NDA Multi-disciplinary Review and Evaluation

Application Type	NDA – 505(b)(2)
Application Number(s)	210361
Priority or Standard	Standard
Submit Date(s)	August 31, 2017
Received Date(s)	August 31, 2017
PDUFA Goal Date	June 30, 2018
Division/Office	DDDP/ODE III
Review Completion Date	See DARRTS electronic signature page
Established Name	Glycopyrronium
(Proposed) Trade Name	QBREXZA
Pharmacologic Class	Anticholinergic agent
Code name	DRM04
Applicant	Dermira, Inc.
Formulation	Cloth
Dosing Regimen	For topical use only. Apply Qbrexza once daily to both axillae using a single cloth
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Qbrexza is an anticholinergic indicated for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older.

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Reviewers of Multi-Disciplinary Review and Evaluation

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Product Quality Team Lead	Yichun Sun, PhD	Branch V/ Division of New Drug Products II	Sections: 1.1, 4.2	**Select one:** ✓ Authored ✓ Acknowledged ✓ Approved
	Signature: Yichun Sun -S Digitally signed by Yichun Sun -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yichun Sun -S, 0.9.2342.19200300.100.1.1=1300393310 Date: 2018.06.18 12:05:28 -04'00'			
Nonclinical Reviewer	Norman See, PhD	ODE III/ DDDP	Sections: 5, 13.3	**Select one:** ✓ Authored ____ Acknowledged ____ Approved
	Signature: Norman A. See -S Digitally signed by Norman A. See -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Norman A. See -S, 0.9.2342.19200300.100.1.1=1300071522 Date: 2018.06.18 12:27:07 -04'00'			
Nonclinical Supervisor	Barbara A. Hill, PhD	ODE III/DDDP	Sections: 5, 13.3	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
	Signature: Barbara A. Hill -S Digitally signed by Barbara A. Hill -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300098991, cn=Barbara A. Hill -S Date: 2018.06.18 13:27:12 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Clinical Pharmacology Reviewer	Jihye Ahn, PharmD	OCP-DCP III	Sections: 6, 13.4	**Select one:** ✓ Authored ___ Acknowledged ___ Approved
	Signature: Jihye Ahn -S (Affiliate) Digitally signed by Jihye Ahn -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001814798, cn=Jihye Ahn -S (Affiliate) Date: 2018.06.18 14:56:07 -04'00'			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP-DCP III	Sections: 6, 13.4	**Select one:** ___ Authored ___ Acknowledged ✓ Approved
	Signature: Chinmay Shukla -S Digitally signed by Chinmay Shukla -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chinmay Shukla -S, 0.9.2342.19200300.100.1.1=2000377244 Date: 2018.06.18 15:01:02 -04'00'			
Biostatistics Reviewer	Rebecca Hager, PhD	OTS/OB/DBIII	Sections: 7.1, 7.2, 7.4, 13.5	**Select one:** ✓ Authored ___ Acknowledged ___ Approved
	Signature: Rebecca S. Hager -S Digitally signed by Rebecca S. Hager -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002201387, cn=Rebecca S. Hager -S Date: 2018.06.18 16:48:19 -04'00'			
Biostatistics Team Leader	Mohamed Alosh, PhD	OTS/OB/DBIII	Sections: 7.1, 7.2, 7.4, 13.5	**Select one:** ___ Authored ___ Acknowledged ✓ Approved
	Signature: Mohamed A. Alosh -S Digitally signed by Mohamed A Alosh -S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0.9 2342 19200300 100 1 1=1300089441 cn=Mohamed A Alosh -S Date: 2018 06 18 16 55:11 04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
OB Division Director (DBIII)	Laura Lee Johnson, PhD	OTS/OB/DBIII	Sections: 7.1, 7.2, 7.4, 13.5	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
	Signature: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011413414, cn=Laura L. Johnson -S Date: 2018.06.18 17:14:10 -04'00'			
Clinical Reviewer	Carol Langley, MD	ODE III/DDDP	Sections: 1.1, 1.2, 1.3, 2, 3, 4.1, 7.1, 7.3, 7.4, 8, 9, 10, 11, 12, 13.1, 13.2	**Select one:** ✓ Authored ____ Acknowledged ____ Approved
	Signature: Carol L. Langley -S Digitally signed by Carol L. Langley -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002148838, cn=Carol L. Langley -S Date: 2018.06.19 13:52:17 -04'00'			
Clinical Team Leader	David Kettl, MD	ODE III/DDDP	Sections: 1.1, 1.2, 1.3, 2, 3, 4.1, 7.1, 7.3, 7.4, 8, 9, 10, 11, 12, 13.1, 13.2	**Select one:** ✓ Authored ____ Acknowledged ✓ Approved
	Signature: David L. Kettl -S Digitally signed by David L. Kettl -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David L. Kettl -S, 0.9.2342.19200300.100.1.1=1300383857 Date: 2018.06.19 14:04:46 -04'00'			
Director - DDDP	Kendall A. Marcus, MD	ODE III/DDDP	Sections: 1	**Select one:** ____ Authored ____ Acknowledged ____ Approved
	Signature: see DARRTS electronic signature page			

Additional Reviewers of Application

Deputy Director	Jill A. Lindstrom, MD, FAAD
Deputy Director for Safety	Tatiana Oussova, MD, MPH
Associate Director for Labeling	Nancy Xu, MD
Associate Director for Regulatory Affairs, ODE III	Wes Ishihara, MEM
OPQ-Drug Substance	Friedrich Burnett, PhD
OPQ-Drug Product	Caroling Strasinger, PhD
OPQ-Microbiology	Xia Xu, PhD
OPQ-Facility	Carl Lee
OPQ-Process	Mesfin Abdi, PhD
OPQ-RBPM	Bamidele (Florence) Aisida
Statistician - DB VI	Malick Mbodj, PhD
OPDP	Laurie Buonaccorsi, /Matthew Falter
DMPP	Shawna Hutchins, MPH, BSN, RN/LaShawn Griffiths, MSHS-PH, BSN, RN
OSI	Bei Yu, PhD/Janice Pohlman, MD, MPH
OSE/DMEPA	Madhuri Patel. PharmD/Sarah Vee, PharmD
OSE-SRPM	Tri Bui-Nguyen, PhD

DB=Division of Biometrics
DCP=Division of Clinical Pharmacology
DDDP=Division of Dermatology and Dental Products
DEPI=Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
OB=Office of Biostatistics
OCP=Office of Clinical Pharmacology
ODE=Office of Drug Evaluation
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE=Office of Surveillance and Epidemiology
OTS=Office of Translational Sciences
RBPM=Regulatory Business Project Manager
SRPM=Safety Regulatory Project Manager

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ANCOVA	analysis of covariance
ASDD	Axillary Sweating Daily Diary
ASDD-C	Axillary Sweating Daily Diary Children
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COA	Clinical Outcome Assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EOP2	End-of-Phase 2
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HDSS	Hyperhidrosis Disease Severity Scale
ICH	International Conference on Harmonization
IND	Investigational New Drug
IQR	interquartile range
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

IWRS	interactive web-based randomization system
LOCF	last observation carried forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
US	United States

1 Executive Summary

1.1. Product Introduction

Dermira, Inc. submitted a 505 (b)(2) application for glycopyrronium cloth for the topical treatment of axillary hyperhidrosis in adults and children 9 years of age and older. The applicant is relying upon certain elements from NDA 22571 for Cuvposa (glycopyrrolate) oral solution, approved 07/28/2010 which is indicated to reduce chronic severe drooling in patients aged 3-16 with neurologic conditions associated with problem drooling (e.g., cerebral palsy). The PDUFA goal date is June 29, 2018.

Glycopyrronium cloth, 2.4%, contains the active ingredient glycopyrronium tosylate monohydrate that belongs to the pharmacological class of anticholinergic agents. Glycopyrronium is a (b) (4) quaternary ammonium compound that inhibits the action of acetylcholine on structures innervated by postganglionic, cholinergic (muscarinic) nerves, such as sweat glands. The proposed indication for glycopyrronium cloth, 2.4% is the "topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older." Glycopyrronium cloth, 2.4%, is to be used as a pre-moistened cloth (an absorbent polypropylene pad or wipe) to facilitate application to the axillae.

The product represents a new salt, and a new dosage form. A related compound, glycopyrrolate (glycopyrronium bromide), also an anticholinergic agent, has been approved for many years in multiple forms (oral, injectable, inhaled) for multiple indications.

The drug product is presented in individually-sealed, single-use, (b) (4) pouches containing a (b) (4) wipe (also referred to as a towelette or pad) with dimensions of approximately 6 × 3.75 inches, wetted with the topical solution containing 2.4% glycopyrronium (equivalent to (b) (4) % w/w of glycopyrronium tosylate monohydrate). The inactive ingredients used in the drug product include: citric acid (b) (4), sodium citrate (b) (4), dehydrated alcohol, and purified water. The recommended expiration dating period of the drug product is 24 months when stored at controlled room temperature.

The investigational product (study drug) may be referred to in this review by various names, including the following:

- Glycopyrronium cloth or topical solution, 2.4%
- DRM04 (glycopyrronium) cloth or topical solution, 2.4%
- DRM04, 2.4%
- DRM04, (b) (4) %

The proposed proprietary name for the product is QBREXZA.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant submitted data from two identically-designed, randomized, double-blind, vehicle-controlled, parallel group pivotal Phase 3 trials (DRM-HH04 and DRM-HH05) examining the effectiveness of glycopyrronium cloth, 2.4% for the topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older. Both trials had the following co-primary endpoints:

- the mean change from baseline in gravimetrically-measured sweat production at Week 4
- the proportion of subjects with at least a 4-point improvement from baseline in the weekly mean score of the Axillary Sweating Daily Diary (ASDD) item #2 at Week 4; this item is a daily assessment that asks subjects to rate their sweating at its worst over the past 24 hours on a scale of 0-10.

In both trials, glycopyrronium was statistically superior to vehicle for the ASDD item #2 co-primary endpoint. For the sweat production co-primary endpoint, pre-specified sensitivity analyses were conducted; all sensitivity analyses for this endpoint were statistically significant in both trials. Thus, the totality of evidence supports the effectiveness of glycopyrronium.

In conclusion, the applicant has demonstrated that glycopyrronium is effective for its intended use in the target population, and has met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Glycopyrronium cloth, 2.4%, contains the active ingredient glycopyrronium tosylate monohydrate that belongs to the pharmacological class of anticholinergic agents. Glycopyrronium is a (b) (4), quaternary ammonium compound that inhibits the action of acetylcholine on structures innervated by postganglionic, cholinergic (muscarinic) nerves, such as sweat glands. The proposed indication for glycopyrronium cloth, 2.4% is the topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older.

Primary axillary hyperhidrosis is a relatively common, chronic disorder involving excessive axillary sweating. Symptoms generally start at puberty, and may persist throughout life, or remit spontaneously as patients age. The prevalence of hyperhidrosis in the US is estimated to range from 1-5%.

There are currently two FDA-approved treatment options for axillary hyperhidrosis: onabotulinumtoxin A (Botox), administered as multiple intradermal axillary injections, and an FDA-cleared device, the miraDry System, which utilizes microwave thermolysis to destroy axillary sweat glands. Other treatment options include local surgical treatment (suction curettage and endoscopic thoracic sympathectomy (ETS).

In two adequate and well controlled trials, glycopyrronium was statistically superior to vehicle for the treatment of hyperhidrosis.

The safety profile for glycopyrronium cloth was adequately characterized during the drug development program. In the pivotal Phase 3 trials, the most common adverse reactions were dry mouth (24.2%), mydriasis (6.8%), oropharyngeal pain (5.7%), headache (5.0%), urinary hesitation (3.5%), vision blurred (3.5%), nasal dryness (2.6%), dry throat (2.6%), dry eye (2.4%), dry skin (2.2%), and constipation (2.0%). Virtually all of these reactions represent anticholinergic effects, consistent with the mechanism of action of glycopyrronium. Local skin reactions were also common, including erythema (17.0% of subjects receiving glycopyrronium), burning/stinging (14.1%), and pruritus (8.1%). Most adverse reactions were mild or moderate in severity, and reversible upon discontinuation of treatment. These identified adverse reactions will be conveyed in product labeling.

Given the potential for anticholinergic effects with glycopyrronium cloth, proposed labeling addresses several key concerns in the Contraindications, Warnings and Precautions, and Drug Interactions sections of labeling, most of which is also contained in existing labeling for other anticholinergic products.

In summary, the available evidence of safety and efficacy supports the approval of glycopyrronium cloth, 2.4%, for the topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older. In view of a favorable overall benefit/risk assessment, approval of this product is recommended.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Primary axillary hyperhidrosis is a relatively common, chronic disorder involving excessive axillary sweating. Symptoms generally start at puberty, and persist throughout life. The prevalence of hyperhidrosis in the US is estimated to range from 1-5%.	Primary axillary hyperhidrosis is a relatively common condition which frequently interferes with normal daily activities. Additional safe and effective treatment options are needed to reduce the burden of this chronic disease on affected individuals.
Current Treatment Options	• Current treatment options for axillary hyperhidrosis include antiperspirants, botulinum toxin, microwave thermolysis, oral medications, and surgery. The only FDA-approved medication for axillary hyperhidrosis is onabotulinumtoxin A (Botox). An FDA-cleared device, the miraDry System, utilizes microwave thermolysis to destroy axillary sweat glands. Other treatment include local surgical treatment (suction curettage), systemic agents, or endoscopic thoracic sympathectomy (ETS). • For other treatment options include local surgical treatment (suction curettage), and endoscopic thoracic sympathectomy	There are currently two FDA-approved treatment options for axillary hyperhidrosis.
Benefit	• Data from Trials DRM-HH04 and DRM-HH05 provided substantial evidence of the effectiveness of glycopyrronium cloth, 2.4%, for the topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older. The trials were identically-designed, randomized, double-blind, vehicle-controlled, parallel group pivotal Phase 3 trials examining the safety and effectiveness of glycopyrronium cloth, 2.4% used daily for 28 days. Both trials had the following co-primary endpoints:	The trials were adequate and well-controlled. The evidence submitted by the applicant to support the approval of glycopyrronium cloth has met the statutory evidentiary standard for providing substantial evidence of effectiveness under the proposed conditions of use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ the mean change from baseline in gravimetrically-measured sweat production at Week 4 ○ the proportion of subjects with at least a 4-point improvement from baseline in the weekly mean score of the Axillary Sweating Daily Diary (ASDD) item #2 at Week 4; this item is a daily assessment that asks subjects to rate their sweating at its worst over the past 24 hours on a scale of 0-10. • In both trials, glycopyrronium was statistically superior to vehicle for the ASDD item #2 co-primary endpoint. For the sweat production co-primary endpoint, pre-specified sensitivity analyses were conducted; all sensitivity analyses for this endpoint were statistically significant in both trials.	
Risk	• The safety profile for glycopyrronium cloth was adequately characterized during the drug development program. The primary safety database consisted of pooled data from the pivotal Phase 3 Trials, DRM04-HH04 and DRM04-HH05, including data from 459 subjects treated with glycopyrronium, and 232 who received vehicle. The applicant evaluated long-term safety in an open-label 44-week extension trial (DRM04-HH06) enrolling 550 subjects. The overall clinical development program included eight trials, with 1269 subjects who received at least one dose of study drug, 393 who were dosed for at least six months, and 114 who were dosed for at least twelve months. The size of the safety database was adequate to identify and characterize relevant safety issues. • Across the eight trials in the development program, there was one death, considered not related to study drug, and 12 serious adverse	Overall, the majority of adverse events observed with exposure to glycopyrronium cloth reflect anticholinergic effects, consistent with the mechanism of action of glycopyrronium, and local skin reactions. Most adverse reactions were mild or moderate in severity, , and reversible.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	events (SAE), all in subjects receiving study drug. Two SAEs, both events of unilateral mydriasis, were considered related. Both these events were categorized as SAEs because the subjects were hospitalized to rule out possible CNS causes. • In the pivotal Phase 3 trials, the most common adverse reactions were dry mouth (24.2%), mydriasis (6.8%), oropharyngeal pain (5.7%), headache (5.0%), urinary hesitation (3.5%), vision blurred (3.5%), nasal dryness (2.6%), dry throat (2.6%), dry eye (2.4%), dry skin (2.2%), and constipation (2.0%). Local skin reactions were also common, including erythema (17.0% of study drug subjects), burning/stinging (14.1%), and pruritus (8.1%).	
Risk Management	• A REMS is not required for this program.	The risks associated with this drug can be adequately managed through product labeling and pharmacovigilance in the post-marketing setting.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 7.2 Study endpoints (7.2.1, 7.2.5)
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 7.4.5.2, Local Skin Reactions
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	X	Other: (Please specify)		References/publications examining patient experience; discussed in Section 2.1
X	Patient experience data that were not submitted in the application, but were considered in this review:			
		X	Input informed from participation in meetings with patient stakeholders	Sections 2.1 and 7.2 – input from PFDD meeting 11/13/17
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Hyperhidrosis is a condition of excessive sweating beyond what is physiologically required to regulate normal body temperature. Hyperhidrosis is most often a primary, idiopathic condition; however, a number of disorders, including endocrine, neurologic, cardiovascular and metabolic conditions, and a number of medications, can cause secondary hyperhidrosis.

Primary hyperhidrosis is generally localized and symmetric, most often affecting the axillae, palms and soles, though it can also involve the face, scalp, trunk and intertriginous areas. The diagnosis is clinical. Symptoms generally start in late childhood or adolescence, following puberty, and may persist throughout life or spontaneously remit with age. Estimates of prevalence in the US range from 1 to 5 percent of the population[1]. A 2016 survey estimated the prevalence of hyperhidrosis at 4.8 %, which represents approximately 15.3 million people in the United States[2]. Though the pathophysiology of primary hyperhidrosis is not completely understood, the sweat glands are generally histologically and functionally normal; rather, excessive sweating in primary hyperhidrosis appears to be an exaggerated central (cortical) response to normal emotional stress[1].

A study examining Canadian and Chinese dermatology patients found that the prevalence of anxiety and depression was 21.3% and 27.2% in patients with hyperhidrosis, and 7.5% and 9.7% in patients without hyperhidrosis, respectively[3]. Increased severity of hyperhidrosis was also correlated with higher rates of anxiety and depression.

The impact of hyperhidrosis on the daily lives of patients was among the topics discussed at an external Patient-Focused Drug Development Meeting for hyperhidrosis held on November 13, 2017. Patients who attended the meeting described the effects of the condition on their quality of life, as well as the patient experience with the available treatment modalities. The final summary report of the meeting is expected to be published in the second-half of 2018.

2.2. Analysis of Current Treatment Options

The major therapeutic options for axillary hyperhidrosis include antiperspirants, botulinum toxin, microwave thermolysis, and surgery. The FDA-approved medication for axillary hyperhidrosis is onabotulinumtoxin A (Botox). There is also an FDA-cleared device, the miraDry System, which utilizes microwave thermolysis to destroy axillary sweat glands. Other treatment

[1] C. Christopher Smith, MD, David Pariser, MD; Primary focal hyperhidrosis; UpToDate.com; updated January 16, 2018
[2] Doolittle J, Walker P, Mills T, Thurston J (2016). Hyperhidrosis: an update on prevalence and severity in the United States. Arch Dermatol Res 308:743–749
[3] Bahar R, Zhou P, Liu Y, Huang Y, et al (2016). The prevalence of anxiety and depression in patients with or without Hyperhidrosis. J Am Acad Dermatol 75: 1126-33.

options include local surgical treatment (suction curettage), or endoscopic thoracic sympathectomy (ETS).

FDA-approved treatments

Onabotulinumtoxin A (Botox) was approved in 2004 for the treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients[4]. The recommended dose is 50 units per axilla, given as intradermal injections. The efficacy of Botox was demonstrated in two randomized, double-blind, placebo-controlled studies[5]; in these studies, the median duration of response was 201 days. Adverse reactions included injection site pain and hemorrhage and non-axillary sweating.

A relatively recent approach to treating axillary hyperhidrosis, **microwave thermolysis**, involves the use of microwave energy to destroy axillary sweat glands[1]. A commercial device for microwave thermolysis, the miraDry System, was cleared by FDA in 2011. Microwave thermolysis is a non-invasive, office-based procedure, typically involving two 30-60 minute sessions three months apart. The most common side effects of treatment are altered skin sensation, pain, and other local reactions.

Non-approved treatments

Topical antiperspirants are generally considered the first line of treatment for axillary hyperhidrosis as they are readily available, inexpensive, and well-tolerated[1]. Nonprescription products may be successful in treating patients with very mild hyperhidrosis; however, most patients with hyperhidrosis will require higher-dose, prescription antiperspirants, such as 6.25% or 20% aluminum chloride hexahydrate. Many patients experience skin irritation with these products, which may limit their use. Low-potency topical corticosteroids (e.g. 2.5% hydrocortisone cream) may help alleviate axillary irritation.

Suction curettage is a minimally invasive procedure which utilizes cannula suction of the superficial subdermis to remove axillary sweat glands[1]. Limited data are available on efficacy. Adverse effects may include local pain, infection, hematoma, scarring, and persistent or compensatory sweating.

Endoscopic thoracic sympathectomy (ETS) involves severing the upper thoracic sympathetic pathway using cauterization, cutting or clipping. This procedure may be less effective for axillary hyperhidrosis, relative to palmar hyperhidrosis, and is associated with a number of serious adverse effects, including surgical complications, the risk of compensatory hyperhidrosis in other areas of the body, and recurrence of focal hyperhidrosis[1].

[4] BOTOX (onabotulinumtoxin A) Prescribing Information, revised 4/2017

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Glycopyrronium cloth, 2.4%, contains the active ingredient glycopyrronium tosylate that belongs to the pharmacological class of anticholinergic agents. The product represents a new salt, and a new dosage form. Glycopyrronium cloth has not been marketed in any country.

Dermira, Inc., the applicant, submitted a 505 (b)(2) application for the current product, glycopyrronium cloth, for the topical treatment of axillary hyperhidrosis. The applicant is relying upon certain elements from NDA 22571 for Cuvposa (glycopyrrolate) oral solution, referenced above.

The sponsor conducted a review of published literature on generic glycopyrrolate, examining peer-reviewed articles published between 1996 and 2017 that included data on oral or topical administration of glycopyrrolate. This is discussed further in Section 7.3.9, Safety in the Postmarket Setting.

A related compound, glycopyrrolate (glycopyrronium bromide), also an anticholinergic agent, has been approved for many years in multiple forms (oral, injectable, inhaled) for multiple indications. Glycopyrrolate has been on the market in the U.S. since 1961 for treatment of peptic ulcers (Robinul and Robinul Forte tablets), and since 1975 as a preoperative injectable anti-muscarinic agent to reduce gastric, salivary, and tracheobronchial secretions (Robinul Injection).

In addition, glycopyrrolate was approved in the US in 2010 as an oral solution (with a trade name of Cuvposa) to reduce chronic severe drooling in children with neurologic conditions associated with problem drooling (e.g., cerebral palsy), and in 2015 as an inhaled treatment (with a trade name of Seebri) for chronic obstructive pulmonary disease.

3.2. Summary of Presubmission/Submission Regulatory Activity

The product was developed under IND 104160. Milestone interactions with the applicant include those described below.

End-of-Phase 2 Meeting - April 1, 2015

The following issues were addressed at the End of Phase 2 (EOP2) Meeting, held April 1, 2015.

- The Agency noted inconsistencies in the results of the two Phase 2 trials, stating that a consistent dose-response relationship had not been identified; the Agency recommended additional dose ranging to further characterize the performance of the study drug, and to assess treatment estimates for the Phase 3 trials.

There was considerable discussion related to proposed efficacy endpoints.

- There was discussion about establishing a clinical bridge to support the 505(b)(2) pathway using Cuvposa as the Listed Drug. The bridge will be established by comparing pharmacokinetic data on glycopyrronium to pharmacokinetic data in subjects dosed orally with Cuvposa, which will be collected as part of the maximum-use pharmacokinetic trial, DRM04-HH07.

Pre-NDA meeting – February 8, 2017

The following issues were addressed at the Pre-NDA Meeting, held February 8, 2017.

- The sponsor asked again about the size/adequacy of the safety database.
- Given results from the maximum-use PK trial, DRM04-HH07, supportive data from ECGs collected in Phase 3 and Phase 2 subjects, and the known pharmacology of glycopyrronium, the sponsor requested a waiver from the need for a thorough QT/QTc trial. Following review, the Agency agreed that a thorough QT study would not be required.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI Review – Clinical Inspection Summary, NDA 210361

(Review by Bei Yu, Ph.D., dated May 9, 2018)

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Cather and Essink were inspected for Study DRM04-HH05 and Study DRM04-HH04, respectively, which were submitted in support of NDA 210361.

Based on the inspection of Dr. Essink, Study DRM04-HH04 appears to have been conducted adequately at this site and the data generated by this site and as reported by the sponsor to the NDA appears acceptable in support of the respective indication. The final classification of this inspection is No Action Indicated (NAI).

At Dr. Cather's site for Study DRM04-HH05, the observation was made that Dr. Cather failed to follow the investigational plan regarding gravimetric assessment of sweat production, one of the co-primary efficacy endpoints for the study as described in depth below. Based upon the findings, OSI recommends that the review team consider conducting sensitivity analyses taking into account the 12 subjects impacted by the sweat collection time deviations at Dr. Cather's site on the primary efficacy endpoint assessment of mean absolute change from baseline in gravimetrically-measured sweat production at Week 4. The preliminary classification for this inspection is Voluntary Action Indicated (VAI).

II. BACKGROUND

Rationale for Site Selection:

- Site #502 (Jennifer Cather): A discrepancy of efficacy signals for two co-primary endpoints exists in the vehicle group, e.g., there is a lack of efficacy in the vehicle group (0% vs. 88.3% for the active) for one co-primary endpoint "proportion of subjects who have at least 4-point improvement in the weekly mean score of Axillary Sweating Daily Diary (ASDD) item #2 from baseline at week 4"; while, high efficacy in the vehicle group (-191.3 vs. -164.1 in the active) for the other co-primary endpoint "mean absolute change from baseline in gravimetrically-measured sweat production at week 4". This trend is not observed in the active group. The site had a high number of protocol violations reported. The CI has 27 INDs, but had not been previously inspected. She conducted two studies contained within the submission: Studies 05 and 06.
- Site #409 (Brandon Essink): High site efficacy effect was seen. The CI has (b) (4) INDs, but had not been previously inspected.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol # / # of Subjects Enrolled	Inspection Dates	Classification
Site #502 **Jennifer Cather, M.D.** 9101 North Central Expressway, Suite 170 Dallas, TX 75231	DRM04-HH05 Subjects: 14	16 - 19 Jan 2018	VAI*
Site #409 **Brandon Essink, M.D.** 3319 N. 107th St. Omaha, NE 68134	DRM04-HH04 Subjects: 17	29 Jan – 1 Feb 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
* Pending: Classification is preliminary pending issuance of correspondence to the inspected entity

Clinical Investigator Sites

1. Jennifer C. Cather, M.D.

At this site for Protocol DRM04-HH05, a total of 17 subjects were screened and 14 subjects were enrolled, 12 of whom completed the study.

The records for all 14 enrolled subjects were reviewed. These included, but were not limited to, Inform Consent Forms, verification of efficacy endpoints, eligibility, randomization and blinding, adverse events, protocol deviations, IRB correspondence and study approvals, sponsor correspondence, electronic Case Report Forms (eCRF), subject e-Diary, source records, and drug accountability records. The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

However, multiple deviations regarding gravimetric assessments (gauze placement time; temperature) were reported by the site to the sponsor and IRB but were not found in the data line listings. These issues were not identified until the end of the study by the study monitor and no corrective action was created during the study to prevent further deviations.

1) Total Gauze Placement Time Deviations: Based on the protocol, the subject's arm must be holding the gauze in the axilla for five minutes to collect sweat. CIs were to record start time when the gauze was placed and record the stop time when the

gauze was removed. The majority of the deviations as documented in a report to the IRB (copy included in the Establishment Inspection Report) in "total time gauze placed in axilla" were observed to be 6 minutes. However, for 9 of 39 deviations, the total gauze placement time was 7-9 minutes. For example, for Subject 502-5106 at Visit 5, the total time gauze placed in both left and right axilla was 9 minutes.

OSI Reviewer comments: The amount of sweat collected is dependent on the duration of gauze placement in the axilla. The duration of sweat collection in the majority of subjects (12 of 14 enrolled) was prolonged from the protocol-specified 5 minutes to 6 minutes, increasing collection time by 20%.

2) Temperature Deviations: based on the protocol, the gravimetric procedure must be performed at a temperature of 70-76°F. Twenty four recorded temperature values across all visits for 12 subjects fluctuated out of the range of 70-76°F for the approximately 45 minute study assessment procedure. For example, for Subject 502-5102 at Visit 5 (Week 3), the recorded room temperature was at 67-79°F.

The sponsor responded to the Office of Regulatory Affairs investigator's query regarding impact of temperature fluctuations out of range indicating that "the amount of fluctuation in room temperature over the 5-minute period of sweat collection is likely to be small and would not have an appreciable effect on the amount of sweat."

OSI Reviewer Comments: Although a Form FDA 483 was not issued at the conclusion of the inspection, the observation was made that Dr. Cather failed to follow the investigational plan regarding gravimetric assessment of sweat production, one of the co-primary efficacy endpoints for the study. The primary protocol deviation related to prolonged sweat collection times and secondarily, minor deviations in room temperature range over the 35-40-minute collection procedure (30 minutes acclimatizing to room temperature, 5-minute sweat collection time, and pre and post weighing of gauze). These deviations, identified during the final study monitoring visit were reported to the sponsor and subsequently the IRB. The sponsor did not report these deviations in the Clinical Study Report or the NDA data listings

Also noted, the sample case report form for both Study DRM04-HH05 and Study DRM04-HH04 did not contain data fields for reporting the actual time of sweat collection. Therefore, this issue would only have been noted if study monitors were reviewing these source document worksheets.

Based on OSI's recommendation, an information request was sent by the review division to the sponsor regarding the documentation of the gauze placement times, study site monitoring of these times, and whether they were aware of additional deviations at other sites.

The sponsor responded that gauze placement times were recorded for all subjects at each

study site for both studies on the sponsor-provided (or equivalent site developed worksheet) Gravimetric Assessment source document worksheet. The sponsor stated that study site monitors reviewed 100% of source documentation including these worksheets that recorded start and stop times of gauze placement based on their clinical monitoring plans. Additional gauze placement deviations were noted in 13 subjects at 8 other study sites participating in either one of the studies; however only five subjects had deviations at either Baseline (Day 1) or at Week 4/Early Termination that would have potentially had an impact on the primary efficacy endpoint.

2. Brandon Essink, M.D.

At this site for Protocol DRM04-HH04, 20 subjects were screened and 17 subjects were enrolled, 16 of whom completed the study.

The records for all 17 enrolled subjects were reviewed. These included, but were not limited to, the informed consent forms, study records, case report forms, monitoring logs, drug accountability, and comparison of data line listings to the source documents. There were neither discrepancies observed nor concerns noted.

A Form FDA 483 was not issued at the conclusion of the inspection.

Clinical Reviewer Comment:

The Statistical Reviewer, Rebecca Hager, PhD, conducted a sensitivity analysis excluding site 502, Dr. Jennifer Cather's site, from the analysis of the gravimetrically-measured sweat production co-primary endpoint (see Section 7.2.4, Table 19). Excluding site 502 from the analysis does not change the conclusions from the primary analysis.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No

Product Quality Review – Executive Summary

(Review by Yichun Sun, Ph.D. and Product Quality Review Team, dated April 26, 2018)

I. Recommendations and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The facility review team from the Office of Process and Facility (OPF) has issued an "Acceptable" recommendation for the facilities involved in this application.

The revised package insert and mock-up container and carton labels are satisfactory from the CMC perspective.

Therefore, from the OPQ's perspective, this NDA is recommended for APPROVAL with an expiration dating period of 24 months for the drug product when stored at room temperature.

II. Summary of Quality Assessments

A. Product Overview

The NDA of Qbrexza (glycopyrronium) cloth, 2.4% is submitted as a 505(b)(2) application by Dermira, Inc. The listed drug used for the basis of this 505(b)(2) application is NDA 022571 [Cuvposa® (glycopyrrolate) oral solution].

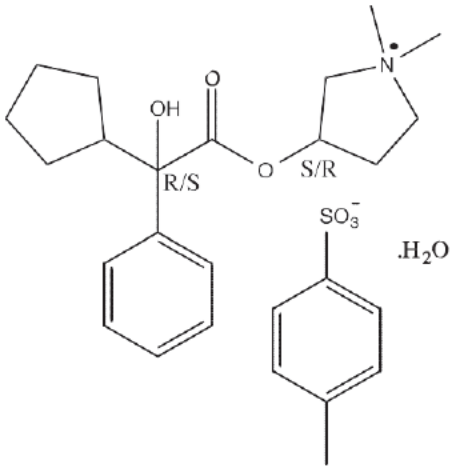
The indication and recommended dose of the drug product are summarized in the following Table.

Proposed Indication(s) including Intended Patient Population	Qbrexza is indicated for topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older.
Duration of Treatment	N/A
Maximum Daily Dose	Qbrexza should not be used more frequently than once every 24 hours.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

Qbrexza (glycopyrronium) Cloth, 2.4 % contains the active ingredient, glycopyrronium tosylate monohydrate (USAN: glycopyrronium tosylate), which is an anticholinergic. It is chemically named as pyrrolidinium, 3-[(2-cyclopentyl- 2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethyl-, 4-methylbenzensulfonate, hydrate (1:1:1). The structural formula is represented below:



It has a molecular formula of $C_{26}H_{37}NO_7S$ and the molecular weight is 507.6 g/mol.

Glycopyrronium tosylate monohydrate has two asymmetric centers in the glycopyrronium moiety and therefore may have four configurational isomers. (b) (4)

(b) (4)

(b) (4)

demonstration batch has been successfully produced using the proposed drug substance manufacturing process. The test results of the demonstration batch indicate that the proposed commercial-scale (b) (4) manufacturing process, and control strategy are adequate to produce the drug substance.

The data and information of elucidation of the chemical structure and characterization of the physiochemical properties of the drug substance were provided in the submission. The origin, identification, characterization and fate of specified organic impurities, observed unspecified organic impurities, starting material impurities, process impurities, and potential genotoxic impurities were adequately addressed by the NDA applicant. The identity, strength, purity and quality of the drug substance are adequately assured by the drug substance specification. The proposed retest period of (b) (4) months is supported by the stability data provided in the submission.

The review on the CMC information of the drug substance in the NDA has been conducted by Dr. Fred Burnett. The NDA is recommended for **approval** from the drug substances perspective (See **CHAPTER I: Review of Drug Substance**).

Drug Product

Qbrexza (glycopyrronium) Cloth is indicated for topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older. The active pharmaceutical ingredient (API), glycopyrronium tosylate monohydrate, used in the topical solution is an anticholinergic.

The drug product is presented in individually-sealed, single-use, (b) (4) pouches containing a target of 2.8 g of the topical solution wetted onto a (b) (4) wipe (also referred to as a towelette or pad) with dimensions of approximately 6 × 3.75 inches. The topical solution contains 2.4% glycopyrronium (equivalent to (b) (4) % w/w of glycopyrronium tosylate monohydrate). The inactive ingredients used in the drug product include: citric acid (b) (4) sodium citrate (b) (4) dehydrated alcohol, and purified water. No novel excipients are used and the levels of the excipients in the drug product are below the limits found in the FDA's Inactive Ingredient Database for topical products approved. All excipients used are compendial and comply with the quality standards set in their respective current USP/NF monographs. The applicant has adequately addressed the concern of a genotoxic impurit (b) (4)

The bulk drug product is prepared (b) (4)

The pouch is formed (b) (4)

(b) (4)

The specification of the drug product specification is deemed adequate to assure the identity, strength, purity, and quality of the drug product.

The long-term stability data up to 18 months and accelerated stability data for 6 months for the three registration batches of the drug product produced at pilot scale ((b) (4) kg, (b) (4) of the production scale) were provided in the NDA submission. The stability data submitted are sufficient to support the proposed expiration dating period of 24 months when stored at controlled room temperature. The results of photostability study indicated that light exposure did not adversely affect the drug product in terms of its assay, impurity level, pH and package integrity. The results of thermal cycling studies indicated that temperature cycle (-20°C and 40°C/75% RH) did not adversely affect the drug product in terms of its assay, weight, pH and package integrity.

The estimated EIC (expected introduction concentration) for the active moiety of the drug substance is estimated to be (b) (4) ppb. The claim of categorical exclusion is deemed acceptable per 21 CFR 25.31 (b).

The drug product is recommended for **approval** from the drug product perspective. The recommended expiration dating period of the drug product is 24 months. The review on the CMC information of the drug product has been conducted by Dr. Caroline Strasinger (See **CHAPTER II: Review of Drug Product**).

Labeling and Labels

The sections of the Package Insert related to CMC, and container and carton labels of the drug product of the NDA have been reviewed by Dr. Caroline Strasinger. The revised package insert and mock-up container and carton labels are now satisfactory from the CMC perspective.

Drug Product Manufacturing Process

(b) (4)

Details of the drug product manufacturing process are discussed in CHAPTER IV: Review of Drug Product Manufacturing Process.

The batch formula, manufacturing process parameters, and in-process controls are found to be adequate to ensure the robustness of the drug product manufacturing process. The NDA is recommended for **approval** from the perspective of drug product manufacturing process. The review on the drug product manufacturing process has been conducted by Dr.

Mesfin Abdi (See **CHAPTER IV: Review of Drug Product Manufacturing Process**).

Quality Microbiology

The drug product is a single-use towelette (polypropylene (b) (4) wipe) pre- moistened with an aqueous, non-sterile, (b) (4) solution.

The drug substance, glycopyrronium tosylate monohydrate, is supplied as non- sterile API. The drug substance is tested for microbial limits and specified microorganisms with the acceptance criteria set in USP <1111> for non-sterile substances for pharmaceutical use.

The drug product is for single-use (b) (4)

Validation results of microbial limits tests indicated that the current USP methods for microbial enumeration (TAMC and TYMC) and specified organisms (*P. aeruginosa and S. aureus*) are suitable to be used for microbial limit tests of the drug product. Validation results for the test method of *B. Cepacia* Complex (Bcc) indicated that test method is suitable to be used for monitoring *Burkholderia cepacia* complex (BCC) in the drug product. The results of stability studies indicated that stability samples of the drug product contained < (b) (4) cfu/g TAMC and TYMC and were absent of *S. aureus* and *P. aeruginosa* during the long-term stability study.

The NDA is recommended for **Approval** from the perspective of quality microbiology. The review on microbiology controls of the drug product of the NDA has been conducted by Dr. Xia Xu (See **CHAPTER V: Review of Quality Microbiology**).

Facilitie s

For discussion of facilities and facility review, see Product Quality Review, **CHAPTER VI: Review of Facilities.** All the facilities are deemed acceptable in their identified functions and responsibilities to support the **approval** of NDA 210361. The facility review of the NDA has been conducted by Consumer Safety Officer, Carl Lee (See **CHAPTER VI: Review of Facilities**).

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Glycopyrronium ion is a competitive inhibitor of acetylcholine receptors that are located on certain peripheral tissues, including sweat glands. Glycopyrronium indirectly reduces the rate of sweat secretion by preventing the stimulation of these receptors. Products containing glycopyrrolate (glycopyrronium bromide) have been approved for the treatment of peptic ulcer disease (Robinul tablets, NDA 012827, approved 11-AUG-1961), as a preoperative medication to reduce salivation while under anesthesia (Robinul injection, NDA 017558, approved 06-FEB-1975), and for the treatment of pathologic chronic moderate to severe drooling in pediatric patients (Cuvposa liquid, NDA 022571, approved 28-JUL-2010). These approved products involved oral or parenteral administration of glycopyrrolate. Under NDA 210361, the sponsor has hypothesized that topical application of glycopyrronium, formulated as the tosylate salt, to the axillary region may prevent or ameliorate hyperhidrosis (excessive sweating).

Formulations containing glycopyrronium tosylate at concentrations of 0%, 2%, 6%, or 20% w/w were topically applied to minipigs once daily for 39 weeks (2.2 mL per application). These exposures equated to approximately 0, 4, 13, and 44 mg/kg/day, although it is unknown what portion of each applied dose was subsequently removed when the site was cleansed. The applications covered approximately 10% of the BSA, and the sites were not covered or occluded following application. There were no apparent effects of treatment, including no effects at the application site, and no effects on survival, clinical signs, mean body weight, ECG, clinical pathology, or histopathology.

Glycopyrrolate was negative in a battery of genetic toxicology studies that included a bacterial reverse mutation (Ames) assay, an in vitro mammalian cell gene mutation assay (a mouse lymphoma assay conducted with L5178Y/TK+/- cells), and an in vivo test for genotoxicity (micronucleus assay with mice). Glycopyrronium tosylate was negative in an Ames assay. Solutions containing up to 4% w/w glycopyrronium tosylate did not induce carcinogenesis when topically applied to rats daily for approximately two years.

