CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213691Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	213691
Priority or Standard	Standard
Submit Date(s)	July 19, 2019
Received Date(s)	July 19, 2019
PDUFA Goal Date	May 19, 2020
Division/Office	Division of Dermatology and Dentistry
Review Completion Date	May 18, 2020
Established/Proper Name	clobetasol propionate lotion, 0.05%
(Proposed) Trade Name	Impeklo Lotion, 0.05%
Pharmacologic Class	Corticosteroids (4025010)
Applicant	Mylan Pharmaceuticals, Inc.
Dosage Form	Lotion
Applicant Proposed Dosing Regimen	Do not use more than (b) (4) pump actuations per application twice daily or (b) (4) pump actuations per day
Applicant Proposed Indication(s)/Population(s)	Corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, in patients 18 years of age or older
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	330901000 |Anti-inflammatory preparations (product)|402753005 |Skin disease attributable to corticosteroid therapy (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if Applicable)	Corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, in patients 18 years of age or older
Recommended Dosing Regimen	Do not use more than 10 pump actuations per application twice daily or 20 pump actuations per day for more than 7 days

Table of Contents

Table of Figures

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OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
PLT, Patient Labeling Team
OSE, Office of Surveillance and Epidemiology
DMEPA, Division of Medication Error Prevention and Analysis

Signatures

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Nonclinical Reviewer	John Dougherty, PhD	Office of Immunology and Inflammation (OII)/ Division of Pharm-Tox for Immunology and Inflammation (DPTII)	Sections: 5, 18.3	**Select one:** _X_ Authored ___ Approved
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	Signature in DARRTS			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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	Signature in DARRTS			

Glossary

ANDA	abbreviated new drug application
BE	bioequivalence
CMC	chemistry, manufacturing, and controls
CRD	corticosteroid-responsive dermatoses
DMF	drug master file
NOEL	no-observed-effect level
REMS	risk evaluation and mitigation strategy

1. Executive Summary

1.1. Product Introduction

The drug product, clobetasol propionate lotion, 0.05% (w/w) formulation in this application was previously approved under Lupin's abbreviated new drug application (ANDA) 209147 on September 22, 2017. In this (505)(b)(2) NDA, Mylan Pharmaceutical, Inc. (the Applicant) is proposing to package the clobetasol propionate formulation developed by Lupin into a metered-dose container closure system containing 68 g of lotion, which is intended to deliver on average 0.3 g of lotion (0.15 mg of clobetasol propionate) per actuation.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness has been established for the listed drug Clobex Lotion (clobetasol propionate, 0.05%). A review of bioequivalence (BE) was conducted under ANDA 209147 by Dr. Manjinder Kaur in the Office of Generic Drugs. Two vasoconstrictor studies were determined to be acceptable for establishing BE. The product under review provides for a new container closure system and so no additional evidence of effectiveness is required.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Clobetasol propionate lotion, 0.05% is a topical corticosteroid product that is approved for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, in patients 18 years of age or older. The Applicant proposes a novel container closure system that delivers the product via actuation of a pump. The Applicant has established bioequivilance to the listed drug Clobex Lotion under ANDA 209147 and may rely on the Agency's findings of safety and effectiveness for approval. The Applicant has provided sufficient chemistry, manufacturing, and controls (CMC) information to assure the identity, purity, strength, and quality of the drug substance, clobetasol propionate, and the drug product, clobetasol propionate lotion, 0.05%, for topical administration.

Labeling negotiations were pending as this review closed. The application is recommended for approval upon achieving agreed upon labeling.

1.4. Patient Experience Data

Not applicable.

2. Therapeutic Context

2.1. Analysis of Condition

Topical corticosteroids have been the treatment of choice for many dermatoses, particularly the inflammation and pruritus associated with conditions characterized by dry, scaly, crusted, or erythematous skin. In a notice published in the Federal Register of April 28, 1971 (36 FF 7982), the Commissioner of Food and Drugs Dr. Charles C. Edwards announced his conclusions regarding the efficacy of corticosteroid drugs for topical use. Determining that the "Indications" section of the labeling for this class of products was unnecessarily complex, the Commissioner found it appropriate to revise it to read, "For relief of the inflammatory manifestations of corticosteroid-responsive dermatoses."

The listed drug for this application, Clobex Lotion, approved in 1985, is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (CRD).

Recently, the Division of Dermatology and Dental Products ceased to recommend CRD as an indication. In the absence of clinical trial information, there does not appear to be a path forward for granting a new indication for this application.

2.2. Analysis of Current Treatment Options

Clobetasol propionate is a dihalogenated corticosteroid, and is classified as the most potent of all topical steroids. Since 1985 it has been marketed specifically for the short-term topical treatment of moderate and severe CRD based on its anti-inflammatory, immunosuppressive, and antimitotic effects. Currently, a number of topical corticosteroid products of various potencies and formulations (e.g., fluocinonide, mometasone furoate, fluticasone propionate, and desonide) are available for the relief of the inflammatory manifestations of CRD.

3. Regulatory Background

3.1. United States Regulatory Actions and Marketing History

This NDA for clobetasol propionate lotion, 0.05% refers to the listed drug, Clobex (clobetasol propionate) Lotion, 0.05%; NDA 021535, approved on July 24, 2003. This application relies on the Food and Drug Administration's (the Agency's) previous findings of safety and effectiveness

of Clobex Lotion, 0.05%. Because the product is bioequivalent to the listed drug Clobex Lotion, 0.05% is intended to be used for the same indication at the same doses, and is to be administered by the same route, the labeling of the reference listed drug was used as the basis for the product labeling. Hence, no nonclinical or clinical studies have been performed.

A review of BE was conducted under ANDA 209147 by Dr. Manjinder Kaur in the Office of Generic Drugs. Two vasoconstrictor studies were determined to be acceptable for establishing BE.

3.2. Summary of Presubmission/Submission Regulatory Activity

A pre-investigational new drug (PIND 130717) teleconference was held on June 29, 2016, and the meeting minutes were provided to the Applicant on July 21, 2016. At this meeting, the Agency agreed with the proposed plan to use the BE studies conducted to support the planned ANDA filing under 505j, to support the proposed NDA filed under 505(b)(2) for clobetasol propionate lotion fitted with a metered-dose pump. Additionally, the Agency stated that the Applicant would need to address the dermal safety of their product.

The Agency provided a written response on November 17, 2016, which stated that dermal safety studies will not be required, assuming a favorable review of the data within the pending ANDA.

The Applicant is requesting a waiver of the requirement for dermal safety studies, because the lotion formulation is identical to that of the generic version, differing only in terms of the delivery device—a metered-dose pump.

Additionally, in the November 17, 2016 written response the Agency stated that this drug/device combination does not trigger the Pediatric Research Equity Act.

The Agency stated that based on information in the briefing package, the product with a metered-dose pump will be considered a drug–device combination product.

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

4.1. Office of Scientific Investigations

There were no clinical study sites for this application; clinical studies were not conducted for this submission.

4.2. Product Quality

Mylan Pharmaceuticals, Inc., has submitted this (505)(b)(2) new drug application for Impeklo (clobetasol propionate) Lotion, 0.05% for topical administration intended for the relief of the inflammatory and pruritic manifestations of CRD only in patients 18 years of age or older.

The Applicant has used Clobex (clobetasol propionate) Lotion, 0.05%, approved under NDA 21535 in 2003 for the same indication as the listed drug. A generic version of clobetasol propionate lotion at the same strength of 0.05% manufactured by Lupin, Ltd. was approved under ANDA 209147 on September 22, 2017.

- The Applicant of this 505(b)(2) NDA has provided sufficient chemistry, manufacturing, and controls (CMC) information to assure the identity, purity, strength, and quality of the drug substance, clobetasol propionate, and the drug product, Impeklo (clobetasol propionate) Lotion, 0.05%, for topical administration.
- Labels/labeling issues have been satisfactorily addressed.
- The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.
- The request for categorical exclusion of the environmental assessment has been granted.

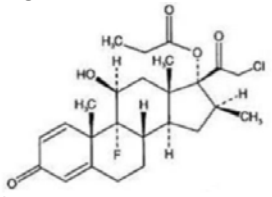
Therefore, from the perspective of the Office of Pharmaceutical Quality, this NDA is recommended for approval with an expiration dating period of 24 months.

Drug Substance

The drug substance, clobetasol propionate, is a synthetic fluorinated corticosteroid and is a compendial drug substance. It belongs to a class of synthetic steroids intended for topical use as anti-inflammatory and antipruritic agents. It is a white to almost white crystalline powder.

Clobetasol propionate is a white to almost-white crystalline powder and is practically insoluble in water. It has the chemical name 21-chloro-9-fluoro-11β, 17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate, an empirical formula of $C_{25}H_{32}ClFO_5$, and a molecular weight of 466.97. The chemical structure is shown in Figure 1.

Figure 1. Chemical Structure of Clobetasol Propionate



Source:

Clobetasol propionate for this application is manufactured and supplied by (b) (4), and is manufactured in accordance with the requirements of current good manufacturing practices and in compliance with the United States Pharmacopeia monograph. It is tested against an adequate specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its proposed retest period of (b) (4) months. Information regarding the manufacture of clobetasol propionate by (b) (4), is provided in drug master file (DMF) (b) (4). This DMF has been reviewed and found to be adequate to support this NDA.

Drug Product

The drug product, Impeklo (clobetasol propionate) Lotion, 0.05% for topical administration is produced as a white to off-white, opaque to translucent, homogeneous, and lump-free lotion that is free of phase separation. It is a preservative-free, non-sterile, aqueous-based lotion formulation and its composition is identical to that of the lotion approved under ANDA 209147. However, this drug product is packaged as 68 g to ensure the delivery of (b) (4) g of lotion in a container closure equipped with a metered-dose pump that delivers on average 0.3 g (0.15 mg of clobetasol propionate) with each actuation.

This drug product was originally designated a drug–device combination based on the use of a metered-dose pump. However, because the pump is not intended to deliver an exact amount of drug product directly to the affected area of skin, the use of the pump was considered a low risk and the Center for Devices and Radiological Health has deferred the review of the metered-dose container closure to the Office of New Drug Products.

Each gram of Impeklo Lotion contains 0.5 mg of clobetasol propionate as the active ingredient and hypromellose (b) (4), carbomer 1342, propylene glycol, mineral oil (b) (4), PEG-6 isostearate, sodium hydroxide, and purified water as inactive ingredients.

The drug product in this application is manufactured by Lupin, Ltd., for Mylan Pharmaceuticals. Lupin, Ltd., is also the manufacturer of the drug product in the approved ANDA 209147. The drug product is manufactured and packaged in accordance with the requirements of current good manufacturing practices and is evaluated against a specification that includes testing and acceptance criteria for all physical and chemical attributes deemed essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout the proposed expiration dating period of 24 months.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant's clobetasol propionate lotion, 0.05% (NDA 213691) contains the same concentration of the same active pharmaceutical ingredient, for the same indication, as the listed drug, Clobex (clobetasol propionate) Lotion, 0.05% (NDA 021535). The current product uses an identical formulation to an approved generic drug product (ANDA 209147, approval date: 09/22/2017), which demonstrated BE to Clobex Lotion, 0.05%. The current product and ANDA 209147 differ only in their container closure systems. The potential leachables of the current product are well below the threshold of toxicological concern; consequently, this difference does not introduce any nonclinical concerns.

The Applicant did not submit any nonclinical studies as part of NDA 213691 because the nonclinical safety of clobetasol propionate lotion, 0.05%, has been adequately evaluated under the listed drug and the identically formulated approved generic. There are no nonclinical safety issues. This NDA is approvable from a nonclinical perspective.

5.2. Referenced NDAs, BLAs, and DMFs

NDA 21535: Clobex (clobetasol propionate) Lotion, 0.05%
ANDA 209147: Clobetasol propionate lotion, 0.05%
DMF (b) (4): Clobetasol propionate

5.3. Pharmacology

Clobetasol propionate is a synthetic corticosteroid with anti-inflammatory, antipruritic, vasoconstrictive, and immunosuppressive properties. Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear.

5.4. Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics

Topically applied corticosteroids, such as clobetasol propionate, can be absorbed across the skin. After absorption, corticosteroids are primarily metabolized by the liver and excreted in urine and bile.

5.5. Toxicology

5.5.1. General Toxicology

No general toxicology information is present in the listed drug (Clobex Lotion, 0.05%) labeling. However, local and systemic toxicities associated with topical corticosteroids have been

established as a result of their clinical use and are included in the labeling. Local adverse reactions to topical corticosteroids may include: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae, miliaria, skin atrophy, and telangiectasia. Adverse reactions resulting from systemic exposure to topically applied corticosteroids may include reversible hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus.

5.5.2. Genetic Toxicology

Genetic toxicology information contained in the listed drug (Clobex Lotion, 0.05%) labeling is provided below.

Clobetasol propionate was negative in the in vitro mammalian chromosomal aberration test and in the in vivo mammalian erythrocyte micronucleus test.

5.5.3. Carcinogenicity

Carcinogenicity and photocarcinogenicity information contained in the listed drug (Clobex Lotion, 0.05%) labeling is provided below. Information concerning the photocarcinogenicity potential of a topical drug product is no longer included in the labeling because, per the International Council on Harmonisation M3(R2) guidance document, the mouse photocarcinogenicity assay does not have clinical relevance.

Clobetasol propionate was not carcinogenic to rats when topically applied for 2 years at concentrations up to 0.005% which correspond to doses up to 11 µg/kg/day (ratio of animal dose to proposed human dose of 0.03 on a mg/m^2/day basis).

Clobetasol propionate at concentrations up to 0.001% did not increase the rate of formation of ultraviolet light-induced skin tumors when topically applied to hairless mice 5 days per week for a period of 40 weeks.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The fertility and early embryonic development information contained in the listed drug (Clobex Lotion, 0.05%) labeling is provided below.

The effect of subcutaneously administered clobetasol propionate on fertility and general reproductive toxicity was studied in rats at doses of 0, 12.5, 25, and 50 µg/kg/day. Males were treated beginning 70 days before mating and females beginning 15 days before mating through day 7 of gestation. A dosage level of less than 12.5 µg/kg/day clobetasol propionate was considered to be the no-observed-effect level (NOEL) for paternal and maternal general toxicity based on decreased weight gain and for male reproductive toxicity based on increased weight of the seminal vesicles. The female reproductive NOEL was 12.5 µg/kg/day (ratio of the animal dose to proposed human dose of 0.03 on a mg/m^2/day basis) based on a reduction in the

number of estrous cycles during the pre-cohabitation period and an increase in the number of nonviable embryos at higher doses.

Embryo-Fetal Development

No specific embryo-fetal development information is present in the listed drug (Clobex Lotion, 0.05%) labeling. However, the listed drug labeling contains the following text:

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and the mouse.

The Applicant did not include the above text in the proposed labeling for the current product. Instead, the Applicant included embryofetal development information from the labeling of an approved drug marketed by the Applicant, Olux (clobetasol propionate) Foam, 0.05% (NDA 021142), which is provided below. Because the Applicant conducted these studies with clobetasol propionate, it is acceptable to include these animal data in the labeling for this clobetasol propionate lotion product.

Embryofetal development studies conducted with clobetasol propionate in mice using the subcutaneous route resulted fetotoxicity at the highest dose tested (1 mg/kg) and malformations at all dose levels tested down to 0.03 mg/kg. The malformations seen included cleft palate and skeletal abnormalities.

