Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Brimonidine (as tartrate)

Proprietary Product Name: Mirvaso

Sponsor: Galderma Australia Pty Ltd

Date of CER:

First round: 18 December 2013

Second round: 28 February 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AESI	adverse events of special interest
AUC	Area under the curve
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve extrapolated to infinity
BA	bioavailability
b.i.d.	twice daily
BID	Twice daily
BLQ	below the limit of quantitation
BMI	body mass index
CD07805/47	Galderma Development Code for brimonidine tartrate drug substance
CEA	Clinician Erythema Assessment
cf	compared with
CI	Confidence interval
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenszel
COL-118	Previous sponsor development code for brimonidine tartrate
COL-118	MIRVASO/CD07805/47
CRF	case report form
CTG	clinician telangiectasia grading
CV	coefficient of variation
ECG	electrocardiogram
FDA	Food and Drug Administration
g	gram
GEE	Generalized Estimating Equation

Abbreviation	Meaning
ICC	Intraclass correlation coefficient
ICF	informed consent form
IGA	Investigators' global assessment
IOP	Intraocular pressure
ISS	Integrated Summary of Safety
ITT	Intent-to-treat (population)
Kel	apparent terminal phase rate constant
LC	liquid chromatography
LLQ	lower limit of quantification
LOQ	Limit of quantification
LTS	Long term study
MAO	Monoamine oxidase
MCII	mean cumulative irritancy
MED	minimal erythema dose - defined as the smallest dose of energy that produced a perceptible redness reaching the borders of the irradiated site.
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MITT	Modified intent to treat
MS-MS	tandem mass spectrometric detection
OTE	Overall Treatment Effect
PAA	Patient Assessment of Appearance
PAW	Patient Assessment of Whitening
PK	Pharmacokinetic
PSA	Patient Self-Assessment
QD	Once daily (Latin: quaque die)

Abbreviation	Meaning
QOL	Quality of life
QTc	QT interval corrected for heart rate
SAE	Serious adverse event
SD	Standard deviation
SOC	system organ class
$t_{1/2}$	half-life
TC	Topical corticosteroid
TEAE	Treatment-emergent adverse event
TeGA	Telangiectasia Grading Assessment
Tmax	time to maximum concentration
UBC	United BioSource Corporation

1. Introduction

This is a category 1 (type C) application to register Mirvaso gel as a new indication, dosage form, formulation and strength of brimonidine tartrate. Brimonidine is currently registered by Allergan Australia as Alphagan (brimonidine tartrate 0.2%, AUST R 60297) and Alphagan P (brimonidine tartrate 0.15%, AUST R 158888) eye drops for the treatment of glaucoma.

The proposed indication is: '*Mirvaso is indicated for the treatment of facial erythema of rosacea.*'

Mirvaso 0.5% gel (5mg/g); One gram of Mirvaso gel contains 5mg (or 0.5%) of brimonidine tartrate.

2. Clinical rationale

Rosacea is one of the most common chronic dermatological diseases, with reports suggesting prevalence between 2% to 10% in both Europe and the United States (Berg 1989, Kyriakis 2005, Powell 2005, van Zuuren 2005). While there is a disproportionately higher frequency of occurrence in fair-skinned people of European and Celtic origin, it also occurs less frequently in other mixed populations (Kyriakis 2005, Powell 2005, van Zuuren 2005). Onset typically occurs between 30 to 50 years of age, and while women are more commonly affected than men, disease manifestations, especially rhinophyma, are frequently more severe in males than in females (Crawford 2004, Powell 2005, van Zuuren 2007). Because the facial skin is the predominant site of involvement, many patients sense that the disease alters their social and professional interactions, leading to problems in the workplace, in relationships, and in other social interactions (Crawford 2004).

An expert committee assembled by the National Rosacea Society in April 2002 (Wilkin 2002) explicitly defined and classified rosacea into 4 different subtypes based upon specific clinical

signs and symptoms: erythematotelangiectatic rosacea (subtype 1), papulopustular rosacea (subtype 2), phymatous rosacea (subtype 3), ocular rosacea (subtype 4), and the variant granulomatous rosacea. Perhaps the most defining characteristic of the disease for both subtypes 1 and 2 is the presence of persistent erythema of the central portion of the face lasting for at least 3 months (Crawford 2004).

The pathophysiology of rosacea is poorly understood and may be multifactorial, involving abnormal vascular reactivity, immune system responses, and follicular microorganisms (Crawford 2004, Nally 2006, Pelle 2008, Wolf 2005). Many of the most cited pathogenic theories on the etiology of the persistent facial erythema of rosacea focus on abnormalities in cutaneous vascular homeostasis, or vasomotor instability, the term commonly used to refer to abnormal involuntary dilatation and reactivity of small subcutaneous resistance arteries. The etiology of vasomotor instability in patients with rosacea is unknown (Crawford 2004, Kyriakis 2005).

Currently, there are no approved pharmaceutical agents in the US or EU that directly target the persistent facial erythema of rosacea. Current pharmaceutical treatments for rosacea available on the US and EU market primarily target the papulopustular rosacea subtype of the disease, reducing rosacea inflammatory lesions through anti-inflammatory/antiparasitic mechanisms. Topical metronidazole targets the papulopustular stage of rosacea, although certain brand products in the US and EU include “erythema” or “acute inflammatory” or “rosacea” statement in the indication[1], it is important to note that topical metronidazole products primarily focus on the papulopustular aspect of the disease, targeting the inflammatory lesion component through anti-inflammatory mechanisms. Metronidazole has no known vasoconstrictive activity, thus, any reduction in general facial erythema, which is not well documented to date, is likely due to focal reductions in transient peri lesional erythema, secondary to the anti-inflammatory action, rather than a true reduction in the persistent generalized erythema of rosacea that is vascular in origin.