The sponsor of NDA 210361 has established a valid clinical bridge to NDA 022571 (Cuvposa liquid), which involves chronic oral ingestion of glycopyrrolate, resulting in systemic exposure to glycopyrronium at substantially higher levels than are associated with NDA 210361. The prior finding of safety associated with NDA 022571 supports the safety of the new topical use of glycopyrronium that is proposed under NDA 210361. The available database, including verbiage taken from the labeling of Cuvposa, as permitted under a 505(b)(2) NDA with a scientifically valid clinical bridge, acceptably addresses all nonclinical issues. No nonclinical post-marketing requirements are necessary. I recommend approval of NDA 210361 with respect to nonclinical concerns. Recommended labeling is presented in this review.

5.2. Referenced NDAs, BLAs, DMFs

NDA 022571 (Cuvposa (Glycopyrrolate, USP) liquid)

5.3. Pharmacology

Primary pharmacology
Glycopyrronium is a nonselective antagonist of muscarinic cholinergic receptors. Glycopyrronium competitively inhibits muscarinic receptors that are located on certain peripheral tissues, including sweat glands. Glycopyrronium indirectly reduces the rate of perspiration by preventing the stimulation of these receptors.

To help establish a bridge to NDA 022571 (Glycopyrrolate, USP), the sponsor conducted a study to demonstrate that the binding properties of glycopyrronium tosylate to muscarinic receptors were similar to those of glycopyrrolate (glycopyrronium bromide).

5.3.1. Glycopyrronium Muscarinic M3 Receptor Binding, study No. SSCG10933

Methods. The relative affinities of glycopyrronium bromide and glycopyrronium tosylate to bind to muscarinic M_3 receptors were assessed in vitro using "GeneBLAzer® M3 NFAT-bla CHO-K1 Cells".

Results. The dose response curves obtained with glycopyrronium tosylate and glycopyrronium bromide were similar. The calculated IC_{50} values for glycopyrronium bromide was 0.108 nM. The calculated IC_{50} for glycopyrronium tosylate was 0.102 nM.

Conclusion. These data suggest that the M_3 muscarinic acetylcholine receptor binding affinities of glycopyrronium tosylate and glycopyrronium bromide are equivalent.

Secondary Pharmacology
Glycopyrronium salts are capable of blocking peripheral muscarinic receptors throughout the body (although as a quaternary amine, glycopyrronium ions do not substantially cross the blood-brain barrier). The secondary pharmacology of glycopyrronium includes inhibition of intestinal motor activity, inhibition of gastric secretion, mydriatic activity, inhibition of lacrimation, inhibition of salivation, and inhibition of vagal input to the heart (which results in increased heart rate and contractile properties). However, these effects were not observed in clinical trials conducted with Qbrexza, presumably because systemic exposure to glycopyrronium is very low following topical application of glycopyrronium tosylate.

Safety Pharmacology
Stand-alone nonclinical safety pharmacology studies were not conducted for glycopyrronium tosylate monohydrate. As mentioned in the ICH S7A guidance, *Safety Pharmacology Studies for*

Human Pharmaceuticals, July 2001, safety pharmacology studies may not be needed for locally applied agents (e.g., dermal or ocular) where the pharmacology of the test substance is well characterized, and where systemic exposure or distribution to other organs or tissues is demonstrated to be low. ICH S7A also notes that safety pharmacology testing may not be needed in the case of a new salt having similar pharmacokinetics and pharmacodynamics to an established reference compound. The effects of glycopyrronium upon CNS, respiratory, cardiovascular and gastrointestinal systems can be predicted from the well-characterized pharmacological profile of glycopyrrolate (NDA 022571, to which the sponsor has established a clinical bridge). As discussed under section 5.5.1 of this review, the sponsor has conducted general toxicology studies in which glycopyrronium tosylate was topically applied to minipigs for extended periods. No effects on ECG were observed in those studies.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Pharmacokinetics of Glycopyrrolate in Male Göttingen Minipigs after a Single Dose via Intravenous or Dermal Routes, No. X7E116.	Following a single IV (bolus) dose of 0.25 mg/kg of glycopyrrolate to male Göttingen minipigs, the mean C_{2min} and $AUC_{0-\infty}$ were 458.5 ng/mL and 76.83 ng•h/mL, respectively. The mean clearance (CL), apparent volume of distribution (Vd) and the $t_{1/2}$ values were 3.71 L/h/kg, 39.35 L/kg and 7.51 hours, respectively. Glycopyrrolate was found to have a high plasma clearance (relative to hepatic blood flow) and a large volume of distribution (relative to total body water). Following dermal administration of glycopyrrolate (~ 6.6 mg/kg) to two male minipigs, absorption was highly variable. C_{max} for the two animals varied by 16-fold (1.13 vs. 0.07 ng/ml), and the AUC_{0-last} varied by 7- fold (4.44 vs. 0.64 ng•h/mL). T_{max} was reached for one animal at the first sampling point of 0.25 hours, while the other exhibited a T_{max} of 3 hours. The apparent bioavailability of glycopyrrolate

Type of Study	Major Findings
	administered dermally was 0.22% and 0.03% in these animals.
Distribution	
Kagiwada K et al., The metabolism of anticholinergic agent, glycopyrrolate (II) studies on the absorption, distribution, metabolism and excretion in mouse. Oyo Yakuri 7:889-901 (1973).	Following IV administration of 0.8 mg glycopyrrolate, spiked with 3.86 µCi ^{14}C-glycopyrrolate, to adult ICR mice, activity was rapidly distributed to all major organs except the brain. The activity was essentially cleared within 24 hours, primarily in the feces, and secondarily in urine.
Metabolism	
Evaluation of NADPH-dependent in vitro Metabolic Stability of Glycopyrrolate in Human, Minipig, Mouse, and Rat Liver Microsomes, No. 2008-DMPK-011-LS.	Liver microsomes from mice (CD-1, male), rats (Sprague Dawley, male), minipigs (Yucatan, male), and humans were incubated with glycopyrrolate (1 and 10 µM) in the presence of β-nicotinamide adenine dinucleotide phosphate (NADPH). Glycopyrrolate (1 and 10 µM) was poorly metabolized by human liver microsomes. At 1 µM glycopyrrolate, only 20% was metabolized after 150 min of incubation in the presence of 2.5 mg/mL microsomal protein. The apparent intrinsic clearance value was 0.64 µL/min/mg protein. In contrast, mouse, rat, and minipig liver microsomes in the presence of NADPH metabolized glycopyrrolate more readily with clearance values of 121, 593 and 346 µL/min/mg protein, respectively. Similar results were observed at a glycopyrrolate concentration of 10 µM. Glycopyrrolate was minimally metabolized in control incubations without NADPH.
Excretion	
Kagiwada K et al. (1973).	See above.
TK data from general toxicology studies 90-Day Dermal Toxicity and Toxicokinetic Study with DRM04 in Rats with a 4-Week	Rat (Day 90), 20% Topical Soln. C_{max}: 14 ng/mL AUC_{0-24h}: 90 ng•h/mL $t_{1/2}$: Not calculated

Type of Study	Major Findings
Recovery Phase, No. 8296392 (sponsor's ref. No. DRM04-TOX-13-07) 39-Week Dermal Toxicology Study with DRM04 Topical Solution in Minipigs with a 4-Week Recovery Phase, No. 8300103 (sponsor's ref. No. DRM04-TOX-14-03)	<u>Minipig (Week 39), 20% Topical Soln.</u> C_{max}: 4 ng/mL AUC_{0-24h}: 33 ng•h/mL $t_{1/2}$: Not calculated
TK data from reproductive toxicology studies TK data not available from label of listed drug.	NA
TK data from Carcinogenicity studies 104-Week Dermal Carcinogenicity and Toxicokinetic Study with DRM04 in Rats, No. 8296393 (sponsor's ref. no. DRM04-TOX-14-04)	<u>Rat (Week 26), 4% Topical Soln.</u> AUC_{0-24h}: Males: 12.8 ng•h/mL Females: 47.6 ng•h/mL

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: 39-Week Dermal Toxicology Study with DRM04 Topical Solution in Minipigs with a 4-Week Recovery Phase

Key Study Findings

- Application of 20% w/w glycopyrronium tosylate in DRM04 topical solution to 10% BSA of male and female minipigs once daily for 39 weeks had no apparent effects, including no effects on skin at the application site, and no effects on survival, clinical signs, mean body weight, ECG, clinical pathology, or histopathology.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

<u>Methods</u>
Dose and frequency of dosing: 2.2 mL of solution containing either 0, 2, 6, or 20% w/w glycopyrronium tosylate, applied once daily
Route of administration: Topical to 10% of the BSA
Formulation/Vehicle: Solution containing citrate, ethanol, and water
Species/Strain: Minipig/Gottingen
Number/Sex/Group: 4 in main study

Age: 2 to 3 months at start of dosing
Satellite groups/ unique design: 2 additional animals/sex/group in control and high-dose groups maintained without treatment for 4 weeks following 39 weeks of treatment (recovery animals)
Deviation from study protocol affecting interpretation of results: None

General toxicology; additional studies
Study title/ number: 90-Day Dermal Toxicity and Toxicokinetic Study with DRM04 in Rats with a 4-Week Recovery Phase, study No. 8296392 (sponsor's ref. No. DRM04-TOX-13-07). Conducted (b) (4) in compliance with GLP regulations, initiation date 09-JAN-2014. Formulations containing glycopyrronium tosylate at concentrations of 0%, 2%, 6%, or 20% w/w were topically applied to Sprague Dawley rats once daily for 92 days (300 µL per application). These exposures equated to approximately 0, 15, 45, and 150 mg/kg/day, although it is unknown what portion of each applied dose was subsequently removed when the site was cleansed. The applications covered approximately 10% of the BSA, and the sites were not covered or occluded following application. The 20% solution induced excessive dermal irritation at the treatment site, resulting in premature sacrifice or cessation of dosing of several animals. Signs of dermal irritation at the treatment site were essentially limited to high-dose animals. In males, reduced mean BW and mean BW change (gain) were observed in groups treated with ≥ 6% solution. In females, no treatment-related effects on mean BW were apparent in any group. There were no apparent effects of treatment on clinical pathology. At the terminal sacrifice, statistically significant decreases in mean absolute mandibular salivary gland weight values were seen in males given 6% or 20% (86% to 89% of controls) and females given 2%, 6%, or 20% (91% to 93% of controls). Treatment-related microscopic lesions were limited to the treatment site of animals that received 20% solution, were of minimal to moderate severity, and included evidence of inflammation. Toxicokinetic data demonstrated that systemic exposure to glycopyrronium increased with increasing concentration of the applied material. Under the conditions of this study, topical application of glycopyrronium tosylate 2% solution may be regarded as being a NOAEL in male rats, while application of glycopyrronium tosylate 6% solution may be regarded as being a NOAEL in female rats.

5.5.2. Genetic Toxicology

<u>In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)</u>
Study title/ number: Bacterial Reverse Mutation Assay/AB36SK.503 (b) (4)
Key Study Findings:

- Glycopyrrolate was negative in an Ames assay, with and without metabolic activation.

GLP compliance: Yes
Test system: Salmonella strains TA98, TA100, TA1535 and TA1537, and E. coli strain WP2 *uvr*A; up to 5000 ug/plate; +/- S9
Study is valid: Yes

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: DRM04 (Glycopyrronium Tosylate monohydrate): Bacterial Reverse Mutation Assay/8298092 (sponsor's ref. No. DRM04-TOX-14-01)

Key Study Findings:

- Glycopyrronium tosylate monohydrate was negative in an Ames assay, with and without metabolic activation.

GLP compliance: Yes

Test system: Salmonella strains TA98, TA100, TA1535 and TA1537, and E. coli strain WP2 *uvr*A; up to 5000 ug/plate; +/- S9

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK$^{+/-}$ Mouse Lymphoma Assay)/AB36SK.704 (b) (4)

Key Study Findings:

- Glycopyrrolate was negative in a mouse lymphoma assay, with and without metabolic activation.

GLP compliance: Yes

Test system: L5178Y cells, clone 3.7.2C; up to 4000 µg/mL; +/-S9

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Mammalian Erythrocyte Micronucleus Test/ AB36SK.123 (b) (4)

Key Study Findings:

- Glycopyrrolate was negative in a micronucleus assay with mice.

GLP compliance: Yes

Test system: ICR mice, bone marrow micronuclei; single intraperitoneal injections of 25, 50, or 100 mg/kg in males and 12.5, 25, and 50 mg/kg in females.

Study is valid: Yes

5.5.3. Carcinogenicity

Topical rat carcinogenicity study: 104-Week Dermal Carcinogenicity and Toxicokinetic Study with DRM04 in Rats, study No. 8296393 (Sponsor's ref. no. DRM04-TOX-14-04). Groups of Sprague Dawley rats were treated topically with solutions that contained 0 (saline), 0 (vehicle), 1%, 2%, or 4% w/w glycopyrronium tosylate once daily at a volume of 300 µL/dose to 10% of the BSA, 7 days per week for approximately two years, in both males and females. The vehicle consisted of water, ethanol, and citrate. The key finding of this study was that topical exposure of rats to glycopyrronium tosylate for a lifetime did not result in a significantly increased incidence of tumors in either males or females. A full review of study No. 8296393 is located in section 13.3 of this review.

Oral rat and mouse carcinogenicity studies: NDA 210361 references the listed drug Cuvposa (NDA 022571). The label of NDA 022571 includes information concerning carcinogenesis assays in which rats and mice were orally dosed with glycopyrrolate for up to two years. Glycopyrrolate was negative in those assays. This information will be included in the label of NDA 210361.

5.5.4. Reproductive and Developmental Toxicology

Reproductive toxicology studies: NDA 210361 references the listed drug Cuvposa (NDA 022571). The label of NDA 022571 includes information concerning effects of glycopyrrolate on fertility of rats, embryofetal development of rats and rabbits, and perinatal development, including maternal function, of rats. This information will be included in the label of NDA 210361.

5.5.5. Other Toxicology Studies

Study title/ number: DRM04: Local Lymph Node Assay in the Mouse (Individual Method), study No. 8292560 (sponsor's ref. No. DRM04-TOX-13-05). A solution containing 20% w/w glycopyrronium tosylate dissolved in a vehicle composed of water, alcohol, (b) (4) citric acid, and sodium citrate (b) (4) (simulating the vehicle of the commercial product), was assessed for potential to induce sensitization in a local lymph node assay with mice. The test article was considered non-sensitizing in this study. These data suggest that the product is unlikely to induce sensitization when topically applied.

6 Clinical Pharmacology

6.1. Executive Summary

Glycopyrronium is a (b) (4) quaternary ammonium compound that inhibits the action of acetylcholine on structures innervated by postganglionic, cholinergic (muscarinic) nerves, such as sweat glands. The applicant is seeking an approval of DRM04 (glycopyrronium) Topical Solution, 2.4% that is to be applied once daily to both the axillae, using a pre-moistened cloth for the treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older.

This NDA is submitted under 505(b)(2) regulatory pathway and the applicant has used Cuvposa® (glycopyrrolate) oral solution (NDA 022571 – date of approval: 07/28/2010) as the Listed Drug.

Topically applied glycopyrronium solution was evaluated in 8 clinical trials and these included two Phase 3 efficacy and safety trials, a Phase 3 long-term safety study, a Phase 2 proof-of-concept study, two Phase 2 studies, a Phase 1 sensitization/irritation study in healthy subjects, and a Phase 1 maximal use pharmacokinetic (MuPK) study. In the Phase 1 MuPK study, relative bioavailability was assessed following application of the to-be-marketed formulation of the proposed topical product (DRM04) applied under maximal use conditions compared to the listed drug (Cuvposa) administered orally. The purpose of this study was to support a clinical bridge. By establishing a clinical bridge with this listed drug, the applicant intended to cross reference nonclinical safety findings, information related to the metabolism, elimination, and use of glycopyrronium in subjects with renal and hepatic impairment.

The key review findings with specific recommendations/comments are summarized in Table 1**.**

Table 1: Summary of Clinical Pharmacology Review

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of glycopyrronium solution for topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older is primarily supported by two Phase 3 trials (DRM04-HH04, DRM04-HH05).
General dosing instruction	The proposed dosing regimen (apply a single-use cloth once daily to both axillae) is acceptable and supported primarily by the safety and efficacy data from two Phase 3 trials.
Dosing in patient subgroups (intrinsic and extrinsic factor)	Intrinsic or extrinsic factors were not evaluated.

Clinical bridge between DRM04 and the Listed Drug	Clinical bridge between DRM04 and Cuvposa™ was established by demonstrating lower systemic exposure of DRM04 under maximal use conditions compared to that of Cuvposa when the dose was titrated to the maximal dose as per the approved labeling.
Bridge between to-be-marketed and clinical trial formulations	PK bridge between to-be-marketed and clinical formulations is not necessary for approval of this NDA because the to-be-marketed formulation was used in the two Phase 3 efficacy and safety trials and in the maximal use PK study.
Drug-Drug Interaction	Two *in vitro* studies evaluating the potential inhibition/induction of CYP450 enzymes were submitted. The results suggested that DRM04 is unlikely to have any drug interaction potential under the conditions of clinical use. In vivo drug-drug interaction studies were deemed not necessary.

6.1.1. Recommendations

From a clinical pharmacology standpoint, this NDA is acceptable provided labeling comments are adequately addressed by the applicant.

6.1.2. Post-Marketing Requirements and Commitment(s)

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Glycopyrrolate is a (b) (4) quaternary ammonium compound with anticholinergic activity as a muscarinic receptor antagonist. Glycopyrrolate inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves, such as sweat glands. Under physiologic conditions, glycopyrrolate dissociates generating the glycopyrronium cation; therefore, the pharmacological activity of glycopyrrolate is mediated by the active moiety glycopyrronium.

Pharmacokinetics of DRM04

Pharmacokinetic characteristics of DRM04 based on the clinical pharmacology program are summarized in Table 2.

Table 2: Summary of Pharmacokinetics of DRM04

Review Issues	Conclusion/Comments
Absorption	Following topical administration of DRM04 cloth for 5 days, the means of Cmax and AUC_{0-6h} were 0.079 ng/mL and 0.195 h*ng/mL in adult subjects and 0.067 ng/mL and 0.178 h*ng/mL in pediatric subjects. The median t_{max} was 1 to 1.5 hour in both adults and pediatric subjects with high inter-subject-variability (ranging from 0 to 10 hours).
Relative Bioavailability (BA)	Following topical administration of DRM04 under maximal use conditions, the systemic concentrations of glycopyrronium were at or near steady state by Day 5. The steady-state systemic exposure of DRM04 were lower than those following oral administration of the listed drug (Cuvposa™) at the highest approved dose levels. This data supports establishment of a clinical bridge between DRM04 and Cuvposa.
Terminal Half-life	Due to sparse detectable concentrations in terminal phase, terminal elimination half-life following topical DRM04 could not be reliably calculated.
Dose Accumulation	No significant dose accumulation was noted in both adult subjects and pediatric subjects when DRM04 was applied once daily for 5 days.
Dose Linearity	A dose-ranging study (DRM04-HH01) was conducted with 4 strengths (1, 2, 3, and 4%) of DRM04B (glycopyrronium (b) (4)) which is a different salt form from the to-be-marketed formulation (glycopyrronium tosylate). Because clinical bridge has not been established between the two formulations, the information from dose ranging study is considered exploratory.
Pediatric Subjects	No notable differences in PK between pediatric and adult subjects were observed. It should be noted that there was only one subject (10 years of age) within the lowest age range of 9 to < 12 years old. Since the relative BA of the topical formulation was lower than Cuvposa and furthermore, Cuvposa is approved in subjects down to 3 years of age; the lack of PK information within the lowest age range, though highly desirable, would not impact approval of this product down to 9 years of age.
Drug-Drug Interaction	Two *in vitro* studies evaluating the potential inhibition/induction of CYP450 enzymes were submitted. The results suggested that DRM04 under the conditions of clinical use is not expected to have any drug-interaction potential.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant has proposed a dosing regimen of topical administration of single-use pre-moistened cloth once daily to both axillae. This regimen is supported by efficacy and safety data from two Phase 3 trials (DRM04-HH04, DRM04-HH05). Refer to Section 7 of this review for efficacy and safety findings.

Therapeutic Individualization

Therapeutic individualization was not evaluated.

Outstanding Issues

There are no outstanding issues that would preclude the approval of DRM04 from a Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The pharmacokinetics (PK) of topically applied DRM04 was evaluated in a Phase 1 maximal use pharmacokinetic (MuPK) study, a Phase 2 proof-of-concept study, and two Phase 2 studies. Two *in vitro* studies were conducted to assess CYP450 inhibition and induction potential of glycopyrrolate. Detailed reviews for individual studies are provided in Appendix 13.4.2.

- Phase 1 MuPK study (DRM04-HH07) is a relative bioavailability study that compared PK of DRM04 under maximal use conditions and the listed drug, Cuvposa™, in order to support a clinical bridge as part of the 505(b)(2) regulatory pathway.
- Phase 2 study (DRM04-HH01) is a dose-ranging trial evaluating efficacy, safety and PK of 4 strengths of DRM04B.
- In a Phase 2 study (DRM04-HH02), plasma concentrations of glycopyrronium in subgroups of the enrolled subjects were measured providing PK characteristics of two different salts of glycopyrronium.
- In a proof-of-concept study (W0266-01), bioavailability of 2 different formulations, each of which contained (b) (4) were evaluated.

Formulations in Clinical Development

During clinical development, two salt forms of glycopyrronium (glycopyrronium (b) (4) [DRM04B] and glycopyrronium tosylate monohydrate [DRM04]) were evaluated. Both glycopyrronium salts dissociate to form the glycopyrronium cation, which was quantifiable in human plasma samples. Glycopyrronium tosylate monohydrate (DRM04) (b) (4)

(b) (4) at a concentration of (b) (4)% (equivalent to glycopyrronium concentration of 2.4%) was chosen as the to-be-marketed formulation and used in two pivotal Phase 3 trials and Phase 1 Maximal Use PK trial. Table 3 provides a summary of the glycopyrronium salts and concentrations evaluated in clinical pharmacology trial and the equivalent glycopyrronium concentration.

Table 3: Clinical Pharmacology Studies and Investigational Drug Formulations Used

Clinical Trial	Study Design	Active Ingredient / Strengths	Equivalent Glycopyrronium Strength
W0266-01	Proof-of-concept, randomized, double-blind, vehicle controlled trial	Glycopyrrolate (b) (4)%, (b) (4)%	(b) (4)%, (b) (4)%
DRM04-HH01	Phase 2, randomized, double-blind, vehicle controlled, parallel group, dose-ranging trial	DRM04B, 1.0%, 2.0%, 3.0%, 4.0%	(b) (4)%, (b) (4)%, 2.4%, (b) (4)%
DRM04-HH02	Phase 2, randomized, double-blind, vehicle controlled, parallel group Trial	DRM04B, (b) (4)%, (b) (4)%	(b) (4)%, 2.4%
		DRM04*, (b) (4)%, (b) (4)%	(b) (4)%, **2.4%**
DRM04-HH07	Phase 1, open label, maximum-use PK trial, conducted in 2 cohorts	**DRM04*, (b) (4)%**	**2.4%**
*To-be-marketed formulation			

Pharmacokinetics of Topically Administered DRM04 Under Maximal Use Conditions

Phase 1 bioavailability (BA) study (DRM04-HH07) was conducted to assess the safety, tolerability and PK of DRM04 Topical Cloth, (b) (4)%, which is to-be-marketed formulation, applied topically under maximum-use conditions in subjects with primary axillary hyperhidrosis (Cohort 1). This study also included a comparative arm, oral glycopyrrolate (Cuvposa™) administered in healthy adults (Cohort 2) to support a clinical bridge by assessing the relative bioavailability between the two products. The purpose of the clinical bridge was to cross reference nonclinical safety findings, information related to metabolism, elimination, and use of glycopyrronium in subjects with renal and hepatic impairment.

A total of 49 subjects were enrolled: 31 subjects in cohort 1 (11 adults and 20 pediatric subjects 10 to 17 years of age) and 18 adult subjects in cohort 2. In Cohort 1, a single cloth was used to apply study drug (DRM04, (b) (4)%) to both axillae once daily in the morning for 5 days. Subjects in Cohort 2 were administered with oral glycopyrrolate (Cuvposa™) for up to a maximum of 15 days (dosing started at 1.0 mg every 8 hours on Day 1 and dose escalated every 5 days based on tolerability, up to a maximum dose of 3 mg every 8 hours). Demographics of the study subjects in DRM04 HH-07 are presented in Table 4.

Reviewer comments: Cuvposa™, glycopyrrolate oral solution, is approved for reducing chronic severe drooling in patients aged 3-16 years with neurologic conditions associated with problem

drooling. Approved dosing regimen is initially at 0.02 mg/kg orally three times daily and titrate in increments of 0.02 mg/kg every 5-7 days. The maximum recommended dosage is 0.1 mg/kg three times daily not to exceed 1.5-3 mg per dose based upon weight. Per labeling of Cuvposa, the recommended dose titration schedule for the subject with ≥ 48 kg is starting of 1 mg three times daily and titrating in increments of 1 mg every 5-7 days up to 3 mg three times a day. Hence, this reviewer opines that it is reasonable to assume that PK data on Day 15 in Cohort 2 (Adults weighted ≥ 48 kg) represents the steady-state PK of oral glycopyrrolate following the doses titrated to maximum tolerated dose per label. The PK data on Day 15 following Cuvposa administration was used to assess establishment of a clinical bridge.

Table 4: Summary of Subjects Demographics

	Cohort 1 Adults DRM04, (b) (4)% (N = 11)	Cohort 1 Pediatric DRM04, (b) (4)% (N = 20)	Cohort 2 Adults Cuvposa (N = 18)
Age (years)			
Mean (SD)	26.0 (8.92)	14.8 (1.64)	44.0 (10.35)
Median	23.0	15.0	46.5
Minimum, Maximum	18, 49	10, 17	18, 58
Sex, n (%)			
Male	4 (36.4)	7 (35.0)	16 (88.9)
Female	7 (63.6)	13 (65.0)	2 (11.1)
Race, n (%)			
White	9 (81.8)	13 (65.0)	9 (50.0)
Black or African American	2 (18.2)	7 (35.0)	8 (44.4)
Other	0	0	1 (5.6)
Ethnicity, n (%)			
Hispanic or Latino	2 (18.2)	0	2 (11.1)
Not Hispanic or Latino	9 (81.8)	20 (100.0)	16 (88.9)
Weight (kg)			
Mean (SD)	87.76 (27.72)	67.15 (16.86)	80.23 (9.82)
Median	79.50	63.60	78.75
Minimum, Maximum	61.7, 156.9	46.3, 108.0	66.7, 98.8
Height (cm)			
Mean (SD)	171.79 (12.40)	167.50 (10.25)	171.56 (7.16)
Median	167.60	166.35	173.75
Minimum, Maximum	154.9, 198.1	150.5, 193.0	153.0, 183.0
BMI (kg/m^2)			
Mean (SD)	29.35 (6.29)	23.88 (5.55)	27.21 (2.35)
Median	29.50	22.15	27.80
Minimum, Maximum	21.9, 40.0	18.6, 40.8	23.5, 30.8

Source: Table 14.1.2.1
DRM04, 3.75% = DRM04 Topical Wipes, 3.75%

Reviewer comments: Comparing adult subjects in Cohort 1 and the subjects in Cohort 2, the subjects in Cohort 1 appears younger, including more female and white subjects comparing to the subjects in Cohort 2. In the pediatric subjects in Cohort 1, the minimum age enrolled in the study was 10 years old. The minimum age studied in this pivotal PK study will be reflected in the labeling language in PK section. In Cohort 2 (comparator arm), minimum weight of enrolled subjects was 46.3 kg. The dosing regimen administered in cohort 2 appears appropriate per labeling of Cuvposa (see the earlier comment).

The applicant performed the primary PK analysis that excluded outliers and the secondary PK analysis that included all data. Concentrations were considered outliers if plasma concentration values were greater than 3 standard deviation from the mean value for a given time point. The applicant also reported that 6 of 31 subject in Cohort 1 from 3 (of a total of 7) study sites had detectable concentrations of glycopyrronium in the pre-dose sample on Day 1, and the reason for observing this is not known. Details regarding outlier data and detectable pre-dose concentrations are provided in individual study report in Appendix 13.4.2. In this review, the results from the analysis including all data was primarily evaluated. High inter-subject variability is expected and was observed following topical administration of DRM04.

The summary of pharmacokinetic parameters and relative bioavailability assessment are presented in Table 5, and Table 6. Following DRM04, (b) (4)% administration, the median t_{max} ranged from 1 to 1.5 hours on both Day 1 and Day 5 in adult and pediatric subjects. The means of Cmax, AUC_{0-6h}, AUC_{0-8h} on Day 5 following DRM04, (b) (4)% administration (Cohort 1) were lower than those following Cuvposa administration at the highest approved dose level for up to 15 days (Cohort 2).

- The mean Cmax on Day 5 in Cohort 1 were 0.325 ng/mL and 0.144 ng/mL in adult and pediatric subjects respectively, while mean Cmax on Day 15 in Cohort 2 was 0.381 ng/mL
- The mean AUC_{0-6h} on Day 5 in Cohort 1 were 0.195 h*ng/mL and 0.272 h*ng/mL in adult and pediatric subjects respectively, while mean AUC_{0-6h} on Day 15 in Cohort 2 was 1.57 h*ng/mL.
- AUC_{0-8h} (0.264 h*ng/mL) on Day 5 in adult subjects in Cohort 1 was lower than AUC_{0-8h} (1.83 h*ng/mL) on Day 15 in adult subjects in Cohort 2.

Table 5: Summary of PK Parameters (Excluding and Including Outlier Data) of DRM04-HH07

	Cohort 1 (DRM04, (b) (4)%)								Cohort 2 (Cuvposa)
	Excluding Outlier Data				Including All Data				
	Adults		Pediatric		Adults		Pediatric		Adults
	Day 1: (N = 11)	Day 5: (N = 11)	Day 1: (N=19)	Day 5: (N=20)	Day 1: (N = 11)	Day 5: (N = 11)	Day 1: (N=19)	Day 5: (N=20)	Day 15: (N = 18)
Cmax (ng/mL)	n=11	n=11	n=19	n=20	n=11	n=11	n=20	n=20	n=18
Mean (SD)	0.139 (0.143)	0.0790 (0.0377)	0.0508 (0.0668)	0.0670 (0.0633)	0.343 (0.533)	0.325 (0.629)	0.109 (0.269)	0.144 (0.260)	0.381 (0.190)

t_{max} (h) **Median** **Range**	n=11 1.5 (0.5, 10)	n=11 1 (0, 10)	n=12 1 (0.5, 6)	n=19 1.5 (0, 6)	n=11 1 (0.5, 10)	n=11 1 .5 (0, 24)	n=13 1 (0.5, 6)	n=19 1.5 (0, 4)	n=18 2 (0.5, 4)
AUC_{0-6h} (h*ng/mL) **Mean** **(SD)**	n=8 0.540 (0.430)	n=10 0.195 (0.140)	n=16 0.136 (0.137)	n=11 0.178 (0.133)	n=9 0.616 (0.556)	n=10 0.195 (0.140)	n=18 0.32 (0.812)	n=11 0.272 (0.232)	n=18 1.57 (0.638)
AUC_{0-8h} (h*ng/mL) **Mean** **(SD)**	n=8 0.672 (0.518)	n=10 0.264 (0.187)	Not Calculated	Not Calculated	n=9 0.871 (0.726)	n=10 0.264 (0.187)	Not Calculated	Not Calculated	n=18 1.83 (0.73)
AUC_{0-24h} (h*ng/mL) **Mean** **(SD)**	n=5 2.57 (1.00)	n=7 0.883 (0.572)	Not Calculated	Not Calculated	n=5 2.71 (1.21)	n=8 3.17 (5.25)	Not Calculated	Not Calculated	n=18 5.50 (2.19)
The information was from Table 40 and Table 41 in the Appendix 13.4.2									

Relative bioavailability (BA) estimated as 90% CI of the ratio of the geometric mean of Cmax and AUC is shown in Table 6. Following DRM04 administration, geometric mean ratio of Cmax, AUC_{0-8h}, and AUC_{0-24h} in adult subjects on Day 5 to those values in Cuvposa on Day 15 were 0.32, 0.14, and 0.24, respectively, and the upper bounds of 90% CI for mean ratios for these parameters were less than 1. Geometric mean ratio of Cmax, and AUC_{0-6h} in pediatric subjects were also less than 1. This confirms lower exposure following topical DRM04 compared to following oral glycopyrrolate at maximum approved dose.

Table 6: Comparison of Relative Exposure: DRM04 on Day 5 vs Cuvposa on Day 15

		Geometric Mean Ratio (90% CI)	
		Excluding Outlier Data	**Including All data**
Cmax (ng/mL)	**Adults**	0.2062 (0.1459, 0.2913)	0.3245 (0.1786, 0.5895)
	Pediatric	0.1313 (0.08508, 0.2026)	0.1694 (0.09646, 0.2973)
AUC_{0-6} (h×ng/mL)	**Pediatric**	0.1015 (0.07078, 0.1454)	0.1300 (0.08334, 0.2028)
AUC_{0-8} (h×ng/mL)	**Adults**	0.1352 (0.09878, 0.1851)	0.1352 (0.09878, 0.1851)
AUC_{0-24} (h×ng/mL)	**Adults**	0.1460 (0.09968, 0.2139)	0.2447 (0.1348, 0.4443)

Reviewer's Summary Assessments of Pharmacokinetics of Topically Administered DRM04

- *Clinical bridge between DRM04 and the listed drug (Cuvposa) has been established. Overall, the lower systemic exposure following administration of DRM04 under maximal use condition was observed compared to Cuvposa at the highest approved dose levels.*

Consistent results were reported with the analysis performed by excluding and including outliers.

- *Observed median t_{max} was1 -1.5 hours; however, inter-subject variability in t_{max} was high with individual t_{max} ranging from 0 to 24h. The high variability is likely due to the outlier data which show unusual high concentrations observed at the later time such as (at 10 hour or at 24 hour). Individual concentration-time profiles are shown in Figure 17 in Appendix 13.4.2.*
- *The systemic exposures on Day 1 were slightly higher than those on Day 5 in adult and pediatric subjects in the analysis with including all data, which is suggestive of lack of dose accumulation. However, in the analysis excluding outliers, slightly greater systemic exposure on Day 5 compare to Day 1 was observed in pediatric subjects. This effect seems to be due to high inter-subject variability and is not of any clinical significance. The data is suggestive of lack of drug accumulation.*
- *Considering the lack of notable dose accumulation following topical DRM04 administration, this reviewer opines that systemic concentration of DRM05 are at or near steady-state by Day 5.*

Pharmacokinetics in Pediatric Subjects

The Phase 1 bioavailability (BA) study (DRM04-HH07) enrolled pediatric subjects age from 10 to 17 in Cohort 1 (DRM04). There is no noticeable difference in systemic exposure between pediatric subjects and adult subjects. Including all data, mean AUC_{0-6h} on Day 5 in pediatric subjects was greater by approximately 40% than that on Day 5 in adult subjects (Table 5). The mean ratio of AUC_{0-6} in pediatric vs adults was 1.12 [90%CI: 0.62-2.03] when including all data (Table 7). However, the analysis excluding the outliers showed comparable or slightly lower mean AUC_{0-6h} in pediatric subjects (Table 7). Due to large inter-subject variability and some outlier concentrations, this difference in exposure when inducing all data does not seem to be of any significance.

Table 7: Comparison of Relative Exposure: DRM04 Pediatrics Day 5 vs DRM04 Adults Day 5

	Geometric Mean Ratio (90% CI)	
	Excluding Outlier Data	**Including All data**
Cmax (ng/mL)	0.6367 (0.3694, 1.0970)	0.5219 (0.2229, 1.2220)
AUC_{0-6} (h×ng/mL)	0.8720 (0.5423, 1.4020)	1.1170 (0.6154, 2.0290)

Reviewer comments: To investigate the discrepancy between two analyses, individual data was evaluated. Among the concentrations measured on Day 5, three exceptionally high concentrations were identified at a single time point in each of three pediatric subjects (Table 8). These identified concentration values were >30 folds greater than the levels observed at adjacent time points. The reason for this >30 folds increase in systemic exposure is not provided by the applicant; however, this reviewer opines that these values do not represent true plasma

*levels of drug and should not be included in calculation of AUC. Excluding these outliers resulted in mean AUC_{0-6h} of 0.178 h*ng/mL on Day 5 in pediatric subjects and 0.195 h*ng/mL on Day 5 in adult subjects (Table 5) with mean ratio of 0.872 [90% CI: 0.54-1.4] (Table 7). Systemic exposure between pediatric subjects and adult subjects appears comparable.*

Table 8: Identified Exceptionally High Concentrations in Pediatric Subjects

	Day 5								
Subject	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**2.5h**	**3h**	**4h**	**6h**
101-0001	0.0284	0.247	0.0231	**1.13***	0.0268	0.0218	0.0221	0.0209	0.0182
101-0006	<0.0100	0.0189	0.0160	<0.0100	<0.0100	**0.479***	<0.0100	0.0168	0.0671
103-0002	0.0209	0.0233	0.0132	0.0626	<0.0100	**0.312***	<0.0100	0.0240	0.0157
*Unusual high concentration measurement Concentration measurement lower than LLOQ is underlined									

It should be noted that there was only one subject (10 years of age) within the lowest age range of 9 to < 12 years old. Since the relative BA of the topical formulation was lower than Cuvposa and furthermore, Cuvposa is approved in subjects down to 3 years of age; based on this, the lack of PK information within the lowest age range, though highly desirable, would not impact approval of this product down to 9 years of age. The adequacy of safety and efficacy data within the lowest age range from the Phase 3 trials is deferred to clinical.

Heathy Subjects vs Patients

All clinical pharmacology studies enrolled patients with axillary hyperhidrosis. The comparison of PK in healthy subjects and patients were not evaluated.

To-be-marketed formulation (DRM04) vs. Developmental formulation (DRM04B)

Since the to-be-marketed formulation was used in the pivotal Phase 3 trials and the relative BA study under maximal use conditions, it is not necessary to establish a bridge between the to-be-marketed formulation and other formulations used during development.

In the Phase 2 study (DRM04-HH02), the applicant compared the pharmacokinetics of 2 strengths of 2 glycopyrronium salts, DRM04B ((b) (4)% and (b) (4)%) (glycopyrronium (b) (4)) and DRM04 ((b) (4)% and (b) (4)%) (glycopyrronium tosylate monohydrate) in subjects with axillary hyperhidrosis in subgroup of the subjects. (b) (4) The PK results are presented in Table 9.

Table 9: DRM04-HH02 Summary of Glycopyrronium Pharmacokinetic Parameters

Group	C_{max} (ng/mL)		T_{max} (h)		AUC_{0-t} (h×ng/mL)	
	N[a]	Mean (SD)	N[a]	Median (Min, Max)	N[a]	Mean (SD)
DRM04B, (b)(4)%	1	0.0263 (ND)	1	3.00 (ND)	1	ND (ND)
DRM04B, %	4	0.307 (0.285)	4	3.26 (2.50, 10.20)	4	3.18 (4.15)
DRM04, (b)(4)%	3	0.0485 (0.0312)	3	1.50 (0.50, 24.10)	3	0.320 (0.316)
DRM04, %	2	0.0575 (0.0433)	2	1.00 (0.50, 1.50)	1	1.13 (ND)

ND = Not determined
Note: At least 3 quantifiable concentration values must have been available for calculation of a subject's AUC.
[a] Number of subjects with detectable plasma concentrations. PK parameters were determined for subjects with detectable levels only.
Source: DRM04-HH02 CSR, Pharmacokinetic Report, Table 2

Comparing PK parameters of two salts forms (b) (4) (DRM04B, (b)(4)% vs. DRM04, (b) (4)%) and (DRM04B, (b)(4)% vs. DRM04, (b)(4)%), it appears that mean Cmax and AUC were highly variable and any trends within or between the salts formulation could not be identified (Table 9). Details of review of this study are provided in Appendix 13.4.2 Individual Study Reports.

Reviewer comments: Due to the limited number of quantifiable concentration levels, any comparisons between the two formulations of different salt forms, DRM04B and DRM04, at either strength were not possible and conclusion on PK bridge between two formulations could not be made. It should be noted that a PK bridge alone would not suffice as PK is not correlated with efficacy, rather it is correlated only with systemic safety. Ideally, in addition to the PK bridge, bridging via assessment of clinical endpoints will be needed. The need for additional Phase 2 studies with the final formulation was deferred to clinical during IND. From a Clinical Pharmacology perspective, the studies to establish a bridge between the 2 glycopyrronium salts was not deemed necessary for the approvability of this NDA as to-be-marketed formulation was used in the Phase 3 trials and the Maximal Use PK study.