In an embryofetal development study in rabbits, subcutaneous administration of clobetasol propionate resulted in malformations at doses of 0.003 and 0.01 mg/kg. The malformations seen included cleft palate, cranioschisis, and other skeletal abnormalities.

Prenatal and Postnatal Development

The prenatal and postnatal development information contained in the listed drug (Clobex Lotion, 0.05%) labeling is provided below.

The effect of clobetasol propionate on pregnancy outcomes and the development of offspring was studied in rat. Clobetasol propionate was administered subcutaneously to female rats twice daily (0, 12.5, 25, and 50 µg/kg/day) from day 7 of presumed gestation through day 25 of lactation or day 24 of presumed gestation for those rats that did not deliver a litter. The maternal NOEL for clobetasol propionate was less than 12.5 µg/kg/day reduced body weight gain and feed consumption during the gestation period. The reproductive NOEL in the dams was 25 µg/kg/day (ratio of the animal dose to the proposed human dose of 0.07 on a mg/m^2/day basis) based on prolonged delivery at a higher dose level. The no-observed-adverse-

effect level for viability and growth in the offspring was 12.5 µg/kg/day (ratio of the animal dose to the proposed human dose of 0.03 on a mg/m^2/day basis) based on the incidence of stillbirths, reductions in pup body weight on days 1 and 7 of lactation, increased pup mortality, increased incidence of umbilical hernia, and increased incidence of cysts on the kidney in pups at higher dose levels during the preweaning period. The weights of the epididymides and testes were significantly reduced at higher dosages. Despite these changes, there were no effects on the mating and fertility of the offspring.

6. Clinical Pharmacology

6.1. Executive Summary

Clobetasol propionate is a super-potent corticosteroid, which has anti-inflammatory, antipruritic, and vasoconstrictive properties. The Applicant is pursuing a 505(b)(2) regulatory pathway with Clobex Lotion (clobetasol propionate, 0.05%) as the listed drug. The proposed product is a drug–device combination product with a container closure system, a bottle fitted with a metered-dose pump. The lotion formulation is identical to that approved under ANDA 209147, but the ANDA 209147 product is not dispensed using a metered-dose pump. Each actuation is intended to deliver on average 0.15 mg of clobetasol propionate in 0.30 g of lotion.

The proposed dosing regimen is to apply the product directly onto the affected areas of skin twice daily, and not to exceed (b) (4) actuations per application or (b) (4) actuations per day.

6.2. Summary of Clinical Pharmacology Assessment

The clinical development program included the following two vasoconstriction studies, which were conducted to support the approval of ANDA 209147:

- Study 11446625: A pilot dose-response study of vasoconstriction in 24 healthy subjects.
- Study 11446626: A phase 1, pivotal randomized, parallel group, BE study comparing the proposed formulation to the listed drug, as measured by the degree of vasoconstriction in 90 healthy subjects.

The proposed formulation (test) met the BE criterion when compared to the listed drug (reference) with a test-to-reference ratio of 103.13 and 90% confidence intervals of 97.37 to 109.23. The BE review for ANDA 209147 conducted by Dr. Manjinder Kaur in the Office of Generic Drugs concluded that the two vasoconstriction studies were acceptable. No new clinical pharmacology studies were performed to support the current NDA application. The BE studies conducted to support the approval of ANDA 209147 will not be re-reviewed and the review findings of Dr. Kaur have been taken into consideration to support approval of this application (see Section 18.4 for the review).

6.2.1. Recommendations

This NDA is approvable from a clinical pharmacology perspective.

6.2.2. Postmarketing Requirements and Commitments

None.

6.2.3. Pharmacology and Clinical Pharmacokinetics

Not applicable as no new studies were conducted to support this application.

6.2.4. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is to apply the product directly onto the affected areas of skin twice daily, and not to exceed (b) (4) actuations per application or (b) (4) actuations per day.

Reviewer comment: *Each actuation is intended to deliver 0.15 mg of clobetasol propionate in 0.30 g of lotion. The maximum weekly dose ((b) (4) actuations; (b) (4) actuations per day × 7 days) equates to (b) (4) g of lotion per week. This amount is (b) (4) higher than the maximum weekly dose for the listed drug, Clobex Lotion, which is 50 g. The (b) (4) higher maximum dose ((b) (4) g of lotion containing (b) (4) mg of clobetasol propionate per week) compared to the listed drug does not appear to be clinically meaningful as the (b) (4) increase in weekly dose is unlikely to have any effect on drug safety (Refer to Section 10.1).*

Therapeutic Individualization

Not applicable.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Not applicable because no new studies were conducted to support this application.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The vasoconstriction studies that concluded that the proposed product is bioequivalent to the listed product provide supportive evidence.

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

Yes.

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

Intrinsic factors have not been evaluated in this application.

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

Drug interactions have not been evaluated in this application.

7. Sources of Clinical Data and Review Strategy

No clinical data has been submitted. The drug product, clobetasol propionate lotion, 0.05% (w/w) formulation, in this application was approved under Lupin's ANDA 209147 on September 22, 2017. A review of BE was conducted under ANDA 209147 by Dr. Manjinder Kaur in the Office of Generic Drugs. Two vasoconstrictor studies were determined to be acceptable for establishing BE. In this (505)(b)(2) NDA, Mylan Pharmaceutical, Inc. is proposing to package the clobetasol propionate formulation developed by Lupin into a metered-dose container closure system.

Mylan is requesting a waiver of the need for dermal safety studies, because the lotion has the same formulation and differs from the generic version only in terms of the delivery device, which is a metered-dose pump. We are in agreement that separate dermal safety studies are not needed to support approval of a new container closure system.

The labeling was reviewed from the clinical perspective.

8. Advisory Committee Meeting and Other External Consultations

Not applicable.

9. Pediatrics

The addition of a new container closure system is not sufficient to trigger the Pediatric Research Equity Act. Pediatric labeling will rely on the successful bridge established between Clobex Lotion and the generic clobetasol lotion approved under ANDA 209147.

10. Labeling Recommendations

10.1. Prescribing Information

The tradename "(b) (4)" has been determined to be unacceptable because of the potential to overstate the efficacy of the drug. The new tradname "Impeklo" is under review.

Nonclinical pharmacology/toxicology labeling is presented in Section 18.3. Laurie Buonaccorsi, Regulatory Review Officer, from the Office of Prescription Drug Promotion (OPDP) provided comments regarding the PI (Review dated 3/19/2020).

No clinical data has been submitted for this application. The proposed labeling relies on approved labeling from Clobex Lotion which is also the same labeling for this drug product that was approved as bioequivalent under ANDA 209147 on September 22, 2017. The Applicant's proposed labeling differs from the labeling of the listed drug in aspects related to the novel pump container. There are also proposed changes to content and format for compliance with the Pregnancy and Lactaion Labeling Rule (PLLR). The proposed labeling maintains the indication for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, in patients 18 years of age or older. In the absence of clinical trial information, there does not appear to be a path forward for modifying the indication in labeling.

The labeling was reviewed from a clinical perspective as to the impact of administering a dose by pump actuation. Each actuation is expected to deliver 0.30 g of lotion based on the average amount delivered. However, it has been demonstrated that the pump may dispense up to 0.4 g of lotion per actuation. The Applicant is proposing to supply 68g of lotion per bottle.

Clobetasol propionate is a well characterized Class I steroid that has the potential for HPA axis suppression at high doses and/or prolonged use. Clobex Lotion labeling restricts dosing to no more than 50 g per week. The Applicant proposes to address the dose restriction with the following:

> *Do not use more than (b) (4) pump actuations per application or (b) (4) pump actuations per day.*

As proposed, the maximum weekly dose ((b) (4) actuations; (b) (4) actuations per day × 7 days) equates to (b) (4) g of lotion per week based on the average amount delivered. This amount is (b) (4) g higher than the maximum weekly dose for the listed drug, Clobex Lotion. However, maximum delivery of the pump has potential to deliver (b) (4) g out of the available 68 g of lotion, exceeding the maximum weekly dose by (b) (4) g.

A dose that exceeds the weekly limitation by (b) (4) g of lotion ((b) (4) mg of clobetasol propionate) is unlikely to have a clinically meaningful effect on drug safety. A dose that exceeds the weekly limitation by (b) (4) g may increase the risk of HPA axis suppression. The proposed labeling, limiting the dose to (b) (4) acuations per application, does not adequately address the weekly dose restriction.

The applicant has been asked to address the dose limitation in labeling. Labeling negotiations were pending as this review closed. A path forward may be to limit the dosage to 9-12 actuations per application. A dose of 9 actuations of maximum delivery equates to 50.4 g of lotion while 12 actuations of average delivery would deliver 50.4 g of lotion per week.

10.2. Patient Labeling

The applicant submitted a Patient Package Insert (PPI) and Instructions for Use (IFU). Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments jointly on patient labeling. Refer to the Patient Labeling Review by Susan Redwood, MPH, BSN, RN (dated 3/23/2020) Labeling negotiations were pending as this review closed.

11. Risk Evaluation and Mitigation Strategies

Routine pharmacovigilance and product labelling are recommended as methods for postmarket risk evaluation and mitigation.

12. Postmarketing Requirements and Commitment

No postmarketing requirements or commitments are recommended.

13. Division Director (DHOT) Comments

Not applicable.

14. Division Director (OCP) Comments

Not applicable.

15. Division Director (OB) Comments

Not applicable.

16. Division Director (Clinical) Comments

Not applicable.

17. Office Director (or Designated Signatory Authority) Comments

Not applicable.

18. Appendices

18.1. References

A literature review was not conducted for this application.

18.2. Financial Disclosure

Not applicable. No clinical studies were submitted for this application.

18.3. Nonclinical Pharmacology/Toxicology

18.3.1. Nonclinical Labeling

The recommended changes to the nonclinical information in Sections 8.1, 8.3, 12.1, and 13.1 of the Applicant's proposed labeling are provided below. The Applicant's proposed labeling is largely adapted from that of the listed drug. Notable changes to the nonclinical labeling made by the Applicant include the deletion of prenatal and postnatal development information that was present in the listed drug label and the addition of embryo-fetal development information from the labeling of Olux (clobetasol propionate) Foam, 0.05%. Reviewer-recommended deletions and additions are indicated by ~~struckthrough~~ and underlined text, respectively.

The pharmacologic class for clobetasol propionate lotion is corticosteroid, which is provided in the Highlights of Prescribing Information, Indications and Usage section of the label.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data for the use of Impeklo ~~on clobetasol propionate use in~~during pregnancy~~t~~ ~~women~~ to inform ~~of~~ any drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes~~for adverse developmental outcomes~~.

Published data report a significantly increased risk of low birthweight with the use of greater than 300 grams of a potent or very potent topical corticosteroid during a pregnancy. Advise pregnant women of the potential risk to a fetus and to use [redacted] (b) (4) Impeklo on the smallest area of skin and for the shortest duration possible (see *Data*). In animal reproduction studies, increased malformations, such as cleft palate and skeletal abnormalities, were observed after subcutaneous administration of clobetasol propionate to pregnant mice and rabbits during the period of organogenesis. The available data do not support relevant comparisons of systemic clobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of Impeklo.~~No comparison of animal exposure with human exposure was computed.~~

Data

Animal Data

~~Embryo-fetal development studies conducted with clobetasol propionate in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and malformations at all dose levels tested down to 0.03 mg/kg. Malformations seen included cleft palate and skeletal abnormalities.~~

In embryo-fetal development studies in mice, subcutaneous administration of clobetasol propionate during the period of organogenesis resulted in malformations at all dose levels, which ranged from 0.03 to 1 mg/kg. The malformations included cleft palate and skeletal abnormalities; fetotoxicity was observed at the high dose (1 mg/kg).

In an embryo-fetal development study in rabbits, subcutaneous administration of clobetasol propionate during the period of organogenesis resulted in malformations at doses of 0.003 and 0.01 mg/kg. The malformations ~~seen~~ included cleft palate, cranioschisis, and other skeletal abnormalities.

In a prenatal and postnatal development study in rats, clobetasol propionate was administered subcutaneously to female rats twice daily (0, 12.5, 25, and 50 µg/kg/day) from gestation day 7 through lactation day 25. In dams, body weight gain and food consumption were reduced during gestation at all doses and prolonged delivery occurred at the high dose. A maternal no-observed-effect level (NOEL) could not be determined and the reproductive NOEL for dams was 25 µg/kg/day. In offspring, doses ≥25 µg/kg/day increased the incidence of stillbirths, reduced pup body weight on lactation days 1 and 7, increased pup mortality, increased the incidence of umbilical hernia, increased the incidence of cysts on the kidney, and significantly reduced the epididymides and testes weights. However, no effects were observed on the mating and fertility of the offspring. The no-observed-adverse-effect level for viability and growth in the offspring was 12.5 µg/kg/day.

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in corticosteroid-responsive dermatoses is unknown.~~Like other topical corticosteroids~~ (b) (4) ~~lotion has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids in general is unclear. However, corticosteroids are thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor,~~

~~arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.~~

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

~~Clobetasol propionate was not carcinogenic to rats when topically applied for 2 years at concentrations up to 0.005% which corresponded to doses up to 11 µg/kg/day (ratio of animal dose to proposed human dose of 0.03 on a mg/m²/day basis).~~
In a 2-year carcinogenicity study, clobetasol propionate was topically applied to rats at concentrations up to 0.005%. No drug-related increase in tumor incidence was observed.

~~Clobetasol propionate at concentrations up to 0.001% did not increase the rate of formation of ultra violet light-induced skin tumors when topically applied to hairless mice 5 days per week for a period of 40 weeks.~~

Clobetasol propionate was negative in the ~~*in vitro*~~in vitro mammalian chromosomal aberration test and in the ~~*in vivo*~~in vivo mammalian erythrocyte micronucleus test.

~~The effect of subcutaneously administered clobetasol propionate on fertility and general reproductive toxicity was studied in rats at doses of 0, 12.5, 25, and 50 µg/kg/day. Males were treated beginning 70 days before mating and females beginning 15 days before mating through day 7 of gestation. A dosage level of less than 12.5 µg/kg/day clobetasol propionate was considered to be the no-observed-effect-level (NOEL) for paternal and maternal general toxicity based on decreased weight gain and for male reproductive toxicity based on increased weights of the seminal vesicles. The female reproductive NOEL was 12.5 µg/kg/day (ratio of animal dose to proposed human dose of 0.03 on a mg/m²/day basis) based on reduction in the numbers of estrous cycles during the pre-cohabitation period and an increase in the number of nonviable embryos at higher doses.~~
In a fertility and reproductive toxicity study, clobetasol propionate was administered subcutaneously to rats at doses of 0, 12.5, 25, and 50 µg/kg/day. Males were treated beginning 70 days before mating and females beginning 15 days before mating through day 7 of gestation. A NOEL could not be determined for paternal and maternal toxicity or male reproductive toxicity because of decreased weight gain in both sexes and an increased seminal vesicle weight in males. The female reproductive NOEL was 12.5 µg/kg/day; higher doses reduced the number of estrous cycles during the pre-cohabitation period and increased the number of nonviable embryos.

The revised nonclinical sections are presented as clean-copy text below:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data for the use of Impeklo during pregnancy to inform any drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Published data report a significantly increased risk of low birthweight with the use of greater than 300 grams of potent or very potent topical corticosteroid during a pregnancy. Advise pregnant women of the potential risk to a fetus and to use Impeklo on the smallest area of skin and for the shortest duration possible (see *Data*). In animal reproduction studies, increased malformations, such as cleft palate and skeletal abnormalities, were observed after subcutaneous administration of clobetasol propionate to pregnant mice and rabbits during the period of organogenesis. The available data do not support relevant comparisons of systemic clobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of Impeklo.

