
TEA Triethylamine
TFA Trifluoroacetic acid
THF Tetrahydrofuran

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M_3 mAChR of the present invention are determined by the following in vitro and in vivo functional assays:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described (H. M. Sarau et al, 1999. *Mol. Pharmacol.* 56, 657-663). CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis Mo.), and 4 µM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, Oreg.) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C. in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH_2PO_4, 25 mM $NaHCO_3$, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20 mM HEPES (pH 7.4)). 50 µl of compound (1×10^{-11}-1×10^{-5} M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels. The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced Bronchoconstriction—Potency and Duration of Action

Airway responsiveness to methacholine was determined in awake, unrestrained Balb C mice (n=6 each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine(2). Mice were pre-treated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO) intranasally (i.n.) and were then placed in the plethysmography chamber a given amount of time following drug administration (15 min—96 h). For potency determination, a dose response to a given drug was performed, and all measurements were taken 15 min following i.n. drug administration. For duration of action determination, measurements were taken anywhere from 15 min to 96 hours following i.n. drug administration.

Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software. This experiment allows the determination of duration of activity of the administered compound.

The present compounds are useful for treating a variety of indications, including but not limited to respiratory-tract disorders such as chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis.

Muscarinic Receptor Radioligand Binding Assays

Radioligand binding studies using 0.5 nM [^{3}H]-N-methyl scopolamine (NMS) in a SPA format is used to assess binding of muscarinic antagonists to M_1, M_2, M_3, M_4 and M_5 muscarinic acetylcholine receptors. In a 96-well plate, the SPA beads are pre-incubated with receptor-containing membrane for 30 min at 4° C. Then 50 mM HEPES and the test compound are added and incubated at room temperature (shaking) for 2 hours. The beads are then spun down and counted using a scintillation counter.

Evaluation of Potency and Duration of Action in Isolated Guinea Pig Trachea

Tracheae were removed from adult male Hartely guinea pigs (Charles River, Raleigh, N.C.; 400-600 grams) and placed into modified Krebs-Henseleit solution. Composition of the solution was (mM): NaCl 113.0, KCl 4.8, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25.0 and dextrose 11.0. which was gassed with 95% O_2: 5% CO_2 and maintained at

37° C. Each trachea was cleaned of adherent tissue and opened lengthwise. Epithelium was removed by gently rubbing the luminal surface with a cotton-tipped applicator. Individual strips were cut, approximately 2 cartilage rings in width, and suspended via silk suture in 10-ml water-jacketed organ baths containing Krebs-Henseleit solution and connected to Grass FT03C force-displacement transducers. Mechanical responses were recorded isometrically by MP100WS/Acknowledge data acquisition system (BIOPAC Systems, Goleta, Calif., www.biopac.com) run on Apple G4 computers. The tissues were equilibrated under a resting tension of 1.5 g, determined to be optimal by length-tension evaluation, and washed with Krebs-Henseleit solution every 15 minutes for one hour. After the equilibration period pulmonary tissues were contracted with 10 uM carbachol until reaching plateau, which served as a reference contraction for data analysis. Tissues were then rinsed every 15 minutes over 1 hour until reaching baseline tone. The preparations were then left for at least 30 minutes before the start of the experiment.

Concentration-response curves were obtained by a cumulative addition of carbachol in half-log increments (Van Rossum, 1963, Arch. Int. Pharmacodyn., 143:299), initiated at 1 nM. Each concentration was left in contact with the preparation until the response plateaued before the addition of the subsequent carbachol concentration. Paired tissues were exposed to mAChR antagonist compounds or vehicle for 30 min before carbachol cumulative concentration-response curves were generated. All data is given as mean±standard error of the mean (s.e.m.) with n being the number of different animals.

For superfusion (duration of action) studies, the tissues were continuously superfused with Krebs-Henseleit solution at 2 ml/min for the duration of the experiment. Stock solutions of agonist and antagonist were infused (0.02 ml/min) via 22-gauge needle inserted into the superfusion tubing. Mechanical responses were recorded isometrically using a commercially-available data acquisition system (MP100WS/Acknowledge; BIOPAC Systems, Goleta, Calif., www.biopac.com) interfaced with a Macintosh G4 computer (Apple, Cupertino, Calif. www.apple.com). The tissues were suspended under an optimal resting tension of 1.5 g. After a 60 min equilibration period, the tissues were contracted with carbachol (1 uM) for the duration of the experiment. Upon reaching a sustained contraction isoproterenol (10 uM) was administered to maximally relax the tissue, and this change served as a reference. Isoproterenol exposure was halted and the carbachol-induced tension allowed to recover. Muscarinic receptor antagonists infused at a single concentration per tissue until a sustained level of inhibition was attained. The compound was then removed and, once again, the carbachol-induced tension was allowed to recover.

The following parameters were determined for each concentration of antagonist, and expressed as the mean±S.E.M. for n individual animals. Inhibition of the carbachol-induced contraction was expressed as a percent of the reference response (isoproterenol) and the time required to reach one-half of this relaxation was measured (onset of response). The tension recovery following removal of the compound was determined as was the time required to reach one-half of the maximum tension recovery (offset of response). At 60 and 180 minutes after removal of the antagonist the remaining level of inhibition was determined and expressed as a percent of the isoproterenol reference.

Antagonist concentration-response curves were obtained by plotting the maximal relaxation data at 0, 60 and 180-min following antagonist withdrawal. Recovery, termed shift, was calculated from the ratio of the 0-min inhibition curve IC_{50} and the concentration of compound yielding a similar tension recovery at 60 and 180 minutes.

Halftimes for onset and offset of response were plotted vs. corresponding concentration and the data were fit with non-linear regression. These values were extrapolated at the IC_{50} (determined from the inhibition concentration-response curve) and designated Ot_{50} (time required, at the IC_{50} concentration, to reach half of the onset response) and Rt50 (time required, at the IC_{50} concentration, to reach half of the recovery response).

Formulation-Administration

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative (e.g., salts and esters) thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

Compounds of formula (I) will be administered via inhalation via the mouth or nose.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di- or poly-saccharides (e.g., lactose or starch), organic or inorganic salts (e.g., calcium chloride, calcium phosphate or sodium chloride), polyalcohols (e.g., mannitol), or mixtures thereof, alternatively with one or more additional materials, such additives included in the blend formulation to improve chemical and/or physical stability or performance of the formulation, as discussed below, or mixtures thereof. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20 μg-10 mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients, or may be formed into particles comprising the compound, optionally other therapeutically active materials, and excipient materials, such as by co-precipitation or coating.

Suitably, the medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

By reservoir dry powder inhaler (RDPI) it is meant as an inhaler having a reservoir form pack suitable for comprising multiple (un-metered doses) of medicament in dry powder form and including means for metering medicament dose from the reservoir to a delivery position. The metering means may for example comprise a metering cup or perforated plate, which is movable from a first position where the cup may be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

By multi-dose dry powder inhaler (MDPI) is meant an inhaler suitable for dispensing medicament in dry powder form, wherein the medicament is comprised within a multi-dose pack containing (or otherwise carrying) multiple, define doses (or parts thereof) of medicament. In a preferred aspect, the carrier has a blister pack form, but it could also, for

example, comprise a capsule-based pack form or a carrier onto which medicament has been applied by any suitable process including printing, painting and vacuum occlusion.

The formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

In one aspect, the multi-dose pack is a blister pack comprising multiple blisters for containment of medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of medicament therefrom.

In one aspect, the multi-dose blister pack comprises plural blisters arranged in generally circular fashion on a disk-form blister pack. In another aspect, the multi-dose blister pack is elongate in form, for example comprising a strip or a tape.

Preferably, the multi-dose blister pack is defined between two members peelably secured to one another. U.S. Pat. Nos. 5,860,419, 5,873,360 and 5,590,645 describe medicament packs of this general type. In this aspect, the device is usually provided with an opening station comprising peeling means for peeling the members apart to access each medicament dose. Suitably, the device is adapted for use where the peelable members are elongate sheets which define a plurality of medicament containers spaced along the length thereof, the device being provided with indexing means for indexing each container in turn. More preferably, the device is adapted for use where one of the sheets is a base sheet having a plurality of pockets therein, and the other of the sheets is a lid sheet, each pocket and the adjacent part of the lid sheet defining a respective one of the containers, the device comprising driving means for pulling the lid sheet and base sheet apart at the opening station.

By metered dose inhaler (MDI) it is meant a medicament dispenser suitable for dispensing medicament in aerosol form, wherein the medicament is comprised in an aerosol container suitable for containing a propellant-based aerosol medicament formulation. The aerosol container is typically provided with a metering valve, for example a slide valve, for release of the aerosol form medicament formulation to the patient. The aerosol container is generally designed to deliver a predetermined dose of medicament upon each actuation by means of the valve, which can be opened either by depressing the valve while the container is held stationary or by depressing the container while the valve is held stationary.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum aerodynamic particle size for inhalation into the bronchial system for localized delivery to the lung is usually 1-10 μm, preferably 2-5 μm. The optimum aerodynamic particle size for inhalation into the alveolar region for achieving systemic delivery to the lung is approximately 0.5-3 μm, preferably 1-3 μm. Particles having an aerodynamic size above 20 μm are generally too large when inhaled to reach the small airways. Average aerodynamic particle size of a formulation may measured by, for example cascade impaction. Average geometric particle size may be measured, for example by laser diffraction, optical means.

To achieve a desired particle size, the particles of the active ingredient as produced may be size reduced by conventional means eg by controlled crystallization, micronisation or nanomilling. The desired fraction may be separated out by air classification. Alternatively, particles of the desired size may be directly produced, for example by spray drying, controlling the spray drying parameters to generate particles of the desired size range. Preferably, the particles will be crystalline, although amorphous material may also be employed where desirable. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention, such that the "coarse" carrier is non-respirable. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90 μm and not less than 15% will have a MMD of less than 15 μm. Additive materials in a dry powder blend in addition to the carrier may be either respirable, i.e., aerodynamically less than 10 microns, or non-respirable, i.e., aerodynamically greater than 10 microns.

Suitable additive materials which may be employed include amino acids, such as leucine; water soluble or water insoluble, natural or synthetic surfactants, such as lecithin (e.g., soya lecithin) and solid state fatty acids (e.g., lauric, palmitic, and stearic acids) and derivatives thereof (such as salts and esters); phosphatidylcholines; sugar esters. Additive materials may also include colorants, taste masking agents (e.g., saccharine), anti-static-agents, lubricants (see, for example, Published PCT Patent Appl. No. WO 87/905213, the teachings of which are incorporated by reference herein), chemical stabilizers, buffers, preservatives, absorption enhancers, and other materials known to those of ordinary skill.

Sustained release coating materials (e.g., stearic acid or polymers, e.g. polyvinyl pyrolidone, polylactic acid) may also be employed on active material or active material containing particles (see, for example, Patent Nos. U.S. Pat. No. 3,634,582, GB 1,230,087, GB 1,381,872, the teachings of which are incorporated by reference herein).

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Preferred unit dosage formulations are those containing an effective dose, as herein before recited, or an appropriate fraction thereof, of the active ingredient.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

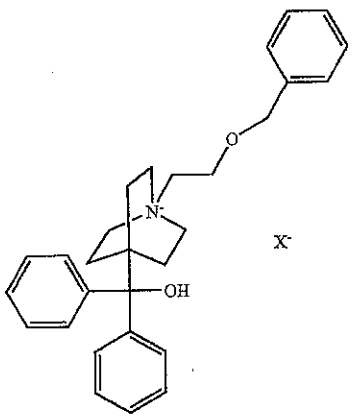
The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. The compound which is 4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide.

2. A pharmaceutical composition comprising 4-[hydroxy (diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide and a pharmaceutically acceptable carrier thereof.

3. The compound



wherein

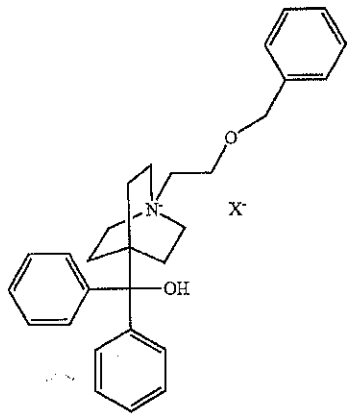
X is a pharmaceutically acceptable anion.

4. The compound according to claim **3** wherein the pharmaceutically acceptable anion is chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate or p-toluenesulfonate.

5. The compound according to claim **3** wherein the pharmaceutically acceptable anion is bromide.

6. The compound according to claim **3** wherein the pharmaceutically acceptable anion is iodide.

7. A pharmaceutical composition comprising the compound



wherein

X is a pharmaceutically acceptable anion, and a pharmaceutically acceptable carrier thereof.

8. The composition according to claim **7** wherein the pharmaceutically acceptable anion is chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate or p-toluenesulfonate.

9. The composition according to claim **7** wherein the pharmaceutically acceptable anion is bromide.

10. The composition according to claim **7** wherein the pharmaceutically acceptable anion is iodide.

11. A pharmaceutical composition according to claim **2** in a form suitable for administration by oral or nasal inhalation.

12. A pharmaceutical composition according to claim **11** wherein the form is suitable for administration by inhalation via a medicament dispenser selected from a reservoir dry powder inhaler, multi-dose dry powder inhaler, or a metered dose inhaler.

13. A pharmaceutical composition according to claim **2** which is a dry powder composition.

14. A pharmaceutical composition according to claim **2** wherein the pharmaceutically acceptable carrier is lactose.

15. A pharmaceutical composition according to claim **7** in a form suitable for administration by oral or nasal inhalation.

16. A pharmaceutical composition according to claim **15** wherein the form is suitable for administration by inhalation via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler, or a metered dose inhaler.

17. A pharmaceutical composition according to claim **7** which is a dry powder composition.

18. A pharmaceutical composition according to claim **7** wherein the pharmaceutically acceptable carrier is lactose.

* * * * *

Customer No.: 20462
Attorney Docket No.: PU60851C1
Confirmation No.: 4033

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Laine et al.	27 June 2008
Serial No.:	11/774,867	Group Art Unit: 1625
Filed:	9 July 2007	Examiner: J. Mabry

For: MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TERMINAL DISCLAIMER

Sir:

Petitioner, Glaxo Group Limited, a company organized under the laws of the United Kingdom, having its registered office and principal place of business as Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, England, represents that it is the assignee of all title and interest in United States Patent Application Serial Number 11/774,867, filed on 9 July 2007 for "Muscarinic Acetylcholine Receptor Antagonists". The present US application is a continuation of US Serial Number 11/568,330 filed on 3 May 2003, which is the §371 national stage entry of PCT/US2005/014386, filed 27 April 2005 by virtue of assignment in said United States Patent Application Serial No. 11/568,330, being duly recorded at Reel 020365 and Frame 0661 in the United States Patent and Trademark Office on 15 January 2008.

Petitioners submit that the evidentiary documents have been reviewed and certify to the best of their knowledge and belief that title is in the Petitioner seeking to take this action.

Petitioner, Glaxo Group Limited, hereby disclaims except as provided below, the terminal part of any patent granted on the above-identified application USSN 11/774,867 which would extend beyond the expiration date of the full statutory term defined in 35 USC §154 and §156 of U.S. application number 11/568,330, and if a patent is granted on U.S. application number 11/568,330 hereby agrees that any patent so granted on the above-identified application shall be enforceable only for, and during, such period that the legal title to said patent shall be the same as the legal title to any patent granted on U.S. application number 11/568,330. This agreement shall

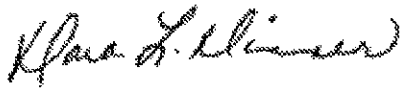
run with any patent granted on the above-identified application and shall be binding upon the grantee, its successors or assigns.

In making the above disclaimer, Petitioner does not disclaim any terminal part of any patent granted on the above-identified application prior to the expiration date of the full statutory term defined in 35 USC §154, and of the term as presently shortened by an terminal disclaimer granted on US application number 11/568,330 in the event that said patent granted on US application number 11/568,330 later expires for failure to pay a maintenance fee, is held unenforceable or is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. §1.321(a), has all claims cancelled by reexamination certificate, or is deemed not to provide the rights conveyed by 35 USC §154 prior to expiration of its full statutory term, except for the separation of legal title as stated above.

This disclaimer shall not be effective against any patent term extensions obtained under 35 U.S.C. §156 for any patent granted on the above-identified application.