Dose Linearity

Dose linearity was assessed in a Phase 2, randomized, vehicle-controlled, parallel group, dose-ranging trial (DRM04-HH01). This study was also designed to assess the safety and efficacy of 4 strengths of DRM04B (1.0%, 2.0%, 3.0%, and 4.0%) compared with vehicle for the treatment of axillary hyperhidrosis. Since this study used a different salt (b) (4) and PK comparability between 2 salts were not adequately established, the study results will not be described in this review as they will not impact approvability of this application.

Bioanalysis and Bioanalytical Methods Validation

Two validated bioanalytical methods that used HPLC with MS/MS, were used to determine plasma glycopyrronium concentrations during clinical development. One of the methods was used to analyze PK samples from the Phase 1 MuPK study while the other method was used to analyze PK samples from the two Phase 2 studies. The bioanalysis results for the bioanalytical assays were submitted for review and were found acceptable. The key components of method validation parameters are presented in Table 10.

Table 10: Method Validation Parameters for the Assays for Measurement of Glycopyrronium in Human Plasma

Validation Report	**LCMSC 655.1**		**LCMSC 655.3**	
Relevant Clinical Trials	**DRM04-HH01** **DRM04-HH02**		**DRM04-HH07 (MuPK study)**	
Analytes	Glycopyrrolate			
Matrix	Human Plasma			
Linearity	0.0200 to 20.0 ng/mL		0.0100 to 10.0 ng/mL	
LLOQ	0.0200 ng/mL		0.0100 ng/mL	
Precision (%CV)	Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
	1.06 to 5.67%	2.25 to 9.15%	0.539 to 9.75%	10.0 to 13.2%
Accuracy (%)	Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
	−9.99 to 8.87%	0.628 to 5.86%	-8.761 to 2.60%	−6.03 to −11.6%
Thawed Matrix Stability	26 hours at room temperature		24 hours at room temperature	
Solution Stability	45 days at -20 °C in acetonitrile		117 days at -20 °C in acetonitrile	
Solution Stress Stability	6.03 hours at room temperature in acetonitrile*		6.03 hours at room temperature in acetonitrile*	
Extract Stability	94 hours at 2 to 8 °C		150.87 hours at 2 to 8 °C	
Freeze-thaw Stability	Five cycles frozen at -20 °C or -70 °C thawed at room temperature		Five cycles frozen at -20 °C or -70 °C and thawed at room temperature	
Frozen Matrix Storage Stability	28 days at -20 °C and -70 °C		37 days at -20 °C and -70 °C	
Long Term Storage Stability	334 days at -20 °C and -70 °C		149 days at -20 °C and -70 °C	
Selectivity	No significant interfering peaks noted in blank plasma samples			
Incurred sample reanalysis (ISR)	Approximately 10% of the study samples were re-assayed. Incurred sample repeats were considered acceptable if the original and re-assay values from two-thirds of the repeated samples had a relative percent difference of ≤ 20%.			
Total % ISR Samples Pass	DRM04-HH01: 100% DRM04-HH02: 78.8%		DRM04-HH07: 86.7%	

Reviewer comments: Overall, the method validation for both bioanalytical assays appears adequate. The range of linearity was 0.1 to 10 ng/mL. This range was adequate as all the plasma concentrations of glycopyrrolate measured in DRM04-HH07 were within the upper limit of the concentration range. In the report LCMSC 655.3 of the assay used in the study DRM04-HH07, glycopyrronium was stable in human plasma for 149 days when stored at −20 °C or −70 °C. The Applicants provided adequate data confirming that all plasma samples from clinical trial DRM04-HH07 were analyzed within the demonstrated stability time frame.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The purpose of maximal use PK study was to assess systemic safety and efficacy was not assessed in this study. The evidence of effectiveness of DRM04 is primarily supported by assessing clinical endpoints in the two Phase 3 trials which demonstrated the efficacy and safety of DRM04 for 28 days in subjects age 9 and older with primary axillary hyperhidrosis. See Section 7 of this multi-disciplinary review for the results of the Phase 3 trials that supported efficacy and safety.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen is primarily supported by efficacy and safety results in the Phase 3 trials which evaluated the proposed dose regimen and demonstrated efficacy for 28 days in subjects with primary axillary hyperhidrosis.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. A dose adjustment is not necessary based on the available efficacy data in Phase 3 trials. Evaluation of the PK of glycopyrronium following administration of topical DRM04 based on intrinsic (e.g., demographic characteristics) and extrinsic (e.g., geographic region, concomitant medications) factors, other than age (see Pharmacokinetics in Pediatric Subjects in Section 6.3.1.), was not performed.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interaction studies are not needed for topical products.

Two *in vitro* studies evaluating the potential inhibition/induction of CYP450 enzymes were submitted. The results suggested that DRM04 under the conditions of clinical use is not expected to have any drug-interaction potential. Detailed reports for these studies are provided in Appendix 13.4.2.

What is the effect of renal and hepatic impairment on the PK of DRM04?

The effect of renal and hepatic impairment on PK of DRM04 was not evaluated by the applicant. The applicant has cross referenced this information from the listed drug (Cuvposa) label.

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The applicant conducted eight clinical trials to evaluate the proposed product in subjects with primary axillary hyperhidrosis. Table 11 below provides a summary of key trials pertinent to the evaluation of the efficacy and safety of glycopyrronium cloth, 2.4% for the treatment of primary axillary hyperhidrosis. For a discussion of the pharmacokinetic trials, the reader should refer to the Clinical Pharmacology Section (Section 6 of this review) and the Clinical Pharmacology Review.

Table 11: Key Clinical Trials Relevant to NDA 210361 – Glycopyrronium cloth, 2.4% for Primary Axillary Hyperhidrosis

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. Centers and Countries
Controlled Studies to Support Efficacy and Safety							
DRM04-HH04	Phase 3 multicenter, randomized, double-blind, vehicle-controlled, parallel group trial	Glycopyrronium cloth, 2.4% (DRM04) or vehicle cloth applied once daily (q HS) to each axilla – topical application	Co-primary: 1) mean absolute change from baseline in gravimetric sweat production at Week 4, and 2) proportion of subjects with ≥ 4-pt improvement in weekly mean score of ASDD Item #2 from baseline at Wk 4	Study product applied daily for 28 days	ITT: 344 DRM04 229, Vehicle 115 Age (yrs) 9-17: 23 ≥ 18: 321 Safety: 341	Male and female subjects age ≥9 years with primary axillary hyperhidrosis, average baseline score of ≥ 4 on Item #2 of the Axillary Sweating Daily Diary (ASDD) and sweat production of ≥ 50 mg over 5 minutes in each axilla	21 sites in the US and 8 sites in Germany
DRM04-HH05	Phase 3 multicenter, randomized, double-blind, vehicle-controlled, parallel group trial	Glycopyrronium cloth, 2.4% (DRM04) or vehicle cloth applied once daily (q HS) to each axilla – topical application	Co-primary: 1) mean absolute change from baseline in gravimetric sweat production at Week 4, and 2) proportion of subjects with ≥ 4-pt improvement in weekly mean score of ASDD Item #2 from baseline at Wk 4	Study product applied daily for 28 days	ITT: 353 DRM04 234, Vehicle 119 Age (yrs) 9-17: 33 ≥ 18: 320 Safety: 350	Male and female subjects age ≥9 years with primary axillary hyperhidrosis, average baseline score of ≥ 4 on Item #2 of the Axillary Sweating Daily Diary (ASDD) and sweat production of ≥ 50 mg over 5 minutes in each axilla	20 sites in the US

Studies to Support Safety							
DRM04-HH06	Phase 3 multicenter, open label long term safety trial	Glycopyrronium cloth, 2.4% (DRM04) applied once daily (q HS) to each axilla – topical application	Safety endpoints: AEs, SAEs, TEAEs, local skin reactions, clinical laboratory results, vital signs, and physical examinations	Study product applied daily for up to 44 weeks	564 subjects Age (yrs) 9-17: 47 ≥ 18: 503 Safety: 550	Male and female subjects age ≥9 years with primary axillary hyperhidrosis who had completed Day 28 of either Study DRM04-HH04 or Study DRM04-HH05 with at least 80% treatment compliance	40 sites in the US and 8 sites in Germany
DRM04-HH08	Phase 1 randomized, controlled trial to evaluate the sensitizing and cumulative irritation potential of glycopyrronium cloth, 2.4%, in healthy volunteers using a Repeat Insult Patch Test and Cumulative Irritation Design	Cohort 2: Cumulative Irritation Potential Test (CIPT) using occlusive patch; stopped early due to anticholinergic AEs; Cohort 2a: CIPT – semi-occlusive patch; Cohort 1: Contact Sensitization Potential	<u>Safety:</u> Signs of irritation and sensitization, AEs	Cohort 2: Study treatments daily x 8 days (stopped early); Cohort 2a: Study treatments daily x 21 day Cohort 1a: 21 day induction period, 10-14 days rest, then 2 days rechallenge	328 adult subjects Cohort 2: 45 Cohort 2a: 41 Cohort 1a: 242	Healthy male and female subjects age ≥ 18 years, any skin type or race with pigmentation allowing the discernment of erythema (Fitzpatrick Scale I-V)	One site in the US

7.1.2. Review Strategy

Data Sources

The sources of data used for the evaluation of the efficacy and safety of glycopyrronium for the proposed indication included final study reports submitted by the applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references. This application was submitted in eCTD format and entirely electronic. The electronic submission including protocols, statistical analysis plans (SAPs), clinical study reports, SAS transport datasets in legacy, Study Data Tabulation Modal (SDTM), and Analysis Data Model (ADaM) format were in the following network path:

- Original submission: \\cdsesub1\evsprod\nda210361\0001\m5\datasets\

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study Design and Endpoints

The applicant conducted two identically-designed, randomized, double-blind, vehicle-controlled, parallel group Phase 3 studies, Trials DRM04-HH04 and DRM04-HH05, hereinafter referred to as Trials HH04 and HH05. Subjects who met the following key inclusion criteria were eligible to be enrolled in the trials:

- Age ≥9 years (Age ≥18 years for sites in Germany)
- Primary axillary hyperhidrosis of at least 6 months duration
- Hyperhidrosis Disease Severity Scale (HDSS; presented in Table 12) grade of 3 or 4 at baseline
- Average Axillary Sweating Daily Diary (ASDD) item #2 (presented in Figure 1 and Figure 2) score of ≥ 4 at baseline. Subjects must have completed 4 to 7 days of the ASDD assessment within 7 days of randomization.
- Sweat production of at least 50 milligrams (mg) over 5 minutes (min) in each axilla assessed gravimetrically. Subjects with a measurement of < 50 mg/each axilla/5 minutes who, in the opinion of the investigator, had a diagnosis of hyperhidrosis could have gravimetric measurements performed up to a total of 3 times within the 35 days prior to randomization.

The following are key criteria that would exclude subjects from enrolling in the trials:

- Prior surgical procedure for hyperhidrosis
- Prior axillary treatment with an anti-hyperhidrosis medical device (approved or investigational) such as miraDry®
- Prior treatment with axillary iontophoresis within 4 weeks of baseline
- Prior treatment with botulinum toxin (e.g., Botox®) for axillary hyperhidrosis within 1 year of baseline
- Previous active treatment in the Dermira Studies DRM04-HH01 or DRM04-HH02

- Axillary use of nonprescription antiperspirants within 1 week or prescription antiperspirants within 2 weeks of baseline
- Secondary axillary hyperhidrosis or presence of a condition that may cause secondary hyperhidrosis (e.g., lymphoma, malaria, severe anxiety not controlled by medication, carcinoid syndrome, substance abuse, hyperthyroidism)

The HDSS is presented in Table 12. The Agency informed the applicant on multiple occasions during the IND stage (the first time in meeting minutes dated September 27, 2013) that the HDSS instrument is not well-defined because it combines two distinct concepts (tolerability of the condition and interference of the condition with daily activities) within the same item. The Agency stated that combining two concepts within the same item limits the interpretation of study results because it is not possible to ascertain which of the two concepts has changed with treatment.

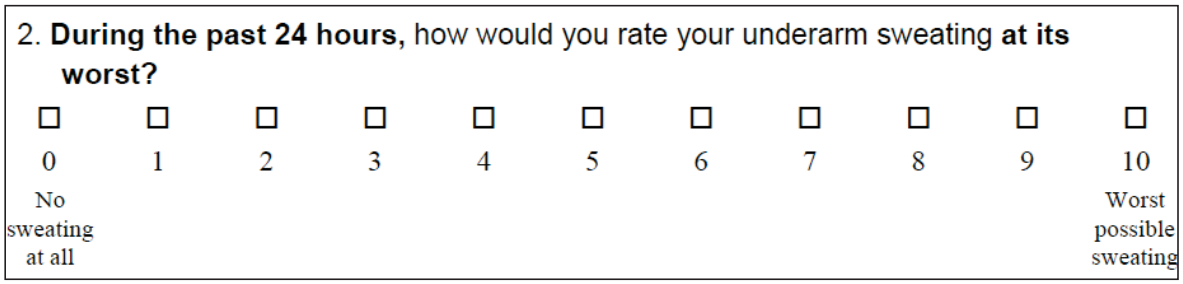
Table 12: Hyperhidrosis Disease Severity Scale (HDSS)

Hyperhidrosis Disease Severity Scale	
Grade	**Definition**
1	My sweating is never noticeable and never interferes with my daily activities
2	My sweating is tolerable but sometimes interferes with my daily activities
3	My sweating is barely tolerable and frequently interferes with my daily activities
4	My sweating is intolerable and always interferes with my daily activities

Source: Appendix C on page 54 of applicant's protocol for Trial HH04

The applicant states that the ASDD presented in Table 50 was developed by Dermira. The Clinical Outcome Assessment (COA) reviewer, Michelle Campbell, concluded in her review dated May 11, 2015 that the applicant had adequately established for age 18 and above the measurement properties for item #2 of the ASDD presented in Figure 1. The Axillary Sweating Daily Diary Children (ASDD-C) presented in Figure 2 is a modified version of the ASDD comprised of only 2 items, and was completed by subjects less than 16 years of age in the trials.

Figure 1: Axillary Sweating Daily Diary (ASDD) Item #2



Source: Appendix D on page 55 of applicant's protocol for Trial HH04

Figure 2: Axillary Sweating Daily Diary Children (ASDD-C)

These questions measure how bad your underarm sweating was last night and today. Please think only about your underarm sweating when answering these questions. Please complete these questions each night before you go to sleep.

1. **Thinking about last night and today**, did you have **any** underarm sweating?

a) Yes

b) No

2. **Thinking about last night and today,** how **bad** was your underarm sweating**?**

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No sweating at all										Worst possible sweating

Source: Appendix E on page 57 of applicant's protocol for Trial HH04

The protocol specifies that eligible subjects were randomized in a 2:1 ratio within study sites to DRM04 or vehicle respectively using a central interactive web-based randomization system (IWRS). Subjects were instructed to apply the study drug via a single wipe once daily in the evening to both axillae for 28 days. Subjects were instructed to apply the study drug to clean, dry axillary skin and were not allowed to apply deodorant or wash the axillae for 4 hours after study drug application. The protocol states that missed doses could be applied provided that there was a 12-hour window until the next scheduled dose. After the baseline visit, subjects had scheduled study visits in the clinic at Weeks 1, 2, 3, and 4 (end of treatment), and a telephone follow-up at Week 5 (study exit).

The protocol specifies that subjects' sweat production was measured gravimetrically at each clinic visit. Prior to the gravimetric procedure, the axillae were shaved if appropriate, and the subject was acclimated to the exam room for 30 minutes. The room was to be at a temperature between 70-75^{o}F and controlled for humidity. Two 4x4 inch gauze pads in a plastic bag were weighed prior to the procedure. After acclimation, one axilla was gently dried with a separate gauze pad. The gauze pads from the bag were removed and placed under the subject's axilla for 5 minutes. After 5 minutes, the gauze pads were placed back in the bag and reweighed. The procedure was repeated for the second axilla.

According to the protocol, subjects were to select the HDSS grade that best described their disease at each clinic visit. Subjects were to be provided with an electronic tablet to complete the ASDD in the evening each day for items #1-4. Item #5 was administered once weekly, and item #6 was asked at the end of treatment. Subjects were to be contacted by the site if the ASDD had not been completed.

The statistical analysis plan (SAP) specifies the following co-primary endpoints:

- Mean absolute change from baseline in gravimetrically-measured sweat production at Week 4
- Proportion of subjects who have at least a 4-point improvement from baseline in the weekly mean score of ASDD item #2 at Week 4

The SAP specifies the following secondary endpoints:

- Proportion of subjects who have at least a 2-grade improvement from baseline in HDSS score at Week 4
- Proportion of subjects who have at least a 50% reduction from baseline in gravimetrically-measured sweat production at Week 4

7.2.2. Statistical Methodologies

The SAP specifies that the intent-to-treat (ITT) population includes all subjects who were randomized and dispensed study drug. The safety population includes all subjects who were randomized and received at least one confirmed dose of study drug. The per protocol (PP) population includes all subjects in the safety population who completed the Week 4 evaluation and did not meet the following exclusion criteria:

- Violated the inclusion/exclusion criteria
- Used an interfering concomitant medication or underwent a prohibited procedure
- Did not attend the Week 4 visit
- Missed more than one post-baseline visit prior to Week 4
- Was not compliant with dosing regimen (i.e., did not apply 80-120% of expected applications of study drug during the treatment)
- Out of the visit window for the Week 4 visit by more than ±2 days

Subjects that discontinued from the study due to an adverse event (AE) related to the study treatment or documented lack of treatment effect were included in the PP population according to the SAP.

Gravimetrically-Measured Sweat Production

Analyses of sweat production were based on the mean of the measurements for the right and left axillae. The SAP specifies that co-primary endpoint of the change from baseline to Week 4 in gravimetrically-measured sweat production was analyzed using an analysis of covariance (ANCOVA) model with factors for treatment group and analysis center, along with baseline sweat production as a covariate.

The SAP specifies that a skewness test based on methods in J.H. Zar (1984)[5] was applied to the residuals from the ANCOVA. If this skewness test was significant at the 0.005 level, then a non-parametric method would be implemented and considered the primary analysis. The non-

[5] Zar, JH, Biostatistical analysis. 2nd edition. Englewood Cliffs, NJ: Prentice-Hall. P 118-119.

parametric method in the SAP specified rank-transforming the change in gravimetrically-measured sweat production data before analysis using the ANCOVA model.

The secondary endpoint of the proportion of subjects who have at least a 50% reduction from baseline in gravimetrically-measured sweat production at Week 4 was analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by analysis center as specified in the SAP.

Patient-Reported Outcomes

ASDD item #2 was intended to be answered by subjects each night during the trial. For each subject, the mean of the responses each week was computed if the subject had responses for at least 4 of the 7 days of the week. If the subject had 3 or fewer responses, the mean weekly value for that item was considered to be missing.

The SAP specifies that the week was defined according to a subject's visit dates using the 7 days prior to the day that the clinic visit occurred. If the subject completed the daily diary, but did not attended the weekly visit, the expected visit date was used to establish the 7 days of data to be used in the mean calculation. Each day was used for only one weekly mean calculation. If the 7 days prior to a visit overlapped with the previous visit, only the diary days on or after the previous visit were used in the calculation of the subsequent weekly mean value.

The SAP specifies analyzing the co-primary endpoint of the proportion of subjects who have at least a 4-point improvement from baseline in the weekly mean score of ASDD item #2 at Week 4 using a CMH test stratified by analysis center.

The HDSS assessment was to be completed at each clinic visit. The SAP specifies analyzing the secondary endpoint of the proportion of subjects who have at least a 2-grade improvement in HDSS from baseline at Week 4 using a CMH test stratified by analysis center.

Pooling of Centers for Analysis

The SAP states that the trial was intended to be conducted such that a minimum of 12 subjects (8 in the DRM04 arm, 4 in the vehicle arm) would be randomized in each site. The SAP pre-specifies a procedure for pooling sites for the analysis in the case that actual enrollment was lower than expected. The SAP states that the site with the smallest enrollment was combined with the site with the largest enrollment of those that did not meet the minimum number of planned subjects. The SAP states, "If there is a further need to combine data, then the data of the Investigator with the second smallest enrollment will be combined with the Investigator's data which had the second largest enrollment, and so on." The applicant refers to the pooled sites as "analysis centers". Version 2 of the SAP dated May 16, 2016 additionally states that United States (US) sites would only be combined with other US sites, and similarly for sites in Germany.

Investigation of Heterogenicity of the Treatment Effect Across Sites

The SAP specifies a plan to investigate efficacy on both co-primary endpoints by the analysis centers to identify centers with extreme results. The mean change from baseline in gravimetrically-measured sweat production at Week 4 was analyzed with an ANCOVA (ranked or unranked) with factors for treatment group, analysis center, and the treatment-by-analysis center interaction, along with baseline sweat production as a covariate. The ASDD item #2 dichotomized endpoint was analyzed with a logistic regression with factors for treatment group, analysis center, and the treatment-by-analysis center interaction. If either of the two analyses of the co-primary endpoints resulted in a significant interaction term (p-value ≤0.10), then further sensitivity analyses would be conducted to identify the center(s) with extreme results.

The SAP specifies analyzing all subsets that could be created by excluding one analysis center. If one or more subsets resulted in an interaction p-value >0.1, then the analysis center excluded from the subset with the largest interaction p-value was deemed to be the extreme analysis center. If all subsets had interaction p-values ≤0.10, then the process would be repeated for all subsets excluding two analysis centers, and so on.

The SAP also specifies investigating the treatment effect within sites prior to the above analyses of analysis centers to determine if "the site-to-site variability is such that it could mask the analysis center effects." The SAP states that if any of the analyses were not computationally feasible due to low enrollment at some sites, then the low-enrolling investigational sites would be excluded from the analysis.

Multiplicity

A gated sequential procedure was pre-specified in the SAP to control the overall Type I error when testing the secondary endpoints. First, the proportion of subjects who have a minimum 2-grade improvement from baseline in HDSS at Week 4 was tested. If that endpoint achieved statistical significance, then the proportion of subjects who have at least a 50% reduction from baseline in gravimetrically-measured sweat production at Week 4 was tested.

Missing Data

The SAP specifies that the primary method for handling missing efficacy data was Markov Chain Monte Carlo (MCMC) multiple imputation (MI). Imputation was conducted separately for each treatment group with variables for the outcomes from each previous visit. The applicant specified conducting at least 5 times nmiss imputations, where nmiss is defined as the maximum number of missing values requiring imputation between the treatment groups. The SAP specifies random number generator seeds to be used for each assessment (i.e. sweat production, ASDD item #2 score, and HDSS score) and treatment group.

For gravimetrically-measured sweat production, the SAP specifies imputing missing right and left axillae measurements separately. If a subject had 3 or fewer responses in a week for ASDD item #2, then the mean weekly value for that item was considered missing and imputed. Any

derived variables from gravimetrically-measured sweat production, ASDD item #2 score, and HDSS score were specified to be calculated from the imputed data.

For the analyses of dichotomous endpoints, the SAP specifies normalizing the CMH test statistics from the imputed data sets using the Wilson-Hilferty transformation prior to combining them using SAS PROC MIANALYZE.

Sensitivity Analyses

The SAP specifies imputing missing data using last observation carried forward (LOCF) and conducting repeated measures analyses as sensitivity analyses for the method of handling missing data. Version 1 of the SAP dated January 11, 2016 specifies conducting a repeated measures ANCOVA analysis for the change from baseline in gravimetrically-measured sweat production with factors for treatment, analysis center, and visit (Weeks 1, 2, 3 and 4), along with a covariate for baseline gravimetrically-measured sweat production. The amended SAP dated May 16, 2016 specifies also including a factor for the treatment-by-visit interaction. The SAP specifies analyzing dichotomous endpoints with a repeated measures logistic regression model (generalized estimating equations) as a sensitivity analysis. Version 1 of the SAP dated January 11, 2016 specifies including factors for treatment, analysis center, and visit (Weeks 1, 2, 3 and 4). The amended SAP dated May 16, 2016 additionally specifies including a factor for the treatment-by-visit interaction. The SAP also specifies analyzing the PP population using LOCF as a sensitivity analysis.

7.2.3. Patient Disposition, Demographic and Baseline Characteristics

Trial HH04 enrolled and randomized 344 subjects, 229 to DRM04 and 115 to vehicle from 21 sites in the US and 8 sites in Germany. Trial HH05 enrolled and randomized 353 subjects, 234 to DRM04 and 119 to vehicle, from 20 sites in the US. Table 13 presents the reasons for discontinuation from the studies. In both trials, there was a greater proportion of subjects who discontinued the trial in the DRM04 arm compared to the vehicle arm, with a greater difference in discontinuation rates observed in Trial HH04. The most common reasons for subjects to drop out in the DRM04 arm were due to adverse event or the subject withdrawing consent.

Table 13: Disposition of Subjects

	Trial HH04		Trial HH05	
ITT Population	**DRM04 N=229**	**Vehicle N=115**	**DRM04 N=234**	**Vehicle N=119**
Discontinued	21 (9.2%)	3 (2.6%)	16 (6.8%)	6 (5.0%)
Adverse event	8 (3.5%)	1 (0.9%)	9 (3.8%)	0
Withdrew consent	6 (2.6%)	1 (0.9%)	5 (2.1%)	5 (4.2%)
Lost to follow-up	5 (2.2%)	1 (0.9%)	0	1 (0.8%)
Noncompliance	1 (0.4%)	0	0	0
Protocol violation	0	0	1 (0.4%)	0
Other	1 (0.4%)	0	1 (0.4%)	0

Source: Reviewer's analysis (same results as applicant's analysis)

The demographics of the trial subjects are presented in Table 14. The demographics were generally balanced across the treatment arms within each trial and across both trials; however, Trial HH04 had a higher proportion of Hispanic or Latino subjects than Trial HH05, and Trial HH04 included sites in Germany, while Trial HH05 solely had sites in the US.

Table 14: Subject Demographics

	Trial HH04		Trial HH05	
ITT Population	DRM04 N=229	Vehicle N=115	DRM04 N=234	Vehicle N=119
Age				
Mean (SD)	32.1 (11.2)	34.0 (13.1)	32.6 (10.9)	32.8 (11.2)
Median	31	32	31	32
Range	11 to 65	9 to 76	12 to 64	12 to 63
< 16 Years	5 (2.2%)	6 (5.2%)	11 (4.7%)	10 (8.4%)
< 18 Years	14 (6.1%)	9 (7.8%)	20 (8.5%)	13 (10.9%)
Sex				
Male	99 (43.2%)	55 (47.8%)	113 (48.3%)	59 (49.6%)
Female	130 (56.8%)	60 (52.2%)	121 (51.7%)	60 (50.4%)
Race				
White	182 (79.5%)	94 (81.7%)	192 (82.1%)	102 (85.7%)
Black	31 (13.5%)	16 (13.9%)	28 (12.0%)	14 (11.8%)
Asian	4 (1.7%)	0	1 (0.4%)	0
American Indian or Alaska Native	2 (0.9%)	0	2 (0.9%)	0
Native Hawaiian or other Pacific Islander	0	2 (1.7%)	0	0
Multiple or Other	10 (4.4%)	3 (2.6%)	11 (4.7%)	3 (2.5%)
Ethnicity				
Hispanic or Latino	46 (20.1%)	23 (20.0%)	28 (12.0%)	15 (12.6%)
Not Hispanic or Latino	183 (79.9%)	92 (80.0%)	206 (88.0%)	104 (87.4%)
Geographic Region				
United States	192 (83.8%)	99 (86.1%)	234 (100%)	119 (100%)
Outside United States	37 (16.2%)	16 (13.9%)	0	0

Source: Reviewer's analysis (same as applicant's analysis)

Table 15 presents the baseline disease characteristics of the trial subjects. In Trial HH04, the mean gravimetrically-measured sweat production at baseline was higher in the DRM04 group than in the vehicle group, and there was a higher proportion of DRM04 subjects with a score of 4 on the HDSS assessment compared to the vehicle group. This indicates that the subjects in the DRM04 group may have had more severe disease at baseline on average than subjects in the vehicle group in Trial HH04. In Trial HH05, the mean gravimetrically-measured sweat production at baseline was lower in the DRM04 group compared to the vehicle group, but the weekly mean ASDD item #2 and HDSS scores appear to be balanced across the treatment groups.

It is of note that there were several subjects who were enrolled into the trials who violated the inclusion criteria. In Trial HH04, there were 6 subjects, 3 in each treatment group, who had a weekly mean ASDD item #2 score less than 4 at baseline. In Trial HH05, 4 subjects, 3 in the DRM04 group and 1 in the vehicle group, had a weekly mean ASDD item #2 score less than 4 at baseline. An additional subject in the vehicle group of Trial HH05 had a HDSS score of 2 at baseline when the entry criteria required a score of 3.

Table 15: Baseline Disease Characteristics

	Trial HH04		Trial HH05	
ITT Population	DRM04 N=229	Vehicle N=115	DRM04 N=234	Vehicle N=119
Weekly Mean ASDD Item #2				
Mean (SD)	7.3 (1.6)	7.1 (1.7)	7.3 (1.6)	7.2 (1.6)
Median	7.5	7.0	7.4	7.4
Range	1.8 to 10.0	1.0 to 10.0	3.0 to 10.0	2.5 to 10.0
Baseline Sweat Production (mg/5 min)				
Mean (SD)	182.9 (266.9)	170.3 (164.2)	162.3 (149.5)	181.9 (160.1)
Median	122.1	112.6	126.9	116.7
Range	50.3 to 3032.4	50.2 to 1047.1	51.1 to 1319.6	51.3 to 857.1
HDSS				
2	0	0	0	1 (0.8%)
3	133 (58.1%)	84 (73.0%)	144 (61.5%)	71 (59.7%)
4	96 (41.9%)	31 (27.0%)	90 (38.5%)	47 (39.5%)

Source: Reviewer's analysis (same as applicant's analysis)

7.2.4. Gravimetrically-Measured Sweat Production Co-Primary Endpoint Results

One of the co-primary endpoints specified in the SAP was the mean change from baseline in gravimetrically-measured sweat production at Week 4. Table 16 presents the proportion of missing data for this endpoint at each study visit. There was generally more missing data in the DRM04 group compared to the vehicle group in both trials, though the difference between the groups at Week 4 was greater in Trial HH04 than in Trial HH05.

Table 16: Missing Gravimetrically-Measured Sweat Production Data by Visit

	Trial HH04		Trial HH05	
ITT Population	DRM04 N=229	Vehicle N=115	DRM04 N=234	Vehicle N=119
Week 1	4 (1.7%)	2 (1.7%)	8 (3.4%)	4 (3.4%)
Week 2	15 (6.6%)	6 (5.2%)	19 (8.1%)	4 (3.4%)
Week 3	21 (9.2%)	4 (3.5%)	23 (9.8%)	5 (4.2%)
Week 4	19 (8.3%)	3 (2.6%)	17 (7.3%)	6 (5.0%)

Source: Reviewer's analysis

Table 17 presents results for the co-primary endpoint of the change from baseline in gravimetrically-measured sweat production at Week 4 for Trial HH04 and Trial HH05 using multiple imputation as the primary method for handling missing data as pre-specified in the SAP.

Table 17 contains two sets of analyses for Trial HH04: those including all subjects in the ITT population, and those excluding subjects from analysis center 14, which was pooled from investigational sites 412 and 419. Note that in the column of results excluding sites 412 and 419, both the multiple imputation and the analysis were performed without data from sites 412 and 419. The applicant identified analysis center 14 as having outlier data according to the methodology that was pre-specified in the SAP applied to the ranked outcome data. Figure 3 depicts the observed data for both the change in sweat production from baseline by visit and the raw sweat production by visit for all subjects in Trial HH04. These plots illustrate that there are several extreme outlier values for sweat production. These extreme outliers are from 4 subjects (412-1107, 412-1110, 412-1111, and 412-1112) who were randomized to DRM04 at site 412, and Figure 4 depicts their sweat production data at each visit.

Subjects (b) (6) had changes in gravimetrically-measured sweat production at Week 4 of -2766.75, 1648.45, and -2233.95 mg/5 min respectively. These 3 subjects also had the highest sweat production at baseline of 3032.4, 1069.6, and 2253.8 mg/5 min respectively. Subject (b) (6) did not have extreme values of sweat production at baseline or Week 4 (358.65 and 237.5 respectively for a change of -121.15 mg/5 min), but had high values of sweat production at the intermediate visits as depicted in Figure 4. In the Study Report, the applicant states, "Source data and study procedures for these subjects were reviewed and verified. No issues were identified either with respect to the data or the procedures for collection of the data." It is of note that when removing analysis center 14 from the analysis, the range and standard deviations of the change in sweat production notably decrease as presented in Table 17.

The results indicate that the data for this co-primary endpoint are skewed as the medians are much smaller than the means. The skewness test pre-specified in the SAP was significant in both trials, indicating that the ranked ANCOVA analysis is considered to be the primary analysis. The results from both the ranked and unranked analyses are presented in Table 17. The ranked analysis on the ITT population in Trial HH04 produces a borderline non-statistically significant result (p=0.065). However, after excluding analysis center 14 with the extreme outliers, the results are statistically significant (p=0.001). All analyses, ranked and unranked, are statistically significant in Trial HH05 for the change from baseline in gravimetrically-measured sweat at Week 4.

Table 17: Gravimetrically-Measured Sweat Production Results

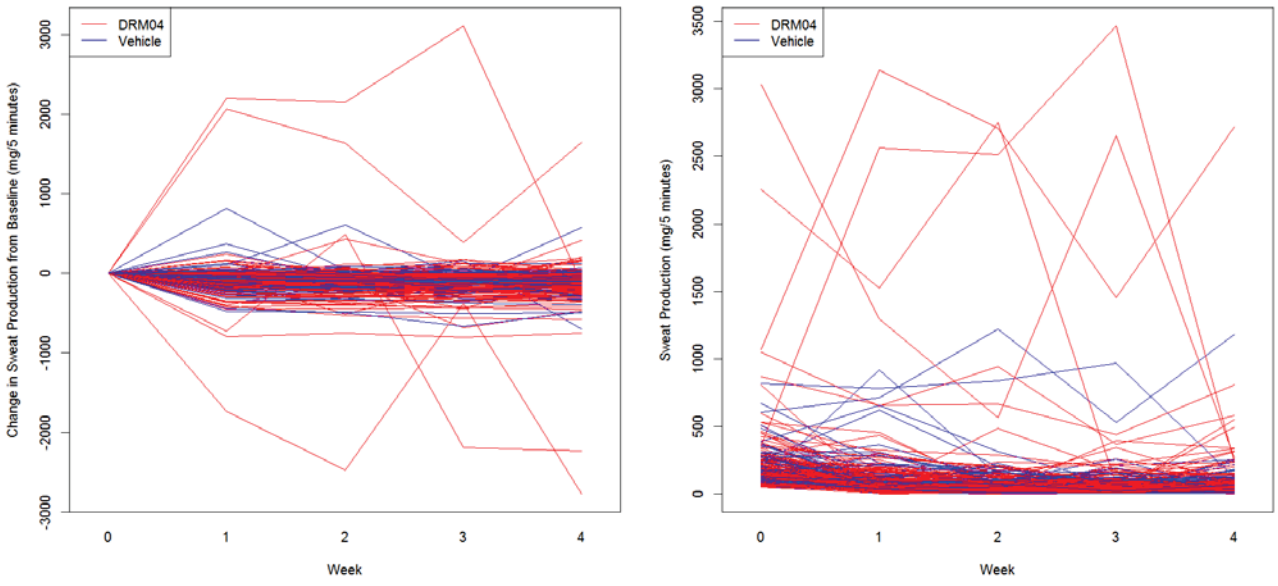
	Trial HH04				Trial HH05	
	ITT Population		Excluding Sites 412 & 419		ITT Population	
	DRM04 N=229	**Vehicle N=115**	**DRM04 N=220**	**Vehicle N=110**	**DRM04 N=234**	**Vehicle N=119**
Baseline, Mean (SD)	183 (267)	170 (164)	157 (114)	168 (165)	162 (149)	182 (160)
Week 4, Mean (SD)	78 (208)	78 (101)	61 (107)	77 (102)	52 (63)	90 (87)
Change, Mean (SD)	-105 (286)	-92 (128)	-96 (126)	-91 (129)	-110 (131)	-92 (153)
Median	-81	-66	-82	-65	-79	-58
IQR	-149, -40	-106, -28	-149, -41	-104, -24	-144, -45	-122, -21
Range	-2767, 1648	-695, 169	-747, 572	-695, 169	-1087, 179	-839, 220
Change, LS Mean (SD)	-102 (176)	-100 (172)	-101 (98)	-88 (96)	-115 (67)	-81 (67)
Skewness p-value[1]	<0.001		<0.001		<0.001	
p-value (unranked) [2]	0.932		0.259		<0.001	
p-value (ranked) [2]	0.065		0.001		<0.001	

Source: Reviewer's analysis (similar to applicant's analysis). Gravimetrically-measured sweat production is measured in mg/5 min. Means, medians, and interquartile ranges (IQRs) averaged over 95 MI datasets for the ITT population in Trial HH04, 90 MI datasets in Trial HH04 excluding sites 412 and 419, and 85 MI datasets for the ITT population in Trial HH05. Standard deviations (SD) from MI datasets are combined using Rubin's formula which differs from the applicant's results slightly, as applicant used the average of standard deviations over the MI datasets.

(1) P-value from a skewness test based on methods in J.H. Zar (1984) and averaged over MI datasets.

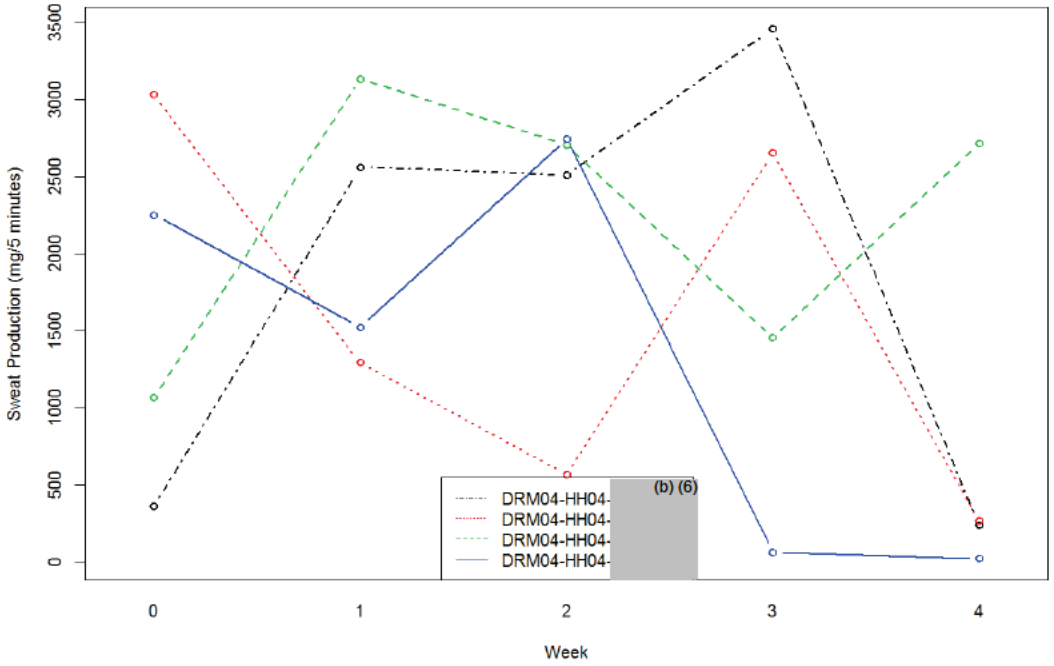
(2) P-values calculated from ANCOVA (unranked or ranked) with factors of treatment group and analysis center and a covariate of baseline gravimetrically-measured sweat production.

Figure 3: Change from Baseline in Sweat Production by Visit and Sweat Production by Visit for Subjects in Trial HH04 (Observed Data)



Source: Reviewer's analysis

Figure 4: Sweat Production by Visit for Extreme Outlier Subjects in Trial HH04



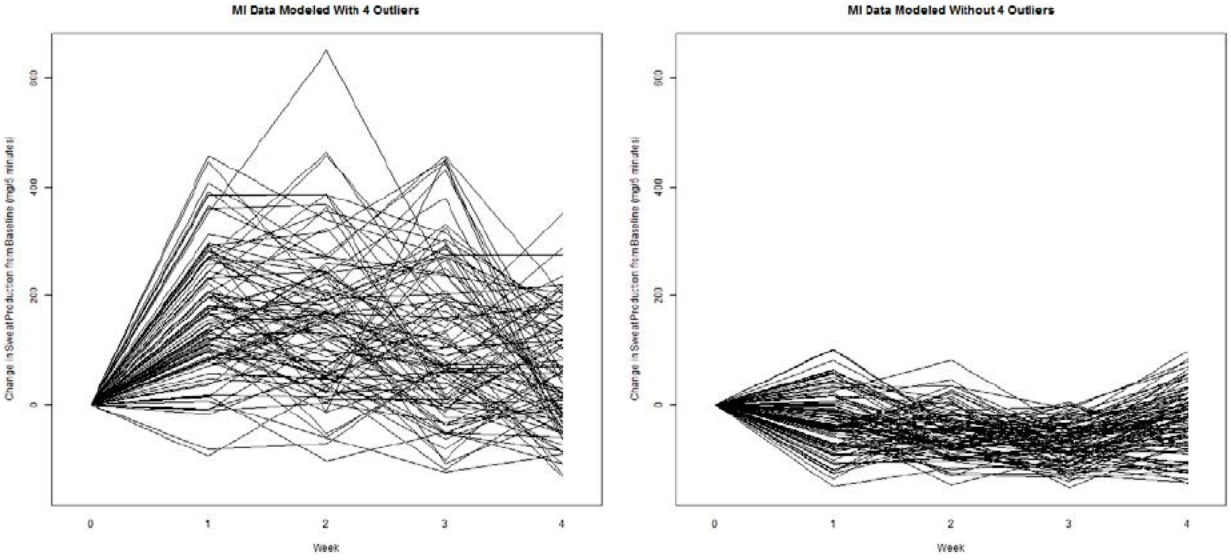
Source: Reviewer's analysis (same as applicant's). Gravimetrically-measured sweat production is measured in mg/5 min.