Data

Animal Data

In embryo-fetal development studies in mice, subcutaneous administration of clobetasol propionate during the period of organogenesis resulted in malformations at all dose levels, which ranged from 0.03 to 1 mg/kg. The malformations included cleft palate and skeletal abnormalities; fetotoxicity was observed at the high dose (1 mg/kg).

In an embryo-fetal development study in rabbits, subcutaneous administration of clobetasol propionate during the period of organogenesis resulted in malformations at doses of 0.003 and 0.01 mg/kg. The malformations included cleft palate, cranioschisis, and other skeletal abnormalities.

In a prenatal and postnatal development study in rats, clobetasol propionate was administered subcutaneously to female rats twice daily (0, 12.5, 25, and 50 µg/kg/day) from gestation day 7 through lactation day 25. In dams, body weight gain and food consumption were reduced during gestation at all doses and prolonged delivery occurred at the high dose. A maternal no-observed-effect level (NOEL) could not be determined and the reproductive NOEL for dams was 25 µg/kg/day. In offspring, doses ≥25 µg/kg/day increased the incidence of stillbirths, reduced pup body weight on lactation days 1 and 7, increased pup mortality, increased the incidence of umbilical hernia, increased the incidence of cysts on the kidney, and significantly reduced epididymides and testes weights. However, no effects were observed on the mating and fertility of the offspring. The no-observed-adverse-effect level for viability and growth in the offspring was 12.5 µg/kg/day.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in corticosteroid-responsive dermatoses is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, clobetasol propionate was topically applied to rats at concentrations up to 0.005%. No drug-related increase in tumor incidence was observed.

Clobetasol propionate was negative in the in vitro mammalian chromosomal aberration test and in the in vivo mammalian erythrocyte micronucleus test.

In a fertility and reproductive toxicity study, clobetasol propionate was administered subcutaneously to rats at doses of 0, 12.5, 25, and 50 µg/kg/day. Males were treated beginning 70 days before mating and females beginning 15 days before mating through day 7 of gestation. A NOEL could not be determined for paternal and maternal toxicity or male reproductive toxicity because of decreased weight gain in both sexes and an increased seminal vesicle weight in males. The female reproductive NOEL was 12.5 µg/kg/day; higher doses reduced the number of estrous cycles during the pre-cohabitation period and increased the number of nonviable embryos.

18.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

The BE review for ANDA 209147:

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	209147	
Drug Product Name	Clobetasol Propionate Lotion	
Strength(s)	0.05% w/w	
Applicant Name	Lupin Limited	
Applicant's Address	Lupin Limited, Off Western Express Highway, 3rd Floor, Kalpataru Inspire, Santacruz (East) Mumbai, Maharashtra, India 400055	
US agent's Name and mailing address	Sudhir Kaushal, Director-Regulatory Affairs, Lupin Pharmaceuticals, Inc., 111 South Calvert Street, Harborplace Tower, 24th Floor, Baltimore, Maryland 21202	
US agent's Telephone Number	410-576-2000 (Extn.: 2338)	
US agent's Fax Number	410-576-2221	
Original Submission Date(s)	04/11/2016 (Refuse to Receive) 05/31/2016 (Resubmission after RTR)	
Submission Date(s) of Amendment(s) Under Review	N/A	
First Generic	☐ YES ☒ NO	
Primary Reviewer	Manjinder Kaur, Ph.D.	
Secondary Reviewer	Suman Dandamudi, Ph.D.	
Tertiary Reviewer	Ke Ren, Ph.D.	
Study Number (s)	11446625	11446626
Study Type (s)	Pilot Dose Duration-Response Relationship Study (un-occluded)	Pivotal Bioequivalence Study (un-occluded)
Strength (s)	0.05%	0.05%
Clinical Site	Novum Pharmaceutical Research Services	
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104, USA	
OSIS INSPECTION RESULT	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A**	**Post October 1, 2014 ANDAs** ☒ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**
Waiver/Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☒ **N/A**	
QC Dissolution	☐ **Pending** ☐ **Adequate** ☐ **Inadequate** ☒ **N/A**	
Formulation	☒ **Adequate** ☐ **Inadequate**	
Will Response to CR Result in	☐ **Possibly** ☐ **No** ☒ **N/A**	

a Reformulation?			
Deficiency Classification	☐ **Major** ☐ **Minor** **IR Eligible?** ☐ **Yes** ☐ **No** ☒ **N/A**		
Overall Review Result	☒ **Adequate** ☐ **Inadequate**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**Pilot Dose Duration-Response Relationship Study**	**0.05%**	☒ **Adequate** ☐ **Inadequate**
1, 2	**Pivotal Bioequivalence Study**	**0.05%**	☒ **Adequate** ☐ **Inadequate**

1 EXECUTIVE SUMMARY

To establish bioequivalence (BE), Lupin Limited conducted a pivotal BE study comparing its test product, Clobetasol Propionate Lotion, 0.05%, to the corresponding reference listed drug (RLD) product, Clobex® (clobetasol propionate) Lotion, 0.05 % (NDA 021535, approved on July 24, 2003). To establish dosing duration time for the pivotal study, the firm first conducted a pilot dose duration-response study (Study No. 11446625) on the RLD product. The pilot dose duration-response study (Study No. 11446625) was designed as an open-label, single exposure non-occluded study on healthy adult (male and female) subjects (N = 24). The pivotal pharmacodynamics BE study (Study No. 11446626) was designed as an open-label, one period, two-treatment, randomized, and non-occluded study on healthy adult (male and female) subjects (N = 88 completed; 63 qualified).

For the pilot-dose duration response study (Study No. 11446625), based on the population fitting of the Chroma Meter dose-response data for 24 subjects, the ED_{50} and Emax values calculated by the reviewer and the firm are as shown in the following table:

Clobetasol Lotion, 0.05% Dose: [10 µL per site – Non Occluded] Pharmacodynamic Parameters, Half-Maximal Dose and Maximal Effect		
Dose Duration-Response Study (Study No. 11446625); N=24		
	ED_{50} (minutes)	**Emax (a scale units*min)**
Calculated by the Firm (Using P-Pharm software): Log Normal Distribution Assumption for ED50	12.44	45.50
Calculated by the Reviewer (Naïve Pooled and Population Fit with Naïve Pooled Method)	10.74	42.43

The reviewer's data fitting results obtained using both naïve pooled and population fit methods are similar to the firm's results in case of both ED50 and Emax values.

For the pivotal pharmacodynamics BE study No. 11446626, the firm used the D_1, ED_{50} and D_2[1] values of 6, 12 and 24 minutes, respectively. The selections of these values are acceptable. The data for 63 of the 88 subjects (71.6%) who completed the study met the $D_2/D_1 \geq 1.25$ criterion,[2] and the data for 36 out of 88 subjects (41%) met the more stringent $D_2/D_1 \geq 2.0$ criterion. These rates of qualified detectors are acceptable and demonstrate a good determination of ED50 through the pilot study. Using Locke's Method, statistical analysis of the data for the subjects who qualified as detectors resulted in the following point estimates and 90% confidence intervals for $AUEC_{0\text{-}24h}$ as shown in the below table.

Clobetasol Lotion, 0.05% Dose: [10 µL per site – Non Occluded] Pharmacodynamic Parameters, Area Under the Effective-Dose Curve, Point Estimates and 90% Confidence Intervals (Locke's Method)					
Pivotal (Vasoconstrictor Assay) Study (Study No. 11446626)					
	Number of Subjects[3]	**$AUEC_{(0.5\text{-}24h)}$***		**Point Estimate**	**90% CI**
		Test	**Reference**		
Calculated by the Firm	63	22.6567	21.9686	103.13%	97.34 – 109.23
Calculated by the Reviewer ($D_2/D_1 \geq$ 1.25)	63	-22.66	-21.97	103.1%	97.34 – 109.23
Calculated by the Reviewer ($D_2/D_1 \geq 2.0$)	36	-19.87	-19.49	102.0%	93.21-111.13

*: The firm calculated AUEC from time 0.5h-24h instead of $AUEC_{(0\text{-}24h)}$, this AUEC calculation is not expected to impact the study outcomes in the current submission. Please see section 4.1.1.3, Comments on Statistical Analysis, for more details.
**: The firm calculated negative AUEC whereas the reviewer calculated AUEC.

[1] Acronyms: Emax: Maximum vasoconstrictor response, a scale units x min
ED50: Half of the maximal vasoconstrictor response, min.
D1: Shorter dose duration calibrator, min, 0.5 x ED50.
D2: Longer dose duration calibrator, min, 2.0 x ED50

[2] As per the FDA Guidance to Industry: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence (Issued 6/2/1996, Posted 3/6/1998)

[3] Number of subjects who meet the criterion of the D2 response/D1 response ≥ 1.25, or ≥ 2.0

Statistical analysis of the data for subjects who met the D2/D1 ≥ 1.25 criterion resulted in the point estimate of approximately 1.03 and 90% confidence intervals (CIs) for $AUEC_{0.5\text{-}24h}$ of 97.34 – 109.23%.

Office of Study Integrity and Surveillance (OSIS) Inspection Status: Since the current ANDA has been submitted in GDUFA year 4, the final inspection status of clinical and analytical sites will be determined by OSIS. Per GDRP, the OSIS inspection status of the current ANDA is "new".

The BE portion of the application is **adequate.**

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[4]

Test Product	Clobetasol Propionate Lotion, 0.05%
Reference Product	Clobex® (clobetasol propionate) Lotion, 0.05%
RLD Manufacturer	Galderma Laboratories L P
NDA No.	021535
RLD Approval Date	July 24, 2003
Indication	Clobex® Lotion is a corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, in patients 18 years of age or older
Potency[5]	Super High Potency

3.2 PK/PD Information[6, 7]

Pharmacokinetics	The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier and occlusion. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and other disease processes in the skin may increase percutaneous absorption. There are no human data regarding the distribution of corticosteroids to body organs following topical application. Nevertheless, once absorbed through the skin, topical corticosteroids are handled through metabolic pathways similar to systemically administered corticosteroids. They are metabolized, primarily in the liver, and are then excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

Dosage and Administration	CLOBEX Lotion, 0.05% should be applied to the affected skin areas twice daily and rubbed in gently and completely. The total dosage should not exceed 50 g (50 mL or 1.75 fl. oz.) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. CLOBEX Lotion, 0.05% contains a super-high topical corticosteroid; therefore treatment should be limited to 2 consecutive weeks. For

[4] Electronic Orange Book, search "Clobex". http://www.accessdata fda.gov/scripts/cder/ob/default.cfm, Last accessed 11/07/2016.
[5] https://dailymed nlm nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=82868
[6] Drugs@FDA, Search: Clobex; http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021535Orig1s003,%20021644Orig1s003lbl.pdf

[7] http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=1264&n=Clobetasol&t=0&enh=1. Last accessed 11/21/2016.

	moderate to severe plaque psoriasis, treatment may be extended for additional 2 weeks for localized lesions (less than 10% body surface area) that have not sufficiently improved. Total dosage should not exceed 50g (50 mL or 1.75 fl.oz.) per week
Occlusion/Non-Occlusion	**Non-Occlusion** of application sites. RLD labeling states ***Do not bandage, cover or wrap your treated areas unless your doctor tells you to.***
ED_{50} (as measured by other in-house ANDAs) **(See details on next page)**	See table below
Drug Specific Issues (if any)	**Warnings and Precautions** Clobetasol propionate is a highly potent topical corticosteroid that has been shown to suppress the hypothalamic-pituitary- adrenal (HPA) axis at the lowest doses tested. Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can also result from systemic absorption of topical corticosteroids. Systemic absorption may require periodic evaluation for HPA axis suppression. Modify use if HPA axis suppression develops. Children may be more susceptible to systemic toxicity from use of topical corticosteroids. Local adverse reactions with topical corticosteroids may occur more frequently with the use of occlusive dressings and higher potency corticosteroids, including clobetasol propionate. These reactions include: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae and miliaria.

ANDA	Firm	Strength	Occluded/ Non-occluded	Dose duration time	ED_{50}-Firm (min)	ED_{50}-Reveiwer (min)	ED_{50}-used in the pivotal study (min)	Study Outcome/ DB decision
205249*	ZYDUS PHARMACEUTICALS USA INC	Lotion, 0.05%	Non-occluded	within 15 minutes, 2, 4, 6, 8, 10, 12, 20, and 24 hours	14.21[8]	17.76[9]	14	BE Inadequate
200302	TARO PHARMACEUTICALS USA INC	Lotion, 0.05%	Non-occluded	10, 20, 40, 60, 90, 120, 240, and 300 minutes	12.88[10]	12.91	14	Approved
078223	ACTAVIS MID ATLANTIC LLC	Lotion, 0.05%	Non-occluded	**0.5, 1, 3, 6,** 12, 30, 60, 90 and 120 minutes	8.5[11]	7.6	6[12]	Approved
208667	TELIGENT PHARMA, INC. (formerly IGI Labs, Inc.)[13]	Lotion, 0.05%	Non-occluded	**1, 3, 6,** 12, 30 minutes, 1, 2, 3, and 4 hours	6.0[14]	6.11	6.0	Adequate

ED_{50} (as measured by other in-house ANDAs)

Reviewer's Comments:

The ED50, as determined in other ANDAs for the same drug, was ranging from 6.11 to 17.76 minutes.

The dose duration times for the current application were **1, 3, 6, 12**, 30 minutes, 1, 2, 3, and 4 hours. There are 4 dose-duration time points prior to 17 minutes for the current pilot study.

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[8] DARRTS, ANDA 205249 EDR 1, Dated: 12/31/2012, Module 5.3.1.2
[9] GDRP for ANDA 205249: http://panorama fda.gov/task/view?ID=542103e400157d8bf43352ffe308a971 by Xuefang Bai, Date Uploaded Jan 27, 2017
[10] DARRTS ANDA 200302 REV-BIOEQ-01 (General Review), Bruce J Lerman, Completed: 02/01/2011.
[11] As provided in bio-summary table #1 for ANDA 078223 (SD #1 dated 3/24/2006)
[12] DARRTS ANDA 078223 REV-BIOEQ-01(General Review), dated 02/15/2007
[13] Effective October 23, 2015, IGI Labs, Inc. has changed its company name to Teligent Pharma, Inc.
[14] DARRTS ANDA 208667-ORIG-1, Bioequivalence Discipline Review, Yoriko Harigaya, Completed : 06/16/2016.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, Pilot and Pivotal

1.	**Type of study:**	Vasoconstrictor Study
	Design:	Pilot dose duration-response study under un-occluded conditions.
	Strength:	0.05%
	Subjects:	Healthy males and nonpregnant females (non-pregnant, non-lactating), general population.
	Additional Comments:	Please refer to the guidance, "Topical Dermatological Corticosteroids: In Vivo Bioequivalence," available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070234.pdf

2.	**Type of study:**	Vasoconstrictor Study
	Design:	Pivotal in vivo bioequivalence study under un-occluded conditions.
	Strength:	0.05%
	Subjects:	Healthy males and females (non-pregnant, non-lactating), general population.
	Additional Comments:	Please see comment above.