In accordance with the fee schedule set forth in 37 C.F.R. § 1.20(d), please charge the required fee of $130.00 to Deposit Account No. 19-2570. Please charge any additional fees under 37 C.F.R. § 1.16 or § 1.17 which may be required by this paper, or credit any overpayment to Deposit Account No. 19-2570. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted



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MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	ENTITY STATUS	ATTY DKT NUMBER
7488827	**$1,130.00**	**$0.00**	**07/25/12**	**11774867**	**02/10/09**	**07/09/07**	**04**	**LARGE**	**PU60851C1**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Jan-2009	IND 104479		umeclidinium (GSK573719) General Memorandum Other	8137bd20

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. The Central Document Control Room	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Other SUBTYPES: Other

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
21-Jan-2009	IND 104479		umeclidinium (GSK573719) General Memorandum Other	8137bd75

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Dr. The Central Document Control Room	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Other SUBTYPES: Other

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
21-Jan-2009	IND 104479		umeclidinium (GSK573719) Response to FDA Request/Comment Other	8141f078

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Martha Anne Auld, R.Ph.	Food and Drug Administration Dr. The Central Document Control Room	FAX/E-mail	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Other SUBTYPES: Other

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
30-Jan-2009	IND 104479; IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) General Correspondence Clinical Meeting Agenda or Details Meeting Request Nonclinical	81384ec5

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Nonclinical; Meeting Request; Clinical; Meeting Agenda or Details SUBTYPES: Nonclinical; Meeting Request; Clinical; Meeting Agenda or Details

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
23-Feb-2009	IND 104479		umeclidinium (GSK573719) General Correspondence Meeting Agenda or Details	813bd480

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Meeting Agenda or Details SUBTYPES: Meeting Agenda or Details

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
26-Feb-2009	IND 104479		umeclidinium (GSK573719) General Memorandum Meeting Agenda or Details	8141f106

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Ms. Miranda B. Raggio	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Meeting Agenda or Details SUBTYPES: Meeting Agenda or Details

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
27-Feb-2009	IND 104479		umeclidinium (GSK573719) General Memorandum Meeting Agenda or Details	8141f2af

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Meeting Agenda or Details SUBTYPES: Meeting Agenda or Details

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
02-Mar-2009	IND 104479; IND 104479		umeclidinium (GSK573719) General Memorandum Meeting Agenda or Details Other	813c640b

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Other; Meeting Agenda or Details SUBTYPES: Other; Meeting Agenda or Details

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:

02-Mar-2009 **IND 104479** umeclidinium (GSK573719) 8141f368
Response to FDA Request/Comment
Other

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug**	**FAX/E-mail**	RESPONSE TO FDA REQUEST/COMMENT
Ms. Mary V. Sides	**Administration**		SUBTYPES: Other
	Ms. Miranda B. Raggio		SUBTYPES: Other

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
24-Mar-2009	**IND 104479; IND 104479**		umeclidinium (GSK573719) General Correspondence Nonclinical Safety	813c0f8e

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug**	**Correspondence**	GENERAL CORRESPONDENCE
Ms. Mary V. Sides	**Administration**		SUBTYPES: Nonclinical; Safety
	Dr. Badrul A. Chowdhury, M.D.		SUBTYPES: Nonclinical; Safety
			SUBINDEXING:
			Protocol: 5DMW039
			Report:WD2006/00147/00
			Protocol: 7DMW030
			Report:WD2008/00503/00
			Protocol: R25984
			Report:WD2005/01079/00
			Protocol: R26274
			Report:WD2005/01422/00
			Protocol: R27343
			Report:WD2007/02012/00
			Protocol: V25982
			Report:WD2005/00750/00
			Reports: CH2006/00011/00
			Reports: FD2005/00208/00

Reports: WD2005/00751/00
Reports: WD2006/00172/00

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
24-Mar-2009	IND 104479; IND 104479		umeclidinium (GSK573719) General Correspondence Nonclinical Safety	813c1001

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety SUBINDEXING: Protocol: 6DMW0136 Report:WD2007/01370/00 Protocol: 7DMW030 Report:WD2008/00503/00 Protocol: M27031 Report:WD2007/00074/00 Protocol: M27293 Report:WD2007/01600/00 Protocol: R25984 Report:WD2005/01079/00 Protocol: V25982 Report:WD2005/00750/00 Reports: CH2006/00011/00 Reports: WD2005/00751/00

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Apr-2009	IND 104479; IND 104479; IND 104479; IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) General Correspondence Briefing Document Clinical CMC Meeting Agenda or Details Nonclinical Safety	81408fae

FROM:
GlaxoSmithKline
Ms. Mary V. Sides

TO:
Food and Drug Administration
Dr. Badrul A. Chowdhury, M.D.

COMMUNICATION:
Correspondence

DOCTYPE & SUBTYPE:
GENERAL CORRESPONDENCE
SUBTYPES: Nonclinical; CMC; Clinical; Safety; Meeting Agenda or Details; Briefing Document
SUBTYPES: Nonclinical; CMC; Clinical; Safety; Meeting Agenda or Details; Briefing Document
Protocol: AC2103473
Protocol: AC2105333
Protocol: AC2105854
Protocol: AC2110664
Protocol: AC4105209
Protocol: AC4105211
Protocol: AC4106889
Protocol: AC4110106
Protocol: AC4113073
Protocol: DB1111581
Protocol: DB2113120
Protocol: AC4108123
Report:GM2008/00079/00
Reports: RM2006/00835/02

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
30-Apr-2009	IND 104479		umeclidinium (GSK573719) Request for Special Protocol Assessment Carcinogenicity	813b3c90

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	REQUEST FOR SPECIAL PROTOCOL ASSESSMENT SUBTYPES: Carcinogenicity SUBTYPES: Carcinogenicity Protocol: 79803 Protocol: 6DMW136 Report:WD2007/01370/00 Protocol: 7DMW030 Report:WD2008/00503/00 Protocol: 8DMW052 Report:WD2009/00030/00 Protocol: M27031 Report:WD2007/00074/00 Protocol: M27293 Report:WD2007/00074/00 Report: WD2007/01600/00 Protocol: R25984 Report:WD2005/01079/00 Protocol: RI05034 Report:CH2006/00011/00 Protocol: V25982 Report:WD2005/00750/00 Protocol: V25983 Report:WD2005/00751/00

DESCRIPTION:

Please refer to our letter dated March 24, 2009 in which we notified the Division of our plan to request a Special Protocol Assessment for a carcinogenicity study to be conducted in the mouse. This protocol will evaluate GSK573719, an orally inhaled potent Quinuclidine derivative that is a pan-active Muscarinic Acetylcholine Receptor (mAChR) antagonist being developed by GSK for the treatment of chronic obstructive pulmonary disease (COPD).

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
30-Apr-2009	IND 104479		umeclidinium (GSK573719)	813b3ccf

Request for Special Protocol Assessment
Carcinogenicity

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	REQUEST FOR SPECIAL PROTOCOL ASSESSMENT SUBTYPES: Carcinogenicity SUBTYPES: Carcinogenicity Protocol: 31114/3 Protocol: 5DMW039 Report:WD2006/00147/00 Protocol: 5DMW076 Report:WD2006/00172/00 Protocol: 7DMW030 Report:WD2008/00503/00 Protocol: BVR739 Report:FD2005/00208/00 Protocol: R25984 Report:WD2005/01079/00 Protocol: R26274 Report:WD2005/01422/00 Protocol: R27343 Report:WD2007/02012/00 Protocol: V25982 Report:WD2005/00750/00 Reports: CH2006/00011/00 Reports: WD2005/00751/00 Reports: WD2009/00030/00

DESCRIPTION:
Please refer to our letter dated March 24, 2009 in which we notified the Division of our plan to request a Special Protocol Assessment for a carcinogenicity study to be conducted in the rat. This protocol will evaluate GSK573719, an orally inhaled potent Quinuclidine derivative that is a pan-active Muscarinic Acetylcholine Receptor (mAChR) antagonist being developed by GSK for the treatment of chronic obstructive pulmonary disease

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
01-May-2009	**IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;**		umeclidinium (GSK573719) General Correspondence Clinical Meeting Agenda or Details	81437e84

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	GENERAL CORRESPONDENCE SUBTYPES: Nonclinical; Meeting Request; Clinical; Safety; Meeting Agenda or Details SUBTYPES: Nonclinical; Meeting Request; Clinical; Safety; Meeting Agenda or Details

DESCRIPTION:
In accordance with the Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products (February 2000), GlaxoSmithKline are requesting a Type C meeting, in the form of a teleconference, to seek agreement on the study designs
and doses for the 3-month combination toxicology study in the dog and the embryofetal study in the rat to support the development of GSK573719A, an inhaled long-acting muscaric antagonist (LAMA) in combination with GW642444M, an inhaled long-acting
beta2-agonist (LABA) for the treatment of COPD.

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
07-May-2009	**IND 104479**		umeclidinium (GSK573719) General Correspondence Meeting Agenda or Details	8143fa79

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration **Dr. Badrul A. Chowdhury, M.D.**	**GlaxoSmithKline** **Ms. Mary V. Sides**	**Correspondence**	GENERAL CORRESPONDENCE SUBTYPES: Meeting Agenda or Details SUBTYPES: Meeting Agenda or Details

DESCRIPTION:
Meeting not required at this time. Questions and supporting materials related to this issue can be submitted in the IND which yoy plan to submit in the fourth quarter of 2009.

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
21-May-2009	IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Clinical Nonclinical Other	81458d13

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Other; Clinical SUBTYPES: Nonclinical; Other; Clinical Protocol: AC4105209 Protocol: AC4105211 Protocol: AC4106889 Protocol: AC4108123 Protocol: AC4110106 Protocol: AC4113073

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
22-May-2009	IND 104479; IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) General Memorandum Clinical Efficacy Meeting Agenda or Details Safety	8145f24f

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Ms. Miranda B. Raggio	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Clinical; Safety; Meeting Agenda or Details; Efficacy SUBTYPES: Clinical; Safety; Meeting Agenda or Details; Efficacy Protocol: AC4106889

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
26-May-2009	IND 104479; IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Topic Clinical Nonclinical Other Safety	8145dcc0

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Mr. Daniel Shurkus	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Trip Report	TOPIC SUBTYPES: Nonclinical; Other; Clinical; Safety SUBTYPES: Nonclinical; Other; Clinical; Safety Protocol: AC4106889

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
03-Jun-2009	IND 104479; IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Clinical Nonclinical Other Safety	8146a978

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:

Food and Drug Administration Dr. Adele Seifried	**GlaxoSmithKline Ms. Mary V. Sides**	**FAX/E-mail**	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Other; Clinical; Safety SUBTYPES: Nonclinical; Other; Clinical; Safety

DESCRIPTION:
Response to carcinogenitic Special Protocol Assessment Request.

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
04-Jun-2009	IND 104479		umeclidinium (GSK573719) Minutes of Meeting N/A	8149264b

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	**GlaxoSmithKline Ms. Mary V. Sides**	**Correspondence**	MINUTES OF MEETING SUBTYPES: N/A SUBTYPES: N/A Protocol: AC4105209 Protocol: AC4105211 Protocol: AC4106889 Protocol: AC4108123 Protocol: AC4110106 Protocol: AC4113073

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
05-Jun-2009	IND 104479; IND 104479;		umeclidinium (GSK573719) Comment/Information Request	81470da4

IND 104479

Nonclinical
Other
Safety

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	**GlaxoSmithKline Ms. Mary V. Sides**	**FAX/E-mail**	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Other; Safety SUBTYPES: Nonclinical; Other; Safety SUBINDEXING: Protocol: M27293 Report:WD2007/01600/00 Protocol: R26274 Report:WD2005/01422/00

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
09-Jun-2009	**IND 104479; IND 104479**		umeclidinium (GSK573719) Response to FDA Request/Comment Nonclinical Safety	81474505

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	**Food and Drug Administration Ms. Miranda B. Raggio**	**FAX/E-mail**	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety SUBINDEXING: Protocol: M27293 Report:WD2007/01600/00 Protocol: R26274 Report:WD2005/01422/00

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Jul-2009	IND 104479; IND 104479; IND 104479; IND 104479; IND 104479; IND 104479	Ser#: 0000	umeclidinium (GSK573719) Ser #: 0000 Initial Investigational New Drug Application CMC Protocol(s) Included Study Reports Protocol Amendment: New Protocol Clinical Protocol Protocol Amendment: New Investigator Investigator Add	8144a948

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INITIAL INVESTIGATIONAL NEW DRUG APPLICATION SUBTYPES: Protocol(s) Included; CMC; Study Reports SUBTYPES: Protocol(s) Included; CMC; Study Reports Protocol: AC2103473 Protocol: AC2105331 Protocol: AC2105333 Protocol: AC2105854 Protocol: AC2106213 Protocol: AC2108378 Protocol: AC2110664 Protocol: AC4105211 Protocol: AC4112014 Protocol: AC4112018 Protocol: AC4113073 Protocol: ACH100539 Protocol: ACH101824 Protocol: BVR1081 Protocol: DB1111581 Protocol: DB2113120 Protocol: DB2113208 Protocol: RES11127 Protocol: SAS10005 Protocol: 1127/895 Report:CD2005/01504/00 Protocol: 1127/900 Report:RD2005/00574/00

Protocol: 1127/905
Report:RD2005/00755/00
Protocol: 181191
Report:FD2005/00164/00
Protocol: 5DMW039
Report:WD2006/00147/00
Protocol: 5DMW049
Report:WD2005/01195/00
Protocol: 5DMW076
Report:WD2006/00172/00
Protocol: 5DMW077
Report:WD2006/00250/00
Protocol: 5DMW105
Report:WD2005/01627/00
Protocol: 5DMW134
Report:WD2006/00073/00
Protocol: 5DMW135
Report:WD2006/00075/00
Protocol: 6DMW065
Report:WD2006/02596/00
Protocol: 6DMW068
Report:WD2006/02657/00
Protocol: 6DMW086
Report:WD2006/03367/00
Protocol: 6DMW136
Report:WD2007/01370/00
Protocol: 724353
Report:WD2006/03154/00
Protocol: 731575
Report:WD2006/03217/00
Protocol: 7DMW030
Report:WD2008/00503/00
Protocol: 7DMW085
Report:WD2008/00001/00
Protocol: 8DMW052
Report:WD2009/00030/00
Protocol: AC4105209
Report:GM2007/00230/00
Protocol: AC4106889
Report:GM2008/00043/00
Protocol: AC4108123
Report:GM2008/00079/00
Protocol: AC4110106
Report:GM2008/00374/00
Protocol: AMES/529
Report:WD2009/00648/00
Protocol: BVR/725

Report:FD2005/00236/00
Protocol: BVR/739
Report:FD2005/00208/00
Protocol: BVR1161
Report:WD2007/01907/00
Protocol: D24638
Report:WD2003/01697/00
Protocol: D24961
Report:WD2004/00489/00
Report: WD2004/00489/01
Protocol: D25886
Report:WD2005/00370/00
Protocol: D26014
Report:FD2005/00097/00
Protocol: D26042
Report:FD2005/00167/00
Protocol: D26053
Report:WD2005/01061/00
Protocol: D26054
Report:WD2005/00841/00
Protocol: D26082
Report:WD2005/00845/00
Protocol: D26275
Report:WD2005/01423/00
Protocol: D26582
Report:WD2006/01711/00
Protocol: D26838
Report:WD2007/01006/00
Protocol: D26864
Report:WD2006/03294/00
Protocol: D26865
Report:WD2006/03228/00
Protocol: D27185
Report:WD2006/03669/00
Protocol: D27338
Report:WD2007/01512/00
Protocol: D28130
Report:WD2008/01504/00
Protocol: D28412
Report:FD2008/00365/00
Protocol: D28415
Report:FD2009/00391/00
Protocol: G05273
Report:CD2005/01385/02
Protocol: G06285
Report:CD2006/02047/00
Protocol: HFL100443/1

Report:WD2006/03251/00
Protocol: I05003
Report:CD2005/00038/00
Protocol: L26578
Report:WD2006/02439/00
Protocol: L26884
Report:WD2006/03186/00
Protocol: L27534
Report:WD2007/00762/00
Protocol: M27031
Report:WD2007/00074/00
Protocol: M27293
Report:WD2007/01600/00
Protocol: R24673
Report:WD2003/01971/00
Protocol: R24960
Report:WD2004/00488/00
Protocol: R25860
Report:WD2004/01556/00
Protocol: R25984
Report:WD2005/01079/00
Protocol: R26052
Report:WD2005/01063/01
Protocol: R26274
Report:WD2005/01422/00
Protocol: R26491
Report:CD2006/01166/01
Protocol: R26581
Report:WD2006/01716/00
Protocol: R26826
Report:WD2006/03225/00
Protocol: R27343
Report:WD2007/02012/00
Protocol: R27391
Report:WD2007/00764/00
Protocol: R27392
Report:WD2007/00763/00
Protocol: R28314
Report:FD2008/00339/00
Protocol: R28416
Report:FD2009/00392/00
Protocol: R60679
Report:VD2005/00625/00
Protocol: RI04088
Report:CH2005/00950/00
Protocol: RI04101
Report:CH2006/00004/00

Protocol: RI04104
Report:CH2006/00001/00
Protocol: RI04108
Report:CH2005/00947/00
Protocol: RI04110
Report:CH2005/00946/00
Protocol: RI04120
Report:CH2006/00012/00
Protocol: RI05017
Report:CH2006/00002/00
Protocol: RI05018
Report:CH2006/00013/00
Protocol: RI05034
Report:CH2006/00011/00
Protocol: V25982
Report:WD2005/00750/00
Protocol: V25983
Report:WD2005/00751/00
Protocol: V26077
Report:FD2005/00109/00
Protocol: V28379
Report:WD2008/01499/00
Protocol: Z26040
Report:FD2005/00063/00
Protocol: Z26041
Report:FD2005/00065/00
Protocol: Z26046
Report:FD2005/00096/00
Protocol: Z26047
Report:FD2005/00095/00
Protocol: Z26103
Report:WD2006/02085/00
Reports: CH2005/00953/00
Reports: CH2005/00954/00
Reports: CH2006/00014/00
Reports: CH2006/00015/00
Reports: CH2006/00018/00
Reports: CH2006/00020/00
Reports: CH2006/00029/00
Reports: CH2006/00030/00
Reports: CH2009/00016/00
Reports: SH2004/00116/00
Reports: SH2006/00079/00
Reports: WD2004/01614/00
Reports: WD2005/00426/00
Reports: WD2005/00427/00
Reports: WD2006/00081/00

Reports: WD2006/03558/00
Reports: WD2006/03559/00
Reports: WD2008/00425/00
Reports: WD2008/00560/00
Reports: WD2008/00583/00
SUBTYPES: Protocol; Clinical
SUBTYPES: Protocol; Clinical
Protocol: AC4113073
SUBTYPES: Investigator Add
SUBTYPES: Investigator Add
SUBINDEXING:
Protocol: AC4113073
Investigator: Gregory J. Feldman, M.D., CPI

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Jul-2009	**IND 104479; IND 104479**	**Ser#: 0001**	umeclidinium (GSK573719) Ser #: 0001 Response to FDA Request/Comment Nonclinical Safety	81494e67