The results in Table 17 show non-statistically significant results (p=0.065) for the co-primary endpoint of the change from baseline in the gravimetrically-measured sweat at Week 4 in Trial HH04 when conducting the pre-specified primary analysis, ranked ANCOVA, on the ITT population. The primary method for handling missing data was MCMC multiple imputation based on sweat production data at previous timepoints. The 4 subjects that the applicant noted for having extreme results (b) (6) were included in the multiple imputation model, which appears to have had a noticeable effect on the imputation of the missing observations.

Figure 5, Figure 6, Figure 7, and Figure 8 depict examples of the imputation for 4 subjects with missing data at Week 4 when including the 4 outlier subjects in the MI and when excluding the 4 outlier subjects in the MI. These 4 subjects whose outcomes are depicted in the figures were selected for being representative of different missing data patterns (e.g. all post-baseline visits missing, last 3 visits missing, last 2 visits missing, and intermediate missing data).

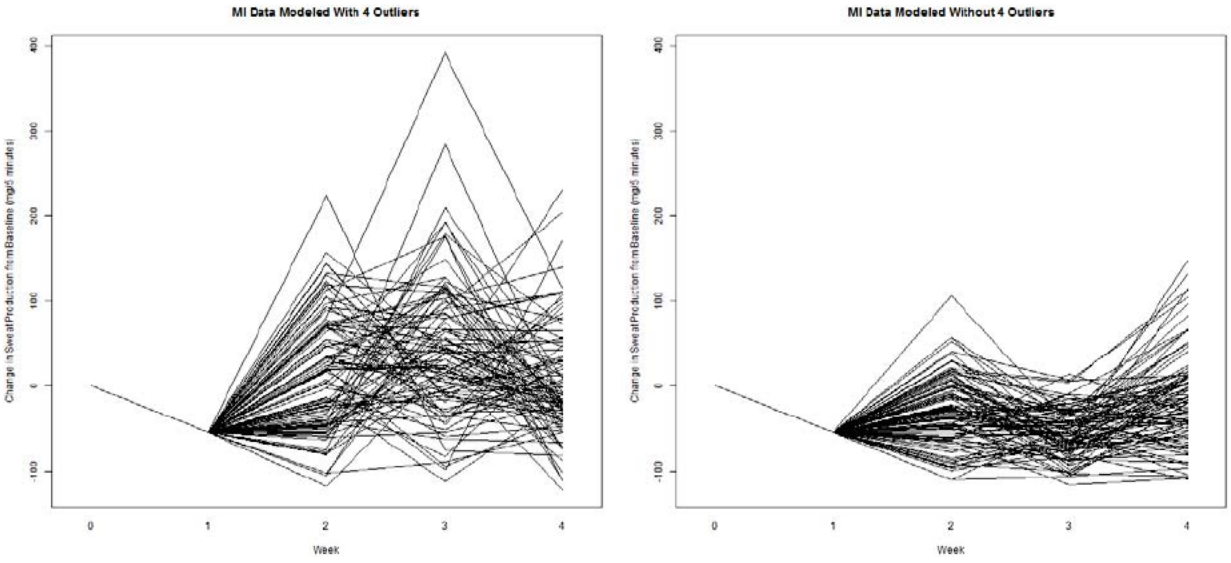
Multiple imputation is conducted prior to ranking the data, so even though the ranked analysis should be robust to a few extreme outliers, the multiple imputation that includes the 4 outlier subjects may cause subjects in the DRM04 treatment group with missing data to be ranked worse than if multiple imputation was conducted without the 4 extreme outlier subjects. As missing data was imputed separately for each treatment group and the extreme outliers were all in the DRM04 group, the imputation of missing data in the vehicle group was unaffected by the extreme outliers.

Figure 5: Effect of 4 Outliers on Multiple Imputation - Subject DRM04-HH04- (b) (6)



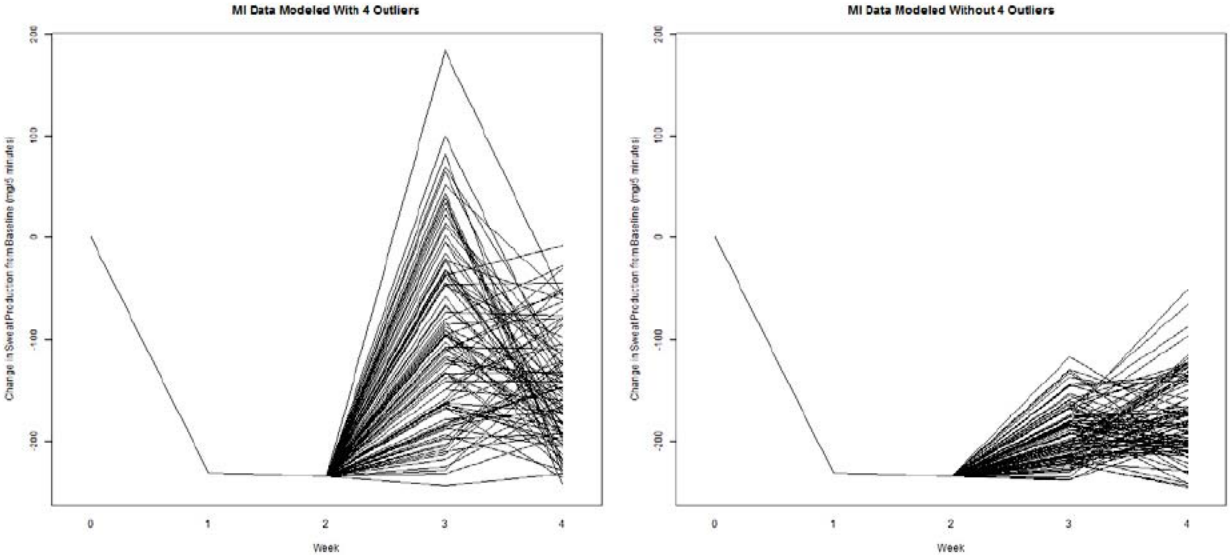
Source: Reviewer's analysis. Gravimetrically-measured sweat production is measured in mg/5 min.

Figure 6: Effect of 4 Outliers on Multiple Imputation - Subject DRM04-HH04- (b) (6)



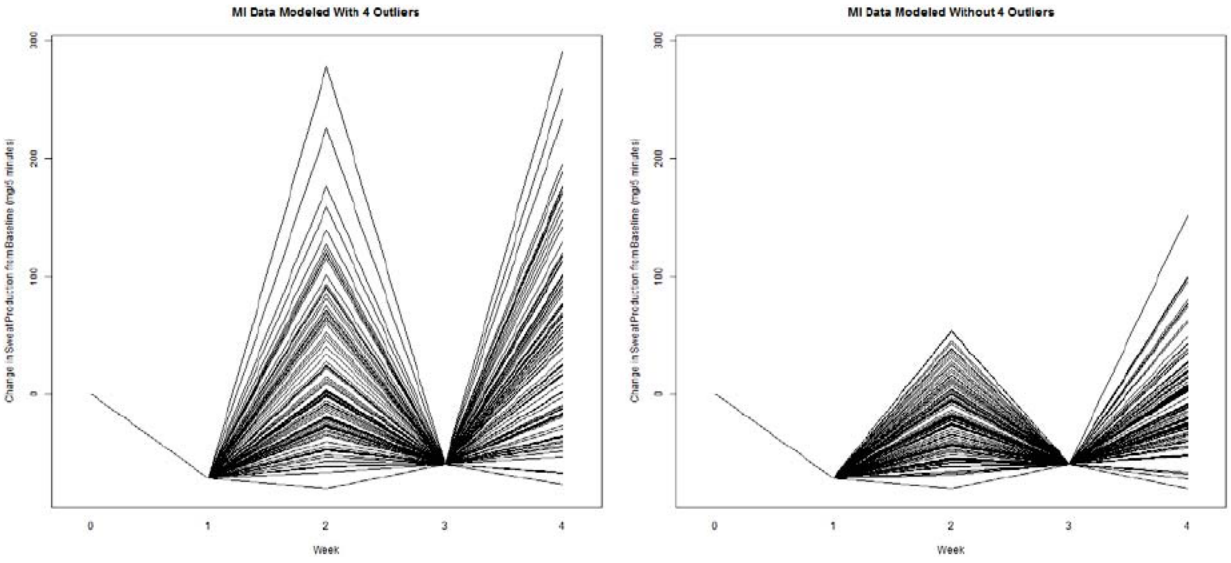
Source: Reviewer's analysis. Gravimetrically-measured sweat production is measured in mg/5 min.

Figure 7: Effect of 4 Outliers on Multiple Imputation - Subject DRM04-HH04- (b) (6)



Source: Reviewer's analysis. Gravimetrically-measured sweat production is measured in mg/5 min.

Figure 8: Effect of 4 Outliers on Multiple Imputation - Subject DRM04-HH04- (b) (6)



Source: Reviewer's analysis. Gravimetrically-measured sweat production is measured in mg/5 min.

The outliers may affect both the multiple imputation and the analysis. Table 17 presents results from a sensitivity analysis where the analysis center with the extreme outliers is excluded from both the multiple imputation and the analysis. To further investigate the impact of the extreme outliers, several additional post-hoc sensitivity analyses were conducted. When multiple imputation is conducted with all ITT subjects and then the analysis is carried out excluding sites 412 and 419, results are statistically significant (p=0.002) for the indicated ranked analysis. The same analyses excluding only site 412 (i.e., still including site 419) produced similar results. When multiple imputation is conducted without the 4 extreme outlier subjects and then the

analysis is conducted on the ITT population, results are also statistically significant (p=0.023) for the indicated ranked analysis.

It is also of note that the SAP specified rank-transforming only the change in gravimetrically-measured sweat production prior to analysis with ANCOVA; however, the baseline gravimetrically-measured sweat production, a covariate in the model, was not rank-transformed. Therefore, the 3 outlier subjects who also had extreme baseline sweat production still affect the ranked ANCOVA model when they are included in the analysis. A post-hoc sensitivity analysis that uses the ranked baseline sweat production as a covariate in the ranked analysis for the ITT population (with MI conducted on the ITT population) produces statistically significant results (p=0.043).

The applicant pre-specified several sensitivity analyses in the SAP, the results of which are presented in Table 18. The SAP specifies analyzing both the ITT population and the PP population using LOCF to handle missing data. Table 18 also presents the results from the SAP-specified repeated measures ANCOVA analysis with factors for treatment, analysis center, visit (Weeks 1, 2, 3 and 4), and the treatment-by-visit interaction along with a covariate for baseline gravimetrically-measured sweat production. The skewness test was statistically significant for each of the sensitivity analyses in Table 18, so the ranked analyses are considered the main analyses as specified in the SAP. The ranked analyses were all statistically significant in favor of DRM04 compared to vehicle.

Table 18: Change in Gravimetrically-Measured Sweat Production from Baseline to Week 4 - Sensitivity Analyses

	Trial HH04		Trial HH05	
	DRM04	**Vehicle**	**DRM04**	**Vehicle**
ITT Population (LOCF)	**N=229**	**N=115**	**N=234**	**N=119**
Change, Mean (SD)	-111 (282)	-93 (129)	-107 (125)	-87 (156)
Change, LS Mean (SD)	-109 (172)	-102 (170)	-112 (81)	-78 (81)
Skewness p-value[1]	<0.001		<0.001	
p-value (unranked) [2]	0.708		<0.001	
p-value (ranked) [2]	0.019		<0.001	
PP Population (LOCF)	**N=180**	**N=97**	**N=192**	**N=99**
Change, Mean (SD)	-122 (313)	-91 (130)	-102 (99)	-100 (138)
Change, LS Mean (SD)	-116 (191)	-107 (187)	-110 (57)	-81 (56)
Skewness p-value[1]	<0.001		<0.001	
p-value (unranked) [2]	0.684		<0.001	
p-value (ranked) [2]	0.009		<0.001	
Repeated measures analysis Based on observed data				
Change, LS Mean (SE)	-110 (12)	-99 (17)	-114 (5)	-78 (6)
Skewness p-value[1]	<0.001		<0.001	
p-value (unranked) [3]	0.612		<0.001	
p-value (ranked) [3]	0.007		<0.001	

Source: Reviewer's analysis (LOCF results are the same as applicant's results). Gravimetrically-measured sweat production is measured in mg/5 min. Results from repeated measures analysis differ slightly from applicant's results.

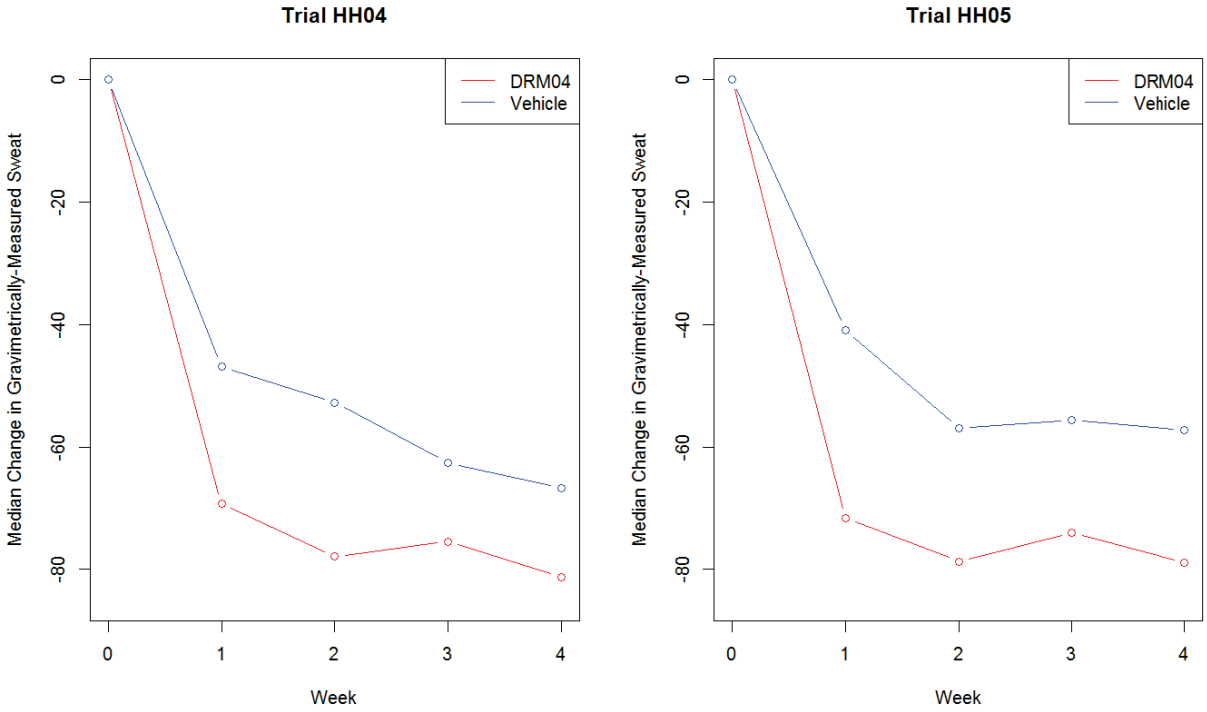
(1) P-value from a skewness test based on methods in J.H. Zar (1984) and averaged over MI datasets.

(2) P-values calculated from ANCOVA (unranked or ranked) with factors of treatment group and analysis center and a covariate of baseline gravimetrically-measured sweat production.

(3) P-values calculated from a repeated measures ANCOVA (unranked or ranked) with factors for treatment, analysis center, visit (Weeks 1, 2, 3 and 4), and the treatment-by-visit interaction, along with a covariate for baseline gravimetrically-measured sweat production.

Figure 9 displays the median change in gravimetrically-measured sweat production by study visit. The median is presented instead of the mean so that the plots are less affected by outliers. The trends are similar across the two trials, with the largest decrease of the median change in sweat production occurring between baseline and Week 1 and smaller additional decreases through Week 4. Plots of the raw median gravimetrically-measured sweat production by study visit appear similar.

Figure 9: Median Change in Gravimetrically-Measured Sweat Production by Study Visit



Source: Reviewer's analysis. Gravimetrically-measured sweat production is measured in mg/5 min. Results combined from 95 MI datasets in Trial HH04 and 85 MI datasets in Trial HH05.

At a clinical site inspection conducted by the Office of Scientific Investigations, the Agency investigator observed protocol deviations in the gauze placement time (i.e., the time that the gauze was placed under the axillae for the measurement of sweat production) at site 502 in Trial HH05. In some instances, sweat was collected for up to 9 minutes, which is almost double the time of the protocol-specified 5 minutes. These protocol deviations were not reported in the original submission of the NDA dated August 31, 2017, nor were the gauze placement times included in the datasets provided by the applicant. The Agency sent an information request to the applicant on April 30, 2018 inquiring whether gauze placement times were recorded for all subjects in both studies and if there were any protocol deviations related to gauze placement times at other sites.

The applicant responded to the information request on May 3, 2018 stating that gauze placement times were recorded for all subjects at each study site for both pivotal trials (Trials HH04 and HH05). The applicant stated that 40 deviations for 13 subjects were observed at site 502, and 13 additional gauze placement deviations in 13 subjects were observed at 8 other study sites participating in either of the pivotal trials. The majority of the protocol deviations are for measurement times of 6 minutes, and the deviations appear to be balanced across the treatment arms.

As site 502 in Trial HH05 had many reported protocol deviations of the gauze placement time, a sensitivity analysis excluding this site from the analysis of the gravimetrically-measured sweat

production co-primary endpoint was conducted. The results of the analysis of all sites and the analysis excluding site 502 are presented in Table 19. Excluding site 502 from the analysis does not change the conclusions from the primary analysis.

Table 19: Sensitivity Analysis Evaluating the Impact of Site 502 in Trial HH05

	Trial HH05			
	ITT Population		Excluding Site 502	
	DRM04 N=234	**Vehicle N=119**	**DRM04 N=224**	**Vehicle N=115**
Baseline, Mean (SD)	162 (149)	182 (160)	160 (150)	177 (157)
Week 4, Mean (SD)	52 (63)	90 (87)	52 (64)	89 (87)
Change, Mean (SD)	-110 (131)	-92 (153)	-108 (131)	-88 (152)
Median	-79	-58	-78	-55
IQR	-144, -45	-122, -21	-143, -45	-118, -18
Range	-1087, 179	-839, 220	-1087, 179	-839, 220
Change, LS Mean (SD)	-115 (67)	-81 (67)	-112 (67)	-79 (67)
Skewness p-value[(1)]	<0.001		<0.001	
p-value (unranked) [(2)]	<0.001		<0.001	
p-value (ranked) [(2)]	<0.001		<0.001	

Source: Reviewer's analysis. Gravimetrically-measured sweat production is measured in mg/5 min. Means, medians, and interquartile ranges (IQRs) averaged over 85 MI datasets for the ITT population in Trial HH05 and 75 MI datasets when excluding site 502 in the analysis of Trial HH05. Standard deviations (SD) from MI datasets are combined using Rubin's formula which differs from the applicant's results slightly, as applicant used the average of standard deviations over the MI datasets.

(1) P-value from a skewness test based on methods in J.H. Zar (1984) and averaged over MI datasets.

(2) P-values calculated from ANCOVA (unranked or ranked) with factors of treatment group and analysis center and a covariate of baseline gravimetrically-measured sweat production.

7.2.5. Axillary Sweating Daily Diary Item #2 Co-Primary Endpoint Results

The other pre-specified co-primary endpoint was the proportion of subjects who have at least a 4-point improvement from baseline in the weekly mean score of ASDD item #2 at Week 4. Table 20 presents the amount of missing weekly mean ASSD item #2 scores by study visit. The mean weekly score was considered to be missing if a subject had 3 or fewer ASDD item #2 responses in a week. The proportion of missing responses increases over time in both trials and treatment arms. By Week 4, the amount of missingness for this assessment is much higher than for the gravimetrically-measured sweat production assessment. This may be due to the burden of answering a questionnaire every night. At most visits, the DRM04 treatment group had a higher proportion of missing data than the vehicle group.

Table 20: Missing Weekly Mean ASDD Item #2 Data by Visit

	Trial HH04		Trial HH05	
ITT Population	DRM04 N=229	Vehicle N=115	DRM04 N=234	Vehicle N=119
Week 1	9 (3.9%)	2 (1.7%)	10 (4.3%)	4 (3.4%)
Week 2	14 (6.1%)	6 (5.2%)	23 (9.8%)	13 (10.9%)
Week 3	30 (13.1%)	8 (7.0%)	30 (12.8%)	10 (8.4%)
Week 4	37 (16.2%)	11 (9.6%)	41 (17.5%)	15 (12.6%)

Source: Reviewer's analysis. Missing was defined as <4 daily entries completed for the week.

The primary method for handling missing data was MCMC multiple imputation as described in Section 7.2.2. Table 21 presents the results for the dichotomous co-primary endpoint, as well as the means and standard deviations of the weekly mean ASDD item #2 scores at baseline, Week 4, and the change from baseline to Week 4. Results were combined from 185 imputed datasets for Trial HH04 (5 multiplied by 37 missing observations in the DRM04 group), and 205 imputed datasets for Trial HH05 (5 multiplied by 41 missing observations in the DRM04 group) according to the plan pre-specified in the SAP.

In both trials, there is a statistically significant difference between the treatment groups in the proportion of subjects who have at least a 4-point improvement from baseline in the weekly mean score of ASDD item #2 at Week 4. The response rate in the DRM04 group was higher in Trial HH05 compared to Trial HH04, while the vehicle response rates were similar across the trials. The mean change from baseline in the weekly mean score of ASDD item #2 at Week 4 (not dichotomized) also support the superiority of DRM04 compared to placebo.

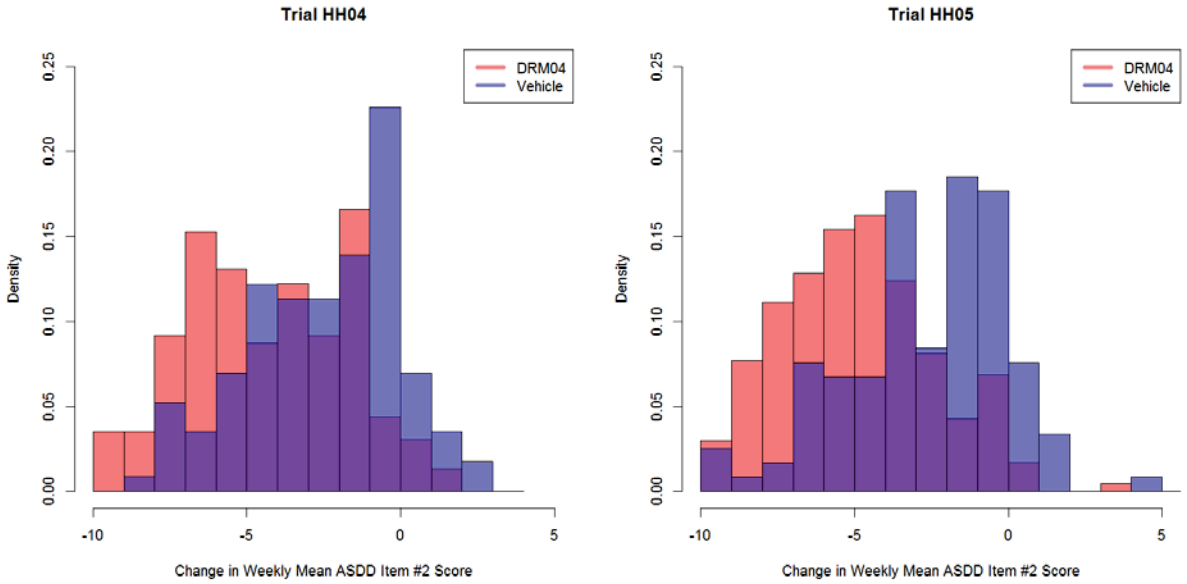
Table 21: Axillary Sweating Daily Diary (ASDD) Item #2 Results

	Trial HH04		Trial HH05	
ITT Population	DRM04 N=229	Vehicle N=115	DRM04 N=234	Vehicle N=119
≥4-point improvement	52.8%	28.3%	66.1%	26.9%
p-value	<0.001		<0.001	
Baseline, Mean (SD)	7.3 (1.6)	7.1 (1.7)	7.3 (1.6)	7.2 (1.6)
Week 4, Mean (SD)	3.0 (2.7)	4.6 (2.5)	2.4 (2.4)	4.7 (2.9)
Change, Mean (SD)	-4.3 (2.7)	-2.5 (2.5)	-4.9 (2.6)	-2.6 (2.7)

Source: Reviewer's analysis (similar to applicant's analysis). Results combined from 185 MI datasets in Trial HH04 and 205 MI datasets in Trial HH05. Standard deviation (SD) estimates for Week 4 and change from baseline results are calculated from Rubin's formula which differs from the applicant's results slightly, as applicant used the average of standard deviations over the MI datasets. P-values calculated from a CMH test stratified by analysis center.

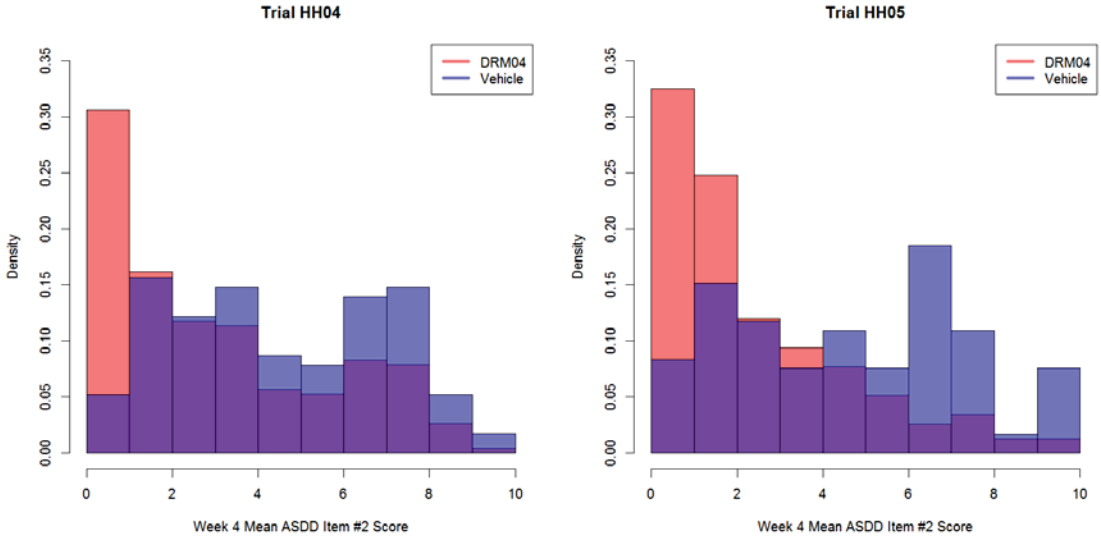
Figure 10 and Figure 11 display the distributions of the changes in the weekly mean ASDD item #2 scores at Week 4 and the raw Week 4 mean ASDD item #2 scores respectively. Red indicates the DRM04 group and blue indicates the vehicle group. The figures depict that the DRM04 group had greater decreases in ASDD item #2 scores and lower raw scores at Week 4 compared to the vehicle group. This supports the conclusion that subjects in the DRM04 group had better outcomes on ASDD item #2 than those in the vehicle group.

Figure 10: Changes in Weekly Mean ASDD Item #2 from Baseline to Week 4 Distribution



Source: Reviewer's analysis. Results combined from 185 MI datasets in Trial HH04 and 205 MI datasets in Trial HH05.

Figure 11: Weekly Mean ASDD Item #2 at Week 4 Distribution



Source: Reviewer's analysis. Results combined from 185 MI datasets in Trial HH04 and 205 MI datasets in Trial HH05.

As presented in Table 20, there were high rates of missing data for the weekly mean ASDD item #2 at Week 4. Results from sensitivity analyses alternative to the MI method used for the primary analysis are presented in Table 22. LOCF was pre-specified by the applicant as a sensitivity analysis. Additionally, results from nonresponder imputation and worst-case imputation are presented in Table 22. Nonresponder imputation imputes subjects with missing data as nonresponders for the dichotomized co-primary endpoint. Worst-case imputation imputes subjects in the DRM04 group with missing data as nonresponders and subjects in the vehicle group with missing data as responders. The results from all 3 additional imputation

methods are statistically significant, except for the worst-case imputation in Trial HH04. Overall, the results support the conclusion of the primary analysis that DRM04 is superior to vehicle. As an additional sensitivity analysis, the SAP specifies analyzing the dichotomized ASDD item #2 co-primary endpoint with a repeated measures logistic regression model using generalized estimating equations including factors treatment, analysis center, visit (Weeks 1, 2, 3 and 4), and the treatment-by-visit interaction. The SAP also specified analyzing the endpoint using the PP population and LOCF to account for missing data. The results of these sensitivity analyses are presented in Table 22, both of which had statistically significant results in favor of the DRM04 treatment group.

Table 22: ASDD Item #2 Sensitivity Analyses

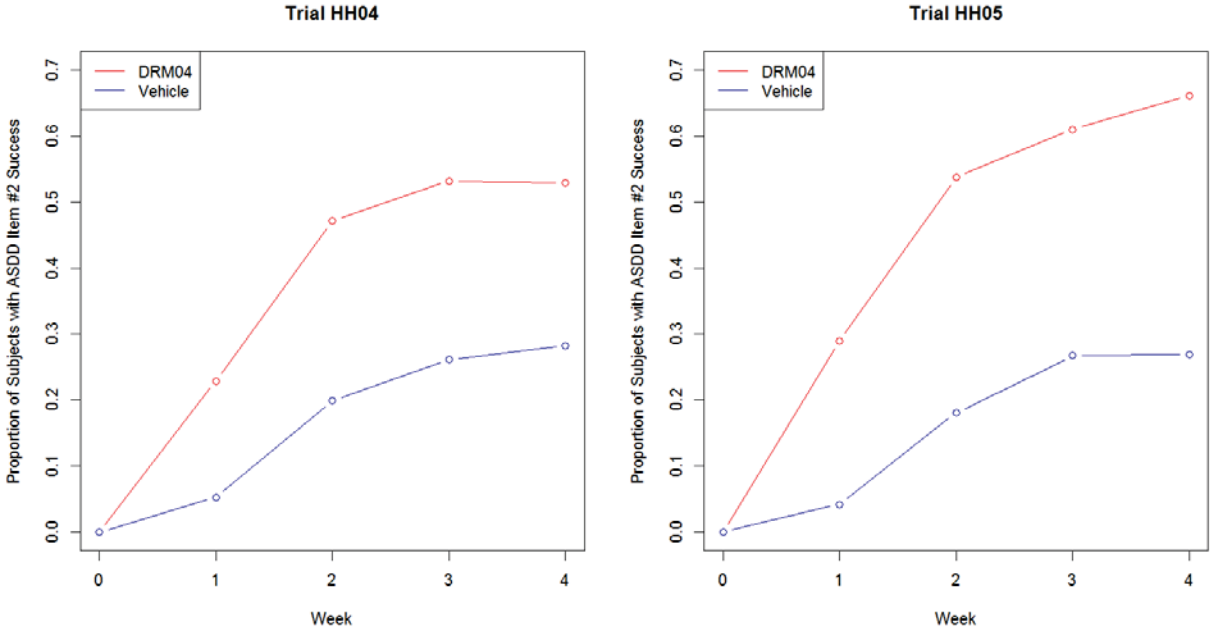
	Trial HH04		Trial HH05	
	DRM04	**Vehicle**	**DRM04**	**Vehicle**
ITT Population	**N=229**	**N=115**	**N=234**	**N=119**
LOCF	51.5%	27.8%	63.2%	26.1%
p-value	<0.001		<0.001	
Nonresponder imputation	44.1%	26.1%	55.1%	25.2%
p-value	<0.001		<0.001	
Worst-case imputation	44.1%	35.7%	55.1%	37.8%
p-value	0.119		0.002	
PP Population	**N=180**	**N=97**	**N=192**	**N=99**
LOCF	52.8%	30.9%	66.1%	26.3%
p-value	<0.001		<0.001	
Repeated measures analysis based on observed data[(1)]	54.1%	28.3%	65.6%	24.4%
p-value	<.0001		<.0001	

Source: Reviewer's analysis (LOCF results are the same as applicant's analysis)

(1) Estimate and p-value based on a repeated measures logistic regression model (generalized estimating equations) treatment, analysis center, visit (Weeks 1, 2, 3 and 4), and the treatment-by-visit interaction terms as independent factors. Estimates differ slightly from applicant's analysis.

Figure 12 depicts the proportion of subjects who achieved success (i.e., improved ≥4 points from baseline) on the ASDD item #2 assessment by visit. The majority of subjects who achieve success achieve it within the first two weeks, while the success rate increases slower in the last two weeks. Plots of the mean change from baseline in the weekly mean ASDD item #2 score show similar trends.

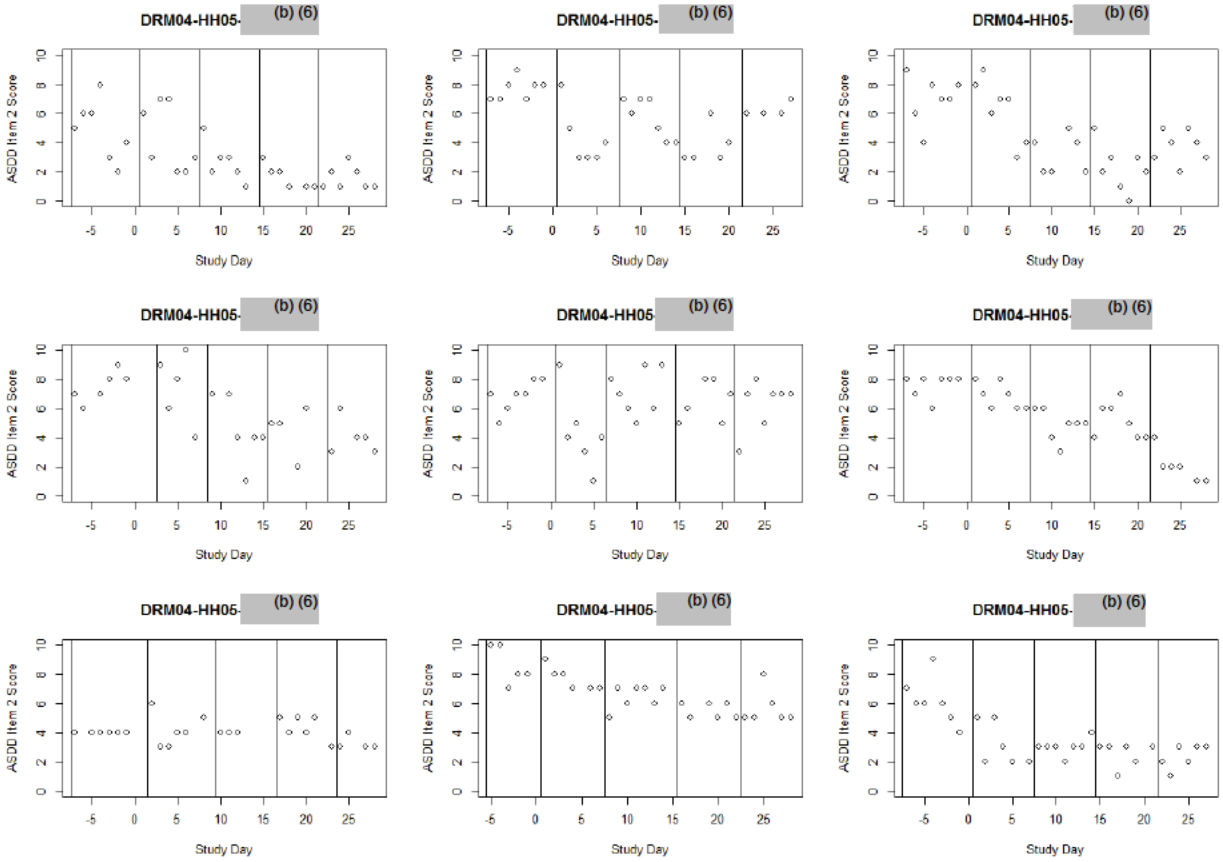
Figure 12: Proportion of Subjects with ASDD Item #2 Success by Visit



Source: Reviewer's analysis. Results combined from 185 MI datasets in Trial HH04 and 205 MI datasets in Trial HH05. Success defined by ≥4-point improvement in weekly mean ASDD item #2 score from baseline.

The pre-specified co-primary endpoint averages the mean ASDD item #2 scores over the 7 days prior to the study visit. Figure 13 displays the observed daily scores for 9 subjects in the vehicle group in Trial HH05. These 9 subjects were chosen to depict trends observed in the data. The vertical lines group together the scores that were averaged to get the weekly mean. The first two rows of subjects appear to show a cyclic effect in their responses, indicating that subjects may have severe sweating on some days, but not on other days. The third row of subjects have scores indicating that the worst severity of sweating is more constant over days of the week.

Figure 13: ASDD Item #2 Daily Results for 9 Vehicle Subjects in Trial HH05 (Observed)



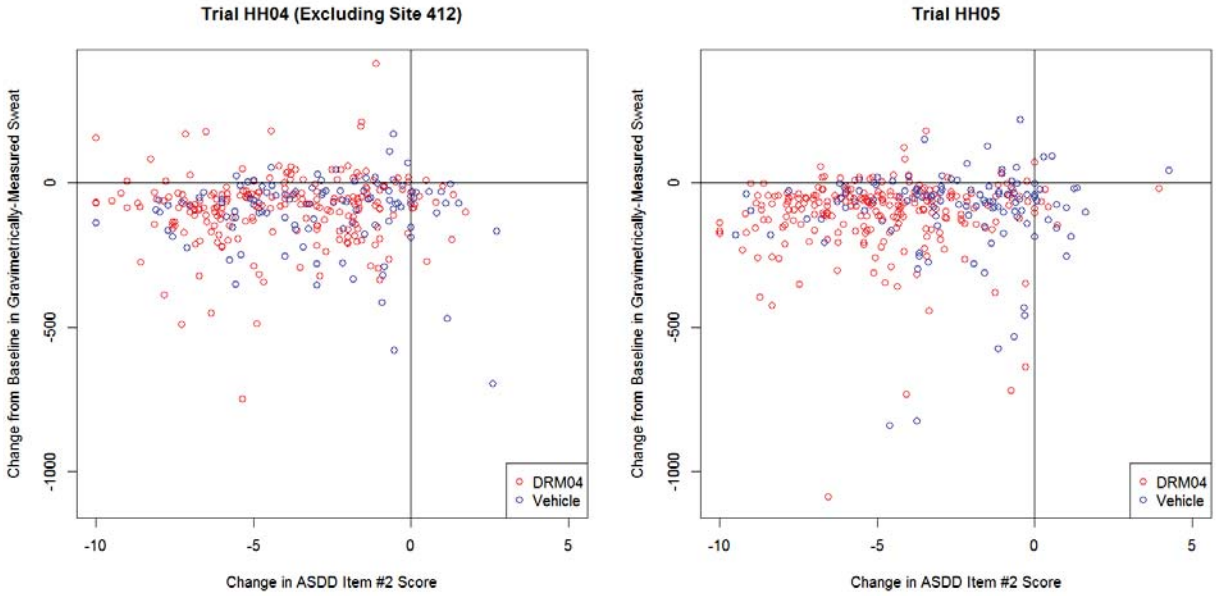
Source: Reviewer's analysis of observed data (no imputation of missing data)

7.2.6. Comparison of Gravimetrically-Measured Sweat and ASDD Item #2

When examining efficacy by site (see Section 7.2.8.2), it was observed that the two co-primary endpoints didn't seem to correspond to each other at some sites. To investigate this further, Figure 14 displays a scatter plot of the change from baseline in gravimetrically-measured sweat production at Week 4 and the change from baseline in weekly mean ASDD item #2 score at Week 4. Data from subjects at site 412 in Trial HH04 are excluded from the plot due to the extreme outliers. The horizontal line at 0 and vertical line at 0 represent no change from baseline. The red circles indicate subjects in the DRM04 group, and the blue circles represent subjects in the vehicle group. It is of note that the majority of subjects in both treatment groups showed some improvement from baseline to Week 4 on both assessments.