Some reported effectiveness of non-pharmaceutical/mechanical treatments for rosacea has been documented in the literature with use of both vascular lasers and intense pulsed light emitters (Pelle 2004, Adamic 2007). There are no large, well-controlled trials to fully substantiate a claim for the reduction of the persistent facial erythema of rosacea with these devices. In general, these procedures have not gained wide-acceptance as a standard of care for rosacea, which may be in part due to their lack of accessibility/availability (for example they can only be performed by a qualified physician, in an office setting, with multiple treatments often required) and high financial costs to patients (Pelle 2004).

The persistent erythema of rosacea, common to both subtype 1 and 2, represents an unmet medical need that is not adequately addressed by currently approved pharmaceutical treatments, and no products have specifically demonstrated reduction in persistent facial erythema to date. Based on the current etiological theories, treatments that stabilize the contractile state of the cutaneous facial blood vessels are expected to have the most beneficial effect in addressing this unmet need. Brimonidine tartrate is a potent and highly selective alpha2-adrenergic receptor agonist that is approximately 1000 fold more selective for the alpha2-adrenoreceptor than the alpha1-adrenoreceptor (Burke 1996). In consideration of the subcutaneous vasoconstrictive activity of brimonidine tartrate, it was expected to offer a positive effect on reducing cutaneous erythema caused by vasomotor instability through direct

[1] Noritate 1% Cream (US) is indicated for the topical treatment of inflammatory lesions and erythema of rosacea; Metrogel 0.75% (UK) is indicated for the treatment of acute inflammatory exacerbation of rosacea; Zyomet Gel 0.75% (UK) is indicated for the treatment of acute inflammatory exacerbations of acne rosacea; Rozex cream or gel 0.75% (broad EU brand) is indicated in the treatment of inflammatory papules, pustules and erythema of rosacea; Metronidazole Actavis 1% cream (EU Nordic countries) is indicated for rosacea.

cutaneous vasoconstriction and the sponsors have investigated Brimonidine Tartrate 0.5% Gel for topical treatment of facial erythema of rosacea in adults.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5:

The clinical development program for Brimonidine Tartrate Gel included a total of 18 clinical trials conducted in adult subjects: 13 clinical trials were conducted by the Applicant and 5 clinical trials were conducted by a previous sponsor. The previous sponsor had named the drug product COL-118 Gel, which was subsequently named CD07805/47 Gel by the applicant. A total of 10 of the 18 clinical trials were conducted in subjects with rosacea, and Brimonidine Tartrate 0.5% Gel (the proposed to be marketed concentration) was evaluated in 6 of the 10 studies in subjects with rosacea. Brimonidine Tartrate 0.5% Gel was also evaluated in 4 studies in healthy subjects.

- Thirteen clinical pharmacology studies, including 3 that provided pharmacokinetic data and 11 that provided pharmacodynamics data.
- Two pivotal efficacy/safety studies- 18140 and 18141.
- 3 dose-finding studies (ROSE 201, 18144, 18161).
- Long-term efficacy and safety study- 18142.
- pooled analyses, meta-analyses, PSURs, Integrated Summary of Efficacy, Integrated Summary of Safety, etcetera.

Module 1

- Application letter; application form, draft Australian product information (PI) and consumer medicine information (CMI).

Module 2:

- *Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety* and literature

Throughout this report, the studies conducted by earlier sponsors are referred to with their prefix (COL-118-ROSE); however, studies conducted by the current sponsors have been referred to without their prefix of RD.06.SRE.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

All studies were conducted in accordance with the ICH E6 Guideline for Good Clinical Practice, the ethical principles originating from the Declaration of Helsinki revised version (Somerset West, 1996) and local regulatory requirements.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies are presented in this report. Table 1 below shows the studies relating to each pharmacokinetic topic.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Primary aim of the study
PK in healthy adults	General PK - Single dose	COL-118-BAPK-101	Relative BA of 0.2% Mirvaso gel compared to 0.2% brimonidine ophthalmic solution
PK in special populations	Target population	RD.06.SRE.18126	Relative BA of 0.18% Mirvaso gel and 0.2% brimonidine ophthalmic solution under conditions of maximum use.
		RD.06.SRE.18143	PK of Mirvaso gel (0.07%, 0.18%, and 0.5%) after 4 weeks treatment compared to PK of brimonidine tartrate ophthalmic solution 0.2% after 1 day.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

4.2.1.1.1. Sites and mechanisms of absorption

Mirvaso is a topical aqueous gel, which is absorbed through the epidermis.

4.2.1.2. Bioavailability

4.2.1.2.1. Absolute bioavailability

Due to the nature of Mirvaso topical gel no absolute bioavailability studies were undertaken.