Pharmacodynamic Measurement	Skin blanching assay (Clobetasol propionate)
Bioequivalence based on (90% CI):	Pivotal vasoconstrictor assay study (Ratio of the mean test and RLD AUEC 0-24h values using Locke's Method)
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	Draft Guidance on Clobetasol Propionate Lotion (Recommended Apr 2016) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM494860.pdf
Summary of OGD or DB History	There are few ANDAs in DARRTS[15] (2 Approved, 2 Pending): Approvals: ANDA 078223 (Actavis Mid Atlantic LLC, approved on 12/04/2008) ANDA 200302 (Taro Pharmaceuticals USA INC, approved on 07/02/2012) Previously Reviewed ANDAs: Yes, ANDA 208667, 205249 There are **control** documents on this product[16]. Yes, There are **protocols** listed in the OGD database for Clobetasol Propionate Lotion[17].

[15] DARRTS, search Clobetasol Propionate Lotion Last accessed 11/07/2016.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Vasoconstrictor Pilot Study	Yes	1
Vasoconstrictor Pivotal Study	Yes	1
Waiver requests	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	

[16] Mercado, Search Clobetasol Propionate Lotion. Last accessed 11/07/2016.
[17] OGD-DB Protocols Tracking Database: Search Clobetasol. Last accessed 11/07/2016.

3.5 Method Validation of Dermal Assessments

Number of Operators	4 for pilot study and 5 for pivotal study
Number of Application Sites	**4 Sites**
Chroma Meter Used	Minolta Model CR-300 (1 for pilot study (RE# 02014 and IC# 291) and 1 for pivotal study (RE# 02015 and IC# 292)
Between Subject Precision Range (%CV)*	14.29% (Pilot) and 4.94% (Pivotal)
Between Site Precision Range (%CV)	7.87% (Pilot) - 3.56% (Pivotal)
Within Site Precision Range (%CV)	3.11-7.47% (Pilot) and 2.08% - 4.01% (Pivotal)
Between Operators Precision Range (%CV)	**9.07% (Pilot)-3.58% (Pivotal)**
Between Instrument Precision Range (%CV)	6.08% (Pilot)-6.82% (Pivotal)
Within Instrument Precision Range (%CV)	5.21% - 8.20% (Pilot) and 1.49% - 3.19% (Pivotal)
Mean Difference vs. Trainer (%CV) ≤ 10% (Y/N)	**Yes**
Method acceptable	**Yes**

* The higher between-subject precision may not solely reflect the precision of the method as it could also be affected by between subject variability.

Table 1. Intra-ChromaMeter and Inter-ChromaMeter Validation

Pilot Dose Duration-Response Study (11446625)

Reading	Chroma Meter 1 #291	Chroma Meter 2 #02014
Date of testing	**11/16/2015**	**11/16/2015**
Replicate 1	(b) (4)	
Replicate 2		
Replicate 3		
Replicate 4		
Replicate 5		
Replicate 6		
Mean	6.97	7.60
% CV	8.20	5.21
Inter-Chroma Meter, Mean	7.29	
Inter-Chroma Meter, % CV	6.08	

Pivotal Bioequivalence Study (11446626)

Reading	Chroma Meter 1 #02015	Chroma Meter 2 #292
Date of testing	**12/14/2015**	**12/14/2015**
Replicate 1	(b) (4)	
Replicate 2		
Replicate 3		
Replicate 4		
Replicate 5		
Replicate 6		
Mean	10.50	9.54
% CV	3.19	1.49
Inter-Chroma Meter, Mean	10.02	
Inter-Chroma Meter, % CV	6.82	

Table 2. Intra- and Inter-site Validation

The firm conducted skin site validation at 4 different sites (one Chroma Meter, one subject and one operator). Submitted data are shown in tables below. The intra- and inter-site precision values (%CV) are both <10. Therefore, the inter-site and intra-site validations are acceptable.

Pilot Dose Duration-Response Study (Study No. 11446625)

Reading	Site 1	Site 2	Site 3	Site 4
Date of testing	11/16/2015	11/16/2015	11/16/2015	11/16/2015
Replicate 1	(b) (4)			
Replicate 2				
Replicate 3				
Replicate 4				
Mean	6.32	5.57	5.66	5.26
% CV	3.11	3.66	3.22	7.47
Inter-Site, Mean	5.70			
Inter-Site, % CV	7.87			

Pivotal Bioequivalence Study (Study No. 11446626)

Reading	Site 1	Site 2	Site 3	Site 4
Date of testing	12/14/2015	12/14/2015	12/14/2015	12/14/2015
Replicate 1	(b) (4)			
Replicate 2				
Replicate 3				
Replicate 4				
Mean	10.28	10.04	10.23	10.89
% CV	3.24	2.99	4.01	2.08
Inter-Site, Mean	10.36			
Inter-Site, % CV	3.56			

Table 3. Intra-Subject and Inter-Subject Validation

Pilot Dose Duration-Response Study (Study No. 11446625)

	Subject	Subject	Subject	Subject
	(b) (6)			
Date of testing	11/16/2015	11/16/2015	11/16/2015	11/16/2015
Site 1	(b) (4)			
Site2				
Site 3				
Site 4				
Mean	5.84	6.78	8.09	7.76
% CV	8.85	12.90	12.93	5.94
Inter-Subject, Mean	7.12			
Inter-Subject, % CV	14.29			

Pivotal Bioequivalence Study (Study No. 11446626)

	Subject	Subject	Subject	Subject
	(b) (6)			
Date of testing	12/14/2015	12/14/2015	12/14/2015	12/14/2015
Site 1	(b) (4)			
Site 2				
Site 3				
Site 4				
Mean	10.14	10.80	11.18	10.12
% CV	3.54	2.77	2.99	8.80
Inter-Subject, Mean	10.56			
Inter-Subject, % CV	4.94			

Table 2. Operator Validation

Operator Validation - Dose Duration-Response Study (Study No. 11446625)

	Operator 1	Operator 2	Operator 3	Operator 4
Date of testing	11/16/2015	11/16/2015	11/16/2015	11/16/2015
Replicate 1	(b) (4)			
Replicate 2				
Replicate 3				
Replicate 4				
Mean	6.32	5.20	5.30	5.66
% CV	3.11	6.99	7.21	1.81
Inter- Operator, Mean	5.62			
Inter- Operator, % CV	9.07			

Operator Validation - Pivotal Bioequivalence Study (Study No. 11446626)

	Operator 1	Operator 2	Operator 3	Operator 4	Operator 5	Operator 6
Date of testing	12/14/2015	12/14/2015	12/14/2015	12/14/2015	12/14/2015	12/14/2015
Replicate 1	(b) (4)					
Replicate 2						
Replicate 3						
Replicate 4						
Mean	10.28	10.91	10.67	11.18	10.33	10.28
% CV	3.24	0.79	0.45	0.89	0.37	0.44
Inter- Operator, Mean	10.61					
Inter- Operator, % CV	3.58					

Table 3. Additional Method Validation Information for Dermal Assessments

	Title	Effective Date
Does the firm submit its standard operating procedures?	(b) (4) (SOP No. (b) (4)	(b) (4)
Is the method validation acceptable?	Yes	

Comments on Method Validation of Dermal Assessments:

- The Chroma Meter validation was conducted by (b) (4) using all of the Chroma Meters assigned to the study.
- Method validation was conducted on 4 subjects to assess reproducibility and precision of the test facility's technique and instrumentation.
- The firm submitted Chroma Meter validation reports. Overall intra-site, inter-site and inter Chroma Meter CV were ≤10%. The inter subject %CV was as high as 14.29% as high variability in Chroma Meter readings is expected between the subjects[18].

The firm's method validation is **adequate.**

[18] \\cdsesub1\evsprod\anda209147\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\11446625\dr-report-body.pdf (APPENDIX 16.1.10).

3.6 Pharmacodynamics Bioequivalence Studies

Table 4A. Summary of the Pilot Study

Study Ref. No.	Study Objective	Study Design	Treatment(s) (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameters		Study Report Location
					E_{max}	ED_{50} (minutes)	
11446625	Dose Response Study of CLOBEX® (clobetasol propionate) Lotion, 0.05%	One Period, Dose Duration-Response Study	**Reference Product:** CLOBEX® (clobetasol propionate) Lotion, 0.05% Marketed by: Galderma Laboratories, L.P. Manufactured by: DPT Laboratories, Ltd. Lot No.: FMER Expiration Date: 10/16 Dose: Nine (9) 10 µL applications of CLOBEX® (clobetasol propionate) Lotion, 0.05% on each forearm. Route: Topical	24 subjects completed the study (12 M/12 F) Healthy subjects Age: 27.88 ± 13.50 Range: 18 - 59	41.10 ± 14.29 (34.77)	11.44 ± 9.68 (84.61)	Module 5.3.1.2

Table 5B. Summary of the Pivotal Study

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameter	Study Report Location
					Negative $AUEC_{0.5\text{-}24hr}$ (n= 63)	
11446626	Bioequivalence Study of Clobetasol Propionate Lotion, 0.05%	One-Period, Two-Treatment, Randomized, Vasoconstrictor Study	**Test Product :** Clobetasol Propionate Lotion 0.05%; Manufactured for: Lupin Pharmaceuticals, Inc. Manufactured by: Lupin Limited Batch Number: K590079 Manufacture Date: Sep. 2015 Expiration Date: 08/2017 Dose: Three (3) 10 µL applications of Clobetasol Propionate Lotion 0.05% on each forearm. Route: Topical	63 Qualifiers (12 M, 51 F) Healthy subjects Age: 31.70 ± 13.86 Range: 18 - 64	22.6567	Module 5.3.1.2
			Reference Product: CLOBEX® (clobetasol propionate) Lotion 0.05% Marketed by: Galderma Laboratories, L.P. Manufactured by: DPT Laboratories, Ltd. Lot No.: FMER Expiration Date: 10/16 Dose: Five (5) 10 µL applications of CLOBEX® (clobetasol propionate) Lotion 0.05% on each forearm. Route: Topical		21.9686	

Table 6. Statistical Summary of the Pilot Dose Duration-Response Study

Clobetasol Lotion, 0.05% Dose: 10 µL per site – Non-Occluded Pharmacodynamic Parameters, Half-Maximal Dose and Maximal Effect Dose Duration-Response Study No. 11446625			
	Distribution Assumption	**ED_{50} (minutes)**	**Emax (a scale units*min)**
Calculated by the Firm (Using P-Pharm software)*	ED_{50} and E_{max} Normal	11.44	41.10
Calculated by the Firm (Using P-Pharm software)*	ED_{50} Log Normal and E_{max} Normal	12.44	45.50
Calculated by the Reviewer (Using Phoenix Software)	i) Normal for ED50 and Emax residuals ii) ED_{50} Log Normal and E_{max} Normal (Population fit model with Naïve pool method)	10.74	42.43

* The model that best fits the data is assuming ED50 log-normal distribution.

Table 7. Statistical Summary of the Pivotal Pharmacodynamic Bioequivalence Study

Name of Drug Product : Clobetasol Propionate Lotion 0.05% Dose: [10 µL per site – Non Occluded, 12 minutes(ED50)] Pharmacodynamic Parameters, Area Under the Effective-Dose Curve, Point Estimates and 90% Confidence Intervals (Locke's Method)					
Pivotal (Vasoconstrictor Study), Study No. 11446626*					
	Number of Subjects[19]	**$AUEC_{(0.5\text{-}24h)}$***		**Point Estimate**	**90% CI (%)**
		Test	**Reference**		
Calculated by the Firm	63	22.6567	21.9686	103.13	97.34 – 109.23
Calculated by the Reviewer ($D_2/D_1 \geq 1.25$)	63	-22.66	-21.97	103.6%	97.34 – 109.23
Calculated by the Reviewer ($D_2/D_1 \geq 2.0$)	36	-19.87	-19.49	102.0%	93.21-111.13

*: The firm calculated AUEC from 0.5h-24h.
Statistical analysis was carried out using Locke's method to determine bioequivalence of the formulations using data for "Detectors" only.
**: The firm calculated negative AUEC whereas the reviewer calculated AUEC.

[19] Number of subjects who meet the criterion of the D2 response/D1 response ≥ 1.25

Reviewer Comments:

Pilot Dose Duration-Response Study

1. Twenty four (24) healthy subjects were enrolled and dosed in the study. All 24 subjects completed the study and data of all 24 subjects were used in the statistical analysis.
2. All treated sites, along with the untreated sites were non-occluded following study drug administration (10 µL each site). The labeling of the RLD product indicated that the drug product should be applied under non-occlusive conditions[20].
3. As stated in the firm's study report, the post-dose ChromaMeter a-value reading at each site and assessment time was adjusted for baseline reading and corrected by the untreated site reading. The baseline-adjustment normalized the ChromaMeter readings for variations in skin tone between the different sites on each subject's forearms. To compensate for skin tone changes that occur over time, the mean base-line adjusted value for the untreated sites on each arm was subtracted from the baseline-adjusted ChromaMeter value for each site on the same arm at each assessment time. These "corrected" base-line adjusted ChromaMeter values were used in all subsequent analyses.

4. The firm used a population fitting technique (non-linear mixed effect model with P-Pharm software) to compute the pharmacodynamic (PD) parameters, Emax and ED_{50}, which are provided in Table 7. The ED_{50} determined by the firm is 12.44 minutes computed by P-Pharm assuming log normal distribution fitted data for ED50, which is similar to that computed by the reviewer (10.74 minutes), using naïve pooled method in Phoenix software. Please note that 0.05% Clobetasol Propionate Lotion has been classified as a high potency corticosteroid[21].

5. The firm selected D_1, ED_{50} and D_2 values of 6, 12 and 24 minutes, respectively, to be used in the pivotal PD bioequivalence study to determine "evaluable" subjects[22].

6. Based on the information of ED50 values as determined in other in-house ANDAs (section 3.2), the current ANDA's ED50 estimation is within the range of other in-house ANDAs.

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[20] http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021535Orig1s003,%20021644Orig1s003lbl.pdf; Last accessed November 11, 2016.

[21] https://ainotes.wikispaces.com/file/view/Topical+Steroid+Potency+Charts.pdf

[22] As per the Guidance - "Evaluable" subjects are those individuals whose mean AUEC values at D1 and D2 are both negative and meet the dose-duration response criterion of mean AUEC at D2/ mean AUEC at D1 ≥ 1.25.

Pivotal PD Bioequivalence Study

1. Ninety (90) healthy adult subjects were enrolled and dosed in the study and eighty eight (88) subjects completed the study. The data for sixty three (63) of the subjects were used in the final statistical analysis.

2. The D_1, ED_{50} and D_2 in the study were 6, 12 and 24 minutes, respectively. The treated and untreated sites were non-occluded in the same manner as the in the pilot dose duration-response study.

3. The firm evaluated the dermal assessment data in pivotal PD bioequivalence study in the same manner as reported in the pilot dose duration-response study.

4. Based on the ChromaMeter results, a total of sixty three (63) of the eighty eight (88) subjects as being "evaluable", and thus their data was used in BE statistical evaluations using Locke's Method (t=1.6698 for calculating the confidence intervals, see Table 4. The 90% confidence interval for AUEC0.5-24h comparing the test and RLD product is 97.34 – 109.23%. The reviewer agrees with the firm's results.

5. In addition to the statistical analysis based on the $D_2/D_1 \geq 1.25$ criterion, the reviewer also analyzed data based on a more stringent $D_2/D_1 \geq 2.0$ criterion. Both of the 90% CI results are within the acceptable limit of 80.00-125.00%.