It is expected that there would be some differences in the outcomes of the two assessments; however, it appears that the endpoints don't correspond to each other. Scatter plots of the raw scores at Week 4 and baseline also show this lack of trend between the co-primary endpoints.

Figure 14: Change from Baseline in Gravimetrically-Measured Sweat Production Versus Change in Weekly Mean ASDD Item #2 Score at Week 4



Source: Reviewer's analysis. Results combined from MI datasets.

It should be noted that the gravimetrically-measured sweat production is measured over 5 minutes at visits once a week during the study. The ASDD item #2 is a daily assessment that asks subjects to evaluate their sweating at its worst in the past 24 hours. As shown in Figure 13, the daily results from the ASDD item #2 assessment indicate that sweating can be cyclic or episodic, so some subjects may have severe sweating one day and more mild sweating the next day. This could explain the high variability and highly skewed data observed in the sweat production endpoint. Therefore, it is not clear that a 5-minute measurement of gravimetrically-measured sweat production once a week is sufficient to characterize the severity of disease.

On November 13, 2017, there was a Patient Focused Drug Development meeting organized by the International Hyperhidrosis Society[6]. During that meeting, some patients with axillary hyperhidrosis expressed that they could not qualify for clinical trials because they did not sweat sufficiently during the gravimetrically-measured sweat production assessment at screening. One patient in particular expressed that her sweating was not constant, but episodic. This also supports the supposition that the gravimetrically-measured sweat production endpoint as measured over 5 minutes is not an accurate characterization of the disease.

7.2.7. Results for the Secondary Endpoints

The applicant pre-specified the secondary endpoints of the proportion of subjects who have at least a 50% reduction from baseline in gravimetrically-measured sweat production at Week 4 and the proportion of subjects who have at least a 2-grade improvement from baseline in HDSS

[6] https://www.sweathelp.org/taking-action/patient-focused-drug-development.html

at Week 4. The applicant adjusted these endpoints for multiplicity, and the results are statistically significant as presented in Table 23; however, in an advice letter dated August 20, 2015, the Agency stated that given the high vehicle response rate in the Phase 2 data, it was not clear that a threshold of 50% reduction in sweat production was clinically meaningful. Additionally, the Agency communicated to the applicant on multiple occasions that the HDSS instrument is not well-defined because it combines two distinct concepts (tolerability of the condition and interference of the condition with daily activities) within the same item. Therefore, it is difficult to interpret the results for this secondary endpoint, as it is not possible to ascertain which of the two concepts has changed with treatment.

Table 23: Results for the Secondary Endpoints at Week 4

	Trial HH04		Trial HH05	
ITT Population	**DRM04 N=229**	**Vehicle N=115**	**DRM04 N=234**	**Vehicle N=119**
≥50% reduction of sweat production	72.4%	53.2%	77.3%	53.3%
p-value	<0.001		<0.001	
≥2-grade improvement on HDSS	56.5%	23.7%	61.6%	27.8%
p-value	<0.001		<0.001	
HDSS score at Week 4				
1	36.2%	10.2%	43.3%	16.4%
2	47.0%	53.6%	47.8%	39.7%
3	12.6%	27.5%	7.5%	29.7%
4	4.1%	8.7%	1.4%	14.1%

Source: Reviewer's analysis (same as applicant's analysis). Sweat production results combined from 95 MI datasets in Trial HH04 and 85 MI datasets in Trial HH05. HDSS results combined from 90 MI datasets in Trial HH04 and 80 MI datasets in Trial HH05. P-values calculated from a CMH test stratified by analysis center.

7.2.8. Findings in Special/Subgroup Populations

7.2.8.1. Sex, Race, Age, and Geographic Region

Table 24 presents the results of the co-primary endpoint of the proportion of subjects who have at least a 4-point improvement from baseline in the weekly mean score of ASDD item #2 at Week 4 by sex, race (White, Black or African American, and other), ethnicity (Hispanic or Latino and not Hispanic or Latino), and by various age groups (<16 years and ≥16 years, <18 years and ≥18 years, and <the median age and ≥ the median age).

Figure 15 presents boxplots of the results by these subgroups for the change from baseline in gravimetrically-measured sweat production at Week 4. The boxplots are presented instead of the means due the highly skewed data. The data from the 3 extreme outliers at Week 4 in Trial HH04 (subjects (b) (6)) are not included in the plots for presentation purposes. Table 51 in the Appendix presents the median and interquartile range (IQR) for the change from baseline in sweat production endpoint. Results for the co-primary endpoints are also presented by geographic region (US vs. outside US) for Trial HH04 in Table

24 and Figure 16. All sites were in the US for Trial HH05, so results are not broken down by geographic region for this trial.

In the pivotal trials, there appears to be higher response rates for males compared to females, and higher efficacy for White subjects compared to Black or African American subjects in both trials on the ASDD item #2 assessment. In Trial HH04, Hispanic or Latino subjects had lower response rates than those who were not, though this trend was not reproduced in Trial HH05, and the sample sizes of the Hispanic or Latino subgroups are relatively small. The pediatric age groups that were investigated had small sample sizes and no clear trend of better or worse efficacy compared to adult subjects. In Trial HH04, subjects at sites in Germany had lower efficacy than subjects at sites in the US, though the number of subjects in Germany was small.

Table 24: ASDD Item #2 Success at Week 4 by Gender, Age, Race, and Geographic Region

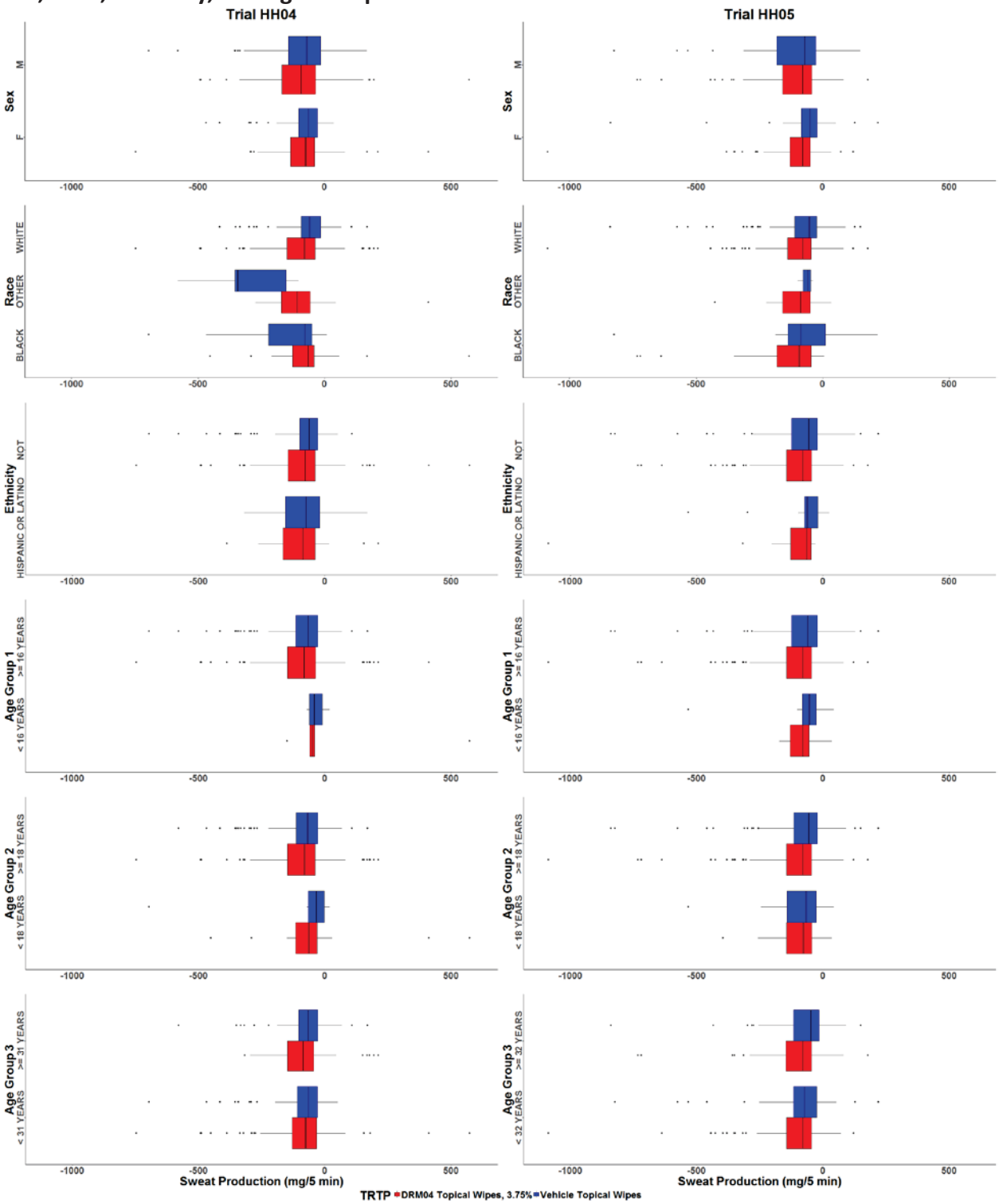
	Trial HH04			Trial HH05		
ITT Population	(N_D, N_V)[1] (229, 115)	DRM04	Vehicle	(N_D, N_V)[2] (234, 119)	DRM04	Vehicle
Sex						
Male	(99, 55)	57.4%	33.6%	(113, 59)	72.0%	36.8%
Female	(130, 60)	49.4%	23.4%	(121, 60)	60.6%	17.1%
Race						
White	(182, 94)	55.1%	28.6%	(192, 102)	68.2%	25.3%
Black or African American	(31, 16)	37.9%	22.7%	(28, 14)	52.4%	30.0%
Other	(16, 5)	56.2%	40.3%	(14, 3)	64.3%	66.7%
Ethnicity						
Hispanic or Latino	(46, 23)	36.9%	17.4%	(28, 15)	67.3%	20.8%
Not Hispanic or Latino	(183, 92)	56.9%	31.0%	(206, 104)	65.9%	27.7%
Age						
<16 years	(5, 6)	78.6%	16.7%	(11, 10)	40.8%	10.5%
≥16 years	(224, 109)	52.3%	28.9%	(223, 109)	67.3%	28.4%
<18 years	(14, 9)	60.1%	11.1%	(20, 13)	56.3%	12.0%
≥18 years	(215, 106)	52.4%	29.7%	(214, 106)	67.0%	28.7%
<31 years	(113, 54)	54.7%	25.0%	(118, 56)	66.2%	19.2%
≥31years	(116, 61)	51.1%	31.2%	(116, 63)	66.0%	33.6%
Geographic Region[2]						
United States	(192, 99)	54.2%	26.8%			
Outside United States	(37, 16)	45.9%	37.5%			

Source: Reviewer's analysis (same as applicant's analysis). Success defined by ≥4-point improvement in weekly mean ASDD item #2 score from baseline. Missing values were handled using multiple imputation and results were combined from 185 MI datasets in Trial HH04 and 205 MI datasets in Trial HH05.

(1) N_D = subgroup sample size in the DRM04 arm and N_V = subgroup sample size in the vehicle arm.

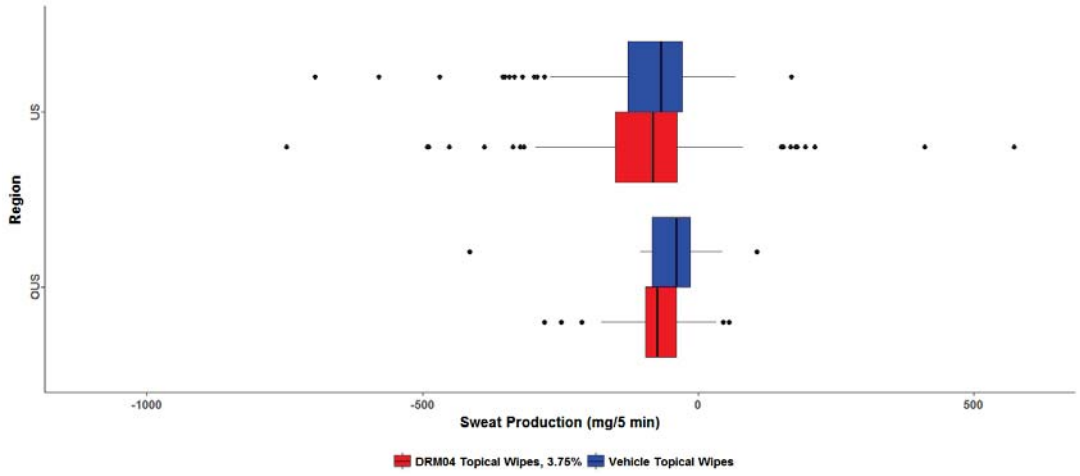
(2) Only Trial HH04 had sites outside of the United States.

Figure 15: Change from Baseline in Gravimetrically-Measured Sweat Production at Week 4 by Sex, Race, Ethnicity, and Age Group



Source: Reviewer's analysis. Gravimetrically-measured sweat production is measured in mg/5 min. Plots for Trial HH04 exclude 3 extreme outliers (subjects [redacted] (b) (6)) for presentation.

Figure 16: Change from Baseline in Gravimetrically-Measured Sweat Production at Week 4 by Region – Trial HH04



Source: Reviewer's analysis. Gravimetrically-measured sweat production is measured in mg/5 min. Plot excludes 3 extreme outliers (subjects (b) (6)) for presentation.

7.2.8.2. Other Special/Subgroup Populations

Efficacy by site was examined for both co-primary endpoints. Table 25 presents results by sites in Trial HH04 and Table 26 presents results by sites in Trial HH05. Site 409 has high efficacy on both endpoints compared to the other sites. It is of note that the two endpoints don't correspond with each other in some sites, specifically at sites 412, 505, and 502. These sites show a high mean decrease in sweat production in the vehicle arm, but the corresponding efficacy on the ASDD item #2 endpoint is low. Section 7.2.6 discusses this disparity between the co-primary endpoints further. For discussion about the outliers found in site 412, see Section 7.2.4. Boxplots of the change from baseline in gravimetrically-measured sweat at Week 4 by site are presented in Figure 19 in the Appendix.

Table 25: Efficacy Results by Site – Trial HH04

	Sample Sizes			ASDD Item #2 Success[1]		Change in Sweat Production[2]	
Site ID	Total	DRM04	Vehicle	DRM04	Vehicle	DRM04	Vehicle
401	33	22	11	18.1%	18.2%	-102 (106)	-114 (108)
418	27	18	9	50.0%	33.3%	-116 (70)	-70 (113)
404	26	17	9	48.2%	11.5%	-49 (241)	-209 (234)
405	26	17	9	70.6%	11.5%	-85 (104)	-42 (139)
416	19	13	6	61.2%	59.6%	-78 (117)	-136 (120)
409	17	11	6	71.6%	16.7%	-286 (199)	-60 (109)
421	17	11	6	18.6%	33.6%	-83 (104)	-48 (47)
407	16	11	5	57.1%	56.9%	-107 (132)	-193 (223)
408	16	10	6	56.4%	50.0%	-117 (169)	-127 (126)
451	15	10	5	50.0%	40.0%	-61 (51)	-21 (92)
406	13	8	5	56.0%	20.0%	-38 (53)	-116 (106)
410	12	8	4	61.5%	50.0%	-80 (44)	-35 (25)
413	12	8	4	87.5%	25.0%	-93 (95)	-21 (42)
412	11	7	4	42.9%	0.0%	-483 (1515)	-137 (116)
455	11	8	3	24.8%	33.3%	-64 (110)	-139 (239)
414	10	7	3	71.2%	0.0%	-19 (79)	-78 (44)
411	9	6	3	66.7%	0.2%	-82 (132)	-25 (47)
415	7	5	2	78.2%	100.0%	-46 (43)	-111 (100)
454	7	5	2	40.0%	50.0%	-70 (108)	-64 (40)
402	6	4	2	69.3%	0.0%	-99 (96)	-32 (23)
460	6	4	2	100.0%	50.0%	-111 (68)	-67 (46)
458	5	3	2	33.3%	50.0%	-44 (77)	-34 (13)
403	4	2	2	100.0%	50.0%	-222 (2)	-88 (111)
417	4	3	1	33.3%	0.0%	-60 (231)	-83
456	4	3	1	33.3%	0.0%	-111 (56)	-70
457	4	3	1	33.3%	0.0%	-110 (45)	-14
419	3	2	1	50.0%	0.0%	-107 (74)	-67
420	3	2	1	100.0%	0.0%	-80 (4)	-35
452	1	1	0	100.0%		10	
Overall	**344**	**229**	**115**	**52.8%**	**28.3%**	Mean **-105**	**-92**
						Median **-81**	**-66**

Source: Reviewer's analysis.

(1) Defined as ≥4-point improvement from baseline in ASDD Item #2 at Week 4. Averaged over 185 MI datasets.

(2) Defined as the change from baseline in gravimetrically-measured sweat production at Week 4. Gravimetrically-measured sweat production is measured in mg/5 min. Results averaged over 95 MI datasets and presented as mean (standard deviation), where standard deviation was calculated using Rubin's formula.

Table 26: Efficacy Results by Site – Trial HH05

	Sample Sizes			ASDD Item #2 Success[1]		Change in Sweat Production[2]	
Site ID	Total	DRM04	Vehicle	DRM04	Vehicle	DRM04	Vehicle
513	34	22	12	83.9%	41.7%	-128 (103)	-68 (96)
507	33	22	11	70.8%	36.4%	-116 (221)	-133 (159)
511	30	20	10	64.0%	12.5%	-136 (150)	-75 (182)
514	28	18	10	72.2%	60.0%	-74 (78)	-82 (93)
505	24	16	8	50.9%	25.0%	-99 (199)	-245 (291)
515	22	14	8	64.0%	12.9%	-101 (112)	-77 (102)
510	19	12	7	68.6%	6.1%	-131 (85)	-79 (76)
520	19	13	6	61.5%	32.0%	-77 (71)	-60 (119)
512	18	12	6	75.3%	33.3%	-150 (190)	-152 (349)
516	18	12	6	85.5%	16.7%	-73 (83)	-58 (22)
504	17	11	6	73.1%	16.7%	-136 (140)	-65 (128)
501	14	10	4	47.4%	50.0%	-56 (54)	-5 (26)
502	14	10	4	88.3%	0.0%	-164 (141)	-191 (172)
508	14	10	4	57.1%	25.0%	-111 (90)	-73 (57)
518	14	9	5	22.2%	0.0%	-138 (96)	-50 (45)
503	13	9	4	55.6%	27.1%	-76 (51)	-128 (112)
506	12	8	4	47.9%	6.0%	-94 (88)	-40 (57)
519	7	4	3	100.0%	66.7%	-160 (90)	20 (61)
517	2	2	0	0.0%	0.0%	-12 (31)	
509	1	0	1	0.0%	0.0%		-41.6
Overall	**353**	**234**	**119**	**66.1%**	**26.9%**	Mean **-110**	**-92**
						Median **-79**	**-58**

Source: Reviewer's analysis

(1) Defined as ≥4-point improvement from baseline in ASDD Item #2 at Week 4. Results averaged over 205 MI datasets.

(2) Defined as the change from baseline in gravimetrically-measured sweat production at Week 4. Gravimetrically-measured sweat production is measured in mg/5 min. Results averaged over 85 MI datasets and presented as mean (standard deviation) where standard deviation was calculated using Rubin's formula.

7.3. Review of Safety

7.3.1. Safety Review Approach

Studies/Clinical Trials Used to Evaluate Safety

The drug development program for glycopyrronium cloth included eight clinical trials, summarized in Table 27. The clinical safety review focused in particular on the two Phase 3 pivotal trials, DRM04-HH04 and DRM04-HH05. These two trials shared a virtually identical study design and study population, consisting of subjects with primary axillary hyperhidrosis – adults and children, 9 years of age and older. Given the common design and study population of these two trials, the applicant pooled the data from these trials for safety analyses; the pooled data (as defined below) constitute the core Safety Database, referred to as the Pooled Safety Database. Similarly, this safety review will focus on data from this database.

This review also includes analysis of the open-label long-term safety extension trial DRM04-HH06, which involved enrollment of subjects from the two Phase 3 trials following study completion, with subsequent open-label treatment with study drug for an additional 44 weeks. Data from this study (as defined below) will be referred to as the Long-Term Safety Database. In addition, this review includes examination of data from study DRM04-HH08, which assessed the skin sensitization and irritation potential of the investigational product in healthy volunteers (see Section 7.4.7). Analysis of safety data is conducted separately for each of these two studies.

This review examined serious adverse events (SAEs) and deaths across all eight studies.

Given the mechanism of action of glycopyrronium, an anticholinergic agent, the Phase 3 trials included a particular focus on anticholinergic effects, several of which were designated as adverse events of special interest (AESI), discussed further in Section 7.4.5. Additional discussion of local skin reactions is also provided in Section 7.4.5.

7.3.2. Review of the Safety Database

Overall Exposure

Definition of the study population: All subjects who were randomized and received at least one confirmed dose of study drug were included in the Safety Database (see Table 27).

Pooling of data: As discussed in the Safety Review Approach Section (Section 7.3.1), as the two pivotal Phase 3 trials shared a common design and study population, the applicant pooled data from these trials for safety analyses. Pooling of data was discussed in correspondence with the sponsor in September 2016, with the Agency indicating support for pooling of data from these two studies for safety analyses.

Table 27: Safety Database for Glycopyrronium: Safety Population, Size and Denominators

Safety Database for Glycopyrronium (Individuals exposed to the study drug in this development program for indication under review) N=1269[1]			
Clinical Trial Groups	Trial	Study Drug (n=1269)	Vehicle (n=635)
Controlled trials conducted for this indication			
	DRM04-HH04[2,3]	227	114
	DRM04-HH05[3,4]	232	118
	DRM04-HH08[5]	328	328
	W0266-01[6]	24	14
	DRM04-HH01[7]	155	39
	DRM04-HH02	83	22
All other than controlled trials conducted for this indication			
	DRM04-HH06[8]	189	NA
	DRM04-HH07	31	NA
Controlled trials conducted for other indications		NA	NA

Reviewer Table.
[1] N represents total number of unduplicated subjects who received at least one dose of glycopyrronium, summed from trials above
[2] Source – CSR, DRM04-HH04, Table 8, p. 49
[3] Trials DRM04-HH04 and DRM04-HH05 are pivotal Phase 3 trials; data from these studies were pooled to create the Pooled Safety Database
[4] Source – CSR, DRM04-HH05, Table 8, p. 47
[5] DRM04-HH08 is dermal safety study; all subjects were exposed to study drug, vehicle and other controls.

[6] Source – CSR, W0266-01; per study synopsis, 38 evaluated for safety
[7] Source – CSR, DRM04-HH01; per study synopsis, safety population included 155 from four study drug arms, 39 from vehicle arm
[8] DRM04-HH06 is open-label extension study; 189 subjects were in vehicle arm in the initial Phase 3 pivotal trials (DRM04-HH04 or DRM04-HH05), then switched to study drug in open label extension.

Table 28 below provides a summary of exposure to the drug across the entire development program, including duration of exposure.

Table 28: Summary of Extent of Exposure (DRM04-HH01, DRM04-HH02, DRM04-HH04, DRM04-HH05, DRM04-HH06, DRM04-HH07, DRM04-HH08, and W0266-01 Pooled)

	DRM04 (N=1269)
No. of subjects who received at least one dose of study drug	1269
No. of subjects dosed for at least 6 months	393
No. of subjects dosed for at least 12 months	114

Note: Pooled data were restricted to subjects who received at least one dose of study drug. Six (6) and 12 months of dosing were determined as greater than or equal to 168 and 336 trial days, respectively.
Source: Adapted from ISS Table 11

As discussed in EOP2 and pre-NDA meetings with the sponsor, indication is considered a chronic indication for a non-life threatening condition, and therefore ICH E1A is applicable. Based on the extent of exposure documented above, it appears that the sponsor has met the minimum requirements for subjects exposed for 6 months and 12 months. However, the number of subjects with short term exposure – 1269 – falls short of the E1A recommended total of 1500.

The shortfall is not sizeable, as the number of subjects who received at least one dose, 1269, represents about 85% of the recommended total of 1500. Further, the safety database does appear adequate for subjects with longer-term exposure (6 months and 12 months).

The treatment regimen in the pivotal Phase 3 trials involved application of study drug or vehicle once daily to both axillae for 28 days. Examining the extent of exposure for subjects in the Pooled Safety Database, the mean duration of exposure was 26.7 days for those receiving study drug, and 27.7 days for those receiving vehicle; the median duration was 28.0 days in both treatment groups (per ISS Table 12).

Relevant characteristics of the safety population:

Demographic characteristics – Pooled Safety Population

Demographic characteristics are summarized for the Pooled Safety Population from the two pivotal Phase 3 trials in Table 29. Demographics were generally similar between the study drug and vehicle groups. The mean age was 32.7 years, with age ranging from 9 to 76 years. Overall,

8.1% (56/691) were <18 years of age. Most subjects were white [82.1% (567/691)]. There were more females than males in both treatment groups.

Table 29: Summary of Subject Demographic Characteristics (DRM04-HH04 and DRM04-HH05 Pooled; Safety Population)

	DRM04, (b) (4)% (N=459)	Vehicle (N=232)	Total (N=691)
Age (years)			
Mean (SD)	32.4 (11.07)	33.3 (12.11)	32.7 (11.43)
Median	31.0	32.0	31.0
Min to Max	11, 65	9, 76	9, 76
<16 Years	16 (3.5%)	16 (6.9%)	32 (4.6%)
≥16 Years	443 (96.5%)	216 (93.1%)	659 (95.4%)
<18 Years	34 (7.4%)	22 (9.5%)	56 (8.1%)
≥18 Years	425 (92.6%)	210 (90.5%)	635 (91.9%)
Sex, n (%)			
Male	210 (45.8%)	112 (48.3%)	322 (46.6%)
Female	249 (54.2%)	120 (51.7%)	369 (53.4%)
Ethnicity, n (%)			
Hispanic or Latino	74 (16.1%)	38 (16.4%)	112 (16.2%)
Not Hispanic or Latino	385 (83.9%)	194 (83.6%)	579 (83.8%)
Race, n (%)			
American Indian or Alaska Native	4 (0.9%)	0 (0.0%)	4 (0.6%)
Asian	5 (1.1%)	0 (0.0%)	5 (0.7%)
Black or African American	58 (12.6%)	28 (12.1%)	86 (12.4%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	2 (0.9%)	2 (0.3%)
White	371 (80.8%)	196 (84.5%)	567 (82.1%)
Other	21 (4.6%)	6 (2.6%)	27 (3.9%)

Max = maximum; Min = minimum; SD = standard deviation
Source: ISS Table 14; ISS Table 14.1.1.3

Hyperhidrosis history was generally similar between treatment groups (see ISS Table 16). Overall, subjects had been experiencing axillary hyperhidrosis for a mean of 15.5 years. Half of subjects (50.4%) reported hyperhidrosis limited to the axillae. However, involvement of other areas was relatively common. In addition to axillary hyperhidrosis, subjects reported hyperhidrosis involving palms (34.4%), soles (29.4%), face (12.0%), scalp (10.9%), and trunk

(15.5%). Most subjects (75.0%) reported no prior treatment for hyperhidrosis; a small percentage reported prior treatment with botulinum toxin (5.4%), oral anticholinergics (4.3%), topical anticholinergics (4.6%), or other treatments (13.6%).

Adequacy of the safety database:

The total subject exposure to study drug, as described above, provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population.
Therefore, the safety database presented by the applicant is sufficient to characterize the safety profile of glycopyrronium for the treatment of primary axillary hyperhidrosis.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety of the investigational product. Data quality and fitness were evaluated in conjunction with the JumpStart team. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

Categorization of Adverse Events

AEs were categorized by system-organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.0. The coding of adverse events in the NDA submission appeared adequate and allowed for accurate estimation of AE risks.

Investigators monitored each subject regularly for AEs or serious AE (SAEs) occurring throughout the trial. AEs and SAEs were recorded and reported from the time of informed consent through to end of the study.

Investigators categorized AE for seriousness, intensity, causality, duration, and action taken with study drug. Each AE or SAE was categorized as mild, moderate or severe. All AEs or SAEs were followed until satisfactory resolution or a clinically stable or baseline status.

Given the mechanism of action of glycopyrronium, which acts as an anticholinergic agent, the sponsor also monitored specific anticholinergic effects. Treatment-emergent AEs of special interest (AESI) were defined to include blurry vision, mydriasis, and urinary hesitancy/retention, which were tabulated and listed separately.

The definition of AE, TEAE, and SAE are acceptable. The classification system used by investigators to describe the severity of AE as well as the causal relationship between AE and study product are also acceptable. The applicant's identification and presentation of AE of special interest was appropriate.

Routine Clinical Tests

In the pivotal Phase 3 trials (the pooled safety analysis set), the evaluation of safety was conducted during visits to the clinic. Scheduled visits occurred at Screening, Baseline (Day 1), Week 1, 2, 3 and 4 (End of Treatment). The evaluation of safety included clinical laboratory tests, vital signs, physical examinations, and ECGs. Safety monitoring also included recording of adverse events, discussed in the previous section.

Clinical laboratory evaluation, including serum chemistry, hematology, and urinalysis, was conducted at Screening and Week 4. Urine pregnancy testing was performed at Screening, Baseline (Day 1) and Week 4 (End of Treatment).

Vital signs were assessed at every clinic visit during the trials [Screening, Baseline (Day 1), Week 1, 2, 3 and 4 (End of Treatment)]. Height and weight were measured at Screening; weight was also measured at Week 4

Physical examinations, including a complete examination of the skin, were performed at Screening. All subjects were also assessed for any signs or symptoms of Local Skin Reactions, including burning/stinging, pruritus, edema, erythema, dryness and scaling; this assessment was conducted at Baseline, Week 1, 2, 3 and 4. As needed, a symptom directed physical exam was offered at Baseline, Week 1, 2, 3 and 4 to assess the subject.

Supine 12-lead ECGs were performed at Screening and Week 4.

Overall, the safety assessments performed seem reasonable for the population, disease, and indication under investigation.

7.3.4. Safety Results

Deaths

Across the 8 trials in the development program, one death occurred, in a subject enrolled in DRM04-HH08 (dermal safety study).

Study DRM04-HH08, Subject #(b) (6): A 57 year old black female, postmenopausal but otherwise with negative medical history, participated in the dermal safety study from Day 1 to Day 15 (last application). On Day 18, the subject died of a SAE of possible myocardial infarction; the subject's recorded cause of death was based on a report from a friend and could not be validated through medical records or information from family or others. The subject reported no AEs during the study. The investigator considered the SAE not related to study drug. This reviewer notes the limited information available but agrees the SAE is unlikely to be related particularly since this trial involved limited product exposure.

Serious Adverse Events

Across the 8 trials in the drug's development program, there were a total of 12 SAEs. All SAEs occurred in subjects who were receiving study drug. One SAE (possible myocardial infarction) was fatal, 3 were severe (diverticulitis, infectious colitis, and suicide attempt), and the remainder were mild or moderate. Ten of the 12 SAEs were considered by investigators to be unrelated to treatment, and 2 SAEs (both events of unilateral mydriasis) were considered related. Mydriasis, reported as SAE for 2 subjects, was the only SAE reported for > 1 subject. Both these events of unilateral mydriasis were categorized as SAEs because the subjects were hospitalized to rule out possible CNS causes.

Overall, SAEs were uncommon. Across the 8 trials, considering all subjects who received at least one dose of study drug, SAEs occurred in 12/1269 (0.9%) subjects. In the pivotal Phase 3 trials, where subjects were treated for 4 weeks, SAEs were reported in 2/459 (0.4%) subjects receiving study drug. In the long-term safety (open label extension) trial (DRM04-HH06), where subjects were followed for an additional 44 weeks, SAEs were reported in 7/550 (1.3%) subjects receiving study drug.

Table 30 below lists all subjects who experienced a SAE across the eight trials:

Table 30: Summary of Subjects Who Had a Serious Adverse Event

Trial No. Subject No.	Age/Sex	AE: MedDRA PT	Severity	Relationship to Study Drug	Day of Onset/ Resolution
Death					
DRM04-HH08					
(b) (6)	57/F	Myocardial infarction	Severe/Fatal	Not related	18/18
Other SAEs					
DRM04-HH01					
(b) (6)	59/M	Malignant melanoma in situ	Moderate	Not related	22/50
DRM04-HH04					
(b) (6)	20/F	Mydriasis (unilateral)	Moderate	Related	10/18
DRM04-HH05					
(b) (6)	34/M	Dehydration	Moderate	Not related	37/40
DRM04-HH06					
(b) (6)	25/F	Concussion	Moderate	Not related	19/20
	30/M	Diverticulitis	Severe	Not related	104/109
	35/F	Suicide attempt	Severe	Not related	52/55
	20/F	Mydriasis (unilateral)	Mild	Related	12/14

(b) (6)	44/M	Chest pain	Moderate	Not related	214/214
	28/M	Affective disorder	Moderate	Not related	135/143
	38/M	Infectious colitis	Severe	Not related	177/185
DRM04-HH08					
(b) (6)	47/F	Diverticulum	Moderate	Not related	38/43

Source: Clinical Overview, Table 26

The following are narratives of selected subjects who experienced SAEs during treatment with study drug:

- Study DRM04-HH04, Subject # (b) (6): A 20 year old female with no prior medical history developed unilateral mydriasis of moderate severity on Day 10. The subject's last application of study drug was on Day 9; with the onset of mydriasis, study drug was stopped and not resumed. The subject was hospitalized to rule out a CNS event, as she had experienced a recent blow to the head. A CNS cause was ruled out, and her symptoms resolved on Day 18. The investigator considered the SAE to be related to study drug; this reviewer concurs.
- Study DRM04-HH06, Subject # (b) (6): A 30 year old male with a history of diverticulitis and perforated colon, hypertension; and rosacea was hospitalized for diverticulitis from Day 104 to Day 109. The SAE was categorized as severe. He was treated with antibiotics with resolution of his symptoms. Study drug was discontinued during the hospitalization but resumed afterwards, continuing through Day 259. While previously on study drug in the DRM04-HH04 trial, the subject temporarily discontinued study drug due to dry mouth and flushing; these symptoms did not recur. Given his prior history of diverticulitis and the lack of constipation or other reported anticholinergic effects at the time of this episode, the investigator felt that the SAE of diverticulitis was not related to study drug. This reviewer agrees the SAE is unlikely to be related.
- Study DRM04-HH06, Subject # (b) (6): A 35 year old female with a history of depression, sinusitis, and hysterectomy was hospitalized for a suicide attempt from Day 52 to 55. The SAE was categorized as severe. She was treated with antidepressants and discharged with a diagnosis of stable depression. Details of the hospitalization were not available. The study drug was continued through Day 114; no other AEs or anticholinergic effects were reported. The investigator considered the suicide attempt as not related to study drug. This reviewer agrees the SAE is unlikely to be related.
- Study DRM04-HH06, Subject # (b) (6): A 38 year old male with a history of psoriasis, seasonal allergy, and appendectomy was hospitalized with infectious colitis. The patient noted abdominal pain, vomiting, and hematochezia on Days 174 to 176, and was hospitalized with a diagnosis of infectious colitis from Day 177 to Day 185. The SAE was categorized as severe. He responded to treatment with antibiotics and intravenous fluids. Study drug was briefly interrupted during hospitalization, then resumed. The patient had

previously experienced AEs including nausea, upper respiratory infection, and sinus congestion, none of which required a change in study drug dosing. Of note, the subject had been taking adalimumab for two years for psoriasis. The investigator felt that the SAE was not related to study drug. This reviewer agrees the SAE is unlikely to be related.

Dropouts and/or Discontinuations Due to Adverse Effects

Pooled Phase 3 trials (DRM04-HH04, DRM04-HH05): Seventeen (17) subjects (3.7%) in the DRM04 group and 1 subject (0.4%) in the vehicle group prematurely discontinued from the trials due to a TEAE; all subjects were followed until the TEAE resolved. In the DRM04 group, TEAEs that led to discontinuation from the trial for > 1 subject included dry mouth (5 subjects [1.1%]), urinary retention and mydriasis (4 subjects [0.9%] each), urinary hesitation (3 subjects [0.7%]), and vision blurred (2 subjects [0.4%]). In the vehicle group, only one subject discontinued from the trial due to abnormal laboratory tests (i.e., a high AST value and a low percent of neutrophils). Most TEAEs leading to discontinuation from the trial were mild or moderate in severity and most were considered by the investigator as related to study drug.

Long-term safety study (DRM04-HH06): 44 (8.0%) of subjects had a TEAE that led to discontinuation from the trial. TEAEs leading to discontinuation were similar to those described in the pooled Phase 3 studies, with the addition of application site dermatitis. The most commonly reported TEAEs leading to discontinuation from the trial in DRM04-HH06 (i.e., those reported for ≥ 5 subjects) were vision blurred (10 subjects [1.8%]), dry mouth (9 subjects [1.6%]), application site dermatitis (5 subjects [0.9%]), and urinary hesitation (5 subjects [0.9%]). Most TEAEs leading to discontinuation were mild or moderate in severity and most were considered by the investigator as related to study drug. The majority of TEAEs leading to discontinuation from the trial occurred within the first 12 weeks of the trial.

Significant Adverse Events

As noted in the discussion of methodology in Section 7.4.3, investigators categorized AEs with regard to seriousness, intensity, causality, duration, and action taken with study drug. Each AE or SAE was categorized as mild, moderate or severe. All AEs or SAEs were followed until satisfactory resolution or a clinically stable or baseline status.

Pooled Phase 3 trials (DRM04-HH04, DRM04-HH05):

Table 31 below shows an overview of TEAEs reported in the pooled safety population of the pivotal Phase 3 trials, including seriousness, severity and discontinuation due to AEs. Of subjects receiving study drug, 4 (0.9%) reported a severe AE, relative to no subjects in the vehicle arm.

Table 31: Overview of Treatment-Emergent Adverse Events (DRM04- HH04 and DRM04-HH05 Pooled; Safety Population)

	DRM04, (b) (4) % (N=459)	Vehicle (N=232)
No. (%) of subjects reporting at least 1 AE	257 (56.0%)	75 (32.3%)
No. (%) of subjects reporting at least 1 SAE	2 (0.4%)	0 (0.0%)
Discontinued from the trial due to an AE	17 (3.7%)	1 (0.4%)
Maximum Severity		
Mild	170 (37.0%)	53 (22.8%)
Moderate	83 (18.1%)	22 (9.5%)
Severe	4 (0.9%)	0 (0.0%)

Source: Adapted from ISS, Table 23

Severe TEAEs included dry mouth [3 subjects (0.7%)], mydriasis [1 subject (0.2%)], urinary retention [1 subject (0.2%)], application site rash [1 subject (0.2%)], and anhidrosis [1 subject (0.2%)]. Following are narratives for the four subjects who experienced one or more severe AEs during treatment with study drug:

- Study DRM04-HH05, Subject # (b) (6): A 34 year old female developed severe dry mouth on Day 3; the event resolved on the same day without intervention or change in study drug dosing.
- Study DRM04-HH05, Subject # (b) (6): A 16 year old male developed four severe TEAEs (dry mouth, mydriasis, urinary retention, and anhidrosis), all of which started on Day 3. Study drug was discontinued, with the subject's last dose on Day 3, and the subject was discontinued from the trial. All TEAEs resolved within 2 to 6 days.
- Study DRM04-HH05, Subject # (b) (6): A 57 year old male noted severe dry mouth on Day 2. The subject took oral lozenges, discontinued study drug, with the last dose on Day 7, and discontinued from the trial. Symptoms resolved on Day 16.
- Study DRM04-HH04, Subject # (b) (6): A 24 year old female noted a severe application site rash on Day 24; the event resolved on the same day without intervention or change in study drug dosing.

Long-term safety study (DRM04-HH06):

Table 32 below shows an overview of TEAEs reported in the safety population of the long-term safety study, including seriousness, severity and discontinuation due to AEs. 28 subjects (5.1%) reported a severe AE, a higher rate than that observed in subjects receiving study drug in the pivotal Phase 3 trials (0.9%). This is likely due in part to the longer period of observation (up to 44 weeks in the long-term safety study, relative to 4 weeks in the pivotal Phase 3 trials). Of note, incidence rates for individual AEs were relatively similar; for example, severe dry mouth

was reported by 0.7% subjects receiving study drug in the pivotal trials, and by 0.9% subjects in the long term safety trial.

Table 32: Overview of Treatment-Emergent Adverse Events (DRM04-HH06; Safety Population)

	DRM04, (b) (4) % (N=550)
No. (%) of subjects reporting at least 1 AE	329 (59.8%)
No. (%) of subjects reporting at least 1 SAE	7 (1.3%)
Discontinued from the study due to an AE	44 (8.0%)
Maximum Severity	
Mild	148 (26.9%)
Moderate	153 (27.8%)
Severe	28 (5.1%)

Source: Adapted from ISS, Table 24

For severe TEAEs reported in the long term safety study, those reported for 2 or more subjects (0.4%) were dry mouth (0.9%), application site pruritus (0.7%), application site dermatitis (0.5%), application site pain (0.5%), application site erythema (0.4%), dry eye (0.4%), nasal dryness (0.4%), and nephrolithiasis (0.4%).