4.2.1.2.2. Bioavailability relative to an ophthalmic solution

4.2.1.2.2.1. Healthy subjects

Study COL-118-BAPK-101 to determine the relative bioavailability of 0.2% (2 mg brimonidine) Mirvaso facial gel compared to 0.2% brimonidine ophthalmic solution in 16 healthy subjects. Following facial administration of 0.2% Mirvaso gel, plasma levels of brimonidine for all subjects were below LLQ and therefore no PK analysis could be performed. By contrast, following ocular administration of a 0.2% (0.2 mg brimonidine) solution, brimonidine readily appeared in plasma with median T_{max}, mean C_{max} and AUC_{0-t} values of 2.00 hours, 0.0506 ng/mL and 0.152 ng.hr/mL, respectively.

4.2.1.2.2.2. Target population

A second study (RD.06.SRE.18126) examined the relative bioavailability of 0.18% Mirvaso facial gel and 0.2% brimonidine ophthalmic solution under conditions of maximum use in subjects with moderate to severe erythematous rosacea. The gel was to be applied to the face once in the morning at hour 0 and reapplied at hour 4 (1 g at each time point). The ophthalmic solution was to be administered 1 drop per eye, at hour 0. Systemic exposure to 0.18% Mirvaso facial gel was below the LLQ (25 pg/mL) in all of the collected plasma samples, with the exception of one isolated sample, whereas following ocular administration of the 0.2% brimonidine tartrate ophthalmic solution, quantifiable plasma concentrations were observed in 11 of the 18 subjects. Relative bioavailability was calculated using the highest C_{max} obtained with the ophthalmic solution (100 pg/mL) and, as a conservative approach, the LLQ (25 pg/mL) was set as the C_{max} for 0.18% Mirvaso facial gel. Based on this calculation, the dermal bioavailability relative to the ophthalmic route was lower than 3%.

> **Comments:** It is not clear why the less sensitive analytical method, which had a LLQ of 25 pg/mL, rather than the method from study RD.06.SRE.18143, which had a LLQ of 10 pg/mL, was used to determine plasma concentrations of brimonidine in the 2 initial BA studies. Furthermore, the 0.5% Mirvaso gel was not examined in the BA studies in healthy subjects, that is the to-be-marketed concentration, as the higher dose may have been easier to detect in plasma. These questions have been raised in section 12.2 of this report.

4.2.1.2.3. Bioequivalence of clinical trial and market formulations

Not examined.

4.2.1.2.4. Bioequivalence of different dosage forms and strengths

A single formulation and strength is proposed for marketing in which one gram of Mirvaso gel contains 5mg (or 0.5%) of brimonidine tartrate.

4.2.1.2.5. Bioequivalence to relevant registered products

Not applicable.

4.2.1.2.6. Influence of food

Not applicable.

4.2.1.2.7. Dose proportionality

No studies examined dose-proportionality following a single administration of Mirvaso gel in healthy subjects.

4.2.1.2.8. Bioavailability during multiple-dosing

No studies examined bioavailability following multiple-dosing of Mirvaso gel in healthy subjects.

4.2.1.2.9. Effect of administration timing

No studies examined the effect of administration timing in healthy subjects.

4.2.1.3. Distribution

4.2.1.3.1. Volume of distribution

No studies examined the volume of distribution following administration of Mirvaso gel in healthy subjects

4.2.1.3.2. Plasma protein binding

No studies examined plasma protein binding of Mirvaso gel in healthy subjects, nor has the protein binding of brimonidine been studied.

4.2.1.3.3. Erythrocyte distribution

Not examined.

4.2.1.3.4. Tissue distribution

Not examined.

4.2.1.4. Metabolism

4.2.1.4.1. Interconversion between enantiomers

Not examined.

4.2.1.4.2. Sites of metabolism and mechanisms / enzyme systems involved

Not examined for Mirvaso gel; however, brimonidine is extensively metabolised by the liver.

4.2.1.4.3. Non-renal clearance

Not examined.

4.2.1.4.4. Metabolites identified in humans

4.2.1.4.4.1. Active metabolites

Not examined.

4.2.1.4.4.2. Other metabolites

Not examined.

4.2.1.4.5. Pharmacokinetics of metabolites

Not examined.

4.2.1.4.6. Consequences of genetic polymorphism

Not examined.

4.2.1.5. Excretion

4.2.1.5.1. Routes and mechanisms of excretion

Not examined for Mirvaso gel; however, urinary excretion is the major route of elimination of brimonidine and its metabolites.

4.2.1.5.2. Mass balance studies

Not examined.

4.2.1.5.3. Renal clearance

Not examined.

4.2.1.6. Intra- and inter-individual variability of pharmacokinetics

Not examined in healthy subjects; however, following administration of 0.5% Mirvaso gel in patients with facial erythema of rosacea for one day the coefficient of variation (%CV) on the C_{max} and AUC values were 60.0% and 79.9%, respectively, and following 28 days of treatment were 95.5% and 83.5%, respectively.

4.2.2. Pharmacokinetics in the target population

Two studies (Study RD.06.SRE.18126, and Study RD.06.SRE.18143) examined the PK of Mirvaso gel in patients with facial erythema of rosacea.

4.2.2.1. PK of the to-be-marketed strength (0.5%) of Mirvaso gel following a single dose.

Study RD.06.SRE.18143 examined the PKs of 0.5% Mirvaso gel following a single application in 23 patients with facial erythema of rosacea. Quantifiable plasma levels of brimonidine were detected in samples from 17 (74%) of the patients treated. Following statistical analysis of the data, in which the values below the limit of quantification were replaced by LLQ of 10 pg/mL, the mean C_{max} and $AUC_{0\text{-}24h}$ values for brimonidine were 19.44 pg/mL (SD: 11.67) and 262.11 pg.h/mL (209.39) respectively.