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety SUBINDEXING: Protocol: M27293 Report:WD2007/01600/00 Protocol: R26274 Report:WD2005/01422/00

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
22-Jul-2009	IND 104479		umeclidinium (GSK573719) Acknowledgement IND # Assigned	814bbd9f

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	Correspondence	ACKNOWLEDGEMENT SUBTYPES: IND # Assigned SUBTYPES: IND # Assigned

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
07-Aug-2009	IND 104479	Ser#: 0002	umeclidinium (GSK573719) Ser #: 0002 Request for Special Protocol Assessment Carcinogenicity	814c518a

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	REQUEST FOR SPECIAL PROTOCOL ASSESSMENT SUBTYPES: Carcinogenicity SUBTYPES: Carcinogenicity SUBINDEXING: Protocol: R26826 Report:WD2006/03225/00

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Aug-2009	IND 104479		umeclidinium (GSK573719) General Memorandum Status Update	814d4e4b

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Status Update SUBTYPES: Status Update

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Aug-2009	IND 104479		umeclidinium (GSK573719) General Memorandum Request Status Update	814d7692

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Ms. Miranda B. Raggio	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Request Status Update SUBTYPES: Request Status Update

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Aug-2009	IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Nonclinical Protocol Safety	814d6296

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Mr. Timothy W. Robison	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Protocol; Nonclinical; Safety SUBTYPES: Protocol; Nonclinical; Safety

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Aug-2009	IND 104479	Ser#: 0003	umeclidinium (GSK573719) Ser #: 0003 Protocol Amendment: Change in Protocol Clinical	814d5562

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: CHANGE IN PROTOCOL SUBTYPES: Clinical SUBTYPES: Clinical SUBINDEXING: Protocol: AC4113073 Amendments:01

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
24-Aug-2009	IND 104479; IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request CMC Nonclinical Other Safety	814e3fb1

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; CMC; Other; Safety SUBTYPES: Nonclinical; CMC; Other; Safety

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
25-Aug-2009	IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Response to FDA Request/Comment Nonclinical Other Safety	814ef5de

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Ms. Miranda B. Raggio	FAX/E-mail	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical; Other; Safety SUBTYPES: Nonclinical; Other; Safety

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
25-Aug-2009	IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Nonclinical Other Safety	814ef62b

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Other; Safety SUBTYPES: Nonclinical; Other; Safety

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
25-Aug-2009	IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Response to FDA Request/Comment Nonclinical Other Safety	814ef648

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Ms. Miranda B. Raggio	FAX/E-mail	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical; Other; Safety SUBTYPES: Nonclinical; Other; Safety

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
01-Sep-2009	IND 104479; IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Clinical Nonclinical Other Safety	814ef665

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Other; Clinical; Safety SUBTYPES: Nonclinical; Other; Clinical; Safety

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
17-Sep-2009	IND 104479; IND 104479; IND 104479	Ser#: 0004	umeclidinium (GSK573719) Ser #: 0004 Response to FDA Request/Comment Clinical CMC Nonclinical	814f8d7a

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Sue M. Holmes, M.S.	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical; CMC; Clinical SUBTYPES: Nonclinical; CMC; Clinical Protocol: AC4113073

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No **MEDIA INFORMATION:**

QC COMPLETED: Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
17-Sep-2009	IND 104479	Ser#: 0005	umeclidinium (GSK573719) Ser #: 0005 Protocol Amendment: New Investigator Investigator Add	81500016

FROM:
GlaxoSmithKline
Ms. Mary V. Sides

TO:
Food and Drug Administration
Dr. Badrul A. Chowdhury, M.D.

COMMUNICATION:
Correspondence

DOCTYPE & SUBTYPE:
PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add
SUBTYPES: Investigator Add
SUBINDEXING:
Protocol: AC4113073
Investigator: Joseph A. Boscia, III, M.D., CPI
Investigator: Ravi T. Chandran, M.D.
Investigator: Connie Hsu, M.D.
Investigator: Andras Koser, M.D., FHM, MBA, CCPI
Investigator: Krishna Kumar Pudi, M.D.
Investigator: Robert R. Walker, M.D.

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No **MEDIA INFORMATION:**

QC COMPLETED: Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
28-Sep-2009	IND 104479; IND 104479	Ser#: 0006	umeclidinium (GSK573719) Ser #: 0006 General Correspondence Nonclinical Safety	81510bfb

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety SUBINDEXING: Protocol: D24287 Report:WD2003/01081/00

DESCRIPTION:
Reference is made to the Initial IND submitted on July 14, 2009 (Effective date of August 13, 2009) and to GlaxoSmithKline's request for comment on the 3-month combination toxicology studies provided in Item 10 of that submission. Reference is also made to Division feedback received September 1, 2009. GSK have provided a response to Comments 1a and 1b.

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
29-Sep-2009	IND 104479		umeclidinium (GSK573719) General Memorandum Request Status Update	8151db63

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Ms. Miranda B. Raggio	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Request Status Update SUBTYPES: Request Status Update

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
02-Oct-2009	IND 104479; IND 104479;		umeclidinium (GSK573719) General Memorandum	81517e9b

Status Update
Comment/Information Request
Nonclinical
Safety

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	**GlaxoSmithKline Ms. Mary V. Sides**	**FAX/E-mail**	GENERAL MEMORANDUM SUBTYPES: Status Update SUBTYPES: Status Update SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
06-Oct-2009	**IND 104479; IND 104479; IND 104479; IND 104479**	**Ser#: 0007**	umeclidinium (GSK573719) Ser #: 0007 General Correspondence Nonclinical Safety Response to FDA Request/Comment Nonclinical Safety	8151be8f

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	**Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	GENERAL CORRESPONDENCE SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety SUBINDEXING: Protocol: D24287 Report:WD2003/01081/00 SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety SUBINDEXING: Protocol: D24287 Report:WD2003/01081/00

DESCRIPTION:
Reference is made to the submission of September 28, 2009 (SN:0006) where GlaxoSmithKline provided a response to Division comments on the 3-month combination toxicity studies with GSK573719/GW642444 Inhalation Powder. Reference is also made to the email from Ms. Miranda Raggio on October 2, 2009 requesting clarity on our response. This submission provides a response to the original comments and to the recent Division comments around dose groups and associated rationale for their inclusion and the data that support them (specifically Question 1a). The response to comment 1b remains unchanged from that submitted September 28, 2009.

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No **MEDIA INFORMATION:**

QC COMPLETED: Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
09-Oct-2009	IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Nonclinical Safety General Memorandum Status Update	8152290c

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety SUBTYPES: Status Update SUBTYPES: Status Update

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:**

QC COMPLETED: Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Oct-2009	IND 104479	Ser#: 0008	umeclidinium (GSK573719) Ser #: 0008 Protocol Amendment: New Investigator Investigator Add	81520883

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:

GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add SUBINDEXING: Protocol: AC4113073 Investigator: David R. Erb, M.D., FCCP, CPI Investigator: Gary D. Levinson, M.D.

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
06-Nov-2009	IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request CMC Nonclinical Safety	81580836

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration **Dr. Badrul A. Chowdhury, M.D.**	**GlaxoSmithKline** **Ms. Mary V. Sides**	**Correspondence**	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; CMC; Safety SUBTYPES: Nonclinical; CMC; Safety

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
11-Nov-2009	IND 104479;	Ser#: 0009	umeclidinium (GSK573719)	Ser #: 0009	8154d532

Protocol Amendment: New Investigator
Investigator Add
Other 1572 Change

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change SUBINDEXING: Protocol: AC4113073 Investigator: David I. Bernstein, M.D. Investigator: Amit I. Patel, M.D. PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change SUBINDEXING: Protocol: AC4113073 Investigator: Andras Koser, M.D., FHM, MBA, CCPI

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No
MEDIA INFORMATION:

QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
20-Nov-2009	**IND 104479;** **IND 104479;** **IND 104479**	**Ser#: 0010**	umeclidinium (GSK573719) Ser #: 0010 Protocol Amendment: New Protocol Clinical Protocol Protocol Amendment: New Investigator Investigator Add	815582d2

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW PROTOCOL SUBTYPES: Protocol; Clinical SUBTYPES: Protocol; Clinical Protocol: AC4113589 SUBTYPES: Investigator Add

SUBTYPES: Investigator Add
SUBINDEXING:
Protocol: AC4113589
Investigator: Joseph A. Boscia, III, M.D., CPI

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DOC ID:
81573797

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:
14-Dec-2009	IND 104479; IND 104479	Ser#: 0011	umeclidinium (GSK573719) Ser #: 0011 Protocol Amendment: New Investigator Investigator Add Other 1572 Change

FROM:
GlaxoSmithKline
Ms. Mary V. Sides

TO:
Food and Drug Administration
Dr. Badrul A. Chowdhury, M.D.

COMMUNICATION:
Correspondence

DOCTYPE & SUBTYPE:
PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add; Other 1572 Change
SUBTYPES: Investigator Add; Other 1572 Change
SUBINDEXING:
Protocol: AC4113073
Investigator: Jutta Beier, M.D.
Investigator: Andreas Eich, M.D.
Investigator: Gabriele Illies, M.D.
Investigator: Stephanie Korn, M.D.
Investigator: Susanne Mindt-Prufert, M.D.
Investigator: Isabelle Schenkenberger, MD
Investigator: Henrik Watz, M.D.
Investigator: Dirk Zuechner, M.D.
Protocol: AC4113589
Investigator: Gregory J. Feldman, M.D., CPI
Investigator: Charles M. Fogarty, M.D., CPI
Investigator: Selwyn Spangenthal, M.D.

PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add; Other 1572 Change
SUBTYPES: Investigator Add; Other 1572 Change
SUBINDEXING:
Protocol: AC4113073

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No
MEDIA INFORMATION:

QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
17-Dec-2009	IND 104479	Ser#: 0012	umeclidinium (GSK573719) Ser #: 0012 Information Amendment: Clinical Investigator's Brochure	8157eb12

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Investigator's Brochure SUBTYPES: Investigator's Brochure Protocol: AC4105211

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No
MEDIA INFORMATION:

QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-Jan-2010	IND 104479; IND 104479; IND 104479; IND 104479	Ser#: 0013	umeclidinium (GSK573719) Ser #: 0013 Protocol Amendment: New Protocol Clinical Protocol Protocol Amendment: New Investigator Investigator Add Amendment: Other Transfer of Obligations to Contract Research Organization	8158dc2e

FROM: GlaxoSmithKline

TO: Food and Drug Administration

COMMUNICATION: Correspondence

DOCTYPE & SUBTYPE:
PROTOCOL AMENDMENT: NEW PROTOCOL
SUBTYPES: Protocol; Clinical
SUBTYPES: Protocol; Clinical
Protocol: DB2113950

PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add
SUBTYPES: Investigator Add
SUBINDEXING:
Protocol: DB2113950
Investigator: Steven John Warrington, MA, MD, FRCP, FFPM

AMENDMENT: OTHER
SUBTYPES: Transfer of Obligations to Contract Research Organization
SUBTYPES: Transfer of Obligations to Contract Research Organization
Protocol: DB2113950

DESCRIPTION:
DB2113950: The primary objective of this study is to assess the effects of 240 mg once daily verapamil on the steady-state pharmacokinetics of inhaled GSK573719 and inhaled GSK573719 in combination with inhaled GW642444 in healthy subjects.

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
22-Jan-2010	IND 104479	Ser#: 0014	umeclidinium (GSK573719) Ser #: 0014 Protocol Amendment: New Investigator Investigator Add	8159958b

FROM: GlaxoSmithKline
Ms. Mary V. Sides

TO: Food and Drug Administration
Dr. Badrul A. Chowdhury, M.D.

COMMUNICATION: Correspondence

DOCTYPE & SUBTYPE:
PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add
SUBTYPES: Investigator Add
SUBINDEXING:
Protocol: AC4113073
Investigator: Veronika Richter, Dr. med.
Protocol: AC4113589
Investigator: Bret A. Wittmer, DVM, M.D., CCI

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Feb-2010	IND 104479; IND 104479	Ser#: 0015	umeclidinium (GSK573719) Ser #: 0015 Protocol Amendment: New Investigator Other 1572 Change Investigator Add	815b84bb

FROM:
GlaxoSmithKline
Ms. Judith Silva

TO:
Food and Drug Administration
Dr. Badrul A. Chowdhury, M.D.

COMMUNICATION:
Correspondence

DOCTYPE & SUBTYPE:
PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add; Other 1572 Change
SUBTYPES: Investigator Add; Other 1572 Change
SUBINDEXING:
Protocol: AC4113073
Investigator: Joseph A. Boscia, III, M.D., CPI
Investigator: David R. Erb, M.D., FCCP, CPI
Investigator: Gregory J. Feldman, M.D., CPI
Investigator: Connie Hsu, M.D.
Investigator: Gary D. Levinson, M.D.

PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add; Other 1572 Change
SUBTYPES: Investigator Add; Other 1572 Change
SUBINDEXING:
Protocol: AC4113589
Investigator: Rain Jogi, M.D., Ph.D.
Investigator: Eve-Mai Kuulpak, M.D.
Investigator: Kaiu Prikk, M.D.
Investigator: Priit Samaruutel, M.D.

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: **MEDIA INFORMATION:**

QC COMPLETED: **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Feb-2010	IND 104479	Ser#: 0016	umeclidinium (GSK573719) Ser #: 0016 Protocol Amendment: Change in Protocol Clinical	815be779

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: CHANGE IN PROTOCOL SUBTYPES: Clinical SUBTYPES: Clinical SUBINDEXING: Protocol: DB2113950 Amendments:01

DESCRIPTION:
Amendment 01: This protocol has been amended so that subjects will remain in house for all of period one, as well as period two. This will minimise the chance of confounding period one pharmacokinetic results due to changes in lifestyle between home life and the unit.

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
23-Feb-2010	IND 104479; IND 104479	Ser#: 0017	umeclidinium (GSK573719) Ser #: 0017 Information Amendment: Nonclinical Nonclinical Study Reports	815c4d1f

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Nonclinical; Study Reports SUBTYPES: Nonclinical; Study Reports SUBINDEXING: Protocol: M28691 Report:FD2009/00397/00 Protocol: R42492 Report:RD2009/01098/00 Protocol: R42493 Report:RD2009/01099/00

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
25-Feb-2010	IND 104479; IND 104479	Ser#: 0018	umeclidinium (GSK573719) Ser #: 0018 Information Amendment: Nonclinical Nonclinical Study Reports	815cc623

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Nonclinical; Study Reports SUBTYPES: Nonclinical; Study Reports SUBINDEXING: Protocol: D28415 Report:FD2009/00391/00 Protocol: R28416 Report:FD2009/00392/00

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-Mar-2010	IND 104479	Ser#: 0019	umeclidinium (GSK573719) Ser #: 0019 Protocol Amendment: New Investigator Investigator Add	815da957

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:

GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**

PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add
SUBTYPES: Investigator Add
SUBINDEXING:
Protocol: AC4113589
Investigator: Helen Arievich, M.D.
Investigator: Jutta Beier, M.D.
Investigator: Susanne Mindt-Prufert, M.D.
Investigator: Christine Paschen, M.D.
Investigator: Isabelle Schenkenberger, M.D.
Investigator: Henrik Watz, M.D.
Investigator: Dirk Zuchner, M.D.

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-Mar-2010	**IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479**	**Ser#: 0020**	umeclidinium (GSK573719) Ser #: 0020 General Correspondence Clinical Nonclinical Safety Response to FDA Request/Comment Clinical Nonclinical Safety	815e0ad5

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	GENERAL CORRESPONDENCE SUBTYPES: Nonclinical; Clinical; Safety SUBTYPES: Nonclinical; Clinical; Safety Protocol: AC4110106 Protocol: G09239 Protocol: D09099 Report:CD2009/00970/00 Protocol: L27534 Report:WD2007/00762/00

RESPONSE TO FDA REQUEST/COMMENT
SUBTYPES: Nonclinical; Clinical; Safety
SUBTYPES: Nonclinical; Clinical; Safety
Protocol: AC4110106
Protocol: G09239
Protocol: D09099
Report:CD2009/00970/00
Protocol: L27534
Report:WD2007/00762/00

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DOC ID: 815e4544

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:
18-Mar-2010	IND 104479; IND 104479; IND 104479; IND 104479	Ser#: 0021	umeclidinium (GSK573719) Ser #: 0021 Protocol Amendment: New Protocol Clinical Protocol Protocol Amendment: New Investigator Investigator Add Amendment: Other Transfer of Obligations to Contract Research Organization

FROM:
GlaxoSmithKline
Ms. Mary V. Sides

TO:
Food and Drug Administration
Dr. Badrul A. Chowdhury, M.D.

COMMUNICATION:
Correspondence

DOCTYPE & SUBTYPE:
PROTOCOL AMENDMENT: NEW PROTOCOL
SUBTYPES: Protocol; Clinical
SUBTYPES: Protocol; Clinical
Protocol: AC4112008
SUBTYPES: Investigator Add
SUBTYPES: Investigator Add
SUBINDEXING:
Protocol: AC4112008
Investigator: Steven John Warrington, MA, MD, FRCP, FFPM
SUBTYPES: Transfer of Obligations to Contract Research Organization
SUBTYPES: Transfer of Obligations to Contract Research Organization
Protocol: AC4112008

DESCRIPTION:
Purpose of Study:
GSK573719 is a high affinity specific partially reversible mAChR antagonist that has a rapid on and slow-off kinetics at the human M3 muscarinic receptor subtypes and has been shown to be an effective inhaled long acting bronchodilator in man.