Treatment Emergent Adverse Events and Adverse Reactions

Pooled Phase 3 trials (DRM04-HH04, DRM04-HH05):

As noted in Table 32 above, TEAEs were reported for 56.0% of subjects in the DRM04, (b) (4) % group and 32.3% of subjects in the vehicle group. The table below (Table 33) shows common TEAEs reported in the pooled Phase 3 studies, including all TEAEs occurring in ≥ 1% of subjects on study drug and occurring at a higher rate in subjects on study drug, relative to vehicle.

Table 33: Summary of TEAEs Reported for ≥ 1% of Subjects on Study Drug (Pooled Phase 3 studies, DRM04-HH04 and DRM04-HH05, Safety Population)[1]

MedDRA PT	**DRM04, (b) (4) % (N=459)**	**Vehicle (N=232)**
Dry mouth	111 (24.2%)	13 (5.6%)
Mydriasis	31 (6.8%)	0
Oropharyngeal pain	26 (5.7%)	3 (1.3%)
Headache	23 (5.0%)	5 (2.2%)
Urinary hesitation	16 (3.5%)	0
Vision blurred	16 (3.5%)	0

Upper respiratory tract infection	14 (3.1%)	6 (2.6%)
Nasal dryness	12 (2.6%)	1 (0.4%)
Dry throat	12 (2.6%)	0
Dry eye	11 (2.4%)	1 (0.4%)
Dry skin	10 (2.2%)	0
Constipation	9 (2.0%)	0
Urinary retention	7 (1.5%)	0
Nausea	6 (1.3%)	0
Pruritus	6 (1.3%)	0
Epistaxis	5 (1.1%)	1 (0.4%)

Source: Adapted from Clinical Overview, Table 22

[1]Listing excludes TEAEs occurring at a lower rate in study drug group relative to vehicle, including application site pain (8.7% and 9.5%, respectively); nasopharyngitis (2.0% and 3.9%); and application site pruritus (1.5% and 3.0%)

To determine which of these reported TEAEs represent adverse reactions for the purpose of labeling– i.e. to assess possible causality – a number of factors were considered, outlined in Table 34 below.

- In reviewing rates of TEAEs in the vehicle group, it is notable how many how many TEAEs have a rate of 0 in the vehicle group (e.g. mydriasis, urinary hesitation, vision blurred), suggesting that these events may have a fairly specific association with study drug.
- Many of the reported TEAEs are consistent with the pharmacology of glycopyrronium, a known anticholinergic agent, as indicated in Table 34 below, which is particularly strong evidence for causality.
- Table 34 also includes summary data from investigators' assessments of individual AEs and whether they were related to study drug; e.g. for dry mouth, 109 of 111 cases were felt to be related to study drug. Though investigator assessments clearly represent individual opinions, these data can be supportive, and overall these data are quite consistent with other evidence presented here related to causality.
- Table 34 also includes information on adverse reactions from the label for Cuvposa, the reference-listed drug. Though the information is derived from a very small placebo-controlled trial, overall the reported adverse reactions are similar to the TEAEs described for glycopyrronium.
- The timing of an event relative to the time of drug exposure may also provide support for causality (though this is not always the case, as some subjects developed AE symptoms late, or had rapid resolution of symptoms while still on drug). However, some subjects provided at least anecdotal evidence in terms of timing; note example discussed above (see Significant Adverse Events section, Study DRM04-HH05, Subject # (b) (6)). In this case, a

16 year old male developed four severe TEAEs (dry mouth, mydriasis, urinary retention, and nhidrosis), all of which started on Day 3. Study drug was discontinued following dose on Day 3, and the subject was discontinued from the trial; all TEAEs resolved within 2 to 6 days.

Table 34: Summary of TEAEs Reported

MedDRA PT	DRM04 (b) (4) % (N=459)	Vehicle (N=232)	Anti-cholinergic effect	AE assessed as related to study drug[1]	Reported for Cuvposa[2]
Dry mouth	111 (24.2%)	13 (5.6%)	✓	109/111 (98%)	8/20 (40%)
Mydriasis	31 (6.8%)	0	✓	30/31 (97%)	
Oropharyngeal pain	26 (5.7%)	3 (1.3%)		8/26 (31%)	
Headache	23 (5.0%)	5 (2.2%)		3/23 (13%)	3/20 (15%)
Urinary hesitation	16 (3.5%)	0	✓	16/16 (100%)	
Vision blurred	16 (3.5%)	0	✓	15/16 (94%)	
Upper respiratory tract Infection	14 (3.1%)	6 (2.6%)		1/14 (7%)	3/20 (15%)
Nasal dryness	12 (2.6%)	1 (0.4%)	✓	12/12 (100%)	
Dry throat	12 (2.6%)	0	✓	12/12 (100%)	
Dry eye	11 (2.4%)	1 (0.4%)	✓	11/11 (100%)	
Dry skin	10 (2.2%)	0	✓	8/10 (80%)	
Constipation	9 (2.0%)	0	✓	5/9 (56%)	7/20 (35%)
Urinary retention	7 (1.5%)	0	✓	7/7 (100%)	3/20 (15%)
Nausea	6 (1.3%)	0		1/6 (17%)	
Pruritus	6 (1.3%)	0		4/6 (67%)	
Epistaxis	5 (1.1%)	1 (0.4%)		3/5 (60%)	

Reviewer Table – data sources noted below
[1] Based on investigator's assessment of individual AEs and whether they were related to study drug; e.g. for dry mouth, 109 of 111 cases were felt to be related to study drug. Source: ISS Table 14.3.1.1.5
[2] From Cuvposa label; data is from 8-week placebo-controlled trial where 20 subjects received Cuvposa; data shown represent frequency of adverse reactions reported by ≥ 15% of CUVPOSA-treated subjects

Weighing all the considerations above, most of the reported TEAEs appear to be clearly related to glycopyrronium, with good evidence to support a causal link, particularly those which represent established anticholinergic effects. However, the evidence is not as strong for at least one of the reported AEs, upper respiratory tract infection, which is non-specific, is not associated with an anticholinergic mechanism, was associated with a minimal risk difference

(<1%) between study drug and vehicle, was judged in most cases by investigators to be unrelated to study drug, and lacked significant evidence for causality. Thus, this AE was not felt to be an adverse reaction.

For the final listing of adverse reactions for product labeling, the reviewer proposes to streamline the list by limiting it to TEAEs occurring in ≥2% of subjects on study drug, and also exclude upper respiratory tract infection, as discussed above. The sponsor proposed using a cutoff of >5%, which would result in including only four adverse reactions (dry mouth, application site pain, mydriasis, and oropharyngeal pain).

Table 35 below displays TEAEs occurring in ≥2% of subjects and more frequently with study drug than vehicle in the pooled Phase 3 trials, specifically those determined by the reviewer to be adverse reactions. This table represents the reviewer's recommendation for the presentation of adverse reactions in Section 6 of product labeling.

Table 35: Adverse Reactions Occurring in ≥2% of Subjects

Adverse Reactions	Glycopyrronium (N=459) n (%)	Vehicle (N=232) n (%)
Dry mouth	111 (24.2%)	13 (5.6%)
Mydriasis	31 (6.8%)	0
Oropharyngeal pain	26 (5.7%)	3 (1.3%)
Headache	23 (5.0%)	5 (2.2%)
Urinary hesitation	16 (3.5%)	0
Vision blurred	16 (3.5%)	0
Nasal dryness	12 (2.6%)	1 (0.4%)
Dry throat	12 (2.6%)	0
Dry eye	11 (2.4%)	1 (0.4%)
Dry skin	10 (2.2%)	0
Constipation	9 (2.0%)	0

Reviewer Table

Long-term safety study (DRM04-HH06):

In general, the commonly reported TEAEs and corresponding subject incidences reported during the 44-week, long-term safety study (DRM04-HH06) were similar to those reported with DRM04, (b) (4)% treatment in the 4-week, placebo-controlled trials (DRM04-HH04 and DRM04-HH05). Table 36 below shows TEAEs occurring in > 2% of subjects in Study DRM04-HH06. Of note, application site reactions appear to be more common in Study DRM04-HH06, relative to the pivotal trials. However, in the pivotal trials, application site reactions often

occurred with equal or greater frequency in the vehicle, relative to the study drug group. As TEAEs occurring with greater frequency in the placebo group are generally not included in the final listing of adverse reactions associated with a study drug, the application site reactions do not appear in the final list of ARs above. As the long-term safety study was not placebo-controlled, all TEAEs are included in the listing below.

The proposed labeling for glycopyrronium cloth does include a section listing local skin reactions, in particular erythema, burning/stinging, and pruritus, which were frequent in both the study drug and vehicle groups. Local skin reactions are discussed further in Section 7.3.5.2.

Table 36: Summary of TEAEs Reported for > 2% of Subjects (DRM04-HH06; Safety Population)

MedDRA PT	Total (N=550) n (%)
Dry mouth	93 (16.9%)
Vision blurred	37 (6.7%)
Application site pain	35 (6.4%)
Nasopharyngitis	32 (5.8%)
Mydriasis	29 (5.3%)
Upper respiratory tract infection	27 (4.9%)
Urinary hesitation	23 (4.2%)
Application site dermatitis	21 (3.8%)
Application site pruritus	21 (3.8%)
Application site rash	21 (3.8%)
Nasal dryness	20 (3.6%)
Dry eye	16 (2.9%)
Application site erythema	13 (2.4%)
Pharyngitis	12 (2.2%)

Source: ISS, Table 27

Laboratory Findings

The vast majority of clinical laboratory parameters (hematology and serum chemistry) were within normal limits at the time points measured in the 2 controlled Phase 3 trials (Screening and Week 4/End of Treatment) and the long-term safety trial (Phase 3 trials Week 4 Visit, used as baseline, and Week 44/End of Treatment). Mean changes from screening/baseline over time were relatively small, and no trends were observed.

Shifts from a normal laboratory value at screening/baseline to an above normal or below normal value at a later time point were observed. In the DRM04-HH04 and DRM04-HH05 trials, the laboratory parameters for which these shifts most commonly occurred (i.e., for ≥ 5% of subjects in the DRM04, (b) (4)% or vehicle groups) included the following:

- Alanine aminotransferase [ALT], with a shift from normal to above normal for 4.9% of subjects in the DRM04, (b) (4)% group and 7.2% of subjects in the vehicle group
- Lymphocytes/leukocytes (%), with a shift from normal to below normal for 6.6% of subjects in the DRM04, (b) (4)% group and 7.3% of subjects in the vehicle group
- Neutrophils/leukocytes (%), with a shift from normal to above normal for 8.3% of subjects in the DRM04, (b) (4)% group and 7.3% of subjects in the vehicle group

None of these laboratory deviations are considered clinically significant, and none of these are recommended in labeling.

Vital Signs

Overall, throughout the development program, the vast majority of subjects had vital sign values (systolic and diastolic blood pressure, pulse, respiratory rate, and temperature) that were normal at baseline and remained normal during the study period. Mean changes from baseline were minimal.

For subjects in DRM04-HH04 and DRM04-HH05, an abnormal vital sign was observed in 0.2% to 4.1% of subjects in the DRM04, (b) (4)% group, which was generally similar to that observed in the vehicle group (0.9% to 2.6%). Two subjects across the 2 controlled Phase 3 trials had a TEAE associated with a vital sign. Both subjects were in the DRM04, (b) (4)% group. One subject had blood pressure increased of mild severity and the other subject had hypertension of moderate severity. Neither TEAE was considered by the investigator as related to study drug.

Electrocardiograms (ECGs)

Standardized, 12-lead ECGs were obtained in DRM04-HH01, DRM04-HH02, DRM04-HH04, DRM04-HH05, and DRM04-HH07. Overall, posttreatment ECG intervals were consistent with screening/baseline values, and posttreatment changes in the DRM04 groups were generally small and consistent with changes observed in the corresponding vehicle group.

Across the trials in which ECGs were collected, TEAEs associated with an ECG abnormality were reported for a total of 3 subjects (2 in a DRM04B, (b) (4)% group [1 each in DRM04-HH01 and DRM04-HH02] and 1 in a vehicle group [DRM04-HH05]). The AEs reported for the subjects receiving DRM04B, (b) (4)% were T wave inversion and atrioventricular block first degree; the AE for the subject in the vehicle group was PR prolongation. All 3 AEs were mild and none was considered by the investigator as related to study drug.

QT

At the End of Phase 2 (EOP2) meeting, the sponsor requested a waiver for a QT/QTc trial. The Agency responded that the proposed plan not to conduct this trial appeared reasonable provided the maximal use PK trial confirmed the expectation that systemic exposure from topical application of glycopyrronium cloth was less than that with orally administered Cuvposa (glycopyrrolate). The Agency also recommended baseline and periodic on-therapy (Tmax) ECG monitoring to exclude large effects (EOP2 meeting minutes, April 20, 2015).

The results from the maximum-use PK trial (DRM04-HH07) were discussed at the pre-NDA meeting (Pre-NDA meeting minutes, February 14, 2017). The trial showed that systemic exposure with glycopyrronium cloth was lower than that with orally dosed Cuvposa. In addition, 12-lead ECGs conducted in all subjects in the Phase 3 trials, DRM04-HH04 and DRM04-HH05, as well as the Phase 2 trials, DRM04-HH01 and DRM04-HH02, showed no evidence of QTc prolongation. Further, no QTc prolongation was observed in the maximum-use PK trial. On the basis of these results, the sponsor requested a waiver for a QT/QTc trial. At the pre-NDA meeting, the Agency indicated that a thorough QT trial would not be required and that a formal waiver request should be included in the NDA, which the sponsor has done.

Immunogenicity

Not applicable.

7.3.5. Analysis of Submission-Specific Safety Issues

7.3.5.1. Adverse Events of Special Interest

Given the mechanism of action of glycopyrronium, an anticholinergic agent, the Phase 3 pivotal trials and the long-term safety trial included a particular focus on anticholinergic effects, several of which were designated as adverse events of special interest (AESI). Designated treatment-emergent AEs of special interest (AESI) included 'Blurry Vision', 'Mydriasis', and 'Urinary Hesitancy/Retention'; these were tabulated and listed separately. The corresponding MedDRA PTs are listed below:

Adverse Event of Special Interest (AESI)	MedDRA PT
Blurry vision	Vision blurred
Mydriasis	Mydriasis
Urinary Hesitancy/Retention	Nocturia, Pollakiuria, Urinary hesitation, Urinary retention, Urine flow decreased

Pooled Phase 3 trials (DRM04-HH04, DRM04-HH05):

Treatment-emergent AESIs were reported for 61 subjects (13.3%) in the DRM04, (b) (4)% group and no subject in the vehicle group. For slightly more than half of subjects with an AESI (34 of 61 subjects; 55.7%), the event resolved without study drug interruption or withdrawal. Twenty

subjects (32.7%) had events that resolved following a drug interruption, and 7 subjects (11.5%) discontinued study drug.

The most common AESI was mydriasis, reported for 31 subjects (6.8%). Urinary hesitancy/retention was reported for 26 subjects (5.7%). Blurry vision was reported for 16 subjects (3.5%).

Trial sites were asked to further specify the AESIs of mydriasis and blurry vision as unilateral or bilateral; unilateral events were likely due to inadvertent, local, direct exposure to the eye. Bilateral events could have been due to systemic effects or to bilateral local exposure.

Among the 31 subjects with an AESI of mydriasis, the event was specified as unilateral for 23 subjects (74%); one subject had an episode that was unilateral and another episode that was bilateral. Over half of the subjects with an AESI of mydriasis (20 of 31 subjects; 64.5%) had their event resolve without study drug interruption or withdrawal, while 7 subjects (22.6%) had events that resolved following a drug interruption. Four subjects (12.9%) discontinued study drug following their AESI of mydriasis.

Among the 16 subjects with an AESI of blurry vision, the event was specified as bilateral for 11 subjects and unilateral for 5. Slightly over half the subjects with an AESI of blurry vision (9 of 16; 56.3%) had their event resolve without study drug interruption or withdrawal, while 5 subjects (31.3%) had events that resolved following a drug interruption. Two subjects (12.5%) discontinued study drug following their AESI of blurry vision.

Among the 26 subjects with an AESI of urinary hesitancy/retention, 10 (38.5%) had their event resolve without study drug interruption or withdrawal, 13 (50.0%) had events that resolved following a drug interruption or study drug withdrawal, and 3 (11.5%) discontinued study drug following the AESI of urinary hesitation/retention.

Among subjects with an AESI of urinary hesitancy/retention, one required catheterization. The subject, a 56-year-old man who entered DRM04-HH05 with unrecognized prostatic hypertrophy, had a TEAE of urinary retention and was treated with bladder catheterization; the subject subsequently underwent transurethral resection of the prostate. The urinary retention was attributed to the prostatic hypertrophy in combination with the anticholinergic effects of DRM04. No other subject required catheterization for urinary hesitancy/retention.

Most AESIs were mild or moderate in severity; however, one subject had both severe mydriasis and severe urinary retention, which both resolved after study drug withdrawal. One subject with unilateral mydriasis was hospitalized to rule out a CNS disorder; the event was therefore reported as an SAE. Most AESIs were considered by the investigator to be related to study drug.

The majority of AESIs resolved within 3 to 14 days. Nine events (3 events of vision blurred, 2 events of urinary hesitation, and single events of mydriasis, nocturia, pollakiuria, and urinary retention) lasted for > 14 days.

Long-term safety study (DRM04-HH06):

The overall incidence of AESIs reported over 44 weeks of treatment in DRM04-HH06 was similar to the incidence reported over 4 weeks of treatment with DRM04, (b) (4)% in the controlled Phase 3 trials (14.2% vs 13.3%, respectively). The most commonly reported AESIs were vision blurred (37 subjects [6.7%] had 45 events), mydriasis (29 subjects [5.3%] had 37 events), and urinary hesitation (23 subjects [4.2%] had 26 events). Rates of the most common AESIs were similar or, as expected for this long-term trial, slightly higher compared with the rates of these events reported in the DRM04, (b) (4)% group in the pivotal trials. Most AESIs were mild or moderate in severity; 1 was severe. Most AESIs were considered by the investigator as related to study drug.

Of the 45 reported TEAEs of vision blurred, 40 (88.9%) were bilateral and 5 (11.1%) were unilateral. Of the 37 reported TEAEs of mydriasis, 6 (16.2%) were bilateral and 31 (83.8%) were unilateral.

Most AESIs resolved within 3 to 14 days. However, 24 subjects with vision blurred (24/45, 53.3%), 7 subjects with urinary hesitation (7/24, 29.2%), and 6 subjects with mydriasis (6/36, 16.7%) had AESIs that lasted for > 14 days. Examining the time between discontinuation of study drug and resolution of symptoms, virtually all subjects had resolution of symptoms by 14 to 21 days after discontinuing study drug.

7.3.5.2. Local Skin Reactions

To evaluate local skin effects at the site of application of the investigational product, all subjects were assessed for Local Skin Reactions (LSRs) at each study visit. LSRs included burning/stinging and pruritus (assessed by the subject), and edema, erythema, dryness, and scaling (assessed by the investigator). Each LSR was scored as 0 (None), 1 (Mild), 2 (Moderate) or 3 (Severe) based on a defined scale for each LSR.

In the two pivotal Phase 3 trials, DRM04-HH04 and DRM04-HH05, LSRs were assessed at baseline and Weeks 1, 2, 3, and 4/End of Treatment; at each assessment time point, the majority of subjects had no observed skin reaction. Across all assessment time points, 30.8% of subjects in the DRM04, (b) (4)% group and 30.3% of subjects in the vehicle group had an LSR. Among subjects with at least 1 post-baseline LSR, the most common were: erythema (17.0% of subjects in the DRM04, (b) (4)5% group and 16.9% in the vehicle group), burning/stinging (14.1% of subjects in the DRM04, (b) (4)% group and 16.9% in the vehicle group), and pruritus (8.1% of subjects in the DRM04, (b) (4)% group and 6.1% in the vehicle group). Most LSRs were mild or moderate in severity. Five subjects (3 in the DRM04, (b) (4)% group and 2 in the vehicle group) had a severe LSR (pruritus, erythema, burning/stinging, edema and dryness). For all 5 subjects

with severe LSRs, the reaction occurred in both axillae and did not recur with repeated treatment.

In the long-term safety study, DRM04-HH06, LSRs were assessed at baseline (collected at the Week 4/End of Treatment visit in Studies DRM04-HH04 and DRM04-HH05) and Weeks 2, 4, 8, 12, 16, 20, 28, 36, and 44/End of Treatment. At each assessment time point, the majority of subjects had no observed skin reaction. The most common LSRs were erythema (reported for 21.1% of subjects), burning/stinging (13.3%), and pruritus (12.4%). LSRs were typically mild (21.8%) or moderate (8.0%) in severity; 2.7% had a severe LSR, which included pruritus (2.0%), erythema (1.5%), burning/stinging (1.3%), edema (0.4%), and dryness (0.2%).

Overall, LSRs were relatively common in both the study drug and vehicle groups, though they appeared to be well-tolerated in most cases. Observed rates of LSRs were comparable in the study drug and vehicle groups, indicating that reactions were likely related to components present in the vehicle. LSR rates were relatively comparable in the pivotal trials (treatment period of 4 weeks) and in the long-term safety study (treatment period of up to 44 weeks), suggesting that reactions did not appear to increase with duration of exposure. Given the frequency of these LSRs, the reviewer proposes to note the most common LSRs – erythema, burning/stinging, and pruritus – in Section 6 of product labeling.

7.3.6. Safety Analyses by Demographic Subgroups

A subgroup analysis of TEAEs by age group was conducted for the long-term safety study, DRM04-HH06. TEAEs were summarized by selected age groups (≤ 16, <18 years, ≥ 18 years, and all subjects) and MedDRA PT in Table 37 below. The subject incidences of commonly reported TEAEs (dry mouth, vision blurred, application site pain, nasopharyngitis, and mydriasis) as well as TEAEs overall were generally similar across age groups. Of note, there were only 3 subjects over age 65, all of whom had a TEAE; for this subgroup, there were too few subjects to allow for meaningful comparisons to be made with other age groups.

Table 37: Summary of TEAEs Reported for > 2% of Subjects Overall, by Age Group (DRM04-HH06; Safety Population)

MedDRA PT[a]	Age ≤ 16 y (N=38)	Age < 18 y (N=47)	Age ≥ 18 y (N=503)	Total (N=550)
No. (%) of subjects with at least 1 AE	22 (57.9%)	25 (53.2%)	304 (60.4%)	329 (59.8%)
Dry mouth	6 (15.8%)	6 (12.8%)	87 (17.3%)	93 (16.9%)
Vision blurred	4 (10.5%)	4 (8.5%)	33 (6.6%)	37 (6.7%)
Application site pain	2 (5.3%)	2 (4.3%)	33 (6.6%)	35 (6.4%)
Nasopharyngitis	0	2 (4.3%)	30 (6.0%)	32 (5.8%)
Mydriasis	3 (7.9%)	3 (6.4%)	26 (5.2%)	29 (5.3%)
Upper respiratory tract infection	2 (5.3%)	3 (6.4%)	24 (4.8%)	27 (4.9%)

Urinary hesitation	1 (2.6%)	1 (2.1%)	22 (4.4%)	23 (4.2%)
Application site dermatitis	2 (5.3%)	2 (4.3%)	19 (3.8%)	21 (3.8%)
Application site pruritus	1 (2.6%)	1 (2.1%)	20 (4.0%)	21 (3.8%)
Application site rash	1 (2.6%)	1 (2.1%)	20 (4.0%)	21 (3.8%)
Nasal dryness	1 (2.6%)	1 (2.1%)	19 (3.8%)	20 (3.6%)
Dry eye	0	0	16 (3.2%)	16 (2.9%)
Application site erythema	0	0	13 (2.6%)	13 (2.4%)
Pharyngitis	1 (2.6%)	1 (2.1%)	11 (2.2%)	12 (2.2%)

Source: ISS, Table 59

These results from the long-term safety study suggest that there were no substantial differences in the risk of adverse reactions across different age groups. However, because the trial was not powered for this type of subgroup analysis, the data must be interpreted with caution.

A review of TEAEs by gender and race indicated no significant differences.

7.3.7. Specific Safety Studies/Clinical Trials

To evaluate their topical drug product, the applicant conducted dermal safety studies which included Trial DRM04-HH08 to evaluate the potential for irritation and sensitization (discussed below). The Agency waived the recommended evaluation of phototoxicity and photoallergenicity because none of the components of the drug product absorbed light corresponding to wavelengths of 290 to 700 nm (UVB, UVA, and visible).

Trial DRM04-HH08

Title: A Randomized, Controlled Study to Evaluate the Sensitizing and Cumulative Irritation Potential of DRM04 in Healthy Volunteers Using a Repeat Insult Patch Test and Cumulative Irritation Design

Objectives

- To determine the potential of DRM04 (b) (4)% solution to induce sensitization or to cause irritation with repeated topical application to normal skin of healthy volunteers under controlled conditions
- To assess the safety of DRM04 (b) (4)% solution by evaluation of reported AEs

Trial Design

Study DRM04-HH08 assessed the potential for DRM04, (b) (4)% or vehicle to cause irritation or contact sensitization when applied using repeat insult patch test (RIPT) conditions. The trial was designed as a randomized, controlled, within-subject comparison of DRM04, (b) (4)% and

vehicle in healthy subjects.

Cumulative irritation was assessed in Cohort 2 and Cohort 2a followed by assessment of contact sensitization in Cohort 1a.

Initially subjects in Cohort 2 were tested using occluded patches. However, more anticholinergic TEAEs were observed than anticipated; thus, this cohort was discontinued, and the protocol was amended to change the method of application to a semi-occluded patch. Semi-occlusive conditions were used for all subsequent subjects in the study, for Cohort 2a (cumulative irritation) and Cohort 1a (contact sensitization).

Four study treatments were used to assess irritation and sensitization: DRM04, (b) (4)%; vehicle; 0.2% sodium lauryl sulfate (SLS: positive control); and 0.9% saline (negative control), following a pre-designated schedule of applications in a randomized sequence to the infrascapular area of the back. Application site reactions and AEs were assessed in each subject in all cohorts. Application site reactions were evaluated by a trained, blinded observer. A skin reaction of Grade 3 or higher required discontinuation of patch application to the designated site.

Cohort 2: Cumulative Irritation Potential Test (CIPT)

Forty-five (45) subjects were enrolled for the assessment of cumulative irritation under occlusive patch conditions. Study treatments were applied daily to the same skin sites for 21 consecutive days, remaining in place under occlusive patch conditions for 24 hours.

The cohort was discontinued early due to a higher than expected incidence of anticholinergic TEAEs, particularly dry mouth and urinary hesitation. One event of dry mouth and one of urinary hesitation were severe. The high incidence of anticholinergic TEAEs was thought to be due to enhanced absorption of DRM04 as a result of full occlusion of the patch test site.

Cohort 2a: Semi-occlusive CIPT

The protocol was amended to include a semi-occlusive cumulative irritation patch test design (Cohort 2a). Ten new subjects were enrolled and received applications. On Day 7, a review of AEs occurred. As no severe anticholinergic TEAEs were reported, applications proceeded under semi-occlusive conditions and the remaining 31 subjects in Cohort 2a were enrolled. Study treatments were applied daily to the same sites for 21 consecutive days, remaining in place under semi-occlusive conditions for 24 hours.

Cohort 1a: Contact sensitization potential

Two hundred forty-two (242) subjects were enrolled for the assessment of contact sensitization. Subjects in Cohort 1a underwent a 3-week Induction Period during which study treatments were applied three times per week (e.g., Monday, Wednesday, and Friday) and remained in place under semi-occlusive patch conditions for 48-72 hours.

Following the Induction Period, all subjects entered a 10 to 14-day Rest Period, followed by a Challenge Period. The Challenge Period consisted of a single semi-occlusive patch application placed on a naïve site on the back, which was left in place for 48 hours and then evaluated.

Safety Results

Overall, topical application of DRM04, (b) (4)% under semi-occlusive patch conditions was well tolerated. The results of the safety analysis were as follows:

Adverse Events / Serious Adverse Events / Pregnancies

TEAEs were frequent in Cohort 2 due to the anticholinergic TEAEs occurring under occlusive patch conditions. Thirty-three (33) subjects (73.3%) in Cohort 2 reported at least one TEAE. All TEAEs were considered related to the study drug and ranged from mild to severe. The most common TEAE in Cohort 2 was dry mouth (30 subjects, 66.7%). Sixteen (16) subjects (35.6%) reported an AESI. Thirteen (13) subjects (28.9%) reported AESIs of urinary hesitation.

In Cohort 2a, 11 subjects (26.8%) reported at least one TEAE. One subject (2.4%) had a non-serious TEAE that was considered related to the study drug, while ten subjects (24.4%) had TEAEs that were considered not related. The TEAEs ranged from mild to moderate in severity.

In Cohort 1a, 32 subjects (13.2%) reported at least one TEAE. Nine subjects (3.7%) had TEAEs that were considered related to the study drug, while 23 subjects (9.5%) had TEAEs that were considered not related. The TEAEs ranged from mild to severe.

Two subjects in Cohort 1a experienced SAEs. One experienced diverticulosis that resulted in hospitalization, and one experienced a possible myocardial infarction that resulted in death. Both SAEs were considered unrelated to the study drug. No subjects in Cohorts 2 or 2a had SAEs.

Two subjects became pregnant during the trial. Both were discontinued from the trial; information on pregnancy outcomes was pending at the time of submission of the NDA.

Cumulative Irritation Results

Cohort 2 was terminated by the sponsor due to a high incidence of anticholinergic TEAEs. Subjects in Cohort 2 were included in the Safety Population and assessed for TEAEs; however, subjects in Cohort 2 were not included in the analysis of cumulative irritation.

Analysis of cumulative irritation was based on data from subjects in Cohort 2a. There were no statistical differences between DRM04, (b) (4)% and vehicle, and DRM04, (b) (4)% and 0.9% saline. The positive control, 0.2% SLS, was significantly more irritating than the other treatments studied.

Sensitization Results

Analysis of sensitization was based on data from subjects in Cohort 1a. There were no statistical differences between DRM04, (b) (4)% and vehicle and DRM04, (b) (4)% and 0.9% saline. The positive control, 0.2% SLS, was significantly more irritating than the other treatments studied.

No subjects in the Sensitization Population displayed potential sensitization to DRM04,

(b) (4)% or vehicle during the Challenge Readings. No subjects required re-challenge.

Conclusions

The results of Study DRM04-HH08 are summarized below:

- When DRM04, (b) (4)% was tested under full occlusion, there were more TEAEs associated with anticholinergic activity than anticipated, preventing the assessment of local tolerability in Cohort 2, and resulting in discontinuation of all subjects in this cohort.
- There was no significant difference in the mean cumulative irritation score between DRM04, (b) (4)% and vehicle or between DRM04, (b) (4)% and saline. The positive control, SLS, 0.2%, was significantly more irritating than all other study products.
- No subject displayed reactions indicative of sensitization and no subject was re-challenged for any of the study treatments.

In conclusion, the study drug and vehicle displayed no reactions consistent with sensitization and showed the same level of irritation as the vehicle. No recommendations for labeling are recommended as a result of the dermal safety patch studies. The adverse reaction data from the actual clinical trials is sufficient to provide safety information in the label.

7.3.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

One malignancy was reported across all eight trials in the development program; this was a case of malignant melanoma in situ which occurred in Study DRM04-HH01, a Phase 2 PK/PD and dose-ranging trial. This event was categorized as an SAE. A narrative for this subject is provided below:

- Study DRM04-HH01, Subject # (b) (6): A 59 year old male with a history of melanocytic nevus and eczema, enrolled on study drug (DRM04B (b) (4)%), was noted on exam to have a suspicious looking nevus on the left upper abdomen, which the subject reported had been present since (b) (6) Biopsy confirmed melanoma in situ (Day 22), and on Day 50, the lesion was excised to clear margins, at which point the SAE was considered resolved. The SAE had no impact on the subject's disposition or on study-drug dosing; the subject continued study drug without interruption. The investigator considered the SAE to be of moderate severity and not related to study drug. This reviewer agrees the SAE is unlikely to be related and was distant from the investigational product application sites.

Human Reproduction and Pregnancy

During clinical development, women of childbearing potential who enrolled in any of the clinical trials were required to use an effective form of birth control, have a negative pregnancy test at

screening, and undergo pregnancy testing at all study visits. Women who were lactating were excluded from the trials. If a subject became pregnant during trial participation, study drug was discontinued and the subject was followed until delivery. Adverse pregnancy outcomes such as spontaneous abortion, stillbirth, and congenital anomalies were reported as TEAEs.

Across the 8 clinical trials in the development program, 6 pregnancies were reported, all in subjects receiving active study drug. Of these, 3 pregnancies were ongoing at the time of NDA submission. The 3 remaining pregnancies had the following outcomes: a healthy baby (one subject), a therapeutic abortion (one subject), and a spontaneous abortion (one subject). The spontaneous abortion was reported as a TEAE of mild severity, and was considered by the investigator as not related to study drug.

The information that will be conveyed in labeling (Section 8.1, Pregnancy, and Section 8.2, Lactation) regarding the risks of exposure to glycopyrronium during pregnancy and lactation is presented in Section 5.6 of this review.

Pediatrics and Assessment of Effects on Growth

In accordance with the applicant's approved Pediatric Study Plan (approval letter issued April 2, 2015), the applicant evaluated pediatric subjects in the two pivotal Phase 3 trials, DRM04-HH04 and DRM04-HH05, and the long-term safety trial, DRM04-HH06. In addition, pediatric subjects were evaluated in the maximal use pharmacokinetic trial, DRM04-HH07. All these trials enrolled subjects age 9 years and older.

The applicant has submitted a partial waiver for children under 9 years of age. As noted in the initial Pediatric Study Plan (iPSP), "… children younger than 9 are not expected to have initiated puberty and thus are not expected to develop axillary hyperhidrosis. Thus, the overall prevalence of axillary hyperhidrosis in this age group makes clinical studies in this group impossible or highly impractical."

The Division presented the Pediatric Study Plan to the Pediatric Review Committee (PeRC) on April 11, 2018. The Division noted continued agreement with the plan as presented in the agreed iPSP. Final comments from the PeRC review are forthcoming, but no concerns were raised in the discussion.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was one event reported as an overdose in the glycopyrronium clinical development program. The event, involving Subject No. (b) (6) (DRM04-HH06), was reported as a TEAE of overdose, with up to 6 applications of study medication to each axilla. The following TEAEs were reported with the overdose: urinary hesitation, vision blurred, dry mouth, application site erythema, dry throat, dry eye, and nasal dryness. These TEAEs, consistent with systemic anticholinergic effects, all resolved without sequelae. Four other subjects who reported

adverse events of interest indicated that they applied more than one swipe per axilla prior to the event.

Administration under occlusive conditions may result in increased absorption and an increase in anticholinergic effects and should be avoided.

There were no withdrawal or rebound effects reported in clinical trials of glycopyrronium cloth, and none are anticipated.

7.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Glycopyrronium cloth has not been marketed in any country.

Limited data are available on glycopyrrolate, the active component in the reference-listed drug, Cuvposa. The sponsor reviewed published literature on generic glycopyrrolate, examining peer-reviewed articles published between 1996 and 2017 that included data on oral or topical administration of glycopyrrolate (summarized in ISS, Table 28). The review identified information on 261 subjects exposed to glycopyrrolate - 226 subjects with oral exposure and 35 subjects with topical exposure. Reported AEs were consistent with anti-cholinergic effects, similar to the TEAE profile observed in studies with glycopyrronium cloth.

Expectations on Safety in the Postmarket Setting

Concomitant medications. Coadministration of glycopyrronium with anticholinergic medications may result in additive interaction leading to an increase in anticholinergic effects and should be avoided. This will be specifically addressed in Prescribing Information, Section 7 (Drug Interactions) with a warning to avoid concomitant use of anticholinergic drugs.

Possible off-label use. Patients with primary axillary hyperhidrosis frequently also have hyperhidrosis involving other body areas (e.g. palms, soles, face, scalp, trunk, etc.). Patients may attempt to use glycopyrronium cloth to treat hyperhidrosis in these other areas, creating the potential for increased local and systemic adverse effects. This will be specifically addressed in Prescribing Information, Sections 2 (Dosage and Administration) and 17 (Patient Counseling Information) with a warning not to apply glycopyrronium cloth to other body areas.

7.3.10. Integrated Assessment of Safety

The safety profile for glycopyrronium cloth was adequately characterized during the drug development program, and adequate numbers of subjects were exposed to the investigational products during development. The primary safety database consisted of pooled data from the pivotal Phase 3 Trials, DRM04-HH04 and DRM04-HH05 These trials enrolled 691 subjects with primary axillary hyperhidrosis; 459 were treated with study drug (DRM04, (b) (4) %), and 232 with vehicle, with all subjects applying topical treatment daily for a period of 28 days. Additional data on long-term safety was provided by an open-label, long-term safety extension trial,

DRM04-HH06, which enrolled subjects who had completed one of the pivotal Phase 3 trials, treating them for up to 44 additional weeks with study drug, DRM04, (b) (4)%; this trial had a safety population of 550 subjects. The overall clinical development program included eight trials, with 1269 subjects who received at least one dose of study drug, 393 who were dosed for at least six months, and 114 who were dosed for at least twelve months.

Across the eight trials in the development program, one death was reported. The death occurred in a subject enrolled in the dermal safety study (DRM04-HH08). The subject died of a possible myocardial infarction; the event was considered not related to study drug by either the applicant or this reviewer.

A total of 12 serious adverse events were reported from the eight trials comprising the development program, all in subjects receiving study drug. Overall, SAEs were uncommon; considering all subjects who received at least one dose of study drug, SAEs occurred in 12/1269 (0.9%) subjects. One SAE (possible myocardial infarction) was fatal, 3 were severe (diverticulitis, infectious colitis, and suicide attempt), and the remainder were mild or moderate. Ten of the 12 SAEs were considered by investigators to be unrelated to treatment, and 2 SAEs (both events of unilateral mydriasis) were considered related. Both these events of unilateral mydriasis were categorized as SAEs because the subjects were hospitalized to rule out possible CNS causes.

In the pivotal Phase 3 trials, the most common adverse reactions (AR) were dry mouth (24.2%), mydriasis (6.8%), oropharyngeal pain (5.7%), headache (5.0%), urinary hesitation (3.5%), vision blurred (3.5%), nasal dryness (2.6%), dry throat (2.6%), dry eye (2.4%), dry skin (2.2%), and constipation (2.0%). Virtually all of these reactions represent anticholinergic effects, consistent with the mechanism of action of glycopyrronium.

The most commonly reported local skin reactions were erythema (17.0% of study drug subjects, 16.9% vehicle), burning/stinging (14.1% of study drug subjects, 16.9% vehicle), and pruritus (8.1% of study drug subjects, 6.1% vehicle). Most reactions were mild or moderate in severity. Overall, LSRs were relatively common in both the study drug and vehicle groups, and the vehicle itself is mildly irritating,

To assess dermal safety, 328 subjects were enrolled in a repeat insult patch test study of irritation and contact sensitization. The cloth product was as irritating as the vehicle. No subject displayed reactions indicative of sensitization.

As a 505(b)(2) application, with Cuvposa (oral glycopyrrolate), an established anticholinergic agent as the listed drug, known effects of drugs in this class are relevant to the safety profile for glycopyrronium. Labeling for Cuvposa highlights the importance of careful patient selection. Per labeling, Cuvposa is contraindicated in several medical conditions that preclude anticholinergic therapy (e.g. glaucoma, paralytic ileus, severe ulcerative colitis, toxic megacolon, etc.). The warnings and precautions noted in labeling for Cuvposa relate to additional

anticholinergic effects – e.g., risk of fever and heat stroke with high ambient temperatures due to decreased sweating, risk of blurred vision, etc. Though systemic exposure is less with a topical agent, these anticholinergic effects still pose risks and should be highlighted in the safety profile of glycopyrronium cloth; thus, they will be noted in the Contraindications and Warnings and Precautions sections of labeling (see Section 10.1, "Labeling Recommendations; Prescribing Information"). A warning is also included related to the potential for worsening of urinary retention. Similarly, the Drug Interactions section of labeling for glycopyrronium cloth will include the recommendation to avoid coadministration of glycopyrronium with other anticholinergic agents due to concern about additive effects.

The safety data provides an adequate risk/benefit analysis for the topical treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older.

7.4. SUMMARY AND CONCLUSIONS

7.4.1. Statistical Issues

In Trial HH04, the pre-specified primary analysis for the change in gravimetrically-measured sweat production co-primary endpoint was not statistically significant (p=0.065). Because of the skewness of the data, the pre-specified primary analysis was ANCOVA on the ranked outcome. The primary method of handling missing data was MCMC multiple imputation.