> **Comments:** Further to the evaluator's previous comments, it is interesting to note that although following facial application of a 0.2% dose of Mirvaso gel in the relative bioavailability study, COL-118-BAPK-101, brimonidine could not be detected in plasma, following a single application of 0.5% Mirvaso gel and utilising a more sensitive analytical method in Study RD.06.SRE.18143 plasma levels of brimonidine could be detected in 74% of subjects. Therefore, this study indicates that brimonidine is absorbed systemically, albeit at lower levels, and following a single 0.5% topical administration of Mirvaso gel, the C_{max} and AUC values of brimonidine were approximately 2.8-fold and 2.2-fold lower, respectively, than following brimonidine tartrate ophthalmic solution 0.2% after 1 day treatment comprising 1 drop to each eye every 8 hours over a 24 hour period.

4.2.2.2. Dose proportionality following a single dose

Study RD.06.SRE.18143 also examined the PKs of brimonidine following single applications of 2 strengths of Mirvaso gel, that is containing 0.18% and 0.5% brimonidine. Following administration of the 0.18% formulation once daily (q.d.) plasma levels of brimonidine could only be detected in 8 (32%) of treated subjects and the calculated C_{max} and AUC values reported were 13.07 pg/mL and 72.3 pg.h/mL, respectively. These results suggest that following a single administration of Mirvaso gel formulations containing 0.18% and 0.5% brimonidine, C_{max} of brimonidine increased less than dose-proportionally (ratio = 1.49), whereas by contrast, AUC increased greater than dose proportionally (ratio = 3.63) following single administrations.

4.2.2.3. Dose proportionality following multiple doses

A similar pattern was seen following 29 days of q.d. dosing with formulations of Mirvaso gel containing 0.18% and 0.5% brimonidine and the C_{max} and AUC for the higher dose was 1.35-fold and 3.49-fold higher, respectively, than following the 0.18% dose.

4.2.2.4. Accumulation and steady-state

Although there was evidence that there was increased exposure after 15 days of treatment in the 0.5% q.d. and the 0.18% b.i.d treatment groups, overall systemic exposures for the first day of application were similar to those observed after 29 days (Day 32) of application in all treatment groups, thus suggesting that there was little to no drug accumulation throughout the treatment duration (4 weeks) for any of the tested concentrations and dose regimens and that steady state conditions were achieved.

4.2.2.5. Effect of time of dosing

Study RD.06.SRE.18143 also examined the PKs of brimonidine following b.i.d. dosing of 0.18% Mirvaso gel, that is, total daily dose of 0.36% brimonidine following 29 days of dosing. Compared to the 0.5% dose formulation of Mirvaso gel given q.d. C_{max} was similar for the two treatments (ratio 0.5% q.d./0.18% b.i.d. = 1.07) whereas the AUC was approximately 33% higher for the 0.5% q.d. dose.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

Not examined.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

Not examined.

> **Comments:** Although studies in patients with hepatic or renal impairment would be difficult to conduct reliably due to the low systemic absorption of brimonidine following topical application of Mirvaso gel, PK studies with 0.5% gel indicate that brimonidine can be detected in plasma. Therefore, given that brimonidine is extensively metabolised by the liver and that it is primarily excreted in urine, patients with impaired hepatic and/or renal function would be expected to have higher levels of exposure to brimonidine than healthy subjects and systemic AEs may be more likely to occur in these patients.

4.2.3.3. Pharmacokinetics according to age

Not examined.

4.2.3.4. Pharmacokinetics related to genetic factors

Not examined.

4.2.3.5. Pharmacokinetics {in other special population / according to other population characteristic}

Not examined.

> **Comment:** The PK/PD of Mirvaso has been primarily undertaken in Caucasian subjects therefore the effect of race on the PK/PD is unknown.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

Not examined.

4.2.4.2. Clinical implications of in vitro findings

Not examined.

> **Comments:** Given that brimonidine is absorbed systemically following topical application of 0.5% Mirvaso gel, albeit at lower levels than the ocular route, can the sponsor please justify why drug-drug interaction studies with other pharmaceutical agents used in the treatment of facial rosacea, such as low-dose clonidine, long acting beta-blockers, antibiotics or retinoids have not been conducted?

4.3. Evaluator's overall conclusions on pharmacokinetics

- Mirvaso is a topical aqueous gel, which is absorbed through the epidermis.
- The absolute bioavailability of Mirvaso gel is unknown.
- Dermal bioavailability of 0.18% Mirvaso gel compared to the ophthalmic solution (100 pg/mL) was less than 3%.
- In the target population, quantifiable plasma levels of brimonidine were detected in samples from 74% of the patients following a single application of 0.5% Mirvaso gel and the calculated mean C_{max} and $AUC_{0\text{-}24h}$ values for brimonidine were 19.44 pg/mL and 262.11 pg.h/mL, respectively.