3.7 Formulation

Location in appendix	See, Section 4.2
Is the formulation acceptable?	**ACCEPTABLE**
If not acceptable, why?	--

3.8 Deficiency Comments

None

3.9 Recommendations

1. The Division of Bioequivalence III (DBIII) accepts the pilot dose duration-response study No. 11446625 conducted by Lupin Limited on the reference-listed drug (RLD), Clobex® (clobetasol Propionate) Lotion, 0.05 %, manufactured by Galderma Laboratories, L.P., (Lot No. FMER).

2. The DBIII accepts the pivotal pharmacodynamic bioequivalence study No.11446626 conducted by Lupin Limited comparing its Clobetasol Propionate, 0.05%, Batch No. K490065 to the RLD product, Clobex® (clobetasol) Lotion, 0.05 %, manufactured by Galderma Laboratories, L.P., (Lot No. FMER).

3.10 Comments for Other OGD Disciplines

Discipline	Comment
N/A	--

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Pilot Dose Duration-Response Study

4.1.1.1 Study Design

Table 8 Study Information

Study Number	11446625
Study Title **Clinical Site (Name & Address)**	Dose Response Study of CLOBEX® (clobetasol propionate) Lotion, 0.05% Novum Pharmaceutical Research Services 4801 Amber Valley Parkway Fargo, ND 58104 United States of America (USA)
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	11/21/15
Were the subjects dosed in more than one group?	No
If Yes, specify the screening dates for each group	N/A
If Yes, specify the dosing dates for each group	N/A
If Yes, specify whether the same clinical sites were used for each group	N/A

Table 9. Product Information

Product	**Reference**
Treatment ID	Reference
Product Name	CLOBEX® (clobetasol propionate) Lotion, 0.05%
Manufacturer	Marketed by: Galderma Laboratories, L.P.; Manufactured by: DPT Laboratories, Ltd.
Batch/Lot No.	Lot No.: FMER
Expiration Date	Expiration Date: 10/16
Strength	0.05%
Dosage Form	Lotion
Potency	Assay 100.3%
Homogeneity	NA
Dose Administered	10 µL
Route of Administration	Topical

Table 10. Study Design, Pilot Dose Duration-Response Study

Number of Subjects	Enrolled:	24 (12F+12M)
	Dosed:	24
	Completed:	24
	Analyzed:	24
No. of Periods	1	
No. of Treatments	1	
No. of Groups	1	
Randomization Scheme	DOSE RESPONSE STUDY NO. 11446625 ASSIGNED SITES FOR DURATION OF APPLICATION 240 240 180 180 120 120 60 60 30 30 12 12 6 6 3 3 1 1 RT RT LT LT SUBJECT MIN MIN MIN MIN MIN MIN MIN MIN MIN MIN MIN MIN MIN MIN MIN MIN MIN MIN UNT UNT UNT UNT (b) (6) 	

Preparation of Skin	To ensure the forearm was free of any dirt or particulate matter, the arms of each subject were washed with a mild soap (Liquid Neutrogena® Facial Cleansing Formula) and gently dried at least 30 minutes before baseline ChromaMeter assessments were performed and at least 2 hours before the initial dosing. Eleven (11) sites were designated on the flexor surface of each forearm. An open washer (inside diameter of approximately 1.6 cm) was placed over each of the 11 sites and taped in place on its edges with hypoallergenic tape. Care was taken that sites were not placed within 3 cm of the wrist or antecubital fossa, and the washers were no closer than 2 cm apart, center-to-center. All sites were labeled by number for ease of identification throughout the study (sites 1-11 on the right sites 12-22 on the left arm). Note: All sites were evaluated before dosing for the presence of any skin condition (e.g., coloration, freckles, moles, scratches, etc.) that would interfere with the assessment or response of skin blanching.
Occlusion or Non-Occlusion	Non-Occlusion
Dose Duration Times	1, 3, 6, 12, 30 minutes, 1, 2, 3, and 4 hours (staggered application) prior to simultaneous removal at Time 0 (0.0 hour). In addition, two untreated control sites were designated on each forearm.
Skin Blanching Reading Times	Pre-dose (Before application in duplicate), and at 0.5, 2, 4, 6, 8, 10, 12, 20 and 24 hours (± 5 minutes) after treatment removal.
Application and Removal of Study Drug(s)	**Application of the drug**: Staggered Application (10 µl of CLOBEX ® Lotion) **Removal of the Drug**: The applications at all sites were removed at the same time (Time 0). Drug removal started with the shortest duration application (1 minute). Each treated site was removed by gently wiping with three consecutive cotton balls: 1 damp cotton ball (soaked in a mild, room temperature hypo-allergenic soap solution), 1 damp cotton ball (soaked in room temperature water), and lastly 1 dry cotton ball. The untreated sites were similarly cleaned and wiped at the same time as the treated sites (Time 0). The subjects were dosed on (b) (6) and completed the study about 28
IRB Approval	Yes, approved on 10/27/2015
Informed Consent	Yes, approved on 10/27/2015

Subject Screening	All of the study participants were screened to determine blanching response using a single dose (10 µL) application of Clobex® (clobetasol propionate) lotion. A 10 µl application of the Lotion was applied to the upper arm (above the forearm). The Lotion was left in place for about 2 hours (± 15 minutes) before removal. The Lotion was removed by gently wiping the application site with three consecutive cotton balls: 1 damp cotton ball (soaked in a mild, room temperature hypo-allergenic soap solution), 1 damp cotton ball (soaked in room temperature water), and 1 dry cotton ball. About 6-9 hours after application, the site was visually evaluated for blanching. All subjects were selected based on a demonstrated blanching response (at least 1 on a 0-3 rating scale), and the absence of any clinically significant findings on the medical history or clinical assessment. Selected subjects had no history of allergy or hypersensitivity to any systemic or topical corticosteroid. They had no skin condition or coloration that would interfere with the placement of test sites or the response or assessment of skin blanching.
Length of Confinement	Entire study, > 30 hours (4 hr prior drug application+4 hr application + 24 hr ChromaMeter assessment)
Safety Monitoring	Vital signs were measured at screening, at check-in, and at the discretion of the Investigator. Safety evaluated by collection of adverse events.

Comments on Study Design:

- The study was conducted with all test sites remaining un-occluded during the dose duration period. As per RLD labeling for Clobex® Lotion, the treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician. Therefore, the firm's pilot study design with all sites un-occluded is acceptable.

- Twenty four (24) subjects that met all inclusion and exclusion criteria were enrolled in the study. Data of all 24 subjects were used in the statistical analysis.

- The lotion was applied within the application sites using a calibrated repeating dispenser (Eppendorf). It was evenly spread within the site using a glass rod. All sites were kept non-occluded throughout the study.

- Quantification of skin blanching (assessment period) was obtained by Chroma Meter (Minolta Inc., Model CR-300, IC# 291) during study conduct. The Chroma Meter was programmed to record the a-scale reading.

- The study design is acceptable.

4.1.1.2 Clinical Results

Table 11. Demographics Profile of Subjects Completing the Pilot Dose Duration-Response Study

Study No. 11446625		
		Treatment Groups
		Reference Product N=24
Age[1] (years)	Mean ± SD	27.88 ± 13.50
	Range	18 - 59
Age Groups	< 18	0 (0.00%)
	18 – 40	19 (79.17%)
	41 – 64	5 (20.83%)
	65 – 75	0 (0.00%)
	> 75	0 (0.00%)
Sex	Male	12 (50.00%)
	Female	12 (50.00%)
Hispanic or Latino Race	American Indian or Alaskan Native	0 (0.00%)
	Asian	0 (0.00%)
	Black or African American	0 (0.00%)
	Native Hawaiian or Other Pacific Islander	0 (0.00%)
	White	0 (0.00%)
	Other	0 (0.00%)
Not Hispanic or Latino Race	American Indian or Alaskan Native	0 (0.00%)
	Asian	0 (0.00%)
	Black or African American	0 (0.00%)
	Native Hawaiian or Other Pacific Islander	0 (0.00%)
	White	24 (100.00%)
	Other	0 (0.00%)
BMI (kg/m^2)	Mean ± SD	25.88 ± 3.84
	Range	20.4 – 35.0
Other Factors		
Weight (lb)	Mean ± SD	175.83 ± 32.75
	Range	132 - 229
Tobacco Users[2]	Yes	0 (0.00%)
	No	24 (100.00%)
Fitzpatrick Skin Type	I	0 (0.00%)
	II	9 (37.50%)
	III	15 (62.50%)

[1] Determined at screening.
[2] Defined as current tobacco user (having used tobacco or nicotine-containing products within 30 days before dosing).

Table 12. Dropout Information, Pilot Dose Duration-Response Study

Study No. 11446625				
Subject No.	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
N/A	N/A	N/A	N/A	N/A

Table 13. Study Adverse Events, Pilot Dose Duration-Response Study

Body System/Adverse Event	**Study No. 11446625 Reference Product N = 24 subjects dosed**
	n (%)
No adverse events.	
Total n (%)	**0 (0.00%)**

n = Number of subjects reporting AE
% = (Number of subjects reporting AE / number of subjects dosed with study drug) x 100.
Total n = Number of subjects that reported at least one AE
Total %= (Number of subjects that reported at least one AE / number of subjects dosed with study drug) x 100.

Table 14. Protocol Deviations, Pilot Dose Duration-Response Study

Study No. 11446625	
Type	**Subject #'s**
No protocol deviations.	N/A

Comments on Dropouts/Adverse Events/Protocol Deviations:

There were no dropouts during the pilot study.

There was no adverse event reported during the study conduct. No protocol deviation was reported for the pilot study.

The clinical results are acceptable.

4.1.1.3 Statistical Results

Table 15A. ED_{50} and Emax Values Calculated by the Firm

Model	**Software Used**	**Assumption of Distribution (ED_{50}) (Normal/Log Distribution)**			
Simple EMAX model	PPHARM	Normal Distribution			
Initial Population Parameter Estimates		**Final Population Parameter (Model Derived) Estimates**			
ED_{50}	**E_{max}**	**ED_{50}**	**Emax**	**Maximum Likelihood**	**Akaike Criteria Value**
1	8	10.68	40.75	-839.913	3.907
1	45	10.66	40.74	-839.972	3.907
1	80	10.66	40.74	-839.978	3.907
3	8	10.71	40.75	-839.966	3.907
3	45	10.71	40.76	-839.911	3.907
3	80	10.71	40.76	-839.924	3.907
6	8	10.69	40.73	-839.966	3.907
6	45	10.78	40.80	-840.003	3.907
6	80	10.82	40.82	-839.968	3.907
12	8	10.82	40.75	-840.087	3.908
12	45	11.42	41.08	-839.759	3.906
12	80	11.44	41.10	-839.686	3.906
30	8	11.44	41.07	-839.776	3.906
30	45	11.43	41.09	-839.744	3.906
30	80	11.43	41.09	-839.737	3.906
60	8	11.44	41.08	-839.754	3.906
60	45	11.43	41.09	-839.752	3.906
60	80	11.44	41.09	-839.729	3.906
120	8	11.43	41.07	-839.764	3.906
120	45	11.43	41.09	-839.755	3.906
120	80	11.44	41.09	-839.738	3.906
180	8	11.42	41.07	-839.765	3.906
180	45	11.44	41.10	-839.715	3.906
180	80	11.43	41.09	-839.742	3.906
240	8	11.43	41.07	-839.770	3.906
240	45	11.44	41.09	-839.728	3.906
240	80	11.44	41.10	-839.710	3.906

Table 16B. ED_{50} and Emax Values Calculated by the Firm

Model	**Software Used**	**Assumption of Distribution (ED_{50}) (Normal/Log Distribution)**			
Simple EMAX model	PPHARM	Log-Normal Distribution			
Initial Population Parameter Estimates		**Final Population Parameter (Model Derived) Estimates**			
ED_{50}	**E_{max}**	**ED_{50}**	**Emax**	**Maximum Likelihood**	**Akaike Criteria Value**
1.5	8	12.02	44.99	-829.192	3.857
1.5	45	12.30	45.37	-829.176	3.857
1.5	80	12.44	45.50	-829.174	3.857
3	8	11.99	44.97	-829.194	3.857
3	45	12.42	45.49	-829.170	3.857
3	80	12.44	45.50	-829.175	3.857
6	8	11.93	44.90	-829.199	3.857
6	45	12.42	45.50	-829.169	3.857
6	80	12.44	45.50	-829.178	3.857
12	8	11.93	44.90	-829.199	3.857
12	45	12.43	45.51	-829.171	3.857
12	80	12.45	45.51	-829.177	3.857
30	8	11.95	44.93	-829.196	3.857
30	45	12.45	45.52	-829.169	3.857
30	80	12.45	45.52	-829.178	3.857
60	8	11.93	44.91	-829.199	3.857
60	45	12.46	45.52	-829.170	3.857
60	80	12.45	45.52	-829.178	3.857
120	8	11.98	44.96	-829.193	3.857
120	45	12.45	45.52	-829.169	3.857
120	80	12.45	45.51	-829.177	3.857
180	8	11.93	44.91	-829.199	3.857
180	45	12.46	45.53	-829.170	3.857
180	80	12.46	45.52	-829.177	3.857
240	8	11.93	44.91	-829.197	3.857
240	45	12.45	45.52	-829.171	3.857
240	80	12.46	45.52	-829.177	3.857

Table 17. ED_{50} and Emax Values Calculated by the Reviewer

Model	**Software Used**	**Assumption of Distribution (ED_{50}) (Normal/Log Normal)**
Naïve Pooled Fit Emax	Phoenix	--
Population Fit Emax (using naïve pool method)	Phoenix	Log Normal for ED50 and Normal for Emax

Data Analysis of Pilot Dose Duration-Response Study using Phoenix

Model	Software Used	Assumption of Distribution (ED_{50}) (Normal/Log Normal)
Simple E_{max}	Phoenix	Naive Pooled Method

(b) (4)

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(b) (4)

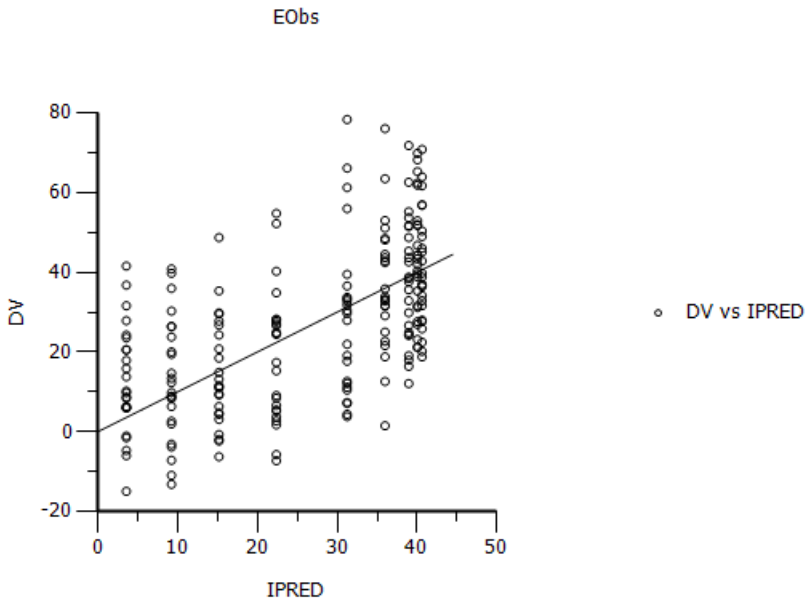
[redacted]

Table 18. Additional Study Information

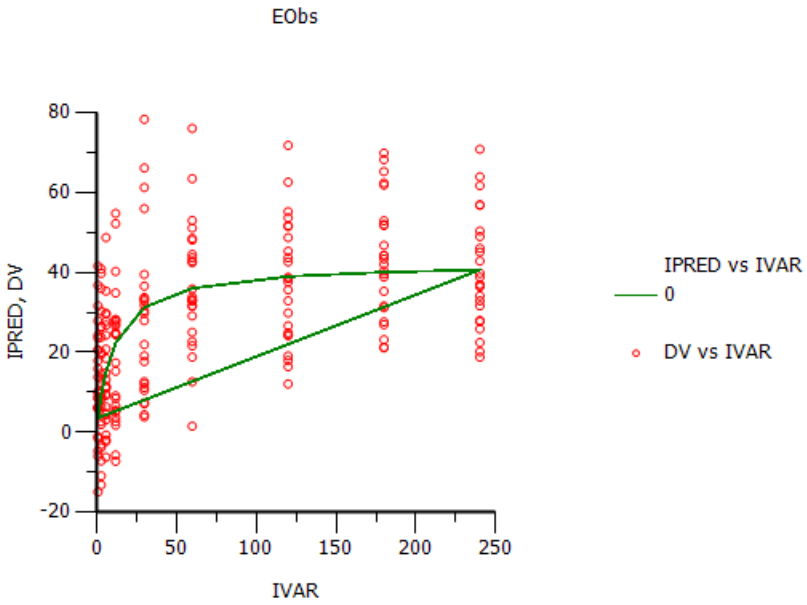
ED_{50} used in the pivotal study	12 min
Does the reviewer agree with the firm's decision?	Yes
If no, why ?	N/A
Reviewer's Comments	Per the FDA Guidance to Industry: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence (Issued 6/2/1996, Posted 3/6/1998), fitting based on nonlinear least squares regression, pooling individual observations from all subjects (naïve pooled data method) is acceptable.