In this analysis, however, the results for the change in gravimetrically-measured sweat production endpoint were influenced by the outcomes from 4 subjects at one site with very large sweat production values during the trial. The 4 subjects with extreme observations not only affected the means and standard deviations, but also affected the values that were imputed during the multiple imputation for subjects with missing outcomes. Notably, the following sensitivity and supportive analyses that were pre-specified in the SAP and either excluded the subjects with extreme values or used methods of missing data handling that were not influenced by the extreme values produced statistically significant results for this endpoint in Trial HH04:

- An analysis removing the analysis center with the extreme outliers
- ITT population using LOCF
- Per protocol population using LOCF
- Observed cases using repeated measures

In Trial HH05, the primary analysis and all sensitivity analyses for gravimetrically-measured sweat production were statistically significant.

In both trials, there is a disparity observed between the two co-primary endpoint assessments, the gravimetrically-measured sweat production and the weekly mean score of ASDD item #2. Gravimetrically-measured sweat production is measured over 5 minutes at visits once a week during the trials, while the ASDD item #2 is a daily assessment that asks subjects to evaluate

their sweating at its worst in the past 24 hours. The daily results on the ASDD item #2 assessment presented in Figure 13 as well as patient input during an externally-led Patient Focused Drug Development meeting indicate that sweating can be episodic for some subjects. Therefore, it is not clear that a 5-minute measurement of gravimetrically-measured sweat once a week is sufficient to characterize the severity of disease. Because of this, high variability and highly skewed data was observed for the gravimetrically-measured sweat production endpoint, along with several extreme outliers. Explorations of other sweat measurement parameters may be recommended for other products who seek axillary hyperhidrosis as an indication.

In the pivotal trials, there was higher response rates for males compared to females, and higher efficacy for white subjects compared to Black or African American subjects for the ASDD item #2 assessment. The pediatric age groups that were investigated had small sample sizes and there was no clear trend of better or worse efficacy compared to adult subjects. In Trial HH04, subjects at sites in Germany had lower efficacy than subjects at sites in the US, though the number of subjects in Germany was small.

7.4.2. Conclusions and Recommendations

To establish the efficacy of DRM04, the applicant submitted data from two identically-designed, randomized, double-blind, vehicle-controlled, parallel group pivotal Phase 3 trials (HH04 and HH05). The trials enrolled subjects 9 years of age and older who had primary axillary hyperhidrosis of at least 6 months duration, a HDSS grade of 3 or 4, an average weekly ASDD item #2 score ≥ 4, and sweat production of at least 50 mg over 5 minutes in each axilla. The co-primary endpoints were the mean change from baseline in gravimetrically-measured sweat production at Week 4 and the proportion of subjects who have at least a 4-point improvement from baseline in the weekly mean score of ASDD item #2 at Week 4.

In both trials, DRM04 was statistically superior to vehicle for the ASDD item #2 co-primary endpoint. Under the pre-specified primary analysis, the sweat production co-primary endpoint was statistically significant in Trial HH05 ($p<0.001$), but not statistically significant in Trial HH04 ($p=0.065$); however, all sensitivity analyses for this endpoint resulted in statistical significance. Section 7.2.4 describes how 4 subjects with extreme outlier data affected the values imputed for subjects with missing data under the pre-specified multiple imputation method, which may have led to the non-statistically significant result for the primary analysis.

8 Advisory Committee Meeting and Other External Consultations

Not applicable. There were no novel or complex regulatory issues that required discussion at a DODAC meeting.

9 Pediatrics

See Section 7.3.8, sub-section on *Pediatrics and Assessment of Effects on Growth*. Subjects as young as nine years of age were included in the trials , and younger pre-pubertal patients are not likely to develop hyperhidrosis.

10 Labeling Recommendations

10.1. Prescribing Information

The applicant submitted proposed Prescribing Information (PI) and carton/container labels for glycopyrronium cloth, 2.4%. The review team provided recommendations regarding PI which are provided throughout this review. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI, proposed patient package insert (PPI), and carton/container. In addition, staff from the Division of Medication Error Prevention and Analysis (DMEPA) provided comments regarding the proposed carton and container labels. Labeling negotiations are currently ongoing as of the date of this review.

10.2. Patient Labeling

The applicant submitted a proposed patient package insert (PPI). The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the PPI. Labeling negotiations are currently ongoing.

11 Risk Evaluation and Mitigation Strategies (REMS)

Based on the overall favorable risk/benefit profile of this topical drug product, risk mitigation measures beyond professional labeling are not warranted at this time. As no additional risk management strategies are required, the subsequent subsections are not applicable for this review and are omitted.

12 Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended for this application.

13 Appendices

13.1. References

See footnotes in text.

13.2. Financial Disclosure

The covered clinical studies as defined in 21 CFR 54.2(e) include Trial DRM04-HH04 and Trial DRM04-HH05 which provide the primary data to establish effectiveness and safety of this drug product.

Covered Clinical Study (Name and/or Number):
DRM04-HH04
DRM04-HH05

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: **DRM04-HH04:** 31 PIs, 57 sub-investigators; **DRM04-HH05:** 20 PIs, 55 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): **None**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **2**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: **1** Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: **1**		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☒	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **34**		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

The applicant provided Form FDA 3455 for the investigator (b) (6), participating in Trial (b) (6) at Site (b) (6) The applicant also included Financial Disclosure forms for this PI dated July 2015, August 2015, October 2015 and June 2017, disclosing equity in Dermira, with over $50,000 in stock. The applicant also provided Form FDA 3455 for the investigator (b) (6) participating in Trial (b) (6) at Site (b) (6) This Principal Investigator was paid for consultation services in excess of $25,000.

Of note, for Study (b) (6) site, # (b) (6) enrolled (b) (6) subjects; (b) (6) site, # (b) (6), enrolled (b) (6) subjects.

The applicant stated that the following steps helped minimize the potential for bias:

- Several studies within the clinical program (DRM04-HH01, DRM04-HH02, DRM04-HH04 and DRM04-HH05) were randomized and double-blinded trials.
- Study treatment was identical in preparation and application between active and vehicle medication.
- In studies (b) (6) disclosed his financial equity information to the IRB before study participation and the information was incorporated into the site-specific informed consent. (b) (6) disclosed his financial equity information for studies (b) (6) after completion of these studies.
- All study endpoints were evaluated by the statistician who had no financial interests/arrangements in Dermira.
- Multiple investigators/sites were used for all the studies.
- In studies DRM04-HH04 and DRM04-HH05, enrollment was capped at each site so one site could not influence the overall conclusions of the trials.

Reviewer Comment:
Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies implemented by the applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

13.3. Nonclinical Pharmacology/Toxicology

Study title: 104-Week Dermal Carcinogenicity and Toxicokinetic Study with DRM04 in Rats

Study no.:	8296393 (Sponsor's ref. no. DRM04-TOX-14-04)
Study report location:	NDA 210361
Conducting laboratory and location:	(b) (4)
Date of study initiation:	24-NOV-2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Glycopyrronium tosylate monohydrate, batch nos. 103513001, 100.32%; 103514001, 99.6%; 103514T49, 100.0%
CAC concurrence:	Yes; ECAC meeting date 26-AUG-2014

Key Study Findings

Sprague Dawley rats were treated topically once daily with glycopyrronium tosylate solutions at concentrations of 0 (vehicle), 1%, 2%, and 4% w/w for both genders. The test materials were administered for up to 24 months. The key finding of this study was that topical exposure of rats to glycopyrronium tosylate for a lifetime did not result in a significantly increased incidence of tumors in either males or females.

Methods

Doses:	Solutions containing 0 (Saline), 0 (vehicle), 1%, 2%, and 4% w/w of glycopyrronium tosylate
Frequency of dosing:	Once daily
Dose volume:	300 µL
Route of administration:	Topical to skin (10% of BSA)
Formulation/Vehicle:	Solution/Vehicle of the product (hydroalcoholic solution containing (b) (4)% w/w citric acid, (b) (4)% sodium citrate, (b) (4)% water, and (b) (4)% (b) (4))
Basis of dose selection:	Data from a 13-week study suggested that a 6% glycopyrronium tosylate monohydrate solution exceeded the MTD
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	60
Age:	8-9 weeks at initiation of dosing
Animal housing:	Individually
Paradigm for dietary restriction:	No
Dual control employed:	No (a saline-treated control group and a vehicle-treated control group were used)
Interim sacrifice:	No
Satellite groups:	Yes; 12 satellite animals/sex/group used for toxicokinetic analysis (6/sex for vehicle control group)
Deviation from study protocol:	NA

The number of survivors in the female saline control group reached the early termination threshold during week 99 of treatment, and all groups of females were terminated at that time, with concurrence of the exec-CAC. All surviving males were sacrificed at the scheduled sacrifice on day 730 (week 105).

Observations and Results

Mortality

There were no statistically significant differences in mortality between the glycopyrronium treated groups and either control group for males or females. The numbers of male rats surviving to terminal necropsy were 24 (40%), 25 (42%), 19 (32%), 29 (48%), and 27 (45%) in the saline control group, vehicle control group, low, medium, and high dose groups, respectively. The numbers of female rats surviving to terminal necropsy were 19 (32%), 28 (47%), 22 (37%), 22 (37%), and 23 (38%) in the saline control group, vehicle control group, low, medium, and high dose groups, respectively. Gylcopyrronium tosylate did not affect survival under the conditions of this study.

Clinical Signs

No remarkable clinical signs were observed, including no apparent relationship between dosage and the number of palpable masses, or the incidence or severity of dermal irritation.

Body Weights

Mean body weight tended to be slightly (circa 5%) reduced among treatment groups and vehicle-treated animals of both genders throughout the study, relative to saline-treated animals.

Feed Consumption

No remarkable effects of treatment were noted on food consumption.

Gross Pathology

All macroscopic findings were considered spontaneous and/or incidental.

Histopathology

Peer Review: Yes

Neoplastic

No significant differences in tumor incidence were observed in rats of either gender according to the statistical standards used by the exec-CAC.

Non Neoplastic

No remarkable non-neoplastic microscopic lesions were observed.

13.3.1. Nonclinical Labeling

I recommend that sections 8.1, 12.1, and 13.1 of the label of the product be phrased as indicated below. Other portions of the proposed label are acceptable with respect to nonclinical issues. As reflected in the draft label, the pharmacologic class of glycopyrronium is "anticholinergic". The information that concerns reproductive toxicology, and oral carcinogenesis assays, is obtained from the label of the listed drug, Cuvposa (NDA 022571). No comparisons of animal exposure with human exposure may be calculated due to minimal systemic exposure in humans after topical administration of Qbrexza. Recommended changes from the sponsor's proposed labeling in regard to section 8.1, 12.1, and 13.1 are indicated below through use of strikeout (deletions) and underline (additions) fonts.

8.1 Pregnancy

Risk Summary

There are no available data (b) (4) on Qbrexza use in pregnant women to inform a

(b) (4)-drug-associated ris (b) (4)for adverse developmental outcomes. In pregnant rats, daily oral administration of glycopyrrolate (glycopyrronium bromide) during organogenesis (b) (4) -did not result in an increased incidence of gross external or visceral defects *[see Data]*. When glycopyrrolate was administered intravenously to pregnant rabbits during organogenesis (b) (4) no adverse effects on embryo-fetal development were seen. The available data do not support relevant comparisons of systemic glycopyrronium exposures achieved in the animal studies to exposures observed in humans after topical use of Qbrexza.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Glycopyrrolate was orally administered to pregnant rats at dosages of 50, 200, and 400 mg/kg/day during the period of organogenesis. (b) (4)

Glycopyrrolate had no effect on maternal survival, but significantly reduced mean maternal body weight gain over the period of dosing at all dosages evaluated. Mean fetal weight was significantly reduced in the 200 and 400 mg/kg/day dose groups. There were two litters with all resorbed fetuses in the 400 mg/kg/day dose group. There were no effects of treatment on the incidence of gross external or visceral defects. Minor treatment-related skeletal effects included reduced ossification of various bones in the 200 and 400 mg/kg/day dose groups; these skeletal effects were likely secondary to maternal toxicity.

Glycopyrrolate was intravenously administered to pregnant rabbits at dosages of 0.1, 0.5, and 1.0 mg/kg/day during the period of organogenesis. (b) (4)

Glycopyrrolate did not affect maternal survival under the conditions of this study. Mean maternal body weight gain and mean food consumption over the period of dosing were lower than the corresponding control value in the 0.5 and 1.0 mg/kg/day treatment groups. There were no effects of treatment on fetal parameters, including fetal survival, mean fetal weight, and the incidence of external, visceral, or skeletal defects.

Female rats that were pregnant or nursing were orally dosed with glycopyrrolate daily at dosages of 0, 50, 200, or 400 mg/kg/day, beginning on day 7 of gestation, and continuing until day 20 of lactation. (b) (4)

(b) (4)
-Mean body weight of pups in all treatment groups was reduced compared to the control group during the period of nursing, but eventually recovered to be comparable to the control group, post-weaning. No other notable delivery or litter parameters were affected by treatment in any group, including no effects on mean duration of gestation or mean numbers of live pups per litter. No treatment-related effects on survival or adverse clinical signs were observed in pups. There were no effects of maternal treatment on behavior, learning, memory, or reproductive function of pups.

12.1 Mechanism of Action

Glycopyrronium is a competitive inhibitor of acetylcholine receptors that are located on certain peripheral tissues, including sweat glands. (b) (4) In hyperhidrosis, glycopyrronium inhibits the action of acetylcholine on sweat glands thereby reducing the extent of sweating.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Glycopyrronium tosylate was not carcinogenic (b) (4) -when topically applied to rats daily for up to 24 months in solution at concentrations of 1%, 2%, and (b) (4) (b) (4) 4% w/w~~,~~ (b) (4)

When (b) (4) glycopyrrolate was administered via oral gavage to mice for up to 24 months at dosages of 2.5, 7, and 20 mg/kg/day in both genders, no significant changes in tumor incidence were observed when compared to control.

When glycopyrrolate was administered via oral gavage to rats for up to 24 months at dosages of 5, 15, and 40 mg/kg/day in both genders, no significant changes in tumor incidence were observed when compared to control.

Glycopyrrolate was negative in a battery of genetic toxicology studies that included a bacterial reverse mutation (Ames) assay, a mouse lymphoma assay conducted with L5178Y/TK$^{+/-}$ cells, and an in vivo micronucleus assay with mice. Glycopyrronium tosylate was negative in an Ames (b) (4) assay.

Glycopyrrolate was assessed for effects on fertility or general reproductive function in rats. (b) (4) Rats of both genders received glycopyrrolate at dosages up to 100 mg/kg/day via oral gavage~~,~~ (b) (4) o treatment-related effects on fertility or reproductive

parameters were observed in either gender.

The revised sections 8.1, 12.1, and 13.1 are presented as clean-copy text below:

8.1 Pregnancy

Risk Summary

There are no available data on Qbrexza use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. In pregnant rats, daily oral administration of glycopyrrolate (glycopyrronium bromide) during organogenesis did not result in an increased incidence of gross external or visceral defects *[see Data]*. When glycopyrrolate was administered intravenously to pregnant rabbits during organogenesis, no adverse effects on embryo-fetal development were seen. The available data do not support relevant comparisons of systemic glycopyrronium exposures achieved in the animal studies to exposures observed in humans after topical use of Qbrexza.

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Glycopyrrolate was orally administered to pregnant rats at dosages of 50, 200, and 400 mg/kg/day during the period of organogenesis. Glycopyrrolate had no effect on maternal survival, but significantly reduced mean maternal body weight gain over the period of dosing at all dosages evaluated. Mean fetal weight was significantly reduced in the 200 and 400 mg/kg/day dose groups. There were two litters with all resorbed fetuses in the 400 mg/kg/day dose group. There were no effects of treatment on the incidence of gross external or visceral defects. Minor treatment-related skeletal effects included reduced ossification of various bones in the 200 and 400 mg/kg/day dose groups; these skeletal effects were likely secondary to maternal toxicity.

Glycopyrrolate was intravenously administered to pregnant rabbits at dosages of 0.1, 0.5, and 1.0 mg/kg/day during the period of organogenesis. Glycopyrrolate did not affect maternal survival under the conditions of this study. Mean maternal body weight gain and mean food consumption over the period of dosing were lower than the corresponding control value in the 0.5 and 1.0 mg/kg/day treatment groups. There were no effects of treatment on fetal parameters, including fetal survival, mean fetal weight, and the incidence of external, visceral, or skeletal defects.

Female rats that were pregnant or nursing were orally dosed with glycopyrrolate daily at dosages of 0, 50, 200, or 400 mg/kg/day, beginning on day 7 of gestation, and continuing until day 20 of lactation. Mean body weight of pups in all treatment groups was reduced compared to the control group during the period of nursing, but eventually recovered to be

comparable to the control group, post-weaning. No other notable delivery or litter parameters were affected by treatment in any group, including no effects on mean duration of gestation or mean numbers of live pups per litter. No treatment-related effects on survival or adverse clinical signs were observed in pups. There were no effects of maternal treatment on behavior, learning, memory, or reproductive function of pups.

12.1 Mechanism of Action

Glycopyrronium is a competitive inhibitor of acetylcholine receptors that are located on certain peripheral tissues, including sweat glands. In hyperhidrosis, glycopyrronium inhibits the action of acetylcholine on sweat glands, thereby reducing the extent of sweating.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Glycopyrronium tosylate was not carcinogenic when topically applied to rats daily for up to 24 months in solution at concentrations of 1%, 2%, and 4% w/w.

When glycopyrrolate was administered via oral gavage to mice for up to 24 months at dosages of 2.5, 7, and 20 mg/kg/day in both genders, no significant changes in tumor incidence were observed when compared to control.

When glycopyrrolate was administered via oral gavage to rats for up to 24 months at dosages of 5, 15, and 40 mg/kg/day in both genders, no significant changes in tumor incidence were observed when compared to control.

Glycopyrrolate was negative in a battery of genetic toxicology studies that included a bacterial reverse mutation (Ames) assay, a mouse lymphoma assay conducted with L5178Y/$TK^{+/-}$ cells, and an in vivo micronucleus assay with mice. Glycopyrronium tosylate was negative in an Ames assay.

Glycopyrrolate was assessed for effects on fertility or general reproductive function in rats. Rats of both genders received glycopyrrolate at dosages up to 100 mg/kg/day via oral gavage. No treatment-related effects on fertility or reproductive parameters were observed in either gender.

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Summary of Bioanalytical Method Validation and Performance

The Applicant used two validated bioanalytical methods to determine serum glycopyrronium concentrations during clinical development. The initial Phase 1 and Phase 2 studies used HPLC with MS/MS (Table 38) and method validation parameters for two assays for measurement of glycopyrronium in human sample are summarized in Table 10 in Section 6.

Table 38: Summary of assays used for quantification of glycopyrronium levels in the clinical development program

Study #	Assay	Validation reports
DRM04-HH01 DRM04-HH02	HPLC with MS/MS Detection	LCMSC 655.1 V 1.00 Whole blood stability – Addendum 1 Analyte stability in frozen matrix – Addendum 2
DRM04-HH07	HPLC with MS/MS Detection	LCMSC 655.3 V 1.00 Additional long-term stability data - Addendum 1

13.4.2. Individual Study Reports

13.4.2.1. Study DRM04-HH07

Title: An Open-Label Safety and Pharmacokinetic Study of DRM04 Applied under Maximum-Use Conditions in Subjects with Primary Axillary Hyperhidrosis

Objectives:

- To assess the safety, tolerability and pharmacokinetics (PK) of DRM04 Topical Wipes, (b) (4)% when applied topically to the axillae under maximum-use conditions
- To assess the safety, tolerability and PK of oral glycopyrrolate (Cuvposa®, titrated to maximum tolerated dose as described in the Cuvposa United States Prescribing Information (USPI))
- To compare the PK of topically applied DRM04 Topical Wipes, (b) (4)% to orally dosed glycopyrrolate (Cuvposa) to support establishment of a clinical bridge

Study Design: This was a Phase 1, open-label study designed to assess the safety, tolerability and relative bioavailability of DRM04 Topical Wipes, (b) (4)% applied topically under maximal-use conditions in subjects with primary axillary hyperhidrosis (Cohort 1) compared to oral glycopyrrolate (Cuvposa) in healthy volunteers (Cohort 2).

Reviewer comments: This was a parallel design study and hence the greater inter-individual variability in PK is anticipated. While this maximal use PK (MuPK) study enrolled the subjects with hyperhidrosis, the comparator arm (Cuvposa) enrolled healthy subjects. Note that Cuvposa is approved in pediatric patients down to 3 years of age. However, only adult subjects were enrolled in Cohort 2 (Cuvposa) and the maximal approved dosing regimen was administered. This is reasonable because due to ethical reasons, it is usually not ideal to dose pediatric subjects with the listed drug with the sole purpose of bridging and dosing in pediatric subjects is not intended to produce any clinical benefit.

Study Population:
Cohort 1: 31 subjects, between 9 and 65 years of age (11 adults + 20 pediatric), with primary axillary Hyperhidrosis were enrolled.

- Featured Inclusion Criteria
  - Male or non-pregnant non-lactating females
  - 9 – 65 years of age

Cohort 2: 18 healthy adult volunteers, between 18 and 65 years of age, were enrolled.

- Featured Inclusion Criteria
  - Healthy male or non-pregnant, non-lactating females assessed by history, physical exam, vital signs, ECG and clinical laboratory tests
  - 18–65 years of age
  - Weight of at least 48 kg and a body mass index (BMI) ≥ 18.0 and ≤ 33.0 (kg/m2)

Treatments:
Cohort 1: Study drug (DRM04 Topical Wipes, (b) (4)%) was applied by study staff once daily to both axillae for 5 days.

Cohort 2: Study staff administered oral glycopyrrolate (Cuvposa). Cuvposa dose started at 1.0 mg every 8 hours on Day 1 and dose escalated every 5 days based on tolerability, up to a maximum dose of 3.0 mg every 8 hours. If a subject could not tolerate a given dose level of Cuvposa, dosing was to have been discontinued and the subject exited the study.

Reviewer comments: Note that both study drug (DRM04) or comparator drug (Cuvposa) were administered by the study staffs. Hence, compliance issues are considered to be minimal. Per labeling of Cuvposa, a high fat meal markedly reduces the oral bioavailability of CUVPOSA. Cuvposa should be taken at least one hour before or two hours after meals. The study protocol indicates that the Applicant requiring the subject to fast for at least 8 hours prior to the first daily dose and at least 2 hours prior to the second and third daily dose.

PK assessment:

Cohort 1

- Adult subjects: PK blood samples were collected prior to the first application of study drug and then at 30 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 24 hours post-application on Day 1 and 5. Pre-dose samples were collected on Day 3 and 4
- Pediatric subjects (9 to < 18 years of age): PK blood samples were collected prior to the first application of study drug and then at 30 minutes, 1, 1.5, 2, 2.5, 3, 4, and 6 hours on Days 1 and 5

Cohort 2: PK blood samples were collected prior to the first dose of study drug and then at 30 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 24 hours post-dose on Days 1, 5, 10 and 15

PK Results:

1) PK analysis

The Applicant performed the primary PK analysis that excluded outliers and the secondary PK analysis that included all data. Concentration were considered outliers and the criteria used was plasma concentration values were greater than 3 Standard Deviation from the mean value for a given time point.

Outlier data excluded in the primary pharmacokinetic analysis: 7 subjects in Cohort 1 had at least one plasma concentration value that was excluded from the analysis of Cmax and AUC. A total of 15 concentration values that were excluded from the primary analysis of Cohort 1. 8 of these 15 concentration values were from one pediatric subject, who was also not evaluable on Day 1 since all plasma concentrations were excluded for Day 1. Concentration-time profile of the individuals with outlier concentrations on Day 1 and Day 5 are provided in Table 39.

Table 39: Concentration-time profile of the individuals with outlier concentrations on Day 1 and Day 5

Outliers Identified in Adult Subjects on Day 1 and Day 5												
Subject	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**2.5h**	**3h**	**4h**	**6h**	**8h**	**10h**	**24h**
Day 1												
101-0003	0.788^	0.039	**1.77***	0.301	0.218	0.264	0.181	0.192	0.162	0.161	0.176	0.0999
107-0001	<0.0100	0.0275	0.0183	0.0171	0.0151	0.0142	0.0486	0.0178	<0.0100	**0.820***	NSR	<0.0100
Day 5												
101-0002	<0.0100	0.0150	0.110	0.0218	0.0296	0.0287	0.0305	0.0400	0.0450	0.0559	0.0450	**2.09***
101-0003	0.101	0.108	0.0891	0.0872	0.0970	0.0897	0.0923	0.0906	0.103	0.0903	**0.834***	0.0577

Outliers Identified in Pediatric Subjects on Day 1 and Day 5									
Subject	**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**2.5h**	**3h**	**4h**	**6h**
Day 1									
104-0001	0.135*^	**1.22***	**1.09***	**0.892***	**0.680***	**0.586***	**0.511***	**0.465***	**0.248***
Day 5									
101-0001	0.0284	0.247	0.0231	**1.13***	0.0268	0.0218	0.0221	0.0209	0.0182
101-0006	<0.010	0.0189	0.0160	<0.010	<0.010	**0.479***	<0.010	0.0168	0.0671
103-0002	0.0209	0.0233	0.0132	0.0626	<0.010	**0.312***	<0.010	0.0240	0.0157
*Outliers Concentration measurement lower than LLOQ is underlined									

Reviewer comments: All outlier data (that was used in calculating PK parameters on Day 1, and Day 5) was carefully examined. As shown in the tables above, the most of outlier concentrations were exceptionally higher (>30 folds) than the concentrations measured at adjacent time points. These could greatly impact on the PK parameters such as tmax, Cmax and AUC calculation. The analysis performed including outliers was primarily reviewed and the results and conclusions between the analyses (including all data and excluding outliers) were compared. If there were discrepancies in results between two analyses, the outliers influencing the results were carefully evaluated.

Detectable concentrations of glycopyrronium in the pre-dose sample on Day 1: The Applicant reported that 6 of 31 subject in Cohort 1 from 3 (of a total of 7) study sites had detectable concentrations of glycopyrronium in the pre-dose sample on Day 1. These 6 measurable pre-dose samples were retested by the assay laboratory for confirmatory duplicate analysis. Upon re-assay, the relative percent difference between the original and re-assay values determined the sample results reported. The median value of all assays results was reported if second and third assay samples were within 20% of the original assay; otherwise, no reportable result was provided. The Applicant reports that in 3 out of 6 subjects, the 2nd and 3rd values from re-assays were within 20% of the 1st measurement. In 3 out of 6 subjects, Day 1 pre-dose sample recorded as no reportable result. The Applicant indicated that the most likely cause of this issues was sample contamination but were not able to provide the definite cause of this issue.

Reviewer comments: Detectable pre-dose concentrations were observed in multiple sites but only in the subjects in Cohort 1 who received topical glycopyrronium (DRM04). Based on the information provided by the Applicant, this reviewer agrees with the Applicant's assessment that detectable pre-dose concentrations were not likely from bioanalysis error but more likely

from sample contamination with exogenous DRM04 during handling of PK samples. However, this reviewer cannot completely rule out the possibility that similar contamination might have occurred in other post-dose samples and there is no way to identify the contamination because most post-dose samples are already quantifiable.
If this truly had occurred because of the exogeneous contamination, this reviewer opines this would only yield increased concentrations rather than decreased concentration values in Cohort 1 which would lead to higher systemic exposures than actual systemic exposure level. Therefore, this reviewer opines that the data submitted is acceptable based on integrating the information including bioanalysis, validation report, individual data, systemic exposure comparison between the study drug and comparator drug.

2) PK Parameters

Table 4 in section 6 presents demographics of the study population in DRM04 HH-07.
The summary of pharmacokinetic parameters and relative ratio of systemic exposure are presented in Table 40 (including all data) and Table 41 (excluding all data).

- Following application of DRM04 Topical Wipes, (b) (4)% to both axillae once daily, plasma glycopyrronium concentrations were quantifiable in most of the subjects up to 24 hours in adults and 6 hours in pediatric subjects.
- Following Cuvposa oral administration, plasma glycopyrronium concentrations were quantifiable in all subjects for the entire sampling period up to 24 hours.
- LLOQ of the bioanalytical assay was 0.01 ng/mL.
- A terminal elimination rate constant was determined in the healthy subjects who received Cuvposa (Cohort 2).
- The Applicant notes that terminal slopes, clearance and volume of distribution were not able to be determined in the DRM04 Topical Wipes, (b) (4)% groups (Cohort 1)

Following application of DRM04, (b) (4)% in adult subjects, mean $AUC_{0\text{-}6h}$, and $AUC_{0\text{-}8h}$ on Day 5 were lower than those values observed on Day1, although mean $AUC_{0\text{-}24h}$ on Day 5 was higher by ~17% than that observed on Day 1. Cmax on Day 1 and Day 5 were comparable (Table 40).

Following application of DRM04, (b) (4)% in pediatric subjects, mean $AUC_{0\text{-}6h}$ on Day 5 was lower than Day 1 in pediatric subjects, while mean Cmax on Day 5 was higher than that observed on Day1 (Table 40).

Reviewer comments: *Based on observed reduction in systemic exposures from Day 1 to Day 5 in adult and pediatric subjects, dose accumulation of DRM04 was not noted from Day 1 to Day 5.*

The median Tmax ranged between 1.00 to 1.50 hours on both Day 1 and Day 5 in adult and pediatric subjects following DRM04, (b) (4)% administration. The median Tmax ranged from 2.00 to 2.75 hours on all PK days (Days 1, 5, 10 and 15) in healthy subjects following oral administration of Cuvposa.

Reviewer comments: *Observed median Tmax (1 -1.5 hour) may be indicative of rapid absorption of topically administered DRM04 (Table 40). But there appears to exist great between individual variability in Tmax ranging from 0 to 24h. Individual concentration-time profiles (Figure 17) suggest that this high variability is likely due to the outlier concentrations which shows unusual high concentration observed at the later time such as (at 10 hour or at 24 hour).*

Table 40: Summary of Pharmacokinetic Parameters (Including All data)

	Cohort 1 (DRM04, (b) (4) %)				**Cohort 2 (Cuvposa)**			
	Adults		**Pediatric**		**Adults**			
Parameter	**Day 1: (N = 11)**	**Day 5: (N = 11)**	**Day 1: (N=19)**	**Day 5: (N=20)**	**Day 1: (N = 18)**	**Day 5: (N = 18)**	**Day 10: (N = 18)**	**Day 15: (N = 18)**
Cmax (ng/mL)	n=11	n=11	n=20	n=20	n=18	n=18	n=18	n=18
Mean (SD)	0.343 (0.533)	0.325 (0.629)	0.109 (0.269)	0.144 (0.260)	0.122 (0.0534)	0.154 (0.118)	0.227 (0.106)	0.381 (0.190)
Range	0.0152, 1.77	0.0209, 2.09	0, 1.22	0, 1.13	0.0445, 0.226	0.0535, 0.544	0.0959, 0.415	0.131, 0.894
Tmax (hour)	n=11	n=11	n=13	n=19	n=18	n=18	n=18	n=18
Mean (SD)	2.95 (3.30)	6.14 (7.53)	2.19 (2.29)	1.68 (1.15)	2.53 (0.606)	2.39 (0.993)	2.86 (1.60)	2.19 (1.10)
Median	1	1.5	1	1.5	2.75	2.5	2.75	2
Range	0.5, 10	0, 24	0.5, 6	0, 4	1, 3	1, 4	0.5, 6	0.5, 4
AUC0-6 (h•ng/mL)	n=9	n=10	n=18	n=11	n=18	n=18	n=18	n=18
Mean (SD)	0.616 (0.556)	0.195 (0.140)	0.32 (0.812)	0.272 (0.232)	0.458 (0.203)	0.613 (0.436)	0.977 (0.405)	1.57 (0.638)
Range	0.075, 1.78	0.0891, 0.569	0, 3.53	0, 0.676	0.156, 0.884	0.202, 2.01	0.438, 1.70	0.643, 2.85
AUC0-8 (h•ng/mL)	n=9	n=10	Not Calculated	Not Calculated	n=18	n=18	n=18	n=18
Mean (SD)	0.871 (0.726)	0.264 (0.187)			0.515 (0.216)	0.708 (0.491)	1.17 (0.499)	1.83 (0.73)
Range	0.0971, 2.1	0.133, 0.762			0.188, 0.960	0.234, 2.28	0.498, 1.98	0.738, 3.27
AUC0-24 (h•ng/mL)	n=5	n=8	Not Calculated	Not Calculated	Not Calculated	n=18	n=18	n=18
Mean (SD)	2.71 (1.21)	3.17 (5.25)				2.12 (1.47)	3.5 (1.5)	5.50 (2.19)
Range	1.43, 4.32	0.37, 15.4				0.702, 6.84	1.49, 5.94	2.21, 9.81

Table 41: Summary of Pharmacokinetic Parameters (Excluding Outliers)

	Cohort 1 (DRM04, (b) (4) %)				Cohort 2 (Cuvposa)			
	Adults		Pediatric		Adults			
Parameter	**Day 1: (N = 11)**	**Day 5: (N = 11)**	**Day 1: (N=19)**	**Day 5: (N=20)**	**Day 1: (N = 18)**	**Day 5: (N = 18)**	**Day 10: (N = 18)**	**Day 15: (N = 18)**
C_{max} (ng/mL)	n=11	n=11	n=19	n=20	n=18	n=18	n=18	n=18
Mean (SD)	0.139 (0.143)	0.0790 (0.0377)	0.0508 (0.0668)	0.0670 (0.0633)	0.122 (0.0534)	0.154 (0.118)	0.227 (0.106)	0.381 (0.190)
Range	0.0152, 0.451	0.0209, 0.149	0, 0.231	0, 0.247	0.0445, 0.226	0.0535, 0.544	0.0959, 0.415	0.131, 0.894
T_{max} (hour)	n=11	n=11	n=12	n=19	n=18	n=18	n=18	n=18
Mean (SD)	2.55 (2.83)	3.18 (4.41)	2.33 (2.33)	1.76 (1.53)	2.53 (0.606)	2.39 (0.993)	2.86 (1.60)	2.19 (1.10)
Range	0.5, 10	0, 10	0.50, 6.00	0, 6.00	1.00, 3.00	1.00, 4.00	0.50, 6	0.50, 4.00
AUC_{0-6} (h•ng/mL)	n=8	n=10	n=16	n=11	n=18	n=18	n=18	n=18
Mean (SD)	0.540 (0.430)	0.195 (0.140)	0.136 (0.137)	0.178 (0.133)	0.458 (0.203)	0.613 (0.436)	0.977 (0.405)	1.57 (0.638)
Range	0.0750, 1.08	0.0891, 0.569	0, 0.365	0, 0.500	0.156, 0.884	0.202, 2.01	0.438, 1.70	0.643, 2.85
AUC_{0-8} (h•ng/mL)	n=8	n=10	Not Calculated	Not Calculated	n=18	n=18	n=18	n=18
Mean (SD)	0.672 (0.518)	0.264 (0.187)			0.515 (0.216)	0.708 (0.491)	1.17 (0.499)	1.83 (0.73)
Range	0.0971, 1.40	0.133, 0.762			0.188, 0.960	0.234, 2.28	0.498, 1.98	0.738, 3.27
AUC_{0-24} (h•ng/mL)	n=5	n=7	Not Calculated	Not Calculated	Not Calculated	n=18	n=18	n=18
Mean (SD)	2.57 (1.00)	0.883 (0.572)				2.12 (1.47)	3.5 (1.5)	5.50 (2.19)
Range	1.43, 3.62	0.370, 1.93				0.702, 6.84	1.49, 5.94	2.21, 9.81

Following Cuvposa administration in healthy subjects, mean AUC_{0-6h}, AUC_{0-8h} and Cmax remarkably increased at each PK sampling periods (i.e from Day1 to Day 5, Day 5 to Day 10, Day 10 to Day 15). These increases were expected given that the doses of Cuvposa was titrated with initial dose of 1.0 mg every 8 hours on Day 1, increase to 2.0 mg every 8 hours on Day 5 and 3.0 mg every 8 hours on Day 10. On Day 15.

Mean AUC_{0-6h}, AUC_{0-8h} and Cmax in both adult or pediatric subjects in DRM04 arm on Day 5 were lower than those values following Cuvposa dosing in healthy subjects on Day 15. The relative ratios of these values were presented in Table 42. Following DRM04 administration,

geometric mean ratio of Cmax, AUC_{0-8h}, and AUC_{0-24h} in adult subjects on Day 5 to those values in Cuvposa on Day 15 were 0.32, 0.13, and 0.24, respectively, and the upper bounds of 90% CI for mean ratios for these parameters were less than 1.

Reviewer comments: The dose of the listed drug Cuvposa was up titrated at a 5-day interval based on tolerability to a maximum approved dose of 3 mg dose. Hence PK data on Day 15 in Table 41. would represent the PK of glycopyrrolate following the maximum approved dose and this data would be used to assess establishment of a clinical bridge. The systemic exposure under maximal use condition of DRM04 on Day5 appears lower than the systemic exposure following administration of Cuvposa with approved maximum dosing regimen, which suggests clinical bridge appears to be establish.

Table 42: Comparison of Relative Exposure (Including All data)

	Geometric Mean Ratio (90% CI)				
	C_{max} (ng/mL)		AUC_{0-6} (h×ng/mL)	AUC_{0-8} (h×ng/mL)[a]	AUC_{0-24} (h×ng/mL)[a]
	Adults	Pediatric	Pediatric	Adults	Adults
DRM04 Day 5 vs Cuvposa Day 5	0.8650 (0.4668, 1.6030)	0.4514 (0.2542, 0.8015)	0.3650 (0.2252, 0.5917)	0.3827 (0.2626, 0.5578)	0.6926 (0.3651, 1.3140)
DRM04 Day 5 vs Cuvposa Day 10	0.5392 (0.2986, 0.9737)	0.2814 (0.1608, 0.4924)	0.2091 (0.1342, 0.3260)	0.2142 (0.1555, 0.2950)	0.3876 (0.2127, 0.7065)
DRM04 Day 5 vs Cuvposa Day 15	0.3245 (0.1786, 0.5895)	0.1694 (0.09646, 0.2973)	0.1300 (0.08334, 0.2028)	0.1352 (0.09878, 0.1851)	0.2447 (0.1348, 0.4443)
DRM04 Pediatrics Day 5 vs DRM04 Adults Day 5	0.5219 (0.2229, 1.2220)		1.1170 (0.6154, 2.0290)	—	—

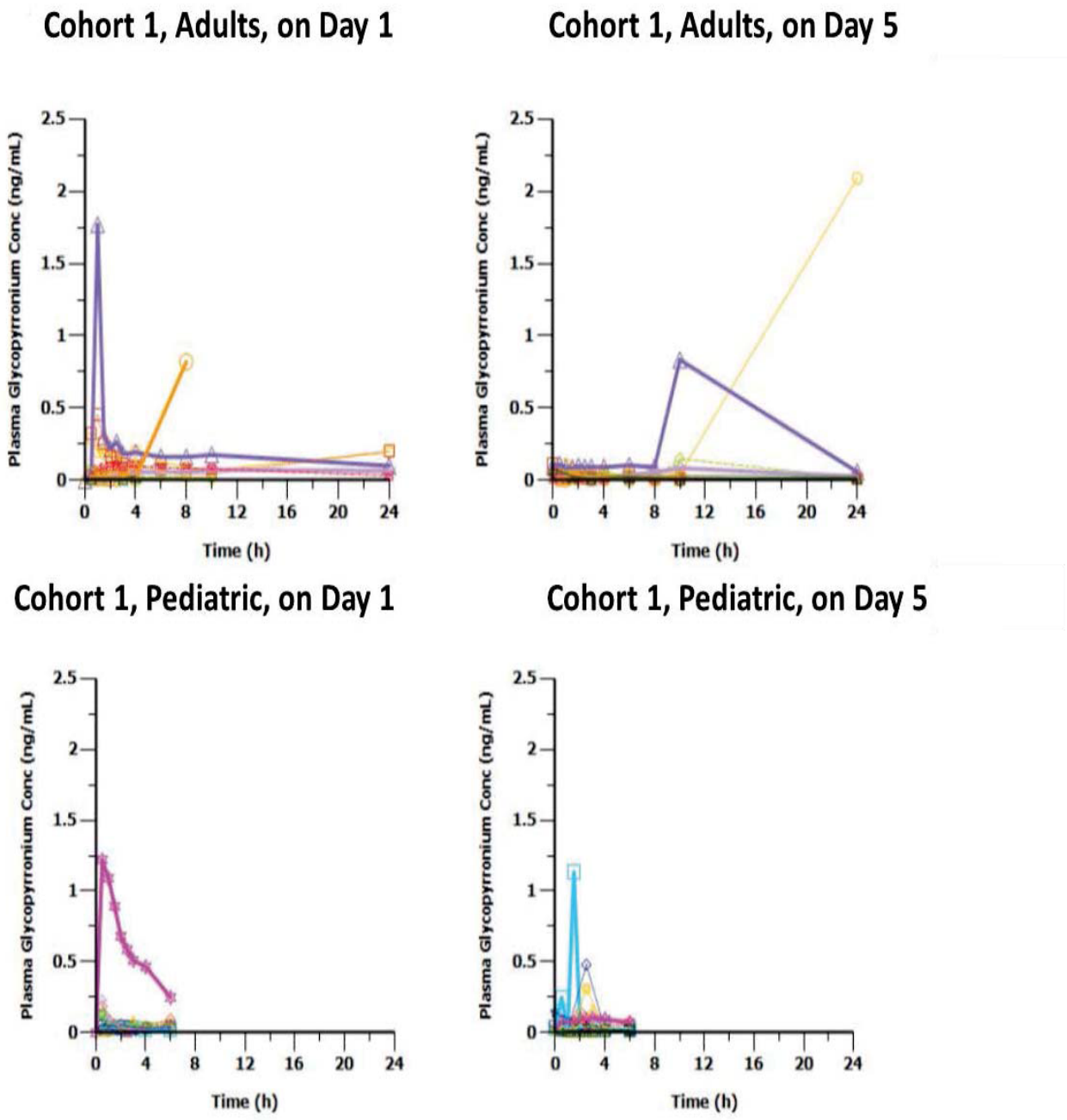
[a] AUC_{0-8} and AUC_{0-24} were calculated for adults only

Table 43: Comparison of Relative Exposure (Excluding Outliers)

	Geometric Mean Ratio (90% CI)				
	Cmax (ng/mL)		AUC0-6 (h×ng/mL)	AUC0-8 (h×ng/mL)a	AUC0-24 (h×ng/mL)a
	Adults	Pediatric	Pediatric	Adults	Adults
DRM04 Day 5 vs Cuvposa Day 5	0.5496 (0.3762, 0.8029)	0.3499 (0.2235, 0.5479)	0.2848 (0.1889, 0.4296)	0.3827 (0.2626, 0.5578)	0.4133 (0.2617, 0.6527)
DRM04 Day 5 vs Cuvposa Day 10	0.3426 (0.2450, 0.4791)	0.2181 (0.1420, 0.3351)	0.1632 (0.1140, 0.2337)	0.2142 (0.1555, 0.2950)	0.2313 (0.1567, 0.3413)
DRM04 Day 5 vs Cuvposa Day 15	0.2062 (0.1459, 0.2913)	0.1313 (0.08508, 0.2026)	0.1015 (0.07078, 0.1454)	0.1352 (0.09878, 0.1851)	0.1460 (0.09968, 0.2139)
DRM04 Pediatrics Day 5 vs DRM04 Adults Day 5	0.6367 (0.3694, 1.0970)		0.8720 (0.5423, 1.4020)	—	—

[a] AUC_{0-8} and AUC_{0-24} were calculated for adults only

Figure 17: Individual Plasma Concentration-Time Profile Including All Data



Reviewer Note DRM04-HH07 (not presented in Section 6)
Detectable pre-dose concentrations raised the concern about potential contamination of PK samples in the study drug arm. Since the cause of this issue is not likely from the bioanalysis errors but from the contamination which may increase the concentration of the samples leading to increased observed systemic exposure than actual systemic exposure. This would not change the conclusion that the clinical bridge was established.