- Following administration of the 0.18% formulation q.d. plasma levels of brimonidine could only be detected in 32% of treated subjects and the calculated C_{max} and AUC values reported were 13.07 pg/mL and 72.3 pg.h/mL, respectively.
- Following a single administrations of Mirvaso gel containing 0.18% or 0.5% brimonidine the C_{max} of brimonidine increased less than dose-proportionally (ratio = 1.49), whereas, AUC increased greater than dose proportionally (ratio = 3.63).
- Following 29 days of q.d. dosing with formulations of Mirvaso gel containing 0.18% and 0.5% brimonidine a similar pattern was seen and the C_{max} and AUC for the higher dose was 1.35-fold and 3.49-fold higher, respectively, than following the 0.18% dose.
- Following 15 days of treatment with either 0.5% q.d. or 0.18% b.i.d exposure to brimonidine increased. However, after 29 days of treatment there was little to no drug accumulation and steady state conditions were achieved.
- Following 29 days administration of either the 0.18% facial gel b.i.d. or the 0.5% dose formulation q.d. the C_{max} Values were similar (ratio 0.5% q.d./0.18% b.i.d. = 1.07), whereas the AUC was approximately 33% for the 0.5% q.d. dose.

4.4. Summary of the evaluator's comments on the PK

- Why was the less sensitive analytical method, which had a LLQ of 25 pg/mL, rather than the method from study RD.06.SRE.18143, which had a LLQ of 10 pg/mL, used to determine plasma concentrations of brimonidine in the 2 initial BA studies?
- Why was 0.5% Mirvaso gel not examined in the BA studies in healthy subjects, that is the to-be-marketed concentration, as the higher dose may have been easier to detect in plasma?
- Following a single 0.5% topical administration of Mirvaso gel, the C_{max} and AUC values of brimonidine were approximately 2.8 fold and 2.2 fold lower, respectively, than following brimonidine tartrate ophthalmic solution 0.2% after 1 day treatment comprising 1 drop to each eye every 8 hours over a 24 hour period.
- Given that brimonidine is extensively metabolised by the liver and that it is primarily excreted in urine, patients with impaired hepatic and/or renal function would be expected to higher levels of exposure than healthy subjects.
- The PK/PD of Mirvaso has been primarily undertaken in Caucasian subjects therefore the effect of race on the PK/PD is unknown.
- Can the sponsor please justify why drug-drug interaction studies with other pharmaceutical agents used in the treatment of facial rosacea, such as low-dose clonidine, long acting beta-blockers, antibiotics or retinoids have not been conducted?

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic.

Table 2. Pharmacodynamic studies.

PD Topic	Subtopic	Study ID	Primary aim of the study
Primary Pharmacology	Single-dose	COL-118-ROSE-101	Dose-response, tolerability and duration of effect
		RD.06.SRE.18144	PD profiles of three different concentrations
		COL-118-ROSE-102	Impact of formulation on the PD profile
	Multiple-dose	COL-118-ROSE-201	PD profiles of three different concentrations
Secondary Pharmacology	Effect on QTc	RD.06.SRE.18139	Thorough QT
	Phototoxicity	COL-118-Phototoxicity-104	Phototoxicity of 0.2% gel
		RD.06.SRE.18189	Phototoxicity of 0.07%, 0.18%, and 0.50% gel
		RD.06.SRE.18124	Photosensitisation potential of 0.07%, 0.18%, and 0.50% gel
	Tolerability	RD.06.SRE.18123	Sensitisation and local tolerability of 0.07%, 0.18%, and 0.5% gel
		RD.06.SRE.18125	Cumulative irritancy following repeated dosing with 0.07%, 0.18%, and 0.5% gel

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

Brimonidine tartrate is a highly selective α2-adrenergic receptor agonist with potent vasoconstrictive/vasostabilising activity. As such, brimonidine tartrate is expected to offer a positive effect on inhibiting and reversing cutaneous erythema caused by vasomotor instability.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

The PK Study RD.06.SRE. also examined the efficacy of 0.18% Mirvaso gel in 20 subjects with moderate to severe erythematous rosacea based upon two subjective markers: Patient's Self-Assessment (PSA) Scale; and the Clinician's Erythema Assessment (CEA) which were assessed pre-dose and up to 8 hours post-dose. Improvement of erythema was observed with both scales (Table 3) and significant correlation coefficients for CEA and PSA were calculated at pre dose and post dose ($p = 0.047$ at Pre-dose and $p \leq 0.001$ at 1 to 8 hours post dose).

Table 3. Study RD.06.SRE.18126. CEA and PSA mean pre dose score and mean change from pre dose

Statistic/ Time Point	Sequence I and II					
	Treatment A N=19		Treatment B N=16 to 18		p-value[a]	
	CEAS	PSA	CEAS	PSA	CEAS	PSA
Mean Score at Pre-dose	2.9	3.1	2.9	3.1	NA	NA
Mean Change from Pre-dose at:						
Hour 1	-0.1	-0.2	0.1	0.0	0.240	0.230
Hour 2	-0.4	-0.5	-0.1	-0.1	0.100	0.015
Hour 3	-0.6	-0.6	-0.2	-0.1	0.074	0.011
Hour 4	-1.2	-0.9	-0.1	-0.2	<0.001	0.005
Hour 5	-1.2	-1.2	0.0	-0.2	<0.001	0.001
Hour 6	-1.3	-1.5	-0.3	-0.4	0.001	<0.001
Hour 7	-1.4	-1.5	-0.3	-0.4	<0.001	<0.001
Hour 8	-1.4	-1.7	-0.2	-0.3	<0.001	<0.001

Sequence I = Treatment A then Treatment B, Sequence II = Treatment B then Treatment A.
Treatment A = COL-118 facial gel + placebo ophthalmic solution, Treatment B = vehicle facial gel + brimonidine tartrate ophthalmic solution.
[a] p-values were calculated for Sequence I and II by using an ANCOVA based on change from Pre-dose at time points from 1 to 8 hours and all variables were analyzed as continuous variables.
NA=not applicable

Further to this study a series of more comprehensive PD studies examined the dose response relationships, duration of effect and the impact of different formulations on the efficacy of Mirvaso gel.