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
30-Mar-2010	IND 104479	Ser#: 0022	umeclidinium (GSK573719) Ser #: 0022 Information Amendment: Chemistry Manufacturing and Controls CMC	815ed740

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Sue M. Holmes, M.S.	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: CHEMISTRY MANUFACTURING AND CONTROLS SUBTYPES: CMC SUBTYPES: CMC Protocol: AC4112008

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-Apr-2010	IND 104479	Ser#: 0023	umeclidinium (GSK573719) Ser #: 0023 Information Amendment: Clinical Study Reports	81600ddc

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports SUBTYPES: Study Reports SUBINDEXING: Protocol: DB2113208

Report:GM2009/00212/00
Keyword: Clinical - Case Report Forms
Keyword: Clinical - Informed Consent Form

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
12-Apr-2010	IND 104479; IND 104479; IND 104479	Ser#: 0024	umeclidinium (GSK573719) General Correspondence Clinical Nonclinical Safety	Ser #: 0024	816035cb

FROM: GlaxoSmithKline

TO: Food and Drug Administration

COMMUNICATION: Correspondence

DOCTYPE & SUBTYPE:
GENERAL CORRESPONDENCE
SUBTYPES: Nonclinical; Clinical; Safety
SUBTYPES: Nonclinical; Clinical; Safety
Protocol: D28843
Protocol: D26275
Report:WD2007/01423/00
Protocol: D26582
Report:WD2006/01711/00
Protocol: D26838
Report:WD2007/01006/00
Protocol: D27338
Report:WD2007/01512/00
Protocol: D28415
Report:FD2009/00391/00

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA:

MEDIA INFORMATION:

QC COMPLETED:

DATE REFERENCED:

No Yes

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Apr-2010	IND 104479	Ser#: 0025	umeclidinium (GSK573719) Ser #: 0025 Protocol Amendment: New Investigator Investigator Add	81609cf5

FROM:
GlaxoSmithKline
Ms. Mary V. Sides

TO:
Food and Drug Administration
Dr. Badrul A. Chowdhury, M.D.

COMMUNICATION:
Correspondence

DOCTYPE & SUBTYPE:
PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add
SUBTYPES: Investigator Add
SUBINDEXING:
Protocol: AC4113589
Investigator: Wlodzimierz Leszczynski, M.D.
Investigator: Robert Marek Mroz, M.D.
Investigator: Grazyna Pulka, M.D., Ph.D.
Investigator: Zenon Siergiejko, M.D.
Investigator: Lucyna Wolak-Sobiczewska, M.D.

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: **MEDIA INFORMATION:**
No

QC COMPLETED: **DATE REFERENCED:**
Yes

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Apr-2010	IND 104479; IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Clinical CMC Nonclinical Safety	8160f2c8

FROM:
Food and Drug Administration
Ms. Miranda B. Raggio

TO:
GlaxoSmithKline
Ms. Mary V. Sides

COMMUNICATION:
FAX/E-mail

DOCTYPE & SUBTYPE:
COMMENT/INFORMATION REQUEST
SUBTYPES: Nonclinical; CMC; Clinical; Safety
SUBTYPES: Nonclinical; CMC; Clinical; Safety
Protocol: AC4112008

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Apr-2010	IND 104479; IND 104479		umeclidinium (GSK573719) General Memorandum Other Status Update	8160f2ee

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Other; Status Update SUBTYPES: Other; Status Update

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
20-Apr-2010	IND 104479; IND 104479; IND 104479; IND 104479	Ser#: 0026	umeclidinium (GSK573719) Ser #: 0026 Response to FDA Request/Comment Clinical CMC Nonclinical Safety	81610596

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury,	Correspondence	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical; CMC; Clinical; Safety SUBTYPES: Nonclinical; CMC; Clinical; Safety

Protocol: AC4112008
Protocol: D26275
Report:WD2005/01423/00
Protocol: R26274
Report:WD2005/01422/00
Protocol: R28314
Report:FD2008/00339/00
Protocol: V28379
Report:WD2008/01499/00

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
21-Apr-2010	IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Nonclinical Safety	81612583

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
22-Apr-2010	IND 104479		umeclidinium (GSK573719)	81613a40

Response to FDA Request/Comment
Other

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Ms. Miranda B. Raggio**	**FAX/E-mail**	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Other SUBTYPES: Other

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
22-Apr-2010	**IND 104479;** **IND 104479**		umeclidinium (GSK573719) General Memorandum Other Status Update	81616d23

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration **Ms. Miranda B. Raggio**	**GlaxoSmithKline** **Ms. Mary V. Sides**	**FAX/E-mail**	GENERAL MEMORANDUM SUBTYPES: Other; Status Update SUBTYPES: Other; Status Update

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
23-Apr-2010	**IND 104479;** **IND 104479**	**Ser#: 0027**	umeclidinium (GSK573719) Ser #: 0027 Response to FDA Request/Comment Nonclinical	81615301

Safety

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety Protocol: AC4112008 Protocol: M28833 Protocol: M28903

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
27-Apr-2010	**IND 104479**	**Ser#: 0028**	umeclidinium (GSK573719) Ser #: 0028 Response to FDA Request/Comment Nonclinical	81618539

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical SUBTYPES: Nonclinical Protocol: M28833 Protocol: M28903

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:

28-Apr-2010 **IND 104479** umeclidinium (GSK573719) 8161c46b
General Teleconference
Other

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	**GlaxoSmithKline Ms. Mary V. Sides**	**Telephone Conversation**	GENERAL TELECONFERENCE SUBTYPES: Other SUBTYPES: Other

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
28-Apr-2010	**IND 104479; IND 104479**		umeclidinium (GSK573719) Comment/Information Request Nonclinical Safety	8161d5d7

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	**GlaxoSmithKline Ms. Mary V. Sides**	**FAX/E-mail**	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Safety SUBTYPES: Nonclinical; Safety Protocol: G09239

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
30-Apr-2010	**IND 104479**	**Ser#: 0029**	umeclidinium (GSK573719)	Ser #: 0029	8161e0b6

Response to FDA Request/Comment
Nonclinical

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical SUBTYPES: Nonclinical SUBINDEXING: Protocol: M28691 Report:FD2009/00397/00 Protocol: M28833 Report:WD2010/00349/00 Protocol: M28903 Report:WD2010/00556/00 Reports: WD2006/03558/00

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
03-May-2010	**IND 104479;** **IND 104479;** **IND 104479**		umeclidinium (GSK573719) Comment/Information Request Clinical Nonclinical Safety	8162b81c

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration **Ms. Miranda B. Raggio**	**GlaxoSmithKline** **Ms. Mary V. Sides**	**FAX/E-mail**	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Clinical; Safety SUBTYPES: Nonclinical; Clinical; Safety Protocol: M28833 Protocol: M28903

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
03-May-2010	IND 104479; IND 104479		umeclidinium (GSK573719) General Memorandum Meeting Agenda or Details Meeting Request	8162b841

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Meeting Request; Meeting Agenda or Details SUBTYPES: Meeting Request; Meeting Agenda or Details

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
04-May-2010	IND 104479; IND 104479; IND 104479	Ser#: 0030	umeclidinium (GSK573719) Ser #: 0030 General Correspondence Clinical Meeting Agenda or Details Other	81622231

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Other; Clinical; Meeting Agenda or Details SUBTYPES: Other; Clinical; Meeting Agenda or Details Protocol: AC4112008

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
10-May-2010	IND 104479		umeclidinium (GSK573719) Comment/Information Request Nonclinical	8162d885

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical SUBTYPES: Nonclinical Protocol: G09239 Protocol: L27534 Report:WD2007/00762/00

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-May-2010	IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Nonclinical Other Safety	81636ccb

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Other; Safety SUBTYPES: Nonclinical; Other; Safety Protocol: M28833

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-May-2010	IND 104479	Ser#: 0031	umeclidinium (GSK573719) Ser #: 0031 Protocol Amendment: New Investigator Other 1572 Change	8162f048

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change SUBINDEXING: Protocol: AC4113589 Investigator: Bret A. Wittmer, M.D.

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-May-2010	IND 104479	Ser#: 0032	umeclidinium (GSK573719) Ser #: 0032 Information Amendment: Clinical Study Reports	8162ed86

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports

Dr. Badrul A. Chowdhury, M.D.

SUBTYPES: Study Reports
SUBINDEXING:
Protocol: AC4105211
Report:GM2009/00207/00

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
27-Aug-2010	IND 104479; IND 104479	Ser#: 0033	umeclidinium (GSK573719) Ser #: 0033 Information Amendment: Nonclinical Nonclinical Study Reports	816d13e6

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Nonclinical; Study Reports SUBTYPES: Nonclinical; Study Reports SUBINDEXING: Protocol: D27185 Report:WD2006/03669/00 Protocol: G09187 Report:CD2010/00187/00 Protocol: L26884 Report:WD2006/03186/00 Protocol: L27534 Report:WD2007/00762/00 Protocol: M28691 Report:FD2009/00397/00 Protocol: M28833 Report:WD2010/00349/00 Protocol: M28903 Report:WD2010/00556/00 Protocol: R26826 Report:WD2006/03225/00 Protocol: R27391 Report:WD2007/00764/00 Protocol: R27392

Report:WD2007/00763/00
Protocol: R42493
Report:RD2009/01099/00
Protocol: Z29060
Report:WD2010/00081/00

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
30-Aug-2010	IND 104479; IND 104479	Ser#: 0034	umeclidinium (GSK573719) Ser #: 0034 Information Amendment: Nonclinical Nonclinical Study Reports	816d14e0

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Nonclinical; Study Reports SUBTYPES: Nonclinical; Study Reports SUBINDEXING: Protocol: D09099 Report:CD2009/00970/00 Protocol: D28412 Report:FD2008/00365/00 Protocol: D28415 Report:FD2009/00391/00 Protocol: D28843 Report:WD2010/00677/00 Protocol: R28416 Report:FD2009/00392/00 Reports: 2010N104308/00

DESCRIPTION:

DESCRIPTORS:
SAFE

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Details

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Reel/Frame: 020365/0661 **Pages:** 5

Recorded: 01/15/2008

Attorney Dkt #: PU60851

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Total properties: 1

1 **Patent #:** 7498440 **Issue Dt:** 03/03/2009 **Application #:** 11568330 **Filing Dt:** 05/03/2007
Publication #: US20070185155 **Pub Dt:** 08/09/2007
Title: MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

Assignors

1	LAINE, DRAMANE I	**Exec Dt:** 04/26/2005
2	PALOVICH, MICHAEL R	**Exec Dt:** 04/26/2005
3	MCCLELAND, BRENT	**Exec Dt:** 04/27/2005
4	NEIPP, CHRISTOPHER	**Exec Dt:** 06/28/2005
5	THOMAS, SONIA M	**Exec Dt:** 06/28/2005

Assignee

1 GLAXO GROUP LIMITED
BERKELEY AVENUE
GREENFORD, MIDDLESEX, UNITED KINGDOM UB6 0NN

Correspondence name and address

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KING OF PRUSSIA, PA 19406

Search Results as of: 01/13/2014 06:32 PM
If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350. v.2.3.4
Web interface last modified: Jul 8, 2013 v.2.3.4

ELECTRONIC MEDIA: No **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
21-Sep-2010	IND 104479; IND 104479	Ser#: 0035	umeclidinium (GSK573719) Ser #: 0035 Information Amendment: Nonclinical Nonclinical Study Reports	816de042

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Nonclinical; Study Reports SUBTYPES: Nonclinical; Study Reports SUBINDEXING: Protocol: D28759 Report:FD2009/00466/00 Protocol: G09239 Report:CD2010/00253/00 Protocol: R28859 Report:FD2009/00467/00

DESCRIPTION:

DESCRIPTORS:
SAFE

ELECTRONIC MEDIA: No **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
01-Oct-2010	IND 104479; IND 104479; IND 104479; IND 104479	Ser#: 0036	umeclidinium (GSK573719) Ser #: 0036 Annual Report Adverse Event Summary Clinical Study Information CMC Investigational Plan	816ffa82

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration	Correspondence	ANNUAL REPORT SUBTYPES: Adverse Event Summary; CMC; Clinical Study Information; Investigational

Dr. Badrul A. Chowdhury, M.D.

Plan

SUBTYPES: Adverse Event Summary; CMC; Clinical Study Information; Investigational

Plan

Protocol: 9DMW069
Protocol: AC4105211
Protocol: AC4110106
Protocol: AC4112008
Protocol: AC4112014
Protocol: AC4113208
Protocol: AC4113377
Protocol: D28759
Protocol: DB2113208
Protocol: DB2113359
Protocol: DB2113361
Protocol: DB2113373
Protocol: DB2113950
Protocol: DB2114417
Protocol: DB2114418
Protocol: DB2114635
Protocol: DB2114636
Protocol: DB2114637
Protocol: G09239
Protocol: M28976
Protocol: R28859
Protocol: R28862
Protocol: 7DMW131
Report:WD2009/00039/00
Protocol: AC4113073
Report:RM2009/00680/00
Protocol: AC4113589
Report:RM2009/00416/00
Protocol: AMES/528
Report:WD2009/00653/00
Protocol: AMES/529
Report:WD2009/00648/00
Protocol: B2C106180
Report:GM2009/00020/00
Protocol: D09099
Report:CD2009/00970/00
Protocol: D28415
Report:FD2009/00391/00
Protocol: D28843
Report:WD2010/00677/00
Protocol: G09187
Report:CD2010/00187/00
Protocol: M28691
Report:FD2009/00397/00

Protocol: M28833
Report:WD2010/00349/00
Protocol: M28903
Report:WD2010/00556/00
Protocol: R28416
Report:FD2009/00392/00
Protocol: R42492
Report:RD2009/01098/00
Protocol: R42493
Report:RD2009/01099/00
Protocol: Z28716
Report:FD2009/00369/00
Protocol: Z28754
Report:FD2009/00404/00
Protocol: Z29060
Report:WD2010/00081/00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
05-Oct-2010	IND 104479		umeclidinium (GSK573719) Comment/Information Request Nonclinical	81716245

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical SUBTYPES: Nonclinical

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
05-Oct-2010	IND 104479		umeclidinium (GSK573719) Response to FDA Request/Comment Nonclinical	81716376

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Eunice H. Chung-Davies, Pharm.D.	FAX/E-mail	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical SUBTYPES: Nonclinical

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
05-Oct-2010	IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Nonclinical Other	8171604d

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Dr. Eunice H. Chung-Davies, Pharm.D.	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Nonclinical; Other SUBTYPES: Nonclinical; Other

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:

No Yes

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
06-Oct-2010	IND 104479; IND 104479	Ser#: 0037	umeclidinium (GSK573719) Ser #: 0037 Information Amendment: Nonclinical Study Reports Response to FDA Request/Comment Nonclinical	81716764

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Study Reports SUBTYPES: Study Reports SUBINDEXING: Protocol: D28759 Report:FD2009/00466/00 RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Nonclinical SUBTYPES: Nonclinical SUBINDEXING: Protocol: D28759 Report:FD2009/00466/00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
21-Oct-2010	IND 104479	Ser#: 0038	umeclidinium (GSK573719) Ser #: 0038 Protocol Amendment: New Investigator Other 1572 Change	8172a34e

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury,	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change

M.D.

Protocol: AC4113073
Protocol: AC4113589

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
02-Nov-2010	IND 104479	Ser#: 0039	umeclidinium (GSK573719) Ser #: 0039 Information Amendment: Clinical Investigator's Brochure	817345de

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Investigator's Brochure SUBTYPES: Investigator's Brochure Protocol: AC4105209 Protocol: AC4105211 Protocol: AC4106889 Protocol: AC4108123 Protocol: AC4110106 Protocol: AC4112008 Protocol: AC4113073 Protocol: AC4113377 Protocol: AC4113589 Protocol: DB2113120 Protocol: DB2113208 Protocol: DB2113950

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
04-Nov-2010	**IND 104479**	**Ser#: 0040**	umeclidinium (GSK573719) Ser #: 0040 Information Amendment: Clinical Study Reports	816f32b5

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports SUBTYPES: Study Reports SUBINDEXING: Protocol: DB2113120 Report:YM2010/00171/00 Protocol: DB2113208 Report:GM2009/00212/00 Protocol: DB2113950 Report:YM2010/00177/00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
04-Nov-2010	**IND 104479; IND 104479**	**Ser#: 0041**	umeclidinium (GSK573719) Ser #: 0041 Information Amendment: Nonclinical Nonclinical Study Reports	8174604f

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Nonclinical; Study Reports SUBTYPES: Nonclinical; Study Reports SUBINDEXING: Protocol: G09239 Report:CD2010/00253/00 Protocol: R28859 Report:FD2009/00467/00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
23-Nov-2010	IND 104479		umeclidinium (GSK573719) Comment/Information Request Other	81766eae

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration	GlaxoSmithKline	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Other SUBTYPES: Other

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
29-Nov-2010	IND 104479; IND 104479		umeclidinium (GSK573719) Response to FDA Request/Comment Clinical Other	817728e2

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	FAX/E-mail	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Other; Clinical SUBTYPES: Other; Clinical Protocol: AC4112008 Protocol: AC4113073 Protocol: AC4113377

Protocol: AC4113589
Protocol: DB2113120
Protocol: DB2113950

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Dec-2010	IND 104479; IND 104479; IND 104479; IND 104479; IND 104479; IND 104479; IND 104479	Ser#: 0042	umeclidinium (GSK573719) Ser #: 0042 Protocol Amendment: New Protocol Clinical Protocol Information Amendment: Nonclinical Nonclinical Study Reports General Correspondence Clinical Nonclinical Protocol Amendment: New Investigator Investigator Add	8174dfcd

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW PROTOCOL SUBTYPES: Protocol; Clinical SUBTYPES: Protocol; Clinical Protocol: DB2113359 INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Nonclinical; Study Reports SUBTYPES: Nonclinical; Study Reports SUBINDEXING: Protocol: D28843 Report:WD2010/00677/01 Protocol: D29332 Report:2010N109790_00 GENERAL CORRESPONDENCE SUBTYPES: Nonclinical; Clinical