13.4.2.2. Study DRM04-HH02

Title: Phase 2, Randomized, Double-Blind, Vehicle Controlled, Comparator Study of the Effect of DRM04B (glycopyrronium (b) (4)) and DRM04 (glycopyrronium tosylate monohydrate) in Subjects with Axillary Hyperhidrosis

Objectives:

- To determine the safety and efficacy of 2 doses of DRM04B ((b) (4)% and (b) (4)%) (b) (4) (b) (4) DRM04 ((b) (4)% and (b) (4)%) or vehicle for the treatment of axillary hyperhidrosis when applied once daily for 4 weeks followed by a 2-week follow-up period.
- To evaluate the pharmacokinetics (PK) of 2 doses of DRM04B ((b) (4)% and (b) (4)%) compared to DRM04 ((b) (4)% and (b) (4)5%) for the treatment of axillary hyperhidrosis when applied once daily for 4 weeks.

Study Design: Approximately, 100 subjects were to be randomized, in a 1:1:1:1:1, to DRM04B ((b) (4)% and (b) (4)%) or DRM04 ((b) (4)% and (b) (4)%) or vehicle treatment. Subjects were instructed to apply study drug to both axillae once daily in the evening for 28 days. Subjects returned to the study center at Week 1, 2, 3, 4, 5, and 6 (study exit) for evaluation of the effect of DRM04B or DRM04 on the qualitative assessment of the severity of hyperhidrosis and the quantitative measure of sweat production.

Study Population: Males and nonpregnant, nonlactating females ≥ 18 years of age, with primary axillary hyperhidrosis for a duration of at least 6 months, an HDSS of 3 or 4, and sweat production (measured gravimetrically) of at least 50 mg over 5 minutes in each axilla. A total of 105 subjects were randomized to each treatment group. Demographic and baseline characteristics of the enrolled subjects are presented in Table 44.

Dose Selection in this Study: In this study, the efficacy, PK, and safety of 2 salt forms of the active moiety glycopyrronium, glycopyrronium (b) (4) (glycopyrrolate; DRM04B) and glycopyrronium tosylate (DRM04), were compared. The selected doses of each salt form ((b) (4)% and (b) (4)% of DRM04B and (b) (4)% and (b) (4)% of DRM04) were consistent with those previously evaluated that had exhibited efficacy and were well tolerated.

Table 44: Summary of Subject Demographics and Baseline Characteristics

	Vehicle (N=22)	DRM04B		DRM04		Overall (N=105)
		(b) (4) % (N=21)	(b) (4) % (N=20)	(b) (4) % (N=22)	(b) (4) % (N=20)	
Age (years)						
Mean (SD)	34.5 (9.9)	31.4 (9.9)	35.6 (14.8)	31.5 (8.5)	33.6 (14.9)	33.3 (11.7)
Median	32.5	29.0	31.0	30.5	30.5	31.0
Minimum, Maximum	23, 63	21, 63	18, 62	18, 47	18, 72	18, 72
Sex, n (%)						
Male	9 (40.9)	13 (61.9)	13 (65.0)	15 (68.2)	7 (35.0)	57 (54.3)
Female	13 (59.1)	8 (38.1)	7 (35.0)	7 (31.8)	13 (65.0)	48 (45.7)
Race, n (%)						
White	20 (90.9)	18 (85.7)	20 (100.0)	16 (72.7)	17 (85.0)	91 (86.7)
Black or African American	2 (9.1)	3 (14.3)	0	3 (13.6)	3 (15.0)	11 (10.5)
Other	0	0	0	3 (13.6)	0	3 (2.9)
Ethnicity, n (%)						
Hispanic or Latino	0	1 (4.8)	1 (5.0)	3 (13.6)	0	5 (4.8)
Not Hispanic or Latino	22 (100.0)	20 (95.2)	19 (95.0)	19 (86.4)	20 (100.0)	100 (95.2)
BMI (kg/m^2)						
Mean (SD)	26.49 (4.48)	29.28 (7.21)	27.40 (5.43)	28.33 (5.53)	30.56 (6.87)	28.38 (6.02)
Median	25.75	28.50	26.80	27.50	30.30	27.80
Minimum, Maximum	18.5, 37.7	18.2, 46.8	17.2, 38.6	21.4, 42.6	18.9, 45.4	17.2, 46.8

Source: Table 14.1.2.1

PK assessment:

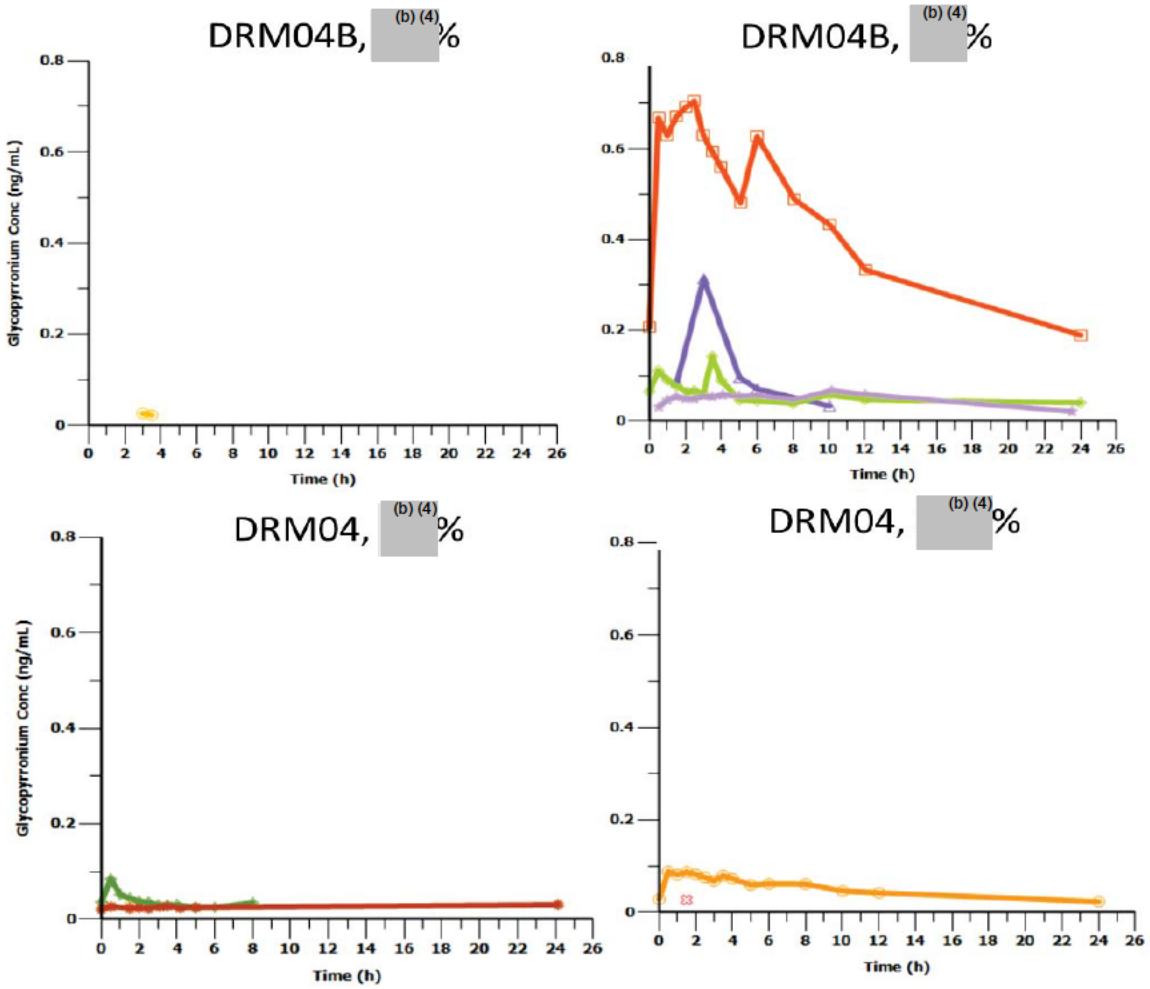
- Full PK subjects: Full PK profiles were determined from a subset of 24 subjects
  - Full PK profiling was collected in 10 subjects at Baseline/Day 1 visit and in 14 subjects at Week 2 visit with a sample drawn at Weeks 4, 5, and 6. On the day of full PK profiling, samples were taken before dose application and 30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 hours post-application.
- Population PK subjects: Pre-dose PK samples were obtained from 79 subjects
  - PK sampling on Day 1, Week 1, 2, 3, 4, 5, and 6 visits

Reviewer comments: *For the full PK subjects, a serial PK sampling was performed at either Day 1 visit OR at the Week 2 visit. The rationale why full PK profiling was conducted at either of Day 1 visit or Week 2 visit was not provided in the study report. PK parameters calculated based on Day 1 would represent PK following a single dose of topical DRM04 and PK parameters calculated based on Week 2 visit would represent PK at steady-state.*

PK results: These results are based on the data from subjects with full plasma concentration-time profiles on PK day. There were 5 subjects each in DRM04B (b)(4)% and DRM04B (b)(4)% groups, 7 subjects in DRM04 (b)(4)% group and 3 subjects in DRM04 (b)(4)% group.

Following application of DRM04B and DRM04 to both axillae once daily, plasma glycopyrronium concentrations were sparsely quantifiable in most of the subjects. The validated lower limit of quantification (LLOQ) of the plasma assay for glycopyrronium was 0.02 ng/mL. Summary of PK parameters is presented in Table 45. Individual plasma concentration-time profiles are presented in Figure 18. There were no subjects with sufficient data to determine the terminal elimination rate constant. Also, PK parameters such as clearance (CL), volume of distribution (Vz) and half-life (T1/2) were not able to be determined due to low rate of quantifiable concentrations and were not reported.

Figure 18: Individual Plasma Concentration-Time Profile



Reviewer comments: *Individual plasma concentration profile indicates topical administrated gylycopyrronium is rapidly absorbed. Full PK profiles were observed in very limited number of subjects.*

Table 45: DRM04-HH02 Summary of Glycopyrronium Pharmacokinetic Parameters

Group	C_{max} (ng/mL)		T_{max} (h)		AUC_{0-t} (h×ng/mL)	
	N[a]	Mean (SD)	N[a]	Median (Min, Max)	N[a]	Mean (SD)
DRM04B, (b) (4)%	1	0.0263 (ND)	1	3.00 (ND)	1	ND (ND)
DRM04B, (b) (4)%	4	0.307 (0.285)	4	3.26 (2.50, 10.20)	4	3.18 (4.15)
DRM04, (b) (4)%	3	0.0485 (0.0312)	3	1.50 (0.50, 24.10)	3	0.320 (0.316)
DRM04, (b) (4)%	2	0.0575 (0.0433)	2	1.00 (0.50, 1.50)	1	1.13 (ND)

ND = Not determined
Note: At least 3 quantifiable concentration values must have been available for calculation of a subject's AUC.
[a] Number of subjects with detectable plasma concentrations. PK parameters were determined for subjects with detectable levels only.
Source: DRM04-HH02 CSR, Pharmacokinetic Report, Table 2

Reviewer comments: *Greater number of quantifiable concentrations of glycopyrronium were observed in the arms that received the higher strengths in a same salt formulation (DRM04B (b) (4)% and DRM04 (b) (4)) compared the arms with the lower strengths. i.e. only 1 out of 5 subjects in DRM04B (b) (4)% group had at least 3 quantifiable concentration values compared to 4 out of 5 subjects showed such in DRM04B (b) (4)%. The PK data from this study provides little information to assess PK difference between two salt formulations.*

Reviewer's Assessment of PK results of DRM04-HH02:

- PK of two doses of DRM04B (glycopyrronium (b) (4)% and (b) (4)%) compared to two doses of DRM04 (glycopyrronium tosylate (b) (4)% and (b) (4)%) were assessed. The percent strengths of DRM04B and DRM04 are (b) (4)
- Great number of the plasma concentrations of glycopyrronium were not quantifiable in this study, which limits determining PK parameters such as terminal elimination rate constant, clearance (CL), volume of distribution (Vz) and half-life (T1/2).
- Individual plasma concentration profile indicates topical administrated glycopyrronium is rapidly absorbed.
- With limited quantifiable data, the differences in PK between the two salts formulations (DRM04B vs. DRM04) and between two doses in the same salt (DRM04B (b) (4)% vs. (b) (4)%, and DRM04 (b) (4)% vs. (b) (4)%) cannot be concluded.

Efficacy assessment

The efficacy of 2 strengths of two salt forms for glycopyrronium, DRM04B ((b) (4)% and (b) (4)%), DRM04 ((b) (4)% and (b) (4)%) were evaluated when applied topically once daily for 4 weeks. Primary efficacy endpoints evaluated in this study include following:

- Proportion of subjects who had a minimum 2-grade improvement in HDSS from baseline at Week 4
- Proportion of subjects who had a minimum 1-grade improvement in HDSS from baseline at Week 4
- Proportion of subjects who had a minimum 1-grade improvement in HDSS from baseline at Week 6
- Absolute change in the gravimetrically measured sweat production (average of left and right axilla measurements) from baseline to Week 4
- Absolute change in the gravimetrically measured sweat production (average of left and right axilla measurements) from baseline to Week 6

Reviewer's note: *Co-primary efficacy endpoints in two Phase 3 trials are the proportion of subjects who had a ≥ 4-point improvement in the weekly mean score of ASDD from baseline at Week 4 and the mean absolute change from baseline in gravimetrically-measured sweat production at Week 4.)*

Safety assessment: Adverse events (AEs), Local skin responses (consisting of burning/stinging, pruritus, edema/swelling, erythema, dryness, and scaling), Safety laboratory tests (serum chemistry, hematology, urinalysis), vital signs, physical examinations (PEs), and electrocardiograms (ECGs).

Reviewer comments: See clinical and biostatistics review for information on efficacy and safety assessments.

13.4.2.3. Study DRM04-HH01

Title: A Phase 2, Randomized, Double-Blind, Vehicle Controlled, Dose-Ranging Study of the Effect of DRM04B in Subjects with Axillary Hyperhidrosis

Primary Objectives:

- The proportion of subjects who had a minimum 2-grade improvement in HDSS from baseline at Week 4
- The absolute change in the gravimetrically measured sweat production (average of left and right axilla measurements) from baseline to Week 4

Secondary Objectives:

- The proportion of subjects who had a minimum 1-grade improvement in HDSS from baseline at Week 4 and at Week 6

- The proportion of subjects who had a minimum 2-grade improvement in HDSS from baseline at Week 6
- The percent change in the gravimetrically measured sweat production (average of left and right axilla measurements) from baseline at Week 4
- The absolute and percent change in the gravimetrically measured sweat production (left and right axilla measured separately) from baseline at Week 4 and at Week 6
- The absolute and percent change in the gravimetrically measured sweat production (average of left and right axilla measurements) from baseline at Week 6
- The absolute change in the Dermatology Life Quality Index (DLQI) score from baseline at Week 4

Study Design: DRM04-HH01 was a Phase 2, randomized, vehicle-controlled, parallel group, dose-ranging trial, designed to assess the safety and efficacy of 4 strengths of DRM04B (1.0%, 2.0%, 3.0%, and 4.0%) compared with vehicle for the treatment of axillary hyperhidrosis. Subjects with axillary hyperhidrosis were randomized in a 1:1:1:1:1 ratio to 1 of the 4 strengths of DRM04B or vehicle treatment. Subjects were instructed to apply study drug to both axillae once daily for 4 weeks.

Study Population: Eligible subjects were males and nonpregnant, nonlactating females ≥ 18 years of age, with primary axillary hyperhidrosis for a duration of at least 6 months, an HDSS of 3 or 4, and sweat production (measured gravimetrically) of at least 50 mg over 5 minutes in each axilla. A total of 198 subjects were randomized to DRM04B (38 subjects to the 1.0% group and 40 subjects to each of the 2.0%, 3.0%, and 4.0% groups) or vehicle.

PK assessment: The PK of topically applied DRM04B was assessed in a subgroup consisting of 32 subjects. Blood samples were collected on Day 1 (at predose and 30 min, 1, 2, 3, 4, and 24 hours postdose); in addition, trough samples were collected at the end of Weeks 1, 2, 3, and 4.

PK results: Table 46 summarizes the serial plasma concentrations of glycopyrronium on Day 1 and trough concentration on subsequent weeks. Plasma concentrations of glycopyrronium were not quantifiable (lower limit of quantitation [LLOQ] = 0.0200 ng/mL) for more than half of the subjects in the DRM04B, 1.0%, 2.0%, and 3.0% groups. Table 47 summarizes PK parameters of 4 dosing groups on Day 1.

Table 46: Summary of Plasma Concentrations of Glycopyrronium (Subgroup of DRM04-HH01)

Plasma Concentrations (ng/mL) by DRM04B Group	Day 1							Week 1 Trough	Week 2 Trough	Week 3 Trough	Week 4 Trough
	Predose	30 min Postdose	1 h Postdose	2 h Postdose	3 h Postdose	4 h Postdose	24 h Postdose				
1.0% Group											
N Total	6	6	6	6	6	6	6	6	6	6	5
N (with detectable level)	0	2	2	2	2	2	1	1	2	2	3
Arithmetic Mean (SD)[a]	—	0.051 (0.027)	0.043 (0.016)	0.066 (0.046)	0.075 (0.049)	0.077 (0.068)	0.038 (—)	0.088 (—)	0.101 (0.027)	0.134 (0.158)	0.115 (0.071)
2.0% Group											
N Total	6	6	6	5[b]	6	6	6	6	6	6	6
N (with detectable level)	0	2	1	1	2	1	1	1	3	3	2
Arithmetic Mean (SD)[a]	—	0.048 (0.026)	0.097 (—)	0.045 (—)	0.038 (0.004)	0.029 (—)	0.021 (—)	0.022 (—)	0.026 (0.009)	0.027 (0.005)	0.062 (0.052)
3.0% Group											
N Total	6	6	6	6	6	6	6	6	6	6	6
N (with detectable level)	0	3	2	2	1	1	1	3	3	3	3
Arithmetic Mean (SD)[a]	—	0.042 (0.032)	0.060 (0.036)	0.054 (0.039)	0.092 (—)	0.103 (—)	0.026 (—)	0.089 (0.040)	0.095 (0.053)	0.074 (0.028)	0.043 (0.032)
4.0% Group											
N Total	7	7	7	7	7	7	7	7	7	7	7
N (with detectable level)	0	5	6	5	5	4	3	4	5	6	6
Arithmetic Mean (SD)[a]	—	0.262 (0.410)	0.302 (0.539)	0.409 (0.657)	0.448 (0.705)	0.457 (0.594)	0.190 (0.116)	0.139 (0.078)	0.327 (0.471)	0.100 (0.053)	0.094 (0.109)

[a] Determined for subjects with detectable levels
[b] A 2-hour PK blood draw was not collected from 1 subject following 2 unsuccessful attempts (DRM04-HH01 CSR Listing 16.2.2).
Source: DRM04-HH01 CSR Table 14.4.1

Table 47: DRM04-HH01 Summary of PK parameters on Day 1

Group	N[a]	C_{max} (ng/mL) Mean (SD)	T_{max} (h) Median (Min, Max)	AUC_{0-t} (h×ng/mL) Mean (SD)
DRM04B, 1.0%	3	0.0753 (0.0471)	0.50 (0.50, 4.00)	0.647 (0.976)
DRM04B, 2.0%	3	0.0537 (0.0372)	1.00 (0.50, 3.00)	0.283 (0.279)
DRM04B, 3.0%	4	0.0471 (0.0376)	2.51 (0.50, 23.93)	0.176 (0.171)
DRM04B, 4.0%	7	0.373 (0.596)	1.03 (0.5, 23.9)	3.77 (5.94)

Note: At least 3 quantifiable concentration values must have been available for calculation of a subject's AUC.
[a] Number of subjects with detectable plasma concentrations. PK parameters were determined for subjects with detectable levels only.
Source: DRM04-HH01 CSR, Pharmacokinetic Report Table 2

Reviewer's Assessment of PK results of DRM04-HH01:

- The formulation used in this study was DRM04B (glycopyrronium (b) (4)) which is a different salt form from the to-be-marketed formulation (glycopyrronium tosylate monohydrate). Therefore, the data reported in this study is considered as exploratory.
- In the lower concentration groups (DRM04B 1%, 2%, 3%), less subjects had quantifiable levels of glycopyrronium than the higher concentration group (DRM04B 4%). Generally lower mean concentrations were observed in lower concentration groups (1, 2, 3%) compared to the DRM04B 4% group.
- Cmax and AUC_{0-t} do not appear dose-proportional within the evaluated doses DRM04B, 1.0%~4.0%). Cmax and AUC_{0-t} is much greater in DRM04B, 4.0% compared to other groups.
- Trough levels in each group fluctuated within a dosing group and a consistent trend was not seen. Therefore, dose accumulation potential was not determined.
- The maximum mean peak plasma concentration was observed at 4 hour post-dose in DRM04B 1, 3, 4 % groups vs. at 1 hour post-dose in DRM04B 2%. Median Tmax was 0.5 - 2.5 hour. After single topical dose of DRM04, Tmax is approximately expected as within 4 hours.

Efficacy assessment: HDSS, the DLQI, and gravimetric assessments of sweat production.

Safety assessment: Treatment-emergent adverse events (TEAEs), Local skin responses (consisting of burning/stinging, pruritus, edema/swelling, erythema, dryness, and scaling), Safety laboratory tests (serum chemistry and hematology), vital signs, physical examinations (PEs), and electrocardiograms (ECGs).

Reviewer comments: See clinical and biostatistics review for information on efficacy and safety assessments.

13.4.2.4. Study W0266-01 (Proof of Concept Study)

Title: A Single-Center, Randomized, Double-Blind, Vehicle-Controlled, Proof-of-Concept Study of Glycopyrrolate in the Treatment of Primary Axillary Hyperhidrosis

Objectives:

- To assess the potential of this product to reduce sweating and to identify the difference in efficacy between 2 doses and placebo and between 2 types of formulations of glycopyrrolate (b) (4) in the treatment of subjects 16 years and older with primary, bilateral, axillary hyperhidrosis
- To evaluate the safety and tolerability of topically applied glycopyrrolate and to evaluate the bioavailability of these doses and formulations of glycopyrrolate

Trial design: 36 subjects 16 years of age or older, with a diagnosis of primary axillary hyperhidrosis, were to be randomized to 1 of the 6 application groups, as shown in Table 48. Subjects who did not complete 2 weeks of treatment were replaced.

Table 48: Randomization of Study Subjects in 6 Groups

	Glycopyrrolate (b) (4)%	Glycopyrrolate (b) (4)%	Vehicle
(b) (4) Formulation	6	6	6
(b) (4) Formulation	6	6	6

Study product was to be applied once daily in the evening for 4 weeks, followed by a 2-week follow-up period. Visits were scheduled at baseline (day 1), week 1, week 2, week 3, week 4, and week 6. Subjects were assessed for efficacy and safety at each visit. Efficacy assessments included a gravimetric assessment of sweating and the subjects' assessment of hyperhidrosis over the last week using the Hyperhidrosis Disease Severity Scale (HDSS). Blood samples were collected at baseline and at weeks 1, 2, 3, and 4 to assess the bioavailability of glycopyrrolate.

Study Population: Males and nonpregnant, nonlactating females ≥ 16 years of age, with primary axillary hyperhidrosis for a duration of at least 6 months, an HDSS of 3 or 4, and sweat production (measured gravimetrically) of at least 50 mg over 5 minutes in each axilla. A total of 38 subjects were enrolled in the trial; 3 subjects discontinued early (2 due to an AE and 1 withdrew consent). Subjects had a mean age of 32.2 years (range: 17–68 years) and the majority were female (58%) and white (87%).

Reviewer comments: In this proof-of-concept study, the Applicant planned to assess bioavailability of 2 different formulations in two dose-levels. The formulations evaluated in this study are not to-be-marketed formulation. Furthermore, the bioanalysis results and validation report for the bioanalytical assay that was used in this trial were not submitted. Therefore, PK results were not reviewed.

13.4.2.5. In vitro Drug-Drug Interaction Studies

1. **Study No. 2110-1014-2300**

Title: In Vitro Assessment of Human Liver Cytochrome P450 Inhibition Potential of Glycopyrrolate

Objective: To assess the potential of glycopyrrolate to inhibit the catalytic activity associated with the formation of metabolites produced by cytochromes P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 (midazolam), and 3A4 (testosterone)

Methods: CYP-specific probe substrates were incubated with pooled human liver microsomes in the presence and absence of standard inhibitors or glycopyrrolate (0, 0.25, 0.5, 1, 2, and 20 µM). In addition, glycopyrrolate (at concentrations previously noted) was pre-incubated for 30 minutes with pooled human liver microsomes before the addition of the CYP-specific probe

substrate to assess potential time-dependent inhibition. The effects of standard inhibitors and glycopyrrolate on the rate of production of the relevant probe substrate metabolites were evaluated. When inhibition reached significant levels (>50%), IC_{50} values for both direct and time-dependent inhibition were determined.

Results:

Direct Inhibition: The tables below show mean % remaining activity of glycopyrrolate effects on CYP activity. Glycopyrrolate at concentrations up to 20 µM did not significantly inhibit any of the isoforms tested. No IC_{50} values are reported for these isoforms. The estimated IC_{50} for glycopyrrolate CYP isoform-specific inhibition in pooled human liver microsomes is greater than 20 µM for all tested enzymes.

Reviewer comment: Maximum mean Cmax of glycopyrrolate observed in the MuPK trial was 0.343 ng/mL (0.68 nM).

Time Dependent (MBI) Inhibition: Following a 30-minute pre-incubation with ß-nicotinamide adenine dinucleotide 2'-phosphate (NADPH), glycopyrrolate showed no significant changes in IC_{50} values for any of the isoforms tested, indicating that glycopyrrolate is not likely a time-dependent (mechanism-based) inhibitor of these isoforms. The results from this CYP in vitro inhibition study indicate that glycopyrrolate is unlikely to play a role in clinical drug-drug interactions related to inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 (midazolam and testosterone) metabolism.

Table 49: Summary (Mean % Remaining Activity) of Glycopyrrolate Effects on CYP Activity

Direct Inhibition

Glycopyrrolate (µM)	1A2	2B6	2C8	2C9	2C19	2D6	3A4 (1OHMDZ)	3A4 (6ßT)
0	100	100	100	100	100	100	100	100
0.25	101	98.6	97.2	99.3	102	103	96.3	104
0.5	103	100	98.4	101	100	103	95.1	79.8
1	100	101	103	104	103	98.4	97.3	90.5
2	99.4	102	95.7	97.3	102	95.7	106	97.2
20	102	99.5	112	103	102	80.1	91.2	100
Positive Control	22.0	34.6	22.6	53.0	40.4	11.8	18.0	15.6

Time-Dependent (MBI) Inhibition

Glycopyrrolate (µM)	1A2	2B6	2C8	2C9	2C19	2D6	3A4 (1OHMDZ)	3A4 (6ßT)
0	100	100	100	100	100	100	100	100
0.25	97.2	99.8	85.4	93.5	96.4	97.2	91.0	102
0.5	102	97.6	93.7	92.4	93.7	96.3	97.5	99.3
1	98.0	102	94.8	102	102	99.0	102	99.3
2	98.4	101	82.2	98.4	95.7	95.1	105	102
20	103	101	83.5	93.8	100	71.9	94.6	84.7
MBI Positive Control	15.7	5.3	32.1	20.8	30.1	<5.0	6.8	4.4

Values reported are the mean of two individual determinations.

Conclusions: DRM04 is not considered an inhibitor of cytochromes P450 enzymes under the conditions of clinical use.

2. **DRM04-TOX-17-01**

Title: Evaluation of Cytochrome P450 Induction After Exposure of Primary Cultures of Human Hepatocytes to DRM04

Objective: To assess the potential of DRM04 to induce human cytochrome P450 (CYP) enzymes (CYP1A2, CYP2B6, and CYP3A4) after exposure to human hepatocytes and to compare the effects with those of prototypical inducers.

Methods: Cryopreserved human hepatocytes from three individual donors were incubated with 0 (vehicle control), 0.5, 5, and 50 µM DRM04 for 72 hours. Positive control inducers omeprazole (CYP1A2), phenobarbital (CYP2B6), and rifampicin (CYP3A4) and the negative control flumazenil were incubated with human hepatocytes concurrently. Induction of cytochromes P450 was assessed by quantitating mRNA levels for each test and control article. Induction was calculated as a fold difference compared with vehicle control for both test and control articles and as a percentage of the positive control for each test article concentration

Results: DRM04 produced maximum fold differences in mRNA levels of 0.81 to 1.59, 1.34 to 2.53, and 1.18 to 2.90 over vehicle controls for CYP1A2, CYP2B6, and CYP3A4, respectively, across donors. In comparison, omeprazole (CYP1A2), phenobarbital (CYP2B6), and rifampicin

(CYP3A4) produced fold differences in mRNA levels of 30.6 to 47.3, 6.4 to 21.5, and 7.1 to 38.2 over solvent controls, respectively, across donors. For DRM04, the maximum fold differences in mRNA levels corresponded to 1.93% to 3.36%, 8.53% to 38.3%, and 5.94% to 41.1% of their respective positive controls for CYP1A2, CYP2B6, and CYP3A4, respectively, across donors. The increases in mRNA elicited by DRM04 were generally independent of incubation concentration.

Conclusions: DRM04 is not considered an inducer of cytochromes P450 enzymes under the conditions of clinical use.

13.5. Clinical/Biostatistics

Table 50: Axillary Sweating Daily Diary (ASDD) Questions

Item No.	Question	Response Options
1	During the past 24 hours, did you have any underarm sweating? *ASDD-C: Thinking about last night and today, did you have any underarm sweating?*	Yes/No *Yes/No*
2	During the past 24 hours, how would you rate your underarm sweating at its worst? *ASDD-C: Thinking about last night and today, how bad was your underarm sweating?*	11-point scale from 0 (no sweating at all) to 10 (worst possible sweating) *11-point scale from 0 (no sweating at all) to 10 (worst possible sweating)*
3	During the past 24 hours, to what extent did your underarm sweating impact your activities?	5 possible responses: not at all; a little bit; a moderate amount; a great deal; an extreme amount
4	During the past 24 hours, how bothered were you by your underarm sweating?	5 possible responses: not at all bothered; a little bothered; moderately bothered; very bothered; extremely bothered
5a	During the past 7 days, did you ever have to change your shirt during the day because of your underarm sweating?	Yes/No
5b	During the past 7 days, did you ever have to take more than 1 shower or bath a day because of your underarm sweating?	Yes/No
5c	During the past 7 days, did you ever feel less confident in yourself because of your underarm sweating?	Yes/No
5d	During the past 7 days, did you ever feel embarrassed by your underarm sweating?	Yes/No
5e	During the past 7 days, did you ever avoid interactions with other people because of your underarm sweating?	Yes/No
5f	During the past 7 days, did your underarm sweating ever keep you from doing an activity you wanted or needed to do?	Yes/No
6	Overall, how would you rate your underarm sweating now as compared to before starting the study treatment?	7-point scale: 1 = much better; 2 = moderately better; 3 = a little better; 4 = no difference; 5 = a little worse; 6 = moderately worse; 7 = much worse

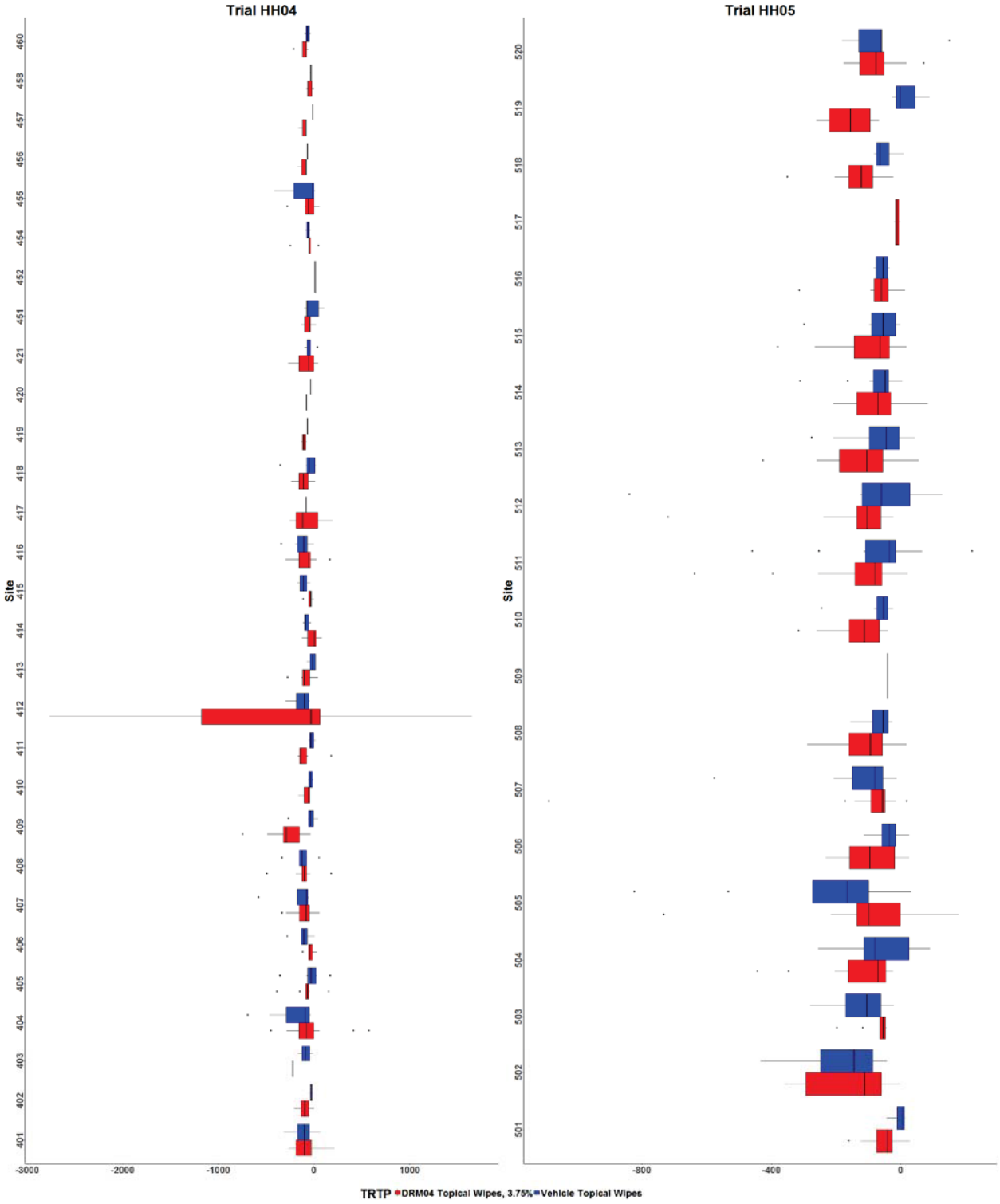
Source: Table 3 on page 32 of applicant's Study Report for Trial HH04

Table 51: Change from Baseline in Gravimetrically-Measured Sweat at Week 4 by Gender, Race, Age, and Geographic Region

	Trial HH04		Trial HH05	
ITT Population[1]	DRM04 N=229	Vehicle N=115	DRM04 N=234	Vehicle N=119
Gender				
Male	N=99 -94 (-181, -38)	N=55 -69 (-145, -15)	N=113 -78 (-160, -42)	N=59 -69 (-182, -27)
Female	N=130 -74 (-135, -41)	N=60 -63 (-102, -29)	N=121 -79 (-131, -49)	N=60 -48 (-84, -20)
Race				
White	N=182 -80 (-148, -39)	N=94 -59 (-92, -16)	N=192 -77 (-140, -45)	N=102 -53 (-115, -23)
Black or African American	N=31 -67 (-155, -40)	N=16 -83 (-251, -47)	N=28 -92 (-191, -44)	N=14 -84 (-143, 17)
Other	N=16 -106 (-169, -56)	N=5 -342 (-354, -154)	N=14 -87 (-162, -48)	N=3 -57 (-97, -38)
Ethnicity				
Hispanic or Latino	N=46 -87 (-169, -42)	N=23 -75 (-160, -10)	N=28 -65 (-132, -48)	N=15 -61 (-76, -2)
Not Hispanic or Latino	N=183 -78 (-147, -40)	N=92 -62 (-100, -28)	N=206 -79 (-145, -45)	N=104 -55 (-126, -22)
Age				
<16 years	N=5 -50 (-60, -41)	N=6 -41 (-67, -3)	N=11 -79 (-142, -54)	N=10 -53 (-87, -26)
≥16 years	N=224 -82 (-149, -40)	N=109 -68 (-115, -28)	N=223 -79 (-145, -45)	N=109 -58 (-125, -21)
<18 years	N=14 -63 (-119, -32)	N=9 -34 (-67, -3)	N=20 -78 (-145, -44)	N=13 -66 (-130, -27)
≥18 years	N=215 -82 (-150, -40)	N=106 -68 (-115, -28)	N=214 -79 (-144, -46)	N=106 -54 (-119, -19)
<Median (31 years in HH04, 32 years in HH05)	N=113 -75 (-128, -36)	N=54 -65 (-116, -27)	N=118 -79 (-143, -45)	N=56 -68 (-127, -24)
≥ Median (31 years in HH04, 32 years in HH05)	N=116 -86 (-158, -48)	N=61 -67 (-104, -28)	N=116 -79 (-150, -46)	N=63 -48 (-119, -15)
Geographic Region[3]				
United States	N=192 -84 (-158, -40)	N=99 -67 (-131, -29)		
Outside United States	N=37 -75 (-95, -40)	N=16 -40 (-86, -14)		

Source: Reviewer's analysis. Gravimetrically-measured sweat production is measured in mg/5 min. Results presented as median (IQR), and are averaged over 95 imputed datasets for Trial HH04 and 85 imputed datasets for Trial HH05.

Figure 19: Change from Baseline in Gravimetrically-Measured Sweat at Week 4 by Site



Source: Reviewer's analysis. Gravimetrically-measured sweat production is measured in mg/5 min.

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/s/

MATTHEW E WHITE
06/28/2018

KENDALL A MARCUS
06/28/2018