5.2.2.1.1. Single administration

The first of these, COL-118-ROSE-101 evaluated the dose response relationship following single administrations of placebo (diluent), 0.0125%, 0.025%, 0.10% or 0.20% Mirvaso gel to a 1 cm^2 area on the malar region of the face of subjects with rosacea with moderate to severe erythema. Efficacy was evaluated by chromameter measurements and by the CEA. The chromameter values were similar pre dosing in all facial areas, with means from 18.8 to 21.1 (overall range 11.7 to 27.3) (Table 4). By 15 minutes post Mirvaso administration, chromameter values had decreased significantly following all concentrations of Mirvaso gel ($p \leq 0.019$), whereas readings were unchanged following placebo. By 2 hours post dose, statistically significant decreases were observed for all Mirvaso gel concentrations, with mean decreases of 1.6, 2.1, 3.0, 3.1, and 4.5 at 0.0125%, 0.025%, 0.05%, 0.1%, and 0.2%, respectively. By contrast, 2 hours following placebo administration there was a mean increase of 0.4. Statistically significant decreases continued through 5 hours with all Mirvaso concentrations, and through 8 hours, the last evaluated time-point, with 0.05%, 0.1%, and 0.2%. The magnitude of the change appeared to be dose related. By contrast, the CEA scores did not change following drug administration, with scores of 3 reported for both cheeks of all patients.

Table 4. Study COL-118-ROSE-101. Summary of chromameter changes from pretreatment by time.

Time	COL-118 Concentration					
	0.00%	0.0125%	0.025%	0.05%	0.1%	0.2%
Pre-dose						
Mean (SD)	18.8 (2.44)	19.5 (2.56)	20.9 (2.79)	21.1 (3.78)	19.8 (3.04)	19.5 (3.09)
15 minutes						
Mean (SD)	0.1 (1.13)	-1.6 (2.23)	-1.5 (2.75)	-2.1 (1.63)	-2.2 (3.34)	-3.0 (2.54)
p-value	0.662	0.003	0.019	< 0.001	0.008	< 0.001
30 minutes						
Mean (SD)	0.1 (1.23)	-1.6 (2.23)	-2.1 (2.91)	-2.3 (2.20)	-2.6 (2.59)	-3.6 (2.35)
p-value	0.602	0.003	0.004	< 0.001	< 0.001	< 0.001
45 minutes						
Mean (SD)	-0.0 (1.01)	-1.7 (2.17)	-2.1 (2.95)	-2.1 (2.39)	-2.5 (2.55)	-4.0 (2.36)
p-value	0.898	0.002	0.005	< 0.001	< 0.001	< 0.001
60 minutes						
Mean (SD)	-0.1 (1.62)	-1.5 (2.20)	-2.2 (2.90)	-2.8 (2.29)	-3.7 (2.60)	-4.3 (2.62)
p-value	0.880	0.006	0.002	< 0.001	< 0.001	< 0.001
2 hours						
Mean (SD)	0.4 (1.37)	-1.6 (2.41)	-2.1 (3.34)	-3.0 (2.42)	-3.1 (2.46)	-4.5 (2.43)
p-value	0.201	0.007	0.010	< 0.001	< 0.001	< 0.001
3 hours						
Mean (SD)	0.5 (1.86)	-1.6 (2.73)	-2.6 (3.50)	-3.2 (2.16)	-3.3 (2.45)	-4.3 (2.59)
p-value	0.244	0.016	0.003	< 0.001	< 0.001	< 0.001
4 hours						
Mean (SD)	0.6 (1.78)	-1.3 (2.68)	-2.0 (3.32)	-3.1 (2.30)	-2.7 (2.69)	-4.1 (2.82)
p-value	0.140	0.036	0.012	< 0.001)	< 0.001	< 0.001
5 hours						
Mean (SD)	0.8 (1.79)	-1.5 (2.44)	-2.0 (3.19)	-3.1 (2.26)	-2.8 (3.31)	-3.8 (2.78)
p-value	0.048	0.012	0.011	< 0.001	< 0.001	< 0.001
6 hours						
Mean (SD)	0.9 (1.27)	-1.5 (2.49)	-1.3 (2.96)	-2.3 (2.54)	-2.2 (3.13)	-3.3 (2.93)
p-value	0.006	0.012	0.060	< 0.001	0.004	< 0.001
7 hours						
Mean (SD)	1.1 (1.25)	-0.5 (1.98)	-0.5 (2.93)	-1.7 (2.35)	-1.5 (3.12)	-2.3 (2.96)
p-value	< 0.001	0.227	0.422	0.004	0.035	0.002
8 hours						
Mean (SD)	0.9 (1.22)	-0.8 (1.96)	-0.3 (2.50)	-1.3 (1.79)	-1.5 (2.44)	-2.1 (2.63)
p-value	0.003	0.091	0.613	0.004	0.009	0.002