SUBTYPES: Nonclinical; Clinical
Protocol: AC4113073
Protocol: DB2113120
Protocol: HZC111348
Protocol: D28412
Report:FD2008/00365/00

PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add
SUBTYPES: Investigator Add
Protocol: DB2113359

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Dec-2010	**IND 104479**	**Ser#: 0043**	umeclidinium (GSK573719) Ser #: 0043 Information Amendment: Clinical Study Reports	816fb29c

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports SUBTYPES: Study Reports SUBINDEXING: Protocol: AC4113073 Report:RM2009/00680/00 Protocol: AC4113377 Report:JM2010/00003/00 Protocol: AC4113589 Report:RM2010/00314/00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-Jan-2011	IND 104479	Ser#: 0044	umeclidinium (GSK573719) Ser #: 0044 Information Amendment: Clinical Investigator's Brochure	81797f24

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Investigator's Brochure SUBTYPES: Investigator's Brochure Protocol: AC4105209 Protocol: AC4105211 Protocol: AC4106889 Protocol: AC4108123 Protocol: AC4110106 Protocol: AC4112008 Protocol: AC4112014 Protocol: AC4113073 Protocol: AC4113377 Protocol: AC4113589 Protocol: DB2113120 Protocol: DB2113208 Protocol: DB2113950

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Jan-2011	IND 104479	Ser#: 0045	umeclidinium (GSK573719) Ser #: 0045 Information Amendment: Chemistry Manufacturing and Controls CMC	81799474

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:

GlaxoSmithKline **Ms. Sue M. Holmes, M.S.**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	INFORMATION AMENDMENT: CHEMISTRY MANUFACTURING AND CONTROLS SUBTYPES: CMC SUBTYPES: CMC SUBINDEXING: Keyword: CMC - Components/Composition Keyword: CMC - Manufacturer (Site)

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
31-Jan-2011	**IND 104479**	**Ser#: 0046**	umeclidinium (GSK573719) General Correspondence Other	Ser #: 0046	8177b3d3

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	GENERAL CORRESPONDENCE SUBTYPES: Other SUBTYPES: Other

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
08-Feb-2011	**IND 104479**	**Ser#: 0047**	umeclidinium (GSK573719) Protocol Amendment: New Investigator Investigator Add	Ser #: 0047	81786812

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:

GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: DB2113359

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	**MEDIA INFORMATION:**	**QC COMPLETED:**	**DATE REFERENCED:**
Yes		Yes	

DATE:	**APPLICATION:**	**SER/SUPP/SEQ #:**	**RE LINE:**	**DOC ID:**
09-Feb-2011	**IND 104479**		umeclidinium (GSK573719) General Memorandum Other	817c2919

FROM:	**TO:**	**COMMUNICATION:**	**DOCTYPE & SUBTYPE:**
Food and Drug Administration **Ms. Miranda B. Raggio**	**GlaxoSmithKline** **Ms. Mary V. Sides**	**FAX/E-mail**	GENERAL MEMORANDUM SUBTYPES: Other SUBTYPES: Other

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	**MEDIA INFORMATION:**	**QC COMPLETED:**	**DATE REFERENCED:**
No		Yes	

DATE:	**APPLICATION:**	**SER/SUPP/SEQ #:**	**RE LINE:**	**DOC ID:**
14-Feb-2011	**IND 104479**		umeclidinium (GSK573719) Response to FDA Request/Comment N/A	817d4be6

FROM:	**TO:**	**COMMUNICATION:**	**DOCTYPE & SUBTYPE:**
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration**	**FAX/E-mail**	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: N/A

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Feb-2011	IND 104479	Ser#: 0048	umeclidinium (GSK573719) Ser #: 0048 General Correspondence Nonclinical	817c5960

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Nonclinical SUBTYPES: Nonclinical Protocol: M28976 Protocol: R28862

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Feb-2011	IND 104479; IND 104479; IND 104479	Ser#: 0049	umeclidinium (GSK573719) Ser #: 0049 Protocol Amendment: New Protocol Clinical Protocol Protocol Amendment: New Investigator Investigator Add	817be47b

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:

GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**

PROTOCOL AMENDMENT: NEW PROTOCOL
SUBTYPES: Protocol; Clinical
SUBTYPES: Protocol; Clinical
Protocol: DB2113361
Protocol: DB2113373
Protocol: DB2114417
Protocol: DB2114418

PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add
SUBTYPES: Investigator Add
Protocol: DB2113361
Protocol: DB2113373
Protocol: DB2114417
Protocol: DB2114418

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	**MEDIA INFORMATION:**	**QC COMPLETED:**	**DATE REFERENCED:**
Yes		Yes	

DATE:	**APPLICATION:**	**SER/SUPP/SEQ #:**	**RE LINE:**	**DOC ID:**
15-Feb-2011	**IND 104479; IND 104479**		umeclidinium (GSK573719) General Correspondence Other Status Update	817d88ba

FROM:	**TO:**	**COMMUNICATION:**	**DOCTYPE & SUBTYPE:**
Food and Drug Administration **Dr. Badrul A. Chowdhury, M.D.**	**GlaxoSmithKline** **Ms. Mary V. Sides**	**Correspondence**	GENERAL CORRESPONDENCE SUBTYPES: Other; Status Update SUBTYPES: Other; Status Update

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No | MEDIA INFORMATION: | QC COMPLETED: Yes | DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
18-Feb-2011	IND 104479; IND 104479		umeclidinium (GSK573719) General Memorandum Other Status Update	817d0b62

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Other; Status Update SUBTYPES: Other; Status Update

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: No | MEDIA INFORMATION: | QC COMPLETED: Yes | DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
24-Feb-2011	IND 104479; IND 104479		umeclidinium (GSK573719) General Memorandum Other Status Update	817d3c47

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Miranda B. Raggio	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Other; Status Update SUBTYPES: Other; Status Update

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: | MEDIA INFORMATION: | QC COMPLETED: | DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
24-Feb-2011	IND 104479; IND 104479; IND 104479	Ser#: 0050	umeclidinium (GSK573719) Ser #: 0050 Protocol Amendment: New Protocol Clinical Protocol Protocol Amendment: New Investigator Investigator Add	817d348f

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW PROTOCOL SUBTYPES: Protocol; Clinical SUBTYPES: Protocol; Clinical Protocol: DB2113374 PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-Mar-2011	IND 104479	Ser#: 0051	umeclidinium (GSK573719) Ser #: 0051 Protocol Amendment: New Investigator Investigator Add	817dc9a3

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: DB2113359

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Mar-2011	IND 104479	Ser#: 0052	umeclidinium (GSK573719) Ser #: 0052 Protocol Amendment: New Investigator Investigator Add	817e9bc4

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: DB2113373

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
29-Mar-2011	IND 104479; IND 104479		umeclidinium (GSK573719) Comment/Information Request Clinical Statistical	81802961

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration	GlaxoSmithKline	FAX/E-mail	COMMENT/INFORMATION REQUEST SUBTYPES: Clinical; Statistical SUBTYPES: Clinical; Statistical Protocol: DB2113360 Protocol: DB2113361

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
07-Apr-2011	IND 104479	Ser#: 0053	umeclidinium (GSK573719) Ser #: 0053 Information Amendment: Clinical Study Reports	817fa5da

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports SUBTYPES: Study Reports SUBINDEXING: Protocol: AC4112008 Report:2010N105452_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-Apr-2011	IND 104479; IND 104479	Ser#: 0054	umeclidinium (GSK573719) Ser #: 0054 Protocol Amendment: New Investigator Investigator Add Other 1572 Change	81808089

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:

GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: DB2113374 PROTOCOL AMENDMENT: NEW INVESTIGATOR

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	**MEDIA INFORMATION:**	**QC COMPLETED:**	**DATE REFERENCED:**
Yes		Yes	

DATE:	**APPLICATION:**	**SER/SUPP/SEQ #:**	**RE LINE:**	**DOC ID:**
19-Apr-2011	**IND 104479; IND 104479**	**Ser#: 0055**	umeclidinium (GSK573719) Ser #: 0055 Protocol Amendment: New Protocol Clinical Protocol	81814ac2

FROM:	**TO:**	**COMMUNICATION:**	**DOCTYPE & SUBTYPE:**
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW PROTOCOL SUBTYPES: Protocol; Clinical SUBTYPES: Protocol; Clinical Protocol: AC4115321 Protocol: AC4115408

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	**MEDIA INFORMATION:**	**QC COMPLETED:**	**DATE REFERENCED:**
Yes		Yes	

DATE:	**APPLICATION:**	**SER/SUPP/SEQ #:**	**RE LINE:**	**DOC ID:**
21-Apr-2011	**IND 104479**	**Ser#: 0056**	umeclidinium (GSK573719) Ser #: 0056 Protocol Amendment: Change in Protocol	81814417

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: CHANGE IN PROTOCOL SUBTYPES: Clinical SUBTYPES: Clinical SUBINDEXING: Protocol: DB2113361 Amendments:01 Protocol: DB2113373 Amendments:01

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
21-Apr-2011	**IND 104479; IND 104479**	**Ser#: 0057**	umeclidinium (GSK573719) Ser #: 0057 Protocol Amendment: New Investigator Investigator Add Other 1572 Change	8181624d

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: DB2113361 Protocol: DB2113373 Protocol: DB2114417 Protocol: DB2114418 PROTOCOL AMENDMENT: NEW INVESTIGATOR

DESCRIPTION:

DESCRIPTORS:

ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
09-May-2011	IND 104479	Ser#: 0058	umeclidinium (GSK573719) Ser #: 0058 Protocol Amendment: New Investigator Investigator Add	8182e6d8

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-May-2011	IND 104479; IND 104479	Ser#: 0059	umeclidinium (GSK573719) Ser #: 0059 Protocol Amendment: New Investigator Other 1572 Change Investigator Add	81835346

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: DB2113361 Protocol: DB2113373 Protocol: DB2114418 PROTOCOL AMENDMENT: NEW INVESTIGATOR

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
20-May-2011	IND 104479	Ser#: 0060	umeclidinium (GSK573719) Ser #: 0060 Protocol Amendment: New Investigator Investigator Add	8183e905

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: AC4115321

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
26-May-2011	IND 104479; IND 104479	Ser#: 0061	umeclidinium (GSK573719) Ser #: 0061 Response to FDA Request/Comment Clinical Statistical	8183f3bc

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: Clinical; Statistical SUBTYPES: Clinical; Statistical Protocol: AC4115408 Protocol: DB2113360

Protocol: DB2113361
Protocol: DB2113373
Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
27-May-2011	IND 104479; IND 104479; IND 104479; IND 104479	Ser#: 0062	umeclidinium (GSK573719) General Correspondence Clinical Draft Protocol Safety Statistical	Ser #: 0062	8180918a

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Clinical; Statistical; Safety; Draft Protocol SUBTYPES: Clinical; Statistical; Safety; Draft Protocol Protocol: AC4105209 Protocol: AC4105211 Protocol: AC4106889 Protocol: AC4108123 Protocol: AC4110106 Protocol: AC4112008 Protocol: AC4113073 Protocol: AC4113377 Protocol: AC4113589 Protocol: B2C106180 Protocol: B2C106996 Protocol: B2C108784 Protocol: B2C109575 Protocol: B2C111045 Protocol: B2C111401 Protocol: DB2113120 Protocol: DB2113208 Protocol: DB2113950 Protocol: DB2114635

Protocol: HZA102934
Protocol: HZA102940
Protocol: HZA105548
Protocol: HZA105871
Protocol: HZC111348

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE;LABA

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
01-Jun-2011	IND 104479; IND 104479; IND 104479; IND 104479	Ser#: 0063	umeclidinium (GSK573719) General Correspondence Clinical Draft Protocol Safety Statistical	Ser #: 0063	81848ea8

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Clinical; Statistical; Safety; Draft Protocol SUBTYPES: Clinical; Statistical; Safety; Draft Protocol Protocol: AC4105209 Protocol: AC4105211 Protocol: AC4106889 Protocol: AC4108123 Protocol: AC4110106 Protocol: AC4113073 Protocol: AC4113377 Protocol: DB2113120 Protocol: DB2113208 Protocol: DB2113950

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-Jun-2011	IND 104479; IND 104479	Ser#: 0064	umeclidinium (GSK573719) Ser #: 0064 Protocol Amendment: New Investigator Investigator Add Other 1572 Change	81851147

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: DB2113359 PROTOCOL AMENDMENT: NEW INVESTIGATOR

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Jun-2011	IND 104479; IND 104479	Ser#: 0065	umeclidinium (GSK573719) Ser #: 0065 Protocol Amendment: New Investigator Investigator Add Other 1572 Change	81859807

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: DB2113361 Protocol: DB2113373 Protocol: DB2114418 PROTOCOL AMENDMENT: NEW INVESTIGATOR

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
30-Jun-2011	IND 104479	Ser#: 0066	umeclidinium (GSK573719) Ser #: 0066 Protocol Amendment: Change in Protocol Clinical	8186a34e

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: CHANGE IN PROTOCOL SUBTYPES: Clinical SUBTYPES: Clinical SUBINDEXING: Protocol: DB2114417 Amendments:01 Protocol: DB2114418 Amendments:01

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-Jul-2011	IND 104479; IND 104479	Ser#: 0067	umeclidinium (GSK573719) Ser #: 0067 Protocol Amendment: New Investigator Investigator Add Other 1572 Change	818755dc

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:

GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: DB2113359 Protocol: DB2113374 PROTOCOL AMENDMENT: NEW INVESTIGATOR

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
14-Jul-2011	**IND 104479**	**Ser#: 0068**	umeclidinium (GSK573719)	Ser #: 0068 Information Amendment: Chemistry Manufacturing and Controls CMC	8187a237

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Sue M. Holmes, M.S.**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	INFORMATION AMENDMENT: CHEMISTRY MANUFACTURING AND CONTROLS SUBTYPES: CMC SUBTYPES: CMC Protocol: AC4115321 Keyword: CMC - Components/Composition Keyword: CMC - Manufacturer (Site)

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
14-Jul-2011	**IND 104479**	**Ser#: 0069**	umeclidinium (GSK573719)	Ser #: 0069	8187de40

Protocol Amendment: Change in Protocol
Clinical

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: CHANGE IN PROTOCOL SUBTYPES: Clinical SUBTYPES: Clinical SUBINDEXING: Protocol: DB2113374 Amendments:01

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Jul-2011	**IND 104479; IND 104479**	**Ser#: 0070**	umeclidinium (GSK573719) Ser #: 0070 Protocol Amendment: New Investigator Investigator Add Other 1572 Change	8187f100

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: DB2113373 Protocol: DB2114418 PROTOCOL AMENDMENT: NEW INVESTIGATOR

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
26-Jul-2011	IND 104479		umeclidinium (GSK573719) General Memorandum Status Update	8188bc3f

FROM: Food and Drug Administration

TO: GlaxoSmithKline

COMMUNICATION: FAX/E-mail

DOCTYPE & SUBTYPE:
GENERAL MEMORANDUM
SUBTYPES: Status Update
SUBTYPES: Status Update
Protocol: DB2114635

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
27-Jul-2011	IND 104479; IND 104479	Ser#: 0071	umeclidinium (GSK573719) General Correspondence Clinical Protocol	Ser #: 0071	8188b30a

FROM: GlaxoSmithKline
Ms. Mary V. Sides

TO: Food and Drug Administration
Dr. Badrul A. Chowdhury, M.D.