Pilot Dose Duration-Response Study Naïve Fit Graphics (From Phoenix):

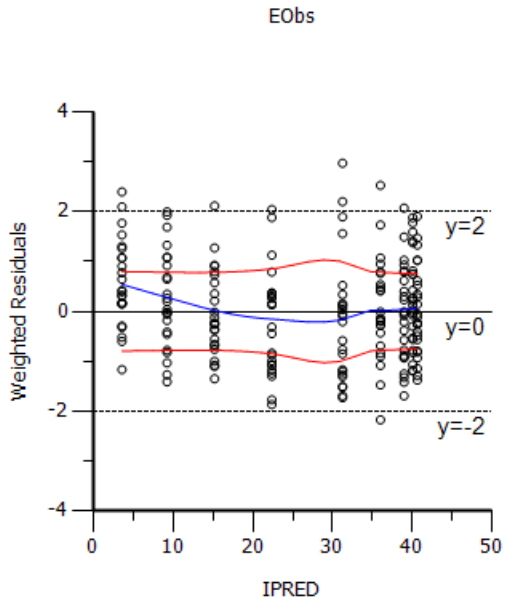
Ind DV vs. IPRED



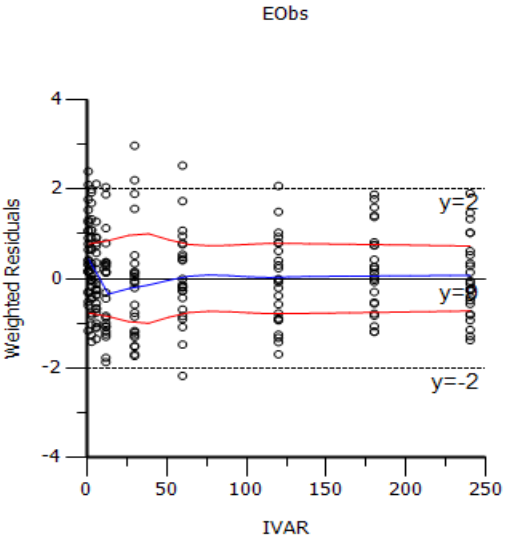
Ind DV, IPRED vs IVAR



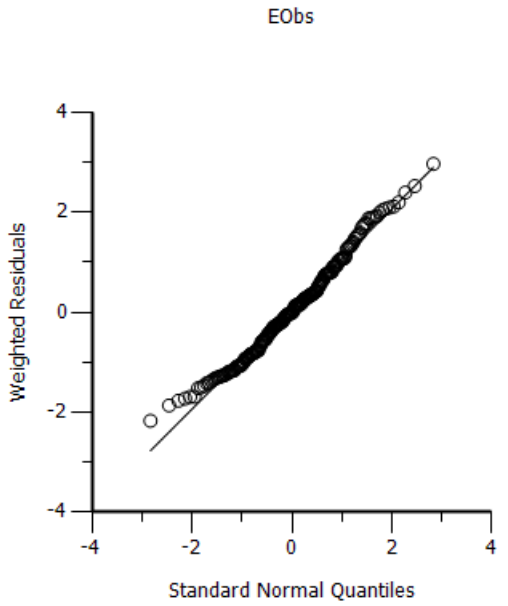
Ind IWRES vs IPRED



Ind IWRES vs IVAR



Ind QQ IWRES



Comments on Statistical Analysis:

- In the pilot dose duration-response study, vasoconstriction response was evaluated by Chroma Meter measurement at pre-dose and at 0.5, 2, 4, 6, 8, 10, 12, 20 and 24 hours (± 5 minutes) after dose removal.

- The Chroma Meter measurements at different time points have been adjusted and corrected by subtracting baseline and control site values. AUECs have been calculated for each dose-duration (1, 3, 6, 12, 30 minutes, and 1, 2, 3, and 4 hours) using the trapezoidal rule.

- The firm performed data analysis using the Agency recommended Simple Emax model for population analysis of the ED50 and Emax using P-Pharm software assuming both normal for ED50 and Emax values and log normal distribution for EC50 (Tables 16A & B). Based on the statistical results provided by the firm, the data fitting with normal distribution is similar to the log-normal distribution. Even, the ED50 value obtained from the normal distribution is (11.44 min) and is similar to that with log normal distribution (12.44 min). The firm used ED50 of 12 minutes for the pivotal BE study. According to the firm, the convergence was judged to be slightly better for the log-normal distribution fitted data as indicated by the smaller range of final ED_{50} estimates (11.93 to 12.46 minutes) as evident from the tables 16A and B. Based on the normal distribution and log normal distribution, the firm's results are provided in the following tables:

With Normal Distribution for ED50:

Duration (minutes)	ChromaMeter (mean $AUEC_{0.5\text{-}24hr}$)
1	12.8
3	13.0
6	14.6
12	19.0
30	28.5
60	36.5
120	37.7
180	43.4
240	40.3
E_{max}	41.10
Standard Deviation	14.29
CV%	34.77
ED_{50} (minutes)	11.44
Standard Deviation	9.68
CV%	84.61

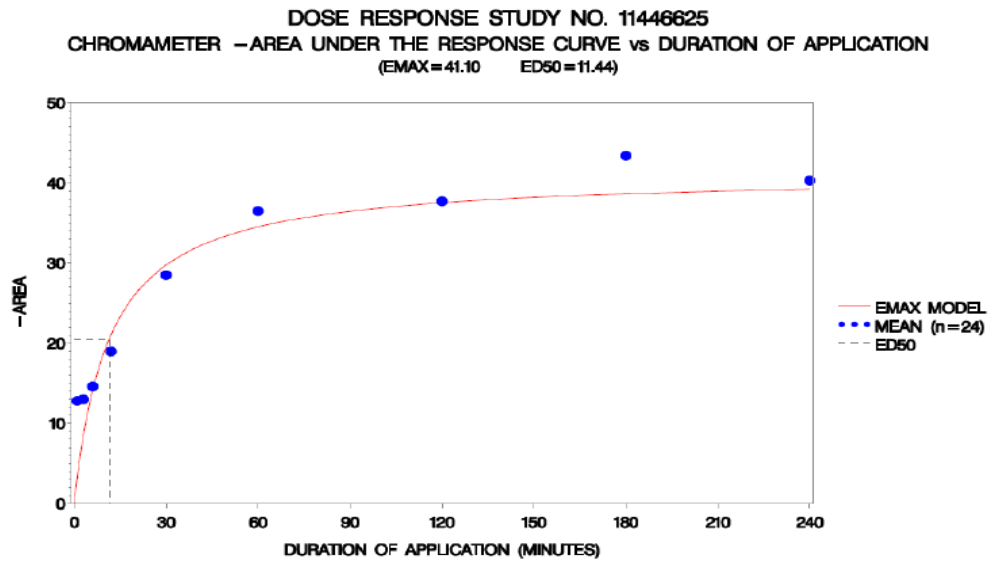
*Initial estimates from normal distribution of $ED_{50} = 240$ and $E_{max} = 80$.

With Log-Normal Distribution for ED50

Duration (minutes)	ChromaMeter (mean $AUEC_{0.5\text{-}24hr}$)
1	12.8
3	13.0
6	14.6
12	19.0
30	28.5
60	36.5
120	37.7
180	43.4
240	40.3
E_{max}	45.50
Standard Deviation	13.17
CV%	28.95
Geometric ED_{50} (minutes)	12.44
Standard Deviation (natural log)	1.51
Geometric CV%	297.96

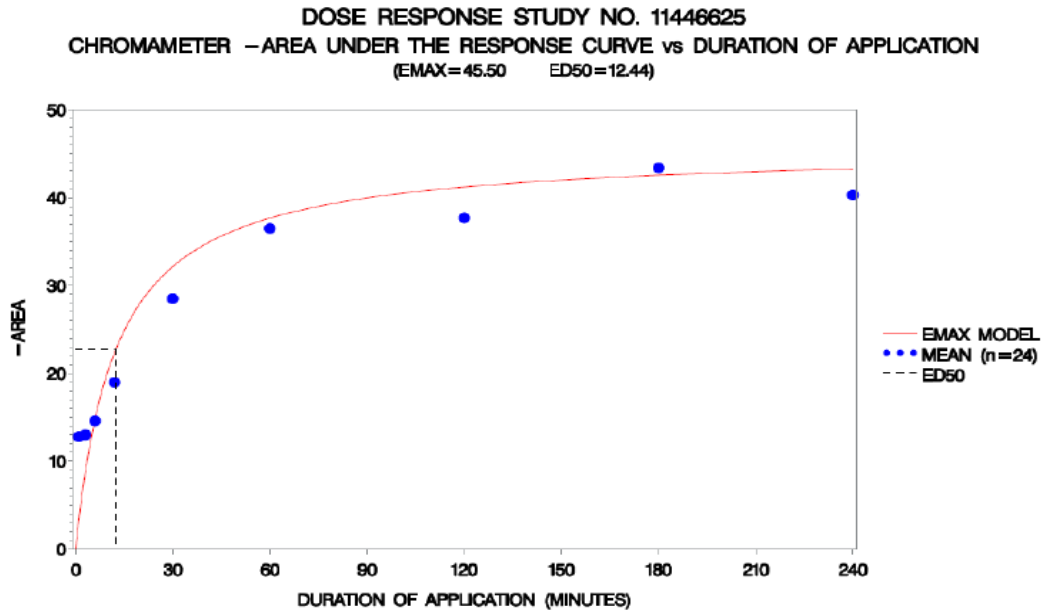
*Initial estimates from log-normal distribution of $ED_{50} = 1.5$ and $E_{max} = 80$.

- The firm provided Pilot Dose Duration-Response Study Plot of Predicted Values vs. Observed Values and mean below:



*Initial estimates from normal distribution of ED_{50} = 240 and E_{max} = 80

With Log-Normal Distribution:



- The reviewer used Phoenix software to fit Emax model to the AUEC0.5-24 hrs for 24 subjects. The reviewer calculated ED50 and Emax based on the assumption of Emax normal and ED50 lognormal distribution in population fit model. The reviewer also employed naïve pooled approach to calculate ED50 and Emax.

Convergence was achieved with both naïve pooled and population fit model. The results are summarized in the table below:

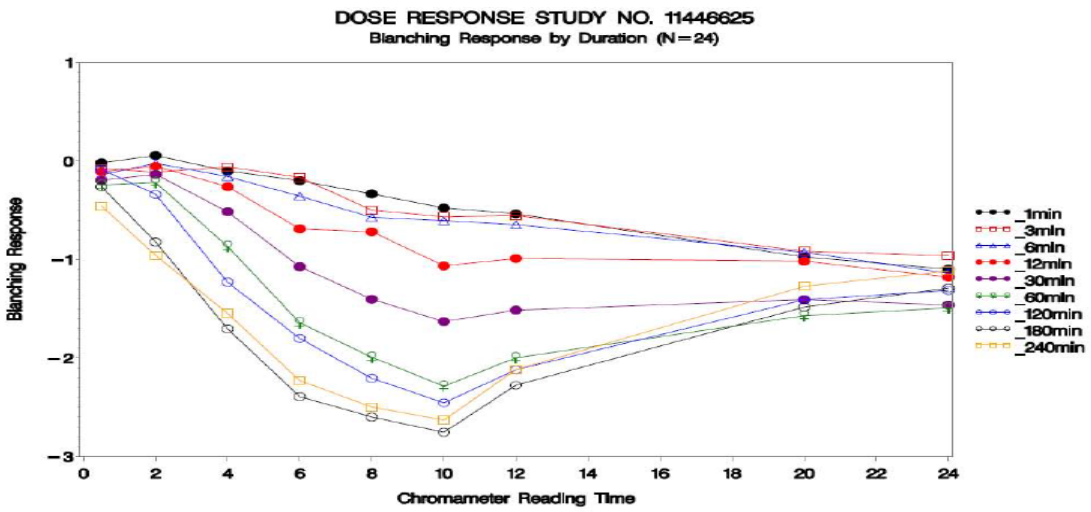
Software	Assumption	ED_{50}	Population %CV for ED_{50}	Emax	Population %CV for Emax	AIC Value
P-Pharm(firm's assumption)	ED_{50} and E_{max} Normal Distribution	11.44	84.61	41.10	34.77	3.907
P-Pharm(firm's assumption)	ED_{50} and E_{max} Log Normal Distribution	12.44	297.96	45.50	28.95	3.857
Phoenix (Reviewer's calculation)	Naïve Pooled method	10.74	25.88	42.43	5.38	1812.7045
Phoenix (Reviewer's calculation)	ED50 log normal and Emax Normal (Population Fit)	10.74	25.88	42.43	5.38	1812.7045

- The reviewer's data fitting results obtained using naïve pooled data method are similar to the firm's results in case of both ED50 and Emax values.

  Based on the above information, the reviewer agrees with the firm's selection of dose duration time and ED50.

- The plot for mean corrected values verses time after dose removal provided by the firm is shown below. As can be seen in the plot that the maximum responses were observed at the different dose-duration times. Therefore, a truncation of vasoconstrictor response under un-occluded condition was not observed.