Study RD.06.SRE.18144 evaluated the PD profiles of three different concentrations of Mirvaso gel (0.07%, 0.18%, and 0.50%), following a single administration to subjects with stable moderate to severe erythematotelangiectatic rosacea (ETR). With the exception of PSA scores, the baseline scores for all other parameters were comparable between treatment groups. Based on the criterion of 1 grade improvement on CEA and PSA, the response rates were 83.9% (0.50%), 80.6% (0.18%), 75% (0.07%), and 28.1% (vehicle). The median times to onset of 1 grade improvement on CEA and PSA were 2.98 hours (0.50%), 2.08 hours (0.18%), and 2.03 hours (0.07%) post dose. For vehicle, the median time to onset was not available because less than 50% of the subjects had a 1 grade improvement in scores. Comparisons of the response curves were statistically significant ($p < 0.05$) for the individual CEA and PSA responses in the 0.50% and 0.18% groups. For the combined CEA and PSA, the comparisons of time to 1 grade improvement were significant ($p < 0.05$) for each active group versus vehicle. The median duration of effect was more than 7 hours in each of the Mirvaso gel groups and approximately 3 hours in vehicle group.

For 2 grade improvement on combined CEA and PSA, the response rates were 54.8% (0.50%), 32.3% (0.18%), 25% (0.07%), and 12.5% (vehicle). The median time to onset of 2 grade improvement was 10.03 hours after dosing for the 0.50% group. For the other groups, the estimates were not available because less than 50% of the subjects reached the response

criterion. Correspondingly, the median duration of effect was approximately 6 hours in the 0.50% group and 3 to 4 hours in the remaining groups.

Although the response rates for maximum improvement on CEA, PSA, and both CEA and PSA did not show a dose ordering trend, higher response rates were observed for each concentration of Mirvaso gel (0.50%, 0.18%, and 0.07%) relative to the vehicle gel group. For the 0.50% and 0.18% groups, the time to maximum improvement was statistically significant for the CEA, PSA, and CEA and PSA Kaplan-Meier curves versus vehicle gel. No dose ordering trend was observed for duration of effect.

The CEA and PSA were to be completed at 13 time points post dose, over a 12 hour observation period. For the mean number of time points with CEA ≤ 1 and both CEA and PSA ≤ 1, the largest effects were seen in the 0.50% group and were statistically significant ($p < 0.05$) versus each of the other active groups as well as versus vehicle. The mean number of time points with CEA ≤ 1 ranged from 0.7 in the vehicle group to 5.0 in the 0.50% group. The mean number of time points with CEA and PSA ≤ 1 ranged from 0.5 in the vehicle group to 2.8 in the 0.50% group.

For the minimum and average changes from baseline for the CEA, each active group showed significant ($p < 0.05$) improvements compared to vehicle (Table 5). Additionally, in the 0.50% group, the minimum and average post dose changes in both CEA and PSA showed significant improvements ($p < 0.05$) for each parameter versus vehicle.

Table 5. Study RD.06.SRE.18144. CEA and PSA mean change from pre dose, ITT population

Criteria During 12-hour Treatment Interval	CD07805/47 Gel			Vehicle Gel N=32
	0.50% N=31	0.18% N=31	0.07% N=28	
Baseline Mean CEA	3.3	3.3	3.2	3.2
Baseline Mean PSA	3.2	3.2	3.5	3.1
Minimum Post-dose				
CEA				
Mean (SD)	1.3 (0.77)	1.4 (0.89)	1.8 (1.07)	2.3 (0.81)
Mean Change (SD)	-2.0 (0.82)	-1.8 (0.82)	-1.4 (0.84)	-0.9 (0.80)
p-value				
vs. 0.18%	0.420	-	-	-
vs. 0.07%	**0.010**	0.068	-	-
vs. Vehicle	**<0.001**	**<0.001**	**0.021**	-
PSA				
Mean (SD)	1.4 (0.89)	1.7 (0.93)	2.0 (1.00)	2.2 (1.00)
Mean Change (SD)	-1.7 (0.96)	-1.4 (0.85)	-1.5 (0.92)	-0.9 (1.01)
p-value				
vs. 0.18%	0.177	-	-	-
vs. 0.07%	0.068	0.575	-	-
vs. Vehicle	**<0.001**	**0.028**	0.136	-
Average Post-dose				
CEA				
Mean (SD)	1.92 (0.727)	2.23 (0.648)	2.48 (0.782)	2.78 (0.561)
Mean Change (SD)	-1.34 (0.634)	-1.03 (0.588)	-0.74 (0.576)	-0.44 (0.541)
p-value				
vs. 0.18%	**0.030**	-	-	-
vs. 0.07%	**<0.001**	0.050	-	-
vs. Vehicle	**<0.001**	**<0.001**	**0.039**	-
PSA				
Mean (SD)	2.06 (0.790)	2.46 (0.691)	2.62 (0.752)	2.60 (0.766)
Mean Change (SD)	-1.10 (0.835)	-0.70 (0.546)	-0.88 (0.529)	-0.46 (0.830)
p-value				
vs. 0.18%	**0.029**	-	-	-
vs. 0.07%	0.064	0.833	-	-
vs. Vehicle	**<0.001**	0.239	0.196	-

P-values were based on ANCOVA model: Change in score = Baseline score, Analysis Center, Treatment.
SD=standard deviation

All active Mirvaso groups demonstrated significant reductions in Chromameter results versus vehicle gel and 0.50% showed statistically significant reductions versus the 0.18% and 0.07% treatment groups.