COMMUNICATION: Correspondence

DOCTYPE & SUBTYPE:
GENERAL CORRESPONDENCE
SUBTYPES: Protocol; Clinical
SUBTYPES: Protocol; Clinical
Protocol: AC4105209
Protocol: AC4115487
Protocol: DB2113361
Protocol: DB2113373
Protocol: AC4113073
Report:RM2009/00068/01
Protocol: AC4113589
Report:RM2010/00314/00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-Aug-2011	IND 104479	Ser#: 0072	umeclidinium (GSK573719) Ser #: 0072 Protocol Amendment: New Investigator Other 1572 Change	81897b3c

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113359 Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Aug-2011	IND 104479; IND 104479	Ser#: 0073	umeclidinium (GSK573719) Ser #: 0073 Protocol Amendment: New Investigator Other 1572 Change Investigator Add	8189f4c5

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: DB2113361

Protocol: DB2113373
Protocol: DB2114418

PROTOCOL AMENDMENT: NEW INVESTIGATOR

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Aug-2011	IND 104479	Ser#: 0074	umeclidinium (GSK573719) Ser #: 0074 Protocol Amendment: New Investigator Investigator Add	818a55d0

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: AC4115321 Protocol: AC4115408

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Aug-2011	IND 104479; IND 104479	Ser#: 0075	umeclidinium (GSK573719) Ser #: 0075 Protocol Amendment: New Protocol Clinical Protocol	818a418c

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW PROTOCOL SUBTYPES: Protocol; Clinical SUBTYPES: Protocol; Clinical Protocol: DB2114635

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-Sep-2011	IND 104479	Ser#: 0076	umeclidinium (GSK573719) Ser #: 0076 Protocol Amendment: New Investigator Other 1572 Change	818ba24f

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113359 Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Sep-2011	IND 104479	Ser#: 0077	umeclidinium (GSK573719) Ser #: 0077 General Correspondence Nonclinical	818c0409

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Nonclinical SUBTYPES: Nonclinical Protocol: R28862

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Sep-2011	IND 104479; IND 104479	Ser#: 0078	umeclidinium (GSK573719) Ser #: 0078 Protocol Amendment: New Investigator Investigator Add Other 1572 Change	818c178a

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: DB2114417 PROTOCOL AMENDMENT: NEW INVESTIGATOR

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
16-Sep-2011	IND 104479	Ser#: 0079	umeclidinium (GSK573719) Ser #: 0079 Protocol Amendment: Change in Protocol	818c2de2

Clinical

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: CHANGE IN PROTOCOL SUBTYPES: Clinical SUBTYPES: Clinical SUBINDEXING: Protocol: DB2113359 Amendments:01

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Sep-2011	**IND 104479**	**Ser#: 0080**	umeclidinium (GSK573719) Ser #: 0080 Protocol Amendment: New Investigator Other 1572 Change	818c4443

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4115321

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
21-Sep-2011	**IND 104479;**		umeclidinium (GSK573719)	818cab08

General Memorandum
Status Update
Comment/Information Request
Nonclinical

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration Ms. Angela Ramsey, R.N.	GlaxoSmithKline Ms. Mary V. Sides	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Status Update SUBTYPES: Status Update SUBTYPES: Nonclinical SUBTYPES: Nonclinical

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
21-Sep-2011	IND 104479; IND 104479; IND 104479; IND 104479	Ser#: 0081	umeclidinium (GSK573719) Ser #: 0081 Annual Report Adverse Event Summary Clinical Study Information CMC Investigational Plan	818c2828

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	ANNUAL REPORT SUBTYPES: Adverse Event Summary; CMC; Clinical Study Information; Investigational Plan SUBTYPES: Adverse Event Summary; CMC; Clinical Study Information; Investigational Plan Protocol: AC4112008 Protocol: AC4112014 Protocol: AC4113073 Protocol: AC4113589 Protocol: AC4115321 Protocol: AC4115408 Protocol: AC4115487 Protocol: DB2113359

Protocol: DB2113360
Protocol: DB2113361
Protocol: DB2113373
Protocol: DB2113374
Protocol: DB2113950
Protocol: DB2114417
Protocol: DB2114418
Protocol: DB2114635
Protocol: DB2114636
Protocol: DB2114637
Protocol: DB2114930
Protocol: DB2114951
Protocol: DB2115362
Protocol: DB2116132
Protocol: DB2116133
Protocol: DB2116134
Protocol: DB2116135
Protocol: DB2116136
Protocol: DB2116137
Protocol: G11095
Protocol: HZA113989
Protocol: HZC102871
Protocol: HZC102970
Protocol: HZC112206
Protocol: HZC112207
Protocol: HZC114156
Protocol: M28976
Protocol: R28862
Protocol: 7DMW131
Report:WD2009/00039/00
Protocol: 9DMW069
Report:2010N105743_00
Protocol: AMES 946
Report:2011N112354_00
Protocol: D10279
Report:2011N111874_00
Protocol: D28759
Report:FD2009/00466/00
Protocol: D28843
Report:WD2010/00677/00
Protocol: G09239
Report:CD2010/00253/00
Protocol: R28859
Report:FD2009/00467/00
Reports: 2010N110596_00
Reports: 2011N111625_00
Reports: WD2010/00669/00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
05-Oct-2011	IND 104479; IND 104479	Ser#: 0082	umeclidinium (GSK573719) Ser #: 0082 General Correspondence Nonclinical Response to FDA Request/Comment Nonclinical	818d77fa

FROM:
GlaxoSmithKline
Ms. Mary V. Sides

TO:
Food and Drug Administration
Dr. Badrul A. Chowdhury, M.D.

COMMUNICATION:
Correspondence

DOCTYPE & SUBTYPE:
GENERAL CORRESPONDENCE
SUBTYPES: Nonclinical
SUBTYPES: Nonclinical
Protocol: R28862
SUBTYPES: Nonclinical
SUBTYPES: Nonclinical
Protocol: R28862

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
06-Oct-2011	IND 104479	Ser#: 0083	umeclidinium (GSK573719) Ser #: 0083 Protocol Amendment: New Investigator Other 1572 Change	818d8815

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113359

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-Oct-2011	IND 104479; IND 104479	Ser#: 0084	umeclidinium (GSK573719) Ser #: 0084 Information Amendment: Nonclinical Nonclinical Study Reports	818dc526

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Nonclinical; Study Reports SUBTYPES: Nonclinical; Study Reports SUBINDEXING: Protocol: 7DMW131 Report:WD2009/00039/00 Protocol: 9DMW069 Report:2010N105743_00 Protocol: D10279 Report:2011N111874_00 Protocol: GSK/009/01 Report:WD2010/00669/00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:

CARDS CHRONOLOGY REPORT
Yes

REPORT DATE RANGE All
Yes

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Oct-2011	IND 104479	Ser#: 0085	umeclidinium (GSK573719) Ser #: 0085 Protocol Amendment: New Investigator Investigator Add	818e1d64

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: DB2114417 Protocol: DB2114418

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Oct-2011	IND 104479	Ser#: 0086	umeclidinium (GSK573719) Ser #: 0086 Protocol Amendment: New Investigator Other 1572 Change	818e5936

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4115321 Protocol: AC4115408

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
04-Nov-2011	IND 104479; IND 104479	Ser#: 0088	umeclidinium (GSK573719) General Correspondence Clinical Statistical	Ser #: 0088	818f75ec

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Clinical; Statistical SUBTYPES: Clinical; Statistical Protocol: DB2113359

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
04-Nov-2011	IND 104479; IND 104479	Ser#: 0087	umeclidinium (GSK573719) General Correspondence Clinical Statistical	Ser #: 0087	818f757d

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Clinical; Statistical SUBTYPES: Clinical; Statistical Protocol: DB2113360 Protocol: DB2113361 Protocol: DB2113373 Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-Nov-2011	IND 104479	Ser#: 0089	umeclidinium (GSK573719) Ser #: 0089 Protocol Amendment: New Investigator Other 1572 Change	818fafeb

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113359

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
09-Nov-2011	IND 104479	Ser#: 0090	umeclidinium (GSK573719) Ser #: 0090 Protocol Amendment: Change in Protocol Clinical	818e8285

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: CHANGE IN PROTOCOL SUBTYPES: Clinical SUBTYPES: Clinical SUBINDEXING: Protocol: DB2113361 Amendments:02 Protocol: DB2113373 Amendments:02

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
16-Nov-2011	IND 104479; IND 104479	Ser#: 0091	umeclidinium (GSK573719) Ser #: 0091 Protocol Amendment: New Investigator Other 1572 Change Investigator Add	819043e2

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: DB2113361 Protocol: DB2113373 PROTOCOL AMENDMENT: NEW INVESTIGATOR

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
17-Nov-2011	IND 104479; IND 104479; IND 104479	Ser#: 0092	umeclidinium (GSK573719) Ser #: 0092 General Correspondence Clinical Protocol Statistical	81904809

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:

GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	GENERAL CORRESPONDENCE SUBTYPES: Protocol; Clinical; Statistical SUBTYPES: Protocol; Clinical; Statistical Protocol: AC4113073 Protocol: AC4115321 Protocol: B2C109575 Protocol: DB2113120 Protocol: HZA113310 Protocol: AC4113589 Report:2011N127531_00 Protocol: AC4115408 Report:2011N127531_00 Protocol: B2C111045 Report:2011N127531_00 Protocol: DB2113359 Report:2011N127531_00 Protocol: DB2113360 Report:2011N127530_00 Report: 2011N127531_00 Protocol: DB2113361 Report:2011N127530_00 Report: 2011N127531_00 Protocol: DB2113373 Report:2011N127530_00 Report: 2011N127531_00 Protocol: DB2113374 Report:2011N127530_00 Report: 2011N127531_00 Protocol: DB2114417 Report:2011N127531_00 Protocol: HZC102871 Report:2011N127531_00 Protocol: HZC102970 Report:2011N127531_00 Protocol: HZC112206 Report:2011N127531_00 Protocol: HZC112207 Report:2011N127531_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: **MEDIA INFORMATION:** **QC COMPLETED:** **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
18-Nov-2011	IND 104479	Ser#: 0093	umeclidinium (GSK573719) Ser #: 0093 Protocol Amendment: New Investigator Other 1572 Change	819079f6

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4115321

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-Dec-2011	IND 104479	Ser#: 0094	umeclidinium (GSK573719) Ser #: 0094 Protocol Amendment: New Investigator Other 1572 Change	81919431

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Dec-2011	IND 104479; IND 104479	Ser#: 0095	umeclidinium (GSK573719) Ser #: 0095 Information Amendment: Nonclinical Nonclinical Study Reports	8191f390

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Nonclinical; Study Reports SUBTYPES: Nonclinical; Study Reports SUBINDEXING: Protocol: AMES/945 Report:2011N111625_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
04-Jan-2012	IND 104479	Ser#: 0096	umeclidinium (GSK573719) Ser #: 0096 General Correspondence Clinical	8192945f

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Clinical SUBTYPES: Clinical Protocol: DB2113360 Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
09-Jan-2012	IND 104479; IND 104479; IND 104479	Ser#: 0097	umeclidinium (GSK573719) Ser #: 0097 Protocol Amendment: New Protocol Clinical Protocol Amendment: Other Transfer of Obligations to Contract Research Organization	81929579

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW PROTOCOL SUBTYPES: Protocol; Clinical SUBTYPES: Protocol; Clinical Protocol: DB2114636 Protocol: DB2114637 AMENDMENT: OTHER SUBTYPES: Transfer of Obligations to Contract Research Organization SUBTYPES: Transfer of Obligations to Contract Research Organization Protocol: DB2114636 Protocol: DB2114637

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
11-Jan-2012	IND 104479	Ser#: 0098	umeclidinium (GSK573719) Ser #: 0098 Protocol Amendment: New Investigator Investigator Add	8192f9c9

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add

SUBTYPES: Investigator Add
Protocol: DB2113373
Protocol: DB2114418

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-Jan-2012	IND 104479	Ser#: 0099	umeclidinium (GSK573719) Ser #: 0099 Protocol Amendment: New Investigator Other 1572 Change	81930c9a

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4115321

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
24-Jan-2012	IND 104479; IND 104479; IND 104479	Ser#: 0100	umeclidinium (GSK573719) Ser #: 0100 Protocol Amendment: New Protocol Clinical Protocol Protocol Amendment: New Investigator Investigator Add	8192f53d

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Vicki Gunto, Ph.D.	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW PROTOCOL SUBTYPES: Protocol; Clinical SUBTYPES: Protocol; Clinical Protocol: ALA116402 SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: ALA116402

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
07-Feb-2012	IND 104479	Ser#: 0101	umeclidinium (GSK573719) Ser #: 0101 Protocol Amendment: New Investigator Other 1572 Change	81949677

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113359

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
07-Feb-2012	IND 104479	Ser#: 0102	umeclidinium (GSK573719) Ser #: 0102 Protocol Amendment: New Investigator	8194969b

Other 1572 Change

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4113589 Protocol: AC4115321

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
10-Feb-2012	**IND 104479**	**Ser#: 0103**	umeclidinium (GSK573719) Ser #: 0103 Protocol Amendment: Change in Protocol Clinical	8194b050

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: CHANGE IN PROTOCOL SUBTYPES: Clinical SUBTYPES: Clinical SUBINDEXING: Protocol: DB2114636 Amendments:01

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:

15-Feb-2012 **IND 104479** **Ser#: 0104** umeclidinium (GSK573719) Ser #: 0104 8194f262
Information Amendment: Clinical Study Reports

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	INFORMATION AMENDMENT: CLINICAL
Ms. Vicki Gunto, Ph.D.	**Dr. Badrul A. Chowdhury, M.D.**		SUBTYPES: Study Reports
			SUBTYPES: Study Reports
			SUBINDEXING:
			Protocol: AC4112014
			Report:2011N115659_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
24-Feb-2012	**IND 104479**	**Ser#: 0105**	umeclidinium (GSK573719) Ser #: 0105 Information Amendment: Clinical Investigator's Brochure	8195c592

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	INFORMATION AMENDMENT: CLINICAL
Ms. Vicki Gunto, Ph.D.	**Dr. Badrul A. Chowdhury, M.D.**		SUBTYPES: Investigator's Brochure
			SUBTYPES: Investigator's Brochure
			Protocol: AC4105209
			Protocol: AC4105211
			Protocol: AC4106889
			Protocol: AC4108123
			Protocol: AC4110106
			Protocol: AC4112008
			Protocol: AC4112014
			Protocol: AC4113073
			Protocol: AC4113377
			Protocol: AC4113589
			Protocol: AC4115321
			Protocol: AC4115487
			Protocol: DB2113120

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
02-Mar-2012	IND 104479	Ser#: 0106	umeclidinium (GSK573719) Ser #: 0106 Information Amendment: Chemistry Manufacturing and Controls CMC	8195fe29

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Sue M. Holmes, M.S.	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: CHEMISTRY MANUFACTURING AND CONTROLS SUBTYPES: CMC SUBTYPES: CMC

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
07-Mar-2012	IND 104479	Ser#: 0107	umeclidinium (GSK573719) Ser #: 0107 Protocol Amendment: New Investigator Other 1572 Change	819677c9

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR

Administration

SUBTYPES: Other 1572 Change
SUBTYPES: Other 1572 Change
Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Mar-2012	IND 104479	Ser#: 0108	umeclidinium (GSK573719) Ser #: 0108 Protocol Amendment: New Investigator Other 1572 Change	8196f64d

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113361 Protocol: DB2114417

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
04-Apr-2012	IND 104479	Ser#: 0110	umeclidinium (GSK573719) Ser #: 0110 Information Amendment: Chemistry Manufacturing and Controls CMC	819802b7

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug	Correspondence	INFORMATION AMENDMENT: CHEMISTRY MANUFACTURING AND CONTROLS

Ms. Sue M. Holmes, M.S. **Administration**
Dr. Badrul A. Chowdhury, M.D.

SUBTYPES: CMC
SUBTYPES: CMC
Protocol: ALA116402
Keyword: CMC - Components/Composition

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-Apr-2012	**IND 104479**	**Ser#: 0111**	umeclidinium (GSK573719) Ser #: 0111 Protocol Amendment: New Investigator Other 1572 Change	81989dbc

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2114417

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
17-Apr-2012	**IND 104479;** **IND 104479;** **IND 104479**	**Ser#: 0112**	umeclidinium (GSK573719) Ser #: 0112 General Correspondence Briefing Document Clinical Draft Protocol	8198a0f6

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Clinical; Draft Protocol; Briefing Document SUBTYPES: Clinical; Draft Protocol; Briefing Document Protocol: AC4116135 Protocol: AC4116136 Protocol: DB2113360 Protocol: DB2113361 Protocol: DB2113373 Protocol: DB2113374 Protocol: DB2114930 Protocol: DB2114951

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-May-2012	IND 104479	Ser#: 0113	umeclidinium (GSK573719) Ser #: 0113 Protocol Amendment: New Investigator Other 1572 Change	819a62aa

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-May-2012	IND 104479		umeclidinium (GSK573719) General Teleconference CMC	819b4b48

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Telephone Conversation	GENERAL TELECONFERENCE SUBTYPES: CMC SUBTYPES: CMC

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
16-May-2012	IND 104479		umeclidinium (GSK573719) General Memorandum CMC	819bd412

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: CMC SUBTYPES: CMC

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
16-May-2012	IND 104479	Ser#: 0114	umeclidinium (GSK573719)	Ser #: 0114	819adb30

Protocol Amendment: New Investigator
Other 1572 Change

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113373 Protocol: DB2114418

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
17-May-2012	**IND 104479**	**Ser#: 0115**	umeclidinium (GSK573719) Ser #: 0115 Protocol Amendment: New Investigator Investigator Add	819b0f54

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: ALA116402

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
25-May-2012	**IND 104479**		umeclidinium (GSK573719)	819d68ba

Comment/Information Request
CMC

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration	**GlaxoSmithKline**	**FAX/E-mail**	COMMENT/INFORMATION REQUEST SUBTYPES: CMC SUBTYPES: CMC

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
01-Jun-2012	**IND 104479; IND 104479**	**Ser#: 0116**	umeclidinium (GSK573719) Ser #: 0116 Information Amendment: Clinical Efficacy Study Reports	819baa17

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports; Efficacy SUBTYPES: Study Reports; Efficacy SUBINDEXING: Protocol: AC4115487 Report:2011N120469_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:

01-Jun-2012 **IND 104479** umeclidinium (GSK573719) 819befbb
General Memorandum
CMC

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**FAX/E-mail**	GENERAL MEMORANDUM SUBTYPES: CMC SUBTYPES: CMC

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
07-Jun-2012	**IND 104479**	**Ser#: 0117**	umeclidinium (GSK573719) Ser #: 0117 Protocol Amendment: New Investigator Other 1572 Change	819c314a

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Jun-2012	**IND 104479**		umeclidinium (GSK573719) Response to FDA Request/Comment	81a72c29

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**FAX/E-mail**	RESPONSE TO FDA REQUEST/COMMENT SUBTYPES: CMC SUBTYPES: CMC

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
18-Jun-2012	**IND 104479**	**Ser#: 0118**	umeclidinium (GSK573719) Ser #: 0118 Protocol Amendment: New Investigator Other 1572 Change	819caa0b

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113373 Protocol: DB2114417

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Jun-2012	**IND 104479; IND 104479**	**Ser#: 0119**	umeclidinium (GSK573719) Ser #: 0119 Protocol Amendment: New Investigator Other 1572 Change	819ccae1

Investigator Add

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: ALA116402 PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: AC4115321

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
05-Jul-2012	**IND 104479**	**Ser#: 0120**	umeclidinium (GSK573719) Ser #: 0120 Protocol Amendment: New Investigator Other 1572 Change	819dbb2e

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113374

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
25-Jul-2012	IND 104479	Ser#: 0121	umeclidinium (GSK573719) Ser #: 0121 Protocol Amendment: New Investigator Other 1572 Change	819efcb6

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: ALA116402

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
26-Jul-2012	IND 104479; IND 104479; IND 104479	Ser#: 0122	umeclidinium (GSK573719) Ser #: 0122 Protocol Amendment: New Protocol Clinical Protocol Protocol Amendment: New Investigator Investigator Add	819e05c5