Figure 14.2.1: Blanching Response by Duration



- According to Guidance for Industry, *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*, the AUEC for each baseline-adjusted, untreated control site-corrected dose duration should be calculated from time zero (0) to 24 hours. In ANDA 208101, similar 0.5-24 hour AUEC calculation (the study was also conducted by Novum Pharmaceutical Research Services, at same clinical site) was observed and the firm was asked to calculate $AUEC_{0-24}$ for the pilot dose response study. In the response to ECD dated 27 May 2015 for ANDA 208101, the firm replied with the following:

  As detailed in the Study Protocol and Clinical Study Report, Study Design and Plan Description (sections 5.1 and 9.1, respectively) for each of these studies, ChromMeter readings were taken from 0.5 hours post-removal through 24 hours post-removal. Therefore, calculation of AUEC0-24 for all subjects for both studies is not possible. The reason for starting ChromaMeter readings at 30 minutes following removal of drug product is that the skin surface is expected to be disrupted by long wear-time of the washer around the drug application area and the drug-removal procedures such that a stabilization period is required for the skin to normalize. Based on in-house experience, Novum has determined that the skin tone and skin color have normalized by 30 minutes post-removal and therefore this time has been chosen as the first post-removal evaluation time. This 30-minute rest period minimizes the variability and optimizes the reliability in the ChromaMeter reading at the initial post-removal evaluation time, because the confounding effects of changes in skin tone from the product-removal procedures on the skin blanching effects from the product itself are eliminated.
  The firm's reasoning was considered acceptable at that time for ANDA208101. The reviewer also considers this explanation acceptable and thus would not ask

the firm to provide justification for not taking Chroma Meter reading at zero time point.

Summary/Conclusions, Pilot Dose Duration-Response Study: The firm's pilot dose-duration response study is **adequate.**

4.1.2 Pivotal Pharmacodynamic Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	11446626
Study Title **Clinical Site (Name & Address)**	Bioequivalence Study of Clobetasol Propionate Lotion, 0.05% Novum Pharmaceutical Research Services 4801 Amber Valley Parkway Fargo, ND 58104 United States of America (USA)
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	12/19/15, 01/05/16, 01/14/16
Where the subjects dosed in more than one group?	Yes
If Yes, specify the screening dates for each group	Group 1: 12/15/15 Group 2: 12/22/15, 12/23/15 Group 3: 12/23/15, 01/04/16, 01/07/16
If Yes, specify the dosing dates for each group	Group 1: 12/19/15 Group 2: 01/05/16 Group 3: 01/14/16
If Yes, specify whether the same clinical sites were used for each group	Yes

Table 20. Product Information

Product	Test	Reference
Treatment ID	Test	Reference
Product Name	Clobetasol Propionate Lotion 0.05%	CLOBEX® (clobetasol propionate) Lotion 0.05%
Manufacturer	Manufactured for: Lupin Pharmaceuticals, Inc. Manufactured by: Lupin Limited	Marketed by: Galderma Laboratories, L.P. Manufactured by: DPT Laboratories, Ltd.
Batch/Lot No.	Batch Number: K590079 [Please refer enclosed Certificate of Analysis]	Lot Number: FMER [Please refer enclosed Certificate of Analysis]
Expiration Date	Expiration Date: 08/2017	Expiration Date: 10/16
Strength		
Dosage Form	Lotion	Lotion
Potency	100.8%	100.3%
Homogeneity	NA	NA
Dose Administered	10 µL	10 µL
Route of Administration	Topical	Topical

Table 21. Study Design, Pivotal Pharmacodynamic Bioequivalence Study

<table>
<tr><td rowspan="4">Number of Subjects</td><td>Enrolled:</td><td>90</td></tr>
<tr><td>Dosed:</td><td>90</td></tr>
<tr><td>Completed:</td><td>88</td></tr>
<tr><td>Analyzed:</td><td>88 (63 included in final analysis)</td></tr>
<tr><td>No. of Periods</td><td colspan="2">1</td></tr>
<tr><td>No. of Treatments</td><td colspan="2">2</td></tr>
<tr><td>No. of Groups</td><td colspan="2">3 Groups:
<table>
<tr><th>Dosing Group</th><th>Subject Nos.</th><th>Dosing Date</th></tr>
<tr><td>1</td><td colspan="2" rowspan="3">(b) (6)</td></tr>
<tr><td>2</td></tr>
<tr><td>3</td></tr>
</table></td></tr>
<tr><td>Randomization Scheme</td><td colspan="2">Staggered application and synchronized removal. \\cdsesub1\evsprod\anda209147\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\11446626\be-16-1-7-random-scheme.pdf</td></tr>
</table>

Preparation of Skin	Before check-in for the study, the subjects were instructed not to use any sprays, lotions, creams, gels, Lotions, emollients, or similar products on the forearms within 24 hours before initial dosing or throughout the entire study. Subjects were also instructed not to use any topical dermatological drug therapy (including topical corticosteroids) on the flexor surface of the forearms in the 30 days before dosing or throughout the entire study. Subjects were also instructed not to use any drug as part of a research study in the 30 days before initial dosing and throughout the entire study. The arms of each subject were washed with a mild soap (Liquid Neutrogena® Facial Cleansing Formula) and gently dried at least 2 hours before initial dosing and before baseline assessments were performed. Ten (10) sites were designated on the flexor surface of each forearm. An open washer (inside diameter of approximately 1.6 cm) was placed over each of the 10 sites and taped in place on its edges with hypoallergenic tape. Care was taken that sites were not placed within 3 cm of the wrist or antecubital fossa, and the washers were no closer than 2 cm apart, center-to-center. All sites were labeled by number for ease of identification throughout the study (sites 1-10 on the right arm; sites 11-20 on the left arm). All sites were evaluated before dosing for the presence of any skin condition (e.g., coloration, freckles, moles, scratches, excessive hair, recently shaved skin, tattoo, etc.) that would interfere with the assessment or response of skin blanching.
Occlusion or Non-Occlusion	Non-Occlusion
Dose Duration Times	D1: 6 min, ED50: 12 min, D2: 24 min
Skin Blanching Reading Times	Evaluations using the ChromaMeter a-scale reading were performed at each site before treatment application (in duplicate) and at 0.5, 2, 4, 6, 8, 10, 12, 20 and 24 hours (± 5 min) after removal. Following treatment removal, the 0.5-hour through 24-hour assessments was performed within approximately 5 minutes of their scheduled time.
Application and Removal of Study Drug(s)	The staggered application with synchronized removal method was used, i.e. the investigational product was applied to skin sites at different times and removed at the same time. At the end of the application period, Each treated site was gently wiped with three consecutive cotton balls: 1 damp cotton ball (soaked in a mild, room temperature hypo-allergenic soap solution), 1 damp cotton ball (soaked in room temperature water), and 1 dry cotton ball. The untreated sites were similarly cleaned and wiped at the same time as the treated sites (Time 0).
IRB Approval	Yes, approved on 12/08/15

Informed Consent	Yes, approved on 12/08/15
Subject Screening	Yes, met the inclusion/exclusion criteria for this study
Length of Confinement	Entire study, 32 hrs (4 hr prior application + 28 hr ChromaMeter assessment)
Safety Monitoring	Vital signs were measured at screening and at the discretion of the Investigator.

Comments on Study Design:

- The study was conducted with all test sites remaining un-occluded during the dose duration period. As per RLD labeling for Clobex® Lotion, the treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician. Therefore, the firm's pivotal study design with all sites un-occluded is acceptable.

- Ninety subjects were pre-screened for vasoconstriction responsiveness using a single dose application of Clobex® Lotion on the upper arm and were enrolled in the study. Subjects were dosed in three groups. Since the subjects were all screened around the same time and same clinical site was used, therefore, it is acceptable to conduct the study in groups.

- A total of 90 subjects were enrolled in the study and had ten sites demarcated on each forearm. 10µL/site of Test product, Clobetasol Propionate Lotion, 0.05% of Lupin Inc, or Reference product Clobex® Lotion of Galderma Laboratories L P was applied in triplicate to the flexor surfaces of each subject's forearm as per randomization schedule for 12 minutes. A 10 µl of the RLD (Clobex® Lotion) was applied to two additional sites for different dose durations D1 (6 min), and D2 (24 min) as determined by the dose duration response study. Two sites on each ventral forearm remained as untreated control sites. All test sites remained un-occluded during the dose duration period. Data from all 88 subjects who completed the study were used in statistical analysis.

- There were 63 subjects (evaluable subjects) who meet the dose-duration response criterion of mean AUEC at D2/ mean AUEC at D1 > 1.25. The percentage responder in the pivotal BE study is 71.59 (63 out of 88 subjects).

- The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Pivotal Pharmacodynamic Bioequivalence Study

Study No. 11446626			
		Treatment Groups	
		Test Product N=63	Reference Product N=63
Age[1] (years)	Mean ± SD	31.70 ± 13.86	31.70 ± 13.86
	Range	18 - 64	18 - 64
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	45 (71.43%)	45 (71.43%)
	41 – 64	18 (28.57%)	18 (28.57%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	12 (19.05%)	12 (19.05%)
	Female	51 (80.95%)	51 (80.95%)
Hispanic or Latino Race	American Indian or Alaskan Native	0 (0.00%)	0 (0.00%)
	Asian	0 (0.00%)	0 (0.00%)
	Black or African American	0 (0.00%)	0 (0.00%)
	Native Hawaiian or Other Pacific Islander	0 (0.00%)	0 (0.00%)
	White	1 (1.59%)	1 (1.59%)
	Other	0 (0.00%)	0 (0.00%)
Not Hispanic or Latino Race	American Indian or Alaskan Native	0 (0.00%)	0 (0.00%)
	Asian	1 (1.59%)	1 (1.59%)
	Black or African American	2 (3.17%)	2 (3.17%)
	Native Hawaiian or Other Pacific Islander	0 (0.00%)	0 (0.00%)
	White	56 (88.89%)	56 (88.89%)
	Other	3 (4.76%)	3 (4.76%)
BMI (kg/m^2)	Mean ± SD	26.30 ± 3.84	26.30 ± 3.84
	Range	19.4 - 34.3	19.4 - 34.3
Other Factors			
Weight (lb)	Mean ± SD	168.48 ± 29.36	168.48 ± 29.36
	Range	107 - 239	107 - 239
Tobacco Users[2]	Yes	0 (0.00%)	0 (0.00%)
	No	63 (100.00%)	63 (100.00%)
Fitzpatrick Skin Type	I	0 (0.00%)	0 (0.00%)
	II	19 (30.16%)	19 (30.16%)
	III	44 (69.84%)	44 (69.84%)

[1] Determined at screening.
[2] Defined as current tobacco user (having used tobacco or nicotine-containing products within 30 days before initial dosing).

Comment: In the firm's study report, it was stated that an interim (futility) statistical analysis of equivalence may be performed after approximately 50% of the subjects meet the qualification criteria (D2/D1 ≥ 1.25). This will be an analysis strictly for futility where the study is stopped only if the test product is deemed not to be equivalent to the reference product. If the results of the interim analysis look promising towards the goal of demonstrating equivalence between test and reference products, then the study will continue as planned and the originally required number of qualifiers (50) would be attained prior to final statistical assessment of bioequivalence.

As per study report, out of the 28 subjects completing Groups 1 through 3, 20 subjects (71 %) had AUEC0.5-24hr data that met the qualification standard of (mean D2 AUEC0.5-24hr)/(mean D1 AUEC0.5-24hr) at least 1.25. These 20 subjects were included in the interim analysis of bioequivalence, conducted per protocol after about 50% of the subjects met the qualification criteria.

Finally, out of the 88 subjects completing Groups 1 through 3, 63 subjects (72 %) had AUEC0.5-24hr data that met the qualification standard of (mean D2 AUEC0.5-24hr)/(mean D1 AUEC0.5-24hr) of at least 1.25. These 63 subjects were included in the final analysis of bioequivalence. All qualified subjects from the last group dosed were included in the statistical analysis of bioequivalence. Similar type of approach was employed by NON-RESPONSIVE . The consult was sent to Office of Research and Standards (ORS) for expert opinion to determine if the firm's interim analysis approach could inflate the Type I error rate and any adjustment of Type I error should be applied in the statistical analysis of firm's sequential study design. In its response to the consult, the ORS concluded that there would be no inflation in the Type I error rate and no adjustment in the significance level for the BE statistical analysis is required[23].

Table 23. Dropout Information, Pivotal Pharmacodynamic Bioequivalence Study

Study No. 11446626				
Subject No.	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Voluntarily withdrew from the study before the 4-hour ChromaMeter assessment because of the adverse events of headache and nausea	single dosing period	No	N/A
	Voluntarily withdrew from the study before the 6-hour ChromaMeter assessment because of the adverse events of headache and nausea	single dosing period	No	N/A

Comment: According to the study report, both the subjects voluntarily withdrew from study due to adverse events of headache and nausea. Therefore, data from these subjects

[23] NON-RESPONSIVE

were excluded from analysis.

Table 24. Study Adverse Events, Pivotal Pharmacodynamic Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups		
	Study No. 11446626		
	Test Product A: N = 90 subjects dosed n (%)	Reference Product B: N = 90 subjects dosed n (%)	Not Assignable N = 90 subjects dosed n (%)
Gastrointestinal disorders			
Nausea	—	—	2 (2.22%)
General disorders and administration site conditions			
Application site pain	—	1 (1.11%)	—
Application site pruritus	—	1 (1.11%)	—
Nervous system disorders			
Headache	—	—	4 (4.44%)
Skin and subcutaneous tissue disorders			
Pruritus	—	—	1 (1.11%)
Total n (%)	**0 (0.00%)**	**1 (1.11%)**	**5 (5.56%)**

n = Number of subjects reporting AE
% = (Number of subjects reporting AE / number of subjects dosed with study drug) x 100.
Total n = Number of subjects that reported at least one AE
Total %= (Number of subjects that reported at least one AE / number of subjects dosed with study drug) x 100.
Simultaneous dosing with Test and Reference products = 90 subjects dosed.

Listing of Adverse Events by Subject

Sub. No.	Adverse Event	ONSET Date	ONSET Time	END Date	END Time	Sev[1]	Rel[2]	Res[3]	SAE[4]	Preferred Term	System/Organ Class
(b) (6)	Application site itching (Site 9 [Reference B])	(b) (6)	2030	(b) (6)	2200	1	4	1	N	Application site pruritus	General disorders and administration site conditions
	Application site burning (Site 9 [Reference B])		2030		2200	1	4	1	N	Application site pain	General disorders and administration site conditions
	Headache		1440		2300	1	2	1	N	Headache	Nervous system disorders
	Nausea		1610		2300	1	1	1	N	Nausea	Gastrointestinal disorders
	Headache		1824		1100	1	2	1	N	Headache	Nervous system disorders
	Nausea		1900		1100	1	1	1	N	Nausea	Gastrointestinal disorders
	Headache		0300		1400	1	1	1	N	Headache	Nervous system disorders
	Headache		0530		1130	1	1	1	N	Headache	Nervous system disorders
	Itching, inside right forearm		1900		0100	1	1	1	N	Pruritus	Skin and subcutaneous tissue disorders

[1] Severity of Adverse Event: 1 = Mild; 2 = Moderate; 3 = Severe.
[2] Relationship to Drug: 1 = Unrelated; 2 = Remote; 3 = Possible; 4 = Probable; 5 = Definite.
[3] Resolution: 1 = Recovered/Resolved; 2 = Recovering/Resolving; 3 = Recovered/Resolved with Sequelae; 4 = Not Recovered/Not Resolved; 5 = Fatal; 6 = Unknown.
[4] Serious Adverse Event: Y = Yes; N = No.

Table 25. Protocol Deviations, Pivotal Pharmacodynamic Bioequivalence Study

Study No. 11446626		
Type	**Subject #'s (Test)**	**Subject #'s (Ref.)**
No protocol deviations.	N/A	N/A

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There are total of 6 adverse events (headache, nausea or itching at application site) reported by 6 subjects in the pivotal study. The adverse events were mild in intensity and considered mostly unrelated or remotely related to the study drug (except itching at application site which is considered probably related to the study drug). The adverse events resolved spontaneously without any medication. No serious adverse events were reported.