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Mr. Kevin C. Fitzgerald, R.Ph.	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW PROTOCOL SUBTYPES: Protocol; Clinical SUBTYPES: Protocol; Clinical Protocol: ILA116213 SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: ILA116213

DESCRIPTION:

DESCRIPTORS:

ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
02-Aug-2012	IND 104479	Ser#: 0123	umeclidinium (GSK573719) Ser #: 0123 General Correspondence Clinical	819f85a9

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Clinical SUBTYPES: Clinical Protocol: DB2114635 Protocol: DB2114636 Protocol: DB2114637

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
06-Aug-2012	IND 104479; IND 104479; IND 104479		umeclidinium (GSK573719) General Memorandum Status Update Comment/Information Request Clinical Statistical	819fc62c

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration	GlaxoSmithKline	FAX/E-mail	GENERAL MEMORANDUM SUBTYPES: Status Update SUBTYPES: Status Update Protocol: AC4116135 Protocol: AC4116136 Protocol: DB2114930

Protocol: DB2114951

COMMENT/INFORMATION REQUEST
SUBTYPES: Clinical; Statistical
SUBTYPES: Clinical; Statistical
Protocol: AC4116135
Protocol: AC4116136
Protocol: DB2114930
Protocol: DB2114951

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Aug-2012	IND 104479	Ser#: 0124	umeclidinium (GSK573719) Ser #: 0124 Protocol Amendment: New Investigator Other 1572 Change	81a060d7

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2114417

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
17-Aug-2012	IND 104479;	Ser#: 0125	umeclidinium (GSK573719) Ser #: 0125	81a08cdf

IND 104479

Protocol Amendment: New Investigator
Investigator Add
Other 1572 Change

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: ILA116213 PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change Protocol: ILA116213

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
23-Aug-2012	**IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479**	**Ser#: 0126**	umeclidinium (GSK573719) Ser #: 0126 Annual Report Changes to Investigator's Brochure Clinical Study Information CMC Development Safety Update Report: DSUR Foreign Marketing Developments Investigational Plan Nonclinical Outstanding Regulatory Business	819ea47f

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	ANNUAL REPORT SUBTYPES: Nonclinical; CMC; Clinical Study Information; Investigational Plan; Foreign Marketing Developments; Outstanding Regulatory Business; Changes to Investigator's Brochure; Development Safety Update Report: DSUR SUBTYPES: Nonclinical; CMC; Clinical Study Information; Investigational Plan; Foreign Marketing Developments; Outstanding Regulatory Business; Changes to Investigator's Brochure;

Development Safety Update Report: DSUR
Protocol: 111391
Protocol: 112185
Protocol: AC4105209
Protocol: AC4105211
Protocol: AC4106889
Protocol: AC4108123
Protocol: AC4110106
Protocol: AC4112008
Protocol: AC4112014
Protocol: AC4113073
Protocol: AC4113377
Protocol: AC4113589
Protocol: AC4115321
Protocol: AC4115408
Protocol: AC4115487
Protocol: AC4116689
Protocol: ALA116402
Protocol: B2C10001
Protocol: B2C101762
Protocol: B2C104604
Protocol: B2C106093
Protocol: B2C106180
Protocol: B2C106181
Protocol: B2C106996
Protocol: B2C108562
Protocol: B2C108784
Protocol: B2C109575
Protocol: B2C110165
Protocol: B2C111045
Protocol: B2C111401
Protocol: B2C112060
Protocol: B2C112205
Protocol: CRT114100
Protocol: CRT116277
Protocol: CRT116436
Protocol: DB1111509
Protocol: DB1111581
Protocol: DB1112017
Protocol: DB1112146
Protocol: DB2113120
Protocol: DB2113208
Protocol: DB2113359
Protocol: DB2113360
Protocol: DB2113361
Protocol: DB2113373
Protocol: DB2113374

Protocol: DB2113950
Protocol: DB2114417
Protocol: DB2114418
Protocol: DB2114634
Protocol: DB2114635
Protocol: DB2114636
Protocol: DB2114637
Protocol: DB2114930
Protocol: DB2114951
Protocol: DB2115362
Protocol: DB2115380
Protocol: DB2116132
Protocol: DB2116133
Protocol: DB2116134
Protocol: DB2116844
Protocol: DB2116975
Protocol: FFA10001
Protocol: FFA10002
Protocol: FFA10003
Protocol: FFA10004
Protocol: FFA10007
Protocol: FFA10008
Protocol: FFA10009
Protocol: FFA10013
Protocol: FFA10022
Protocol: FFA10026
Protocol: FFA10027
Protocol: FFA10028
Protocol: FFA103096
Protocol: FFA106783
Protocol: FFA109684
Protocol: FFA109685
Protocol: FFA109687
Protocol: FFA112059
Protocol: FFA112202
Protocol: FFA114496
Protocol: FFA115283
Protocol: FFA115285
Protocol: FFA115354
Protocol: FFA115440
Protocol: FFA115441
Protocol: FFA20001
Protocol: FFR10001
Protocol: FFR100010
Protocol: FFR100012
Protocol: FFR10002
Protocol: FFR10003

Protocol: FFR10005
Protocol: FFR10006
Protocol: FFR10007
Protocol: FFR10008
Protocol: FFR10010
Protocol: FFR10013
Protocol: FFR100650
Protocol: FFR100652
Protocol: FFR100688
Protocol: FFR101747
Protocol: FFR101782
Protocol: FFR101816
Protocol: FFR101888
Protocol: FFR102123
Protocol: FFR103184
Protocol: FFR104503
Protocol: FFR104861
Protocol: FFR105693
Protocol: FFR106080
Protocol: FFR110537
Protocol: FFR111158
Protocol: FFR113342
Protocol: FFR113406
Protocol: FFR113407
Protocol: FFR114613
Protocol: FFR114614
Protocol: FFR115177
Protocol: FFR115312
Protocol: FFR116179
Protocol: FFR116364
Protocol: FFR116365
Protocol: FFR20001
Protocol: FFR20002
Protocol: FFR30002
Protocol: FFR30003
Protocol: FFR30006
Protocol: FFR30007
Protocol: FFR30008
Protocol: FFS113203
Protocol: FFU105924
Protocol: FFU105927
Protocol: FFU108556
Protocol: FFU109045
Protocol: FFU109047
Protocol: FFU111439
Protocol: FFU112602
Protocol: HZA102928

Protocol: HZA102942
Protocol: HZA106853
Protocol: HZA106855
Protocol: HZA107112
Protocol: HZA108799
Protocol: HZA112018
Protocol: HZA112776
Protocol: HZA112777
Protocol: HZA113310
Protocol: HZA113477
Protocol: HZA113714
Protocol: HZA113719
Protocol: HZA113989
Protocol: HZA114971
Protocol: HZA115150
Protocol: HZA116025
Protocol: HZA116525
Protocol: HZA116863
Protocol: HZA116935
Protocol: HZA116963
Protocol: HZC102972
Protocol: HZC112352
Protocol: HZC113108
Protocol: HZC113684
Protocol: HZC113782
Protocol: HZC114156
Protocol: HZC115057
Protocol: HZC115058
Protocol: HZC115151
Protocol: HZC115247
Protocol: HZC115398
Protocol: HZC115805
Protocol: HZC116338
Protocol: HZC116601
Protocol: ILA115938
Protocol: ILA116213
Protocol: ILA116524
Protocol: LOC113596
Protocol: RLV116974
Protocol: SCO30003
Protocol: TORCH STUDY
Protocol: VER112995
Protocol: 10DMW020
Report:2011N115614_00
Protocol: 11DMW026
Report:2011N121880_00
Protocol: 5DMW138

Report:WD2006/02044/01
Protocol: 9DMW069
Report:2010N105743_00
Protocol: D10279
Report:2011N111874_00
Protocol: D11299
Report:WPT/87/213
Protocol: D27951
Report:WD2008/01441/00
Protocol: D29424
Report:2011N126501_00
Protocol: G07046
Report:CD2007/00973/00
Protocol: G07259
Report:2011N119325_00
Protocol: G07260
Report:2010N109253_00
Protocol: G11095
Report:2011N118595_00
Protocol: HZA102932
Report:2010N110697_01
Protocol: HZA102934
Report:YM2010/00090/01
Protocol: HZA102936
Report:YM2009/00240/01
Protocol: HZA102940
Report:GH2008/00013/01
Protocol: HZA105548
Report:YM2010/00096/00
Protocol: HZA105871
Report:GH2008/00003/01
Protocol: HZA106827
Report:2011N124014_00
Protocol: HZA106829
Report:2011N128470_01
Protocol: HZA106837
Report:2011N116051_00
Protocol: HZA106839
Report:2011N112186_01
Protocol: HZA106851
Report:2010N104747_02
Protocol: HZA111789
Report:2011N112461_01
Protocol: HZA113090
Report:YM2010/00102/00
Protocol: HZA113091
Report:2011N120957_01

Protocol: HZA113126
Report:2011N112458_01
Protocol: HZA113970
Report:2011N112054_00
Protocol: HZA114624
Report:2011N113105_01
Protocol: HZC102871
Report:2011N127966_00
Protocol: HZC102970
Report:2011N121187_00
Protocol: HZC110946
Report:YM2010/00164/01
Protocol: HZC111348
Report:YM2008/00192/01
Protocol: HZC112206
Report:2011N112338_01
Protocol: HZC112207
Report:2011N115017_00
Protocol: HZC113107
Report:2011N126070_01
Protocol: HZC113109
Report:2011N129606_01
Protocol: I11061
Report:2011N114722_00
Protocol: QBR1062268
Report:2011N118910_00
Protocol: R27071
Report:WD2007/00766/00
Protocol: R27955
Report:FD2008/00342/00
Reports: 2011N119347_00
Reports: 2012N135141_00
Reports: 2012N138876_01

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
28-Aug-2012	IND 104479		umeclidinium (GSK573719)	81a14150

Comment/Information Request
Clinical

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
Food and Drug Administration	**GlaxoSmithKline**	**FAX/E-mail**	COMMENT/INFORMATION REQUEST SUBTYPES: Clinical SUBTYPES: Clinical

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
31-Aug-2012	**IND 104479; IND 104479**	**Ser#: 0127**	umeclidinium (GSK573719) Ser #: 0127 General Correspondence Clinical Response to FDA Request/Comment Clinical	81a151f9

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Mr. Kevin C. Fitzgerald, R.Ph.	**Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	GENERAL CORRESPONDENCE SUBTYPES: Clinical SUBTYPES: Clinical Protocol: ILA116213 SUBTYPES: Clinical SUBTYPES: Clinical Protocol: ILA116213

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Sep-2012	IND 104479	Ser#: 0128	umeclidinium (GSK573719) Ser #: 0128 Protocol Amendment: New Investigator Other 1572 Change	81a237b8

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2114418

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Sep-2012	IND 104479	Ser#: 0129	umeclidinium (GSK573719) Ser #: 0129 Protocol Amendment: New Investigator Investigator Add	81a28b69

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: ALA116402

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
03-Oct-2012	IND 104479	Ser#: 0130	umeclidinium (GSK573719) Ser #: 0130 Information Amendment: Chemistry Manufacturing and Controls CMC	81a36ede

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Sue M. Holmes, M.S.	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: CHEMISTRY MANUFACTURING AND CONTROLS SUBTYPES: CMC SUBTYPES: CMC

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
18-Oct-2012	IND 104479	Ser#: 0131	umeclidinium (GSK573719) Ser #: 0131 Protocol Amendment: New Investigator Investigator Add	81a490c7

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: ALA116402

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
24-Oct-2012	IND 104479; IND 104479; IND 104479	Ser#: 0132	umeclidinium (GSK573719) Ser #: 0132 Protocol Amendment: New Protocol Clinical Protocol Protocol Amendment: New Investigator Investigator Add	81a4e67d

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW PROTOCOL SUBTYPES: Protocol; Clinical SUBTYPES: Protocol; Clinical Protocol: ILA116524 PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: ILA116524

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
05-Nov-2012	IND 104479; IND 104479	Ser#: 0133	umeclidinium (GSK573719) Ser #: 0133 Information Amendment: Clinical Efficacy Study Reports	819ee272

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports; Efficacy SUBTYPES: Study Reports; Efficacy SUBINDEXING: Protocol: AC4115408 Report:2011N130819_00 Protocol: DB2113360 Report:2011N128803_00 Protocol: DB2113361

Report:2011N130134_00
Protocol: DB2113373
Report:2011N130136_00
Protocol: DB2113374
Report:2011N128792_00
Protocol: DB2114417
Report:2011N130906_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
08-Nov-2012	IND 104479	Ser#: 0134	umeclidinium (GSK573719) Ser #: 0134 Protocol Amendment: New Investigator Other 1572 Change	81a5f4a8

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113359

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Nov-2012	IND 104479; IND 104479; IND 104479	Ser#: 0135	umeclidinium (GSK573719) Ser #: 0135 Protocol Amendment: New Protocol Clinical	81a32d52

Protocol
Protocol Amendment: New Investigator
Investigator Add

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW PROTOCOL SUBTYPES: Protocol; Clinical SUBTYPES: Protocol; Clinical Protocol: AC4116135 Protocol: AC4116136 SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: AC4116135 Protocol: AC4116136 PROTOCOL AMENDMENT: NEW PROTOCOL

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
15-Nov-2012	**IND 104479**	**Ser#: 0136**	umeclidinium (GSK573719) Ser #: 0136 Protocol Amendment: New Investigator Other 1572 Change	81a66a5e

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113361 Protocol: DB2113373

DESCRIPTION:

DESCRIPTORS:

ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
16-Nov-2012	IND 104479	Ser#: 0137	umeclidinium (GSK573719) General Correspondence Statistical	Ser #: 0137	81a4ee12

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Statistical SUBTYPES: Statistical

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:** **QC COMPLETED:** Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:		DOC ID:
13-Dec-2012	IND 104479	Ser#: 0138	umeclidinium (GSK573719) Protocol Amendment: New Investigator Investigator Add	Ser #: 0138	81a82fac

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: AC4116135

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Dec-2012	IND 104479	Ser#: 0139	umeclidinium (GSK573719) Ser #: 0139 Protocol Amendment: New Investigator Other 1572 Change	81a8b284

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: ALA116402

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
10-Jan-2013	IND 104479	Ser#: 0140	umeclidinium (GSK573719) Ser #: 0140 Protocol Amendment: New Investigator Investigator Add	81a98310

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: AC4116135 Protocol: AC4116136

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Jan-2013	IND 104479	Ser#: 0141	umeclidinium (GSK573719) Ser #: 0141 Protocol Amendment: New Investigator Other 1572 Change	81a9c950

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: DB2113361

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
17-Jan-2013	IND 104479	Ser#: 0142	umeclidinium (GSK573719) Ser #: 0142 Protocol Amendment: New Investigator Other 1572 Change	81aa2ab4

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: ALA116402

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:

MEDIA INFORMATION:

QC COMPLETED:

DATE REFERENCED:

Yes Yes

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
07-Feb-2013	IND 104479	Ser#: 0143	umeclidinium (GSK573719) Ser #: 0143 Protocol Amendment: New Investigator Investigator Add	81abb5ad

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: AC4116135 Protocol: AC4116136

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
07-Mar-2013	IND 104479	Ser#: 0144	umeclidinium (GSK573719) Ser #: 0144 Protocol Amendment: Change in Protocol Clinical	81adffb5

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: CHANGE IN PROTOCOL SUBTYPES: Clinical SUBTYPES: Clinical SUBINDEXING: Protocol: AC4116135 Amendments:01 Protocol: AC4116136 Amendments:01

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-Mar-2013	IND 104479	Ser#: 0145	umeclidinium (GSK573719) Ser #: 0145 Protocol Amendment: New Investigator Investigator Add	81ae95b0

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: AC4116135 Protocol: AC4116136

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-Apr-2013	IND 104479	Ser#: 0146	umeclidinium (GSK573719) Ser #: 0146 Protocol Amendment: New Investigator Other 1572 Change	81b12307

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4116136

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Apr-2013	IND 104479	Ser#: 0147	umeclidinium (GSK573719) Ser #: 0147 Protocol Amendment: New Investigator Other 1572 Change	81b1a49b

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: ALA116402

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
02-May-2013	IND 104479; IND 104479	Ser#: 0148	umeclidinium (GSK573719) Ser #: 0148 Information Amendment: Clinical Investigator's Brochure General Correspondence Other	81b2742d

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Vicki Gunto, Ph.D.	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Investigator's Brochure SUBTYPES: Investigator's Brochure Protocol: AC4115361 Protocol: ALA116402 Protocol: CRT116277 Protocol: DB2116133 Protocol: ILA115938

Protocol: ILA116524
Protocol: AC4105209
Report:GM2007/00230/00
Protocol: AC4105211
Report:GM2009/00207/00
Protocol: AC4106889
Report:2012N140346_00
Report: GM2008/00043/00
Protocol: AC4108123
Report:GM2008/00079/00
Protocol: AC4110106
Report:GM2008/00374/00
Protocol: AC4112008
Report:2010N105452_00
Protocol: AC4112014
Report:2011N115659_00
Protocol: AC4113073
Report:RM2009/00680/00
Protocol: AC4113377
Report:JM2010/00003/00
Protocol: AC4113589
Report:RM2010/00314/00
Protocol: AC4115321
Report:2011N124430_00
Protocol: AC4115408
Report:2011N130819_00
Protocol: AC4115487
Report:2011N120469_00
Protocol: ASQ112989
Report:2010N103856_00
Protocol: D26275
Report:WD2005/01423/00
Protocol: D26864
Report:WD2006/03294/00
Protocol: D27185
Report:WD2006/03669/00
Protocol: D27338
Report:WD2007/01512/00
Protocol: D28759
Report:FD2009/00466/00
Protocol: DB2113120
Report:YM2010/00171/00
Protocol: DB2113208
Report:GM2009/00212/00
Protocol: DB2113359
Report:2011N130683_00
Protocol: DB2113361

Report:2011N130134_00
Protocol: DB2113373
Report:2011N130136_00
Protocol: DB2113374
Report:2011N128792_00
Protocol: DB2113950
Report:YM2010/00177/00
Protocol: DB2114417
Report:2011N130906_00
Protocol: DB2114418
Report:2011N130900_00
Protocol: DB2114635
Report:2011N128710_00
Protocol: DB2114636
Report:2012N140627_00
Protocol: DB2114637
Report:2012N140743_00
Protocol: DB2116975
Report:2012N137814_00
Protocol: M27293
Report:WD2007/01600/00
Protocol: M28976
Report:2012N131664_00
Protocol: R26826
Report:WD2006/03225/00
Protocol: R28859
Report:FD2009/00467/00
Protocol: R28862
Report:2012N131619_00
Protocol: RES113817
Report:2010N104592_00
Protocol: SOBDA EVIDENCE DOSSIER
Report:2012N133680_00
Reports: 2011N114061_00
SUBTYPES: Other
SUBTYPES: Other

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
14-May-2013	IND 104479	Ser#: 0149	umeclidinium (GSK573719) Ser #: 0149 Protocol Amendment: New Investigator Other 1572 Change	81b37eaf

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4116135

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
22-May-2013	IND 104479	Ser#: 0150	umeclidinium (GSK573719) Ser #: 0150 General Correspondence Clinical	81b3ebfb

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	GENERAL CORRESPONDENCE SUBTYPES: Clinical SUBTYPES: Clinical Protocol: AC4116135 Protocol: AC4116136 Protocol: AC4200109 Protocol: AC4200110 Protocol: DB2114930 Protocol: DB2114951 Protocol: DB2116132 Protocol: DB2116133 Protocol: DB2116134 Protocol: DB2116960 Protocol: DB2116961 Protocol: ZEP117115

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Jun-2013	IND 104479	Ser#: 0151	umeclidinium (GSK573719) Ser #: 0151 Protocol Amendment: New Investigator Other 1572 Change	81b5a901

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4116136

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-Jul-2013	IND 104479	Ser#: 0152	umeclidinium (GSK573719) Ser #: 0152 Protocol Amendment: New Investigator Investigator Add	81b77b97

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: AC4116136

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:**

QC COMPLETED: Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
25-Jul-2013	IND 104479; IND 104479; IND 104479; IND 104479; IND 104479	Ser#: 0153	umeclidinium (GSK573719) Ser #: 0153 Protocol Amendment: New Protocol Clinical Protocol Protocol Amendment: New Investigator Investigator Add Information Amendment: Nonclinical Nonclinical Study Reports	81b8208b

FROM:
GlaxoSmithKline
Ms. Vicki Gunto, Ph.D.

TO:
Food and Drug Administration
Dr. Badrul A. Chowdhury, M.D.

COMMUNICATION:
Correspondence

DOCTYPE & SUBTYPE:
PROTOCOL AMENDMENT: NEW PROTOCOL
SUBTYPES: Protocol; Clinical
SUBTYPES: Protocol; Clinical
Protocol: 200109
Protocol: 200110
SUBTYPES: Investigator Add
SUBTYPES: Investigator Add
Protocol: 200109
Protocol: 200110
SUBTYPES: Nonclinical; Study Reports
SUBTYPES: Nonclinical; Study Reports
SUBINDEXING:
Protocol: D30338G
Report:2013N169979_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes **MEDIA INFORMATION:**

QC COMPLETED: Yes **DATE REFERENCED:**

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
01-Aug-2013	IND 104479	Ser#: 0154	umeclidinium (GSK573719) Ser #: 0154 Information Amendment: Clinical Study Reports	81b8da29

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Mr. Kevin C. Fitzgerald, R.Ph.	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports SUBTYPES: Study Reports SUBINDEXING: Protocol: ALA116402 Report:2013N159568_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
07-Aug-2013	IND 104479; IND 104479	Ser#: 0155	umeclidinium (GSK573719) Ser #: 0155 Information Amendment: Clinical Efficacy Study Reports	81b9535b

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Vicki Gunto, Ph.D.	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports; Efficacy SUBTYPES: Study Reports; Efficacy SUBINDEXING: Protocol: DB2116133 Report:2013N165473_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
20-Aug-2013	IND 104479; IND 104479; IND 104479	Ser#: 0156	umeclidinium (GSK573719) Ser #: 0156 Information Amendment: Nonclinical Nonclinical Study Reports Information Amendment: Clinical Study Reports	81b8a518

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	INFORMATION AMENDMENT: NONCLINICAL SUBTYPES: Nonclinical; Study Reports SUBTYPES: Nonclinical; Study Reports SUBINDEXING: Protocol: D30338G Report:2013N169979_00 INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports SUBTYPES: Study Reports SUBINDEXING: Protocol: CTT116415 Report:2013N166039_00

DESCRIPTION:

DESCRIPTORS:
ESG;ECTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
27-Aug-2013	IND 104479	Ser#: 0158	umeclidinium (GSK573719) Ser #: 0158 Information Amendment: Chemistry Manufacturing and Controls CMC	81ba86f2

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:

GlaxoSmithKline **Ms. Sue M. Holmes, M.S.**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	INFORMATION AMENDMENT: CHEMISTRY MANUFACTURING AND CONTROLS SUBTYPES: CMC SUBTYPES: CMC

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
27-Aug-2013	**IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479;** **IND 104479**	**Ser#: 0157**	umeclidinium (GSK573719) Ser #: 0157 Annual Report Adverse Event Summary Changes to Investigator's Brochure Clinical Study Information CMC Development Safety Update Report: DSUR Foreign Marketing Developments Investigational Plan Nonclinical Outstanding Regulatory Business	81baad6e

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	ANNUAL REPORT SUBTYPES: Adverse Event Summary; Nonclinical; CMC; Clinical Study Information; Investigational Plan; Foreign Marketing Developments; Outstanding Regulatory Business; Changes to Investigator's Brochure; Development Safety Update Report: DSUR SUBTYPES: Adverse Event Summary; Nonclinical; CMC; Clinical Study Information; Investigational Plan; Foreign Marketing Developments; Outstanding Regulatory Business; Changes to Investigator's Brochure; Development Safety Update Report: DSUR Protocol: 200109 Protocol: 200110 Protocol: 200284 Protocol: 200286 Protocol: 200699 Protocol: AC4115361 Protocol: AC4116135 Protocol: AC4116136 Protocol: AC4117410

Protocol: ALA116402
Protocol: B2C10001
Protocol: B2C101762
Protocol: B2C104604
Protocol: B2C106093
Protocol: B2C106180
Protocol: B2C106181
Protocol: B2C106996
Protocol: B2C108562
Protocol: B2C108784
Protocol: B2C109575
Protocol: B2C110165
Protocol: B2C111045
Protocol: B2C111401
Protocol: B2C112060
Protocol: B2C112205
Protocol: CRT114100
Protocol: CRT116277
Protocol: CTT116415
Protocol: CTT116853
Protocol: CTT116854
Protocol: CTT116855
Protocol: CTT116856
Protocol: CTT117304
Protocol: CTT200587
Protocol: DB1111509
Protocol: DB1112017
Protocol: DB1112146
Protocol: DB2113360
Protocol: DB2114634
Protocol: DB2114930
Protocol: DB2114951
Protocol: DB2114956
Protocol: DB2115362
Protocol: DB2115380
Protocol: DB2116132
Protocol: DB2116133
Protocol: DB2116134
Protocol: DB2116844
Protocol: DB2116960
Protocol: DB2116961
Protocol: FFA10001
Protocol: FFA10002
Protocol: FFA10003
Protocol: FFA10007
Protocol: FFA10008
Protocol: FFA10009

Protocol: FFA10013
Protocol: FFA10022
Protocol: FFA10026
Protocol: FFA10027
Protocol: FFA10028
Protocol: FFA103096
Protocol: FFA106783
Protocol: FFA109684
Protocol: FFA109685
Protocol: FFA109687
Protocol: FFA112059
Protocol: FFA112202
Protocol: FFA114496
Protocol: FFA115283
Protocol: FFA115285
Protocol: FFA115440
Protocol: FFA115441
Protocol: FFA117156
Protocol: FFA20001
Protocol: FFR10001
Protocol: FFR100010
Protocol: FFR100012
Protocol: FFR10002
Protocol: FFR10003
Protocol: FFR10005
Protocol: FFR10006
Protocol: FFR10007
Protocol: FFR10008
Protocol: FFR10010
Protocol: FFR10013
Protocol: FFR101747
Protocol: FFR101782
Protocol: FFR101816
Protocol: FFR101888
Protocol: FFR102123
Protocol: FFR103184
Protocol: FFR104503
Protocol: FFR104861
Protocol: FFR106080
Protocol: FFR110537
Protocol: FFR110573
Protocol: FFR111158
Protocol: FFR113406
Protocol: FFR114614
Protocol: FFR115312
Protocol: FFR116179
Protocol: FFR116364

Protocol: FFR116365
Protocol: FFR20001
Protocol: FFR20002
Protocol: FFR30002
Protocol: FFR30003
Protocol: FFR30006
Protocol: FFR30007
Protocol: FFR30008
Protocol: FFS113203
Protocol: FFU105924
Protocol: FFU105927
Protocol: FFU108556
Protocol: FFU109045
Protocol: FFU109047
Protocol: FFU111439
Protocol: HZA102928
Protocol: HZA102932
Protocol: HZA102934
Protocol: HZA102936
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Protocol: HZA106829
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Protocol: HZA106855
Protocol: HZA107112
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Protocol: HZA112776
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Protocol: HZA113090
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Protocol: HZA113126
Protocol: HZA113310
Protocol: HZA113477
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Protocol: HZA113719
Protocol: HZA113970
Protocol: HZA113989
Protocol: HZA114624
Protocol: HZA114971

Protocol: HZA115150
Protocol: HZA115199
Protocol: HZA116525
Protocol: HZA116592
Protocol: HZA116863
Protocol: HZC102871
Protocol: HZC102970
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Protocol: HZC110946
Protocol: HZC111348
Protocol: HZC112206
Protocol: HZC112207
Protocol: HZC112352
Protocol: HZC113107
Protocol: HZC113108
Protocol: HZC113109
Protocol: HZC113684
Protocol: HZC113782
Protocol: HZC114156
Protocol: HZC115057
Protocol: HZC115058
Protocol: HZC115151
Protocol: HZC115247
Protocol: HZC115398
Protocol: HZC115805
Protocol: HZC116338
Protocol: HZC116601
Protocol: ILA115938
Protocol: ILA116524
Protocol: LOC113596
Protocol: RLV116533
Protocol: RLV116974
Protocol: VER112995
Protocol: ZEP117115

Protocol: 11DMW019
Report:2011N128400_00

Protocol: AC4105209
Report:GM2007/00230/01

Protocol: AC4105211
Report:GM2009/00207/00

Protocol: AC4106889
Report:GM2008/00043/00

Protocol: AC4108123
Report:GM2008/00079/01

Protocol: AC4110106
Report:GM2008/00374/00

Protocol: AC4112008

Report:2010N105452_00
Protocol: AC4112014
Report:2011N115659_01
Protocol: AC4113073
Report:RM2009/00680/03
Protocol: AC4113377
Report:JM2010/00003/01
Protocol: AC4113589
Report:RM2010/00314/00
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Protocol: AC4115408
Report:2011N130819_01
Protocol: AC4115487
Report:2011N120469_00
Protocol: AC4116689
Report:2012N140346_00
Protocol: ASQ112989
Report:2010N103856_01
Protocol: D11299
Report:WPT/87/213
Protocol: D23588
Report:WD2003/00645/00
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Report:WD2004/00523/00
Protocol: D26275
Report:WD2005/01423/00
Protocol: D26864
Report:WD2006/03294/00
Protocol: D27074
Report:WD2007/00219/00
Protocol: D27185
Report:WD2006/03669/00
Protocol: D27338
Report:WD2007/01512/00
Protocol: D27951
Report:WD2008/01441/00
Protocol: D28759
Report:FD2009/00466/00
Protocol: D29424
Report:2011N126501_00
Protocol: D30068
Report:2013N164836_00
Protocol: D30554
Report:2013N170062_00
Protocol: DB2113120
Report:YM2010/00171/00

Protocol: DB2113208
Report:GM2009/00212/00
Protocol: DB2113359
Report:2011N130683_00
Protocol: DB2113361
Report:2011N130134_00
Protocol: DB2113373
Report:2011N130136_01
Protocol: DB2113374
Report:2011N128792_01
Protocol: DB2113950
Report:YM2010/00177/00
Protocol: DB2114417
Report:2011N130906_00
Protocol: DB2114418
Report:2011N130900_00
Protocol: DB2114635
Report:2011N128710_00
Protocol: DB2114636
Report:2012N140627_00
Protocol: DB2114637
Report:2012N140743_01
Protocol: DB2116975
Report:2012N137814_00
Protocol: F43010N
Report:2013N158964_00
Protocol: G01688
Report:FD2002/00011/01
Protocol: G07046
Report:CD2007/00973/00
Protocol: GSK012/01
Report:2012N145447_00
Protocol: L23338
Report:WD2002/00882/00
Protocol: L42984N
Report:2012N152432_00
Protocol: M23602
Report:WD2003/00100/00
Protocol: M24141
Report:WD2005/00894/00
Protocol: M27293
Report:WD2007/01600/00
Protocol: M28976
Report:2012N131664_00
Protocol: QBR113236QB01
Report:2012N144582_00
Protocol: R23393

Report:WD2002/01055/00
Protocol: R23603
Report:WD2003/00099/00
Protocol: R23653
Report:WD2003/01044/00
Protocol: R24142
Report:WD2005/00895/00
Protocol: R26826
Report:WD2006/03225/00
Protocol: R27071
Report:WD2007/00766/00
Protocol: R27955
Report:FD2008/00342/00
Protocol: R28859
Report:FD2009/00467/00
Protocol: R28862
Report:2012N131619_00
Protocol: RES113817
Report:2010N104592_00
Reports: 2011N114061_00
Reports: 2012N133680_00
Reports: 2012N151093_00
Reports: 2012N156532_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes

MEDIA INFORMATION:

QC COMPLETED: Yes

DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Sep-2013	IND 104479	Ser#: 0159	umeclidinium (GSK573719) Ser #: 0159 Protocol Amendment: New Investigator Other 1572 Change	81bc0249

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4116135 Protocol: AC4116136

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
11-Oct-2013	IND 104479	Ser#: 0160	umeclidinium (GSK573719) Ser #: 0160 Protocol Amendment: New Investigator Other 1572 Change	81bde584

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4116136

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
18-Oct-2013	IND 104479	Ser#: 0161	umeclidinium (GSK573719) Ser #: 0161 Protocol Amendment: New Investigator Investigator Add	81be6199

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury, M.D.	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add SUBTYPES: Investigator Add Protocol: 200109 Protocol: 200110

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Nov-2013	IND 104479	Ser#: 0162	umeclidinium (GSK573719) Ser #: 0162 Protocol Amendment: New Investigator Other 1572 Change	81c01eef

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4116135 Protocol: AC4116136

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA: Yes
MEDIA INFORMATION:
QC COMPLETED: Yes
DATE REFERENCED:

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
19-Nov-2013	IND 104479; IND 104479	Ser#: 0163	umeclidinium (GSK573719) Ser #: 0163 Protocol Amendment: New Investigator Investigator Add Other 1572 Change	81c07719

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline Ms. Mary V. Sides	Food and Drug Administration Dr. Badrul A. Chowdhury,	Correspondence	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Investigator Add; Other 1572 Change SUBTYPES: Investigator Add; Other 1572 Change

Protocol: 200109
Protocol: 200110

PROTOCOL AMENDMENT: NEW INVESTIGATOR
SUBTYPES: Investigator Add; Other 1572 Change
SUBTYPES: Investigator Add; Other 1572 Change
Protocol: 200110

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
12-Dec-2013	IND 104479	Ser#: 0164	umeclidinium (GSK573719) Ser #: 0164 Information Amendment: Clinical Study Reports	81c1eb17

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	Food and Drug Administration	Correspondence	INFORMATION AMENDMENT: CLINICAL SUBTYPES: Study Reports SUBTYPES: Study Reports SUBINDEXING: Protocol: DB2116132 Report:2013N174383_00

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Dec-2013	IND 104479	Ser#: 0165	umeclidinium (GSK573719) Ser #: 0165	81c221ca

Protocol Amendment: New Investigator
Other 1572 Change

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: AC4116136

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
18-Dec-2013	**IND 104479**	**Ser#: 0166**	umeclidinium (GSK573719) Ser #: 0166 Protocol Amendment: New Investigator Other 1572 Change	81c27536

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline **Ms. Mary V. Sides**	**Food and Drug Administration** **Dr. Badrul A. Chowdhury, M.D.**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: Other 1572 Change SUBTYPES: Other 1572 Change Protocol: 200110

DESCRIPTION:

DESCRIPTORS:
ESG;eCTD;SAFE

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
Yes		Yes	

DATE:	APPLICATION:	SER/SUPP/SEQ #:	RE LINE:	DOC ID:
13-Jan-2014	**IND 104479**	**Ser#: 0167**	umeclidinium (GSK573719) Ser #: 0167 Protocol Amendment: New Investigator	81c37c86

N/A

FROM:	TO:	COMMUNICATION:	DOCTYPE & SUBTYPE:
GlaxoSmithKline	**Food and Drug Administration**	**Correspondence**	PROTOCOL AMENDMENT: NEW INVESTIGATOR SUBTYPES: N/A SUBTYPES: N/A

DESCRIPTION:

DESCRIPTORS:

ELECTRONIC MEDIA:	MEDIA INFORMATION:	QC COMPLETED:	DATE REFERENCED:
No		No	