- There were two dropouts in this study. Both the subjects ((b) (6)) voluntarily withdrew from the study.

- No protocol deviation was reported.

- The clinical results are acceptable.

4.1.2.3 Statistical Results

Table 26. Area under the Effective-Dose Curve and 90% Confidence Intervals - Firm and Reviewer Calculated

Name of Drug Product: Clobetasol Propionate Lotion 0.05% Dose: [10 µL per site – Non Occluded, 12 minutes(ED50)] Pharmacodynamic Parameters, Area Under the Effective-Dose Curve, Point Estimates and 90% Confidence Intervals (Locke's Method*)					
Pivotal (Vasoconstrictor Assay) Study (Study No. 11446626)					
	Number of Subjects[24] (b) (6)	**$AUEC_{(0.5-24h)}$**		**Point Estimate**	**90% CI**
		Test	**Reference**		
Calculated by the Firm**		22.6567	21.9686	103.13%	97.34 – 109.23
Calculated by the Reviewer ($D_2/D_1 \geq 1.25$)		-22.66	-21.97	103.1%	97.34 – 109.23
Calculated by the Reviewer ($D_2/D_1 \geq 2.0$)		-19.87	-19.49	102.0%	93.21-111.13

(*) Statistical analysis was carried out using Locke's method to determine bioequivalence of the formulations using data for "Detectors" only.
**: The firm calculated negative AUEC whereas the reviewer calculated AUEC.

Table 27. Mean AUEC Values of Subjects in the Pivotal Study Meeting the Dose Duration-Response Criterion, mean $AUEC_{0.5-24h}$ D_2/ mean $AUEC_{0.5-24h}$ $D_1 \geq 1.25$ (N=63)

Subject	mean $AUEC_{0.5-24h}$ D_2/ mean $AUEC_{0.5-24h}$ $D_1 \geq 1.25$	$AUEC_{0-24h}$ Test Product (Mean)	$AUEC_{0.5-24h}$ Reference Product (Mean)
(b) (6)	1.39838	25.26542	24.59333
	2.798388	23.89292	21.70542
	1.767579	37.73458	24.32208
	7.945322	33.9675	28.89875
	1.862289	15.445	13.62083
	3.482668	32.03458	29.13208
	2.155441	28.38667	31.74583
	1.330205	25.56333	18.13625
	13.79747	10.64083	18.29667
	1.686037	10.81667	13.21417
	3.044614	28.43833	23.50917
	1.791007	14.01167	20.52083
	2.823428	13.02458	21.83167
	1.9918	26.39208	32.31792
	2.262594	25.0725	16.38875
	7.778931	22.73833	24.64583
	1.56497	30.64458	29.11292
	2.374923	22.14375	16.64958

[24] Number of subjects who meet the criterion of the D2 response/D1 response ≥ 1.25 or ≥ 2.0

Subject	mean $AUEC_{0.5\text{-}24h}$ D_2/ mean $AUEC_{0.5\text{-}24h}$ $D_1 \geq 1.25$	$AUEC_{0\text{-}24h}$ Test Product (Mean)	$AUEC_{0.5\text{-}24h}$ Reference Product (Mean)
(b) (6)	12.59259	3.799167	-3.19083
	3.426335	27.50208	28.375
	3.523946	15.085	16.25625
	2.281117	13.685	16.02542
	34.26639	0.055833	8.720417
	2.466925	8.699167	13.43208
	1.807168	20.11875	11.05375
	9.897232	23.8275	24.28167
	1.403742	35.92667	43.98833
	1.38282	25.3275	32.29708
	3.486258	22.06833	11.825
	1.396507	17.95292	4.6925
	2.631561	19.03958	19.6925
	30.98958	28.65458	21.76708
	2.540587	33.25375	35.50208
	2.021917	31.9575	31.635
	2.445703	13.60417	18.885
	3.105933	15.61208	27.41792
	3.957228	6.765417	10.28
	2.447331	39.92708	23.09833
	1.272081	23.98792	13.63667
	2.467367	34.21083	37.5475
	2.069053	17.46833	18.38458
	1.418095	38.08542	38.2425
	1.350067	32.74792	27.4825
	2.805029	9.82875	18.04625
	1.366666	57.27625	53.02875
	1.539764	14.44083	20.20917
	6.491308	28.24375	28.40167
	1.777358	37.80292	36.49292
	4.861444	12.57125	5.834167
	1.581333	47.25292	39.44625
	1.312196	19.32792	19.58042
	2.156999	19.06542	19.10417
	1.484467	26.64292	22.42625
	1.428988	35.22792	40.29292
	1.577785	25.66833	27.095

Subject	mean $AUEC_{0.5\text{-}24h}$ D_2/ mean $AUEC_{0.5\text{-}24h}$ $D_1 \geq 1.25$	$AUEC_{0\text{-}24h}$ Test Product (Mean)	$AUEC_{0.5\text{-}24h}$ Reference Product (Mean)
(b) (6)	1.423906	18.29083	22.01417
	2.120107	7.007083	4.274583
	1.275195	6.6625	7.958333
	4.292822	2.025417	2.681667
	17.65659	6.704583	5.806667
	1.274485	29.0125	31.56458
	2.251149	34.30792	24.59083
	1.958325	14.43083	15.19667

Table 28. Locke's Method: Determination of 90% Confidence Intervals (mean $AUEC_{0-24h}$ D_2/ mean $AUEC_{0-24h}$ $D_1 \geq 1.25$, N=63)

			Arith. Mean	22.66	21.97		E(Xi)^2		E(TEST*REF)
ANDA	209147		EXi	1427.37	1384.02		40370.42	37667.72	37851.12
Date	18-Nov-2016		(EXi)^2	2037375.601	1915499.827				
Reviewer:	Manjinder		((EXi)^2)/n	32339.30	30404.76				
AVETest	22.66								
AVEREF	21.97		Exti/EXri	1.03132					
T/R	1.031		(Exti/Exri)^2	1.06					
DTR	104.74		DTT/DRR	1.11					
DRR	117.14		DTR/DRR	0.89					
DTT	129.53								
Inta Sub Var (%)	19.63		SUBJ	TEST	REF		(TEST)^2	(REF)^2	(TEST)*(REF)
			(b) (6)	25.26542	24.59333		638.34	604.83	621.36
K	0.32			23.89292	21.70542		570.87	471.13	518.61
SQRT(K)	0.57			37.73458	24.32208		1423.90	591.56	917.78
W	0.02			33.9675	28.89875		1153.79	835.14	981.62
n	63			15.445	13.62083		238.55	185.53	210.37
t	1.6698			32.03458	29.13208		1026.21	848.68	933.23
t^2	2.79			28.38667	31.74583		805.80	1007.80	901.16
Gr	0.01			25.56333	18.13625		653.48	328.92	463.62
DRR*W	1.86			10.64083	18.29667		113.23	334.77	194.69
SQRT(DRR*W)	1.36			10.81667	13.21417		117.00	174.61	142.93
				28.43833	23.50917		808.74	552.68	668.56
-CINT	0.973			14.01167	20.52083		196.33	421.10	287.53

+CINT	1.092		(b) (6)	13.02458	21.83167		169.64	476.62	284.35
				26.39208	32.31792		696.54	1044.45	852.94
90% CI:	97.34			25.0725	16.38875		628.63	268.59	410.91
	109.23			22.73833	24.64583		517.03	607.42	560.41
				30.64458	29.11292		939.09	847.56	892.15
				22.14375	16.64958		490.35	277.21	368.68
				3.799167	-3.19083		14.43	10.18	-12.12
				27.50208	28.375		756.36	805.14	780.37
				15.085	16.25625		227.56	264.27	245.23
				13.685	16.02542		187.28	256.81	219.31
				0.055833	8.720417		0.00	76.05	0.49
				8.699167	13.43208		75.68	180.42	116.85
				20.11875	11.05375		404.76	122.19	222.39
				23.8275	24.28167		567.75	589.60	578.57
				35.92667	43.98833		1290.73	1934.97	1580.35
				25.3275	32.29708		641.48	1043.10	818.00
				22.06833	11.825		487.01	139.83	260.96
				17.95292	4.6925		322.31	22.02	84.24
				19.03958	19.6925		362.51	387.79	374.94
				28.65458	21.76708		821.09	473.81	623.73
				33.25375	35.50208		1105.81	1260.40	1180.58
				31.9575	31.635		1021.28	1000.77	1010.98
				13.60417	18.885		185.07	356.64	256.91
				15.61208	27.41792		243.74	751.74	428.05
				6.765417	10.28		45.77	105.68	69.55
				39.92708	23.09833		1594.17	533.53	922.25
				23.98792	13.63667		575.42	185.96	327.12

		(b) (6)						
			34.21083	37.5475		1170.38	1409.81	1284.53
			17.46833	18.38458		305.14	337.99	321.15
			38.08542	38.2425		1450.50	1462.49	1456.48
			32.74792	27.4825		1072.43	755.29	899.99
			9.82875	18.04625		96.60	325.67	177.37
			57.27625	53.02875		3280.57	2812.05	3037.29
			14.44083	20.20917		208.54	408.41	291.84
			28.24375	28.40167		797.71	806.65	802.17
			37.80292	36.49292		1429.06	1331.73	1379.54
			12.57125	5.834167		158.04	34.04	73.34
			47.25292	39.44625		2232.84	1556.01	1863.95
			19.32792	19.58042		373.57	383.39	378.45
			19.06542	19.10417		363.49	364.97	364.23
			26.64292	22.42625		709.85	502.94	597.50
			35.22792	40.29292		1241.01	1623.52	1419.44
			25.66833	27.095		658.86	734.14	695.48
			18.29083	22.01417		334.55	484.62	402.66
			7.007083	4.274583		49.10	18.27	29.95
			6.6625	7.958333		44.39	63.34	53.02
			2.025417	2.681667		4.10	7.19	5.43
			6.704583	5.806667		44.95	33.72	38.93
			29.0125	31.56458		841.73	996.32	915.77
			34.30792	24.59083		1177.03	604.71	843.66
			14.43083	15.19667		208.25	230.94	219.30

Locke, C.S., An exact confidence interval from untransformed data for the ratio of two formulation means. J. Pharmacokinet. Biopharm. 1984 Dec;12(6):649-655

E: Sum

D: Sigma hat in Lockes' method

n: number of subjects

t: Students t value for d.f. = n-1

one tail 0.05, two tail 0.1

Comments on Statistical Analysis:

- The reviewer has verified that the firm calculated pharmacodynamics response from the Chroma Meter readings in a manner consistent with that stated in the Topical BE Guidance (i.e. adjusting Chroma Meter readings at a dosed site for untreated site readings and baseline readings).

- The Dose Ranging Pilot Study suggested a nominal ED_{50} of 11.44 and 12.44 minutes depending upon the distribution assumption. ED50 dose duration of 12 minutes was used in this study. This is acceptable.

- The firm and reviewer used Locke's Method for calculating the 90% confidence intervals (CI).

- The firm and reviewer used the Chroma Meter results from 63 subjects who met the inclusion criteria of (1) $AUEC_{0.5\text{-}24}$ values at D_1 and D_2 are both negative and (2) the mean $AUEC_{0.5\text{-}24h}$ D_2/mean $AUEC_{0.5\text{-}24h}$ $D_1 \geq 1.25$.

- The 90% CI of $AUEC_{0.5\text{-}24h}$ test vs $AUEC_{0.5\text{-}24h}$ reference drug product calculated both by the firm and reviewer is within the acceptable limit of 80.00%-125.00%.

Summary/Conclusions, Pivotal Pharmacodynamics Bioequivalence Study: The pivotal pharmacodynamics bioequivalence study is **adequate.**

4.2 Formulation Data

Table 29. Test Product Formulation

Ingredient	Function	% W/W
Clobetasol Propionate USP [A]	Active Ingredient	0.05
Hypromellose USP (b) (4)	(b) (4)	
Carbomer 1342 NF		
Propylene glycol USP		
Mineral Oil USP (b) (4)		
PEG-6 Isostearate IH		
Sodium hydroxide NF [B]		
Purified water USP [C]		

A (b) (4)

B

C

Table 30. Reference Product Formulation[25]

[NOT TO BE RELEASED UNDER FOIA]

Ingredients	Function	percent (w/w)
Clobetasol propionate	Active ingredient	0.05
Hydroxypropylmethyl cellulose	(b) (4)	
Polyoxyethylene glycol 300 isostearate (PEG-6 isostearate)		
Carbomer 1342 NF (b) (4)		
Mineral oil		
Propylene Glycol		
Sodium hydroxyde		
Purified water		

[25] NDA 021535, Original-1, REV-QUALITY-03 (General Review), dated 06/27/2003

Table 31. Comparative Formulation Data for the Test and Reference Products

Ingredient	Amount (%w/w)	
	Test	Reference
Propylene glycol USP	(b) (4)	
Mineral oil USP		
Polyethylene glycol 300 (PEG 6) isostearate[26]		
Carbomer 1342 NF		
Hydoxypropylmethyl cellulose USP		
Sodium hydroxide NF		

Table 302. Justification of Excipient Amounts in Test Product Formulation

Ingredient	% w/w	Maximum Level Listed in the FDA IIG Database for Approved Drug Products/Unit (Based on Route/Dosage Form)[27]	IIG Limit Reference	Amount exceed or below the IIG limit of approved drug product/unit
(b) (4)				Below
				Below

Note: All other excipients are present in amount either equal to or less than RLD.

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Are all of the inactive ingredients within the FDA's Inactive Ingredient Guide (IIG) limits?	Yes
If no, then why?	N/A
Does the firm provide sufficient information to justify its formulation?	Yes
Is there data available to the Agency which supports the quantity of the inactive ingredient(s) in the test formulation?	Yes

[26] PEG 300 isostearate is synonymous to PEG 6 isostearate
[27] IIG Database, Internal: http://intranetappslb-dev fda.gov/scripts/IIG/ (Last accessed on 11/07/2016)

Comments on the drug product formulation:

- The levels of inactive ingredients used in the test formulation, Clobetasol Propionate Lotion, 0.05% are all within the FDA's Inactive Ingredient Guide (IIG) Database.

- The Maximum Daily Dose for the drug product cannot be determined due to the dosage form of the drug product. The RLD labeling has the following statements about dosage and administration: (b) (4)

- The formulation is acceptable.

4.3 Detailed Regulatory History

N/A

4.4 Consult Reviews

N/A

4.5 Attachment:

209147Emax.phxproj

4.6 OSIS Inspection Status:

Since the current ANDA is submitted in GDUFA year 4, the final inspection status of clinical and analytical sites will be determined by the OSIS.

BIOEQUIVALENCE COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 209147

APPLICANT Lupin Ltd

DRUG PRODUCT: Clobetasol Lotion, USP, 0.05%

The Division of Bioequivalence III (DBIII) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs

4.7 Outcome Page

ANDA: 209174

Reviewer: Kaur, Manjinder **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Clobetasol Propionate Lotion

Items:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Score***	***Subtotal***
29670	5/31/2016	BIO	ANDA Original [1]	1	1
29670	5/31/2016	Complexity	PD Endpoints (Emax, ED50) [1]	1	1
29670	5/31/2016	Parallel	VCA Pilot Study [1]	1	1
29670	5/31/2016	Parallel	VCA Pivotal Study [1]	1	1
29670	11/21/2016	BIOQUALITY	Quality Assessment [1-5]	4	4
				Total:	8

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/s/

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BARBARA A HILL
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SOO HYEON SHIN
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