Study COL-118-ROSE-102 evaluated the impact of different formulations (cream and gel) on the PD profile of Mirvaso gel applied to a 1 cm^2 area on the malar region of the face in subjects diagnosed with rosacea with moderate to severe erythema. The chromameter values were similar pre dosing in all facial areas, with means from 17.8 to 21.0 (overall range 11.0 to 28.8). Fifteen minutes following dosing, chromameter values had decreased significantly with all formulations except gel A, which was too tacky to assess. The decreases from screening were statistically significant for all formulations through 8 hours, the last evaluated time point. Mean T_{max} occurred 3.6 to 4.2 hours following treatment for all formulations, with half of the maximum effect achieved in less than 1 hour for gels A and C, and 1.1 to 1.4 hours for the other formulations. The maximum change from baseline was 4.2 to 5.6. As judged visually by the investigator, for all patients the effect had not been lost at the last time point, 8 hours.

5.2.2.1.2. Multiple-administrations

Study COL-118-ROSE-201 evaluated the dose-response relationship and PD profile of 3 concentrations (0.02%, 0.07% and 0.20%) of Mirvaso gel applied to the faces of subjects with rosacea with moderate to severe erythema and telangiectasia on the malar area. Each patient applied a small amount (approximately 1g) of the assigned study drug to the affected area of the face each morning and as needed thereafter, but no more often than once every 4 hours and no more than 3 times per day for 28 days. The primary endpoint, reduction in erythema, CEA, across all time-points (0-8 hour) and all visits (Day 0, Day 14, and Day 28), showed a clear dose-response relationship (Table 6). Both the 0.2% and 0.07% groups had significantly greater changes from Baseline than the vehicle group ($p < 0.001$ and $p < 0.05$, respectively). A dose response relationship was also apparent using the dataset for the 0 to 4 hour observation period. Correlations of dose and reduction in CEA were statistically significant ($p < 0.001$) for both 0 to 4 and 0 to 8 hour AUCs. The efficacy was consistent and reproducible over the 3 study visits (days 0, 14, and 28; $p < 0.001$). The reduction in investigator's global assessment (IGA) was also dose dependent (Table 7). Averaged across all visits the 0.2% group had significantly greater changes from baseline than the vehicle group ($p < 0.05$ for the 0 to 4 hour evaluation and $p < 0.01$ for the 0 to 8 hour evaluation. The p value for the dose response was statistically significant for the 0 to 4 hour and 0 to 8 hour evaluations across all visits ($p < 0.01$). In the Day 28 responder analysis, with success defined as an IGA score of 0 or 1 or an improvement of at least 2 points, the differences among the treatment groups were statistically significant at Hours 1 through 4 ($p < 0.05$, Mantel-Haenszel Chi Square statistics). At Hour 3, 37.5% of patients in the 0.2% group, 13.6% in the 0.07% group, 15.0% in the 0.02% group, and 0% in the vehicle group were successes. Telangiectasia (CTG) and total inflammatory lesion count neither improved nor worsened following treatment. Peak efficacy was significantly higher in the 0.2% group than in the vehicle group on Days 0, 14, and 28 when represented by the greatest change from Baseline in CEA and on Day 28 when represented by the greatest change from Baseline in IGA. Peak efficacy was consistent and reproducible across the 3 study visits. An onset of effect was seen as early as 15 minutes after study drug application and the duration of effect was about 5 hours.

Table 6. Study COL-118-ROSE-201. Summary of mean CEA derived AUC averaged change scores

Variable	Brimonidine Gel			Vehicle (N = 28)
	0.2% (N = 27)	0.07% (N = 29)	0.02% (N = 26)	
CEA				
AUC 0-4 hours				
Mean (SD)	-4.140 (2.691)	-3.316 (2.714)	-2.529 (2.426)	-1.795 (2.104)
p-value[a]	< 0.0001	< 0.0001	< 0.0001	0.0001
AUC 0-8 hours				
Mean (SD)	-5.782 (4.061)	-4.609 (3.981)	-3.452 (3.606)	-2.211 (2.549)
p-value[a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001

p-value testing the null hypothesis that each AUC mean change is zero.

Table 7: Study COL-118-ROSE-201. Summary of mean IGA and CTG derived AUC averaged change scores

Variable	Brimonidine Gel			Vehicle (N = 28)
	0.20% (N = 27)	0.07% (N = 29)	0.02% (N = 26)	
IGA				
AUC 0-4 hours				
Mean (SD)	-2.918 (2.449)	-2.171 (2.038)	-1.747 (1.764)	-1.472 (1.885)
p-value[a]	< 0.0001	< 0.0001	< 0.001	0.0003
AUC 0-8 hours				
Mean (SD)	-4.048 (3.428)	-3.142 (3.206)	-2.446 (2.943)	-1.787 (2.371)
p-value[a]	< 0.0001	< 0.0001	0.0003	0.0005
CTG				
AUC 0-4 hours				
Mean (SD)	-2.133 (2.425)	-2.034 (1.925)	-1.553 (1.720)	-2.146 (2.163)
p-value[a]	0.0001	< 0.0001	0.0001	< 0.0001
AUC 0-8 hours				
Mean (SD)	-3.225 (4.094)	-2.943 (2.942)	-2.450 (3.032)	-2.920 (3.058)
p-value[a]	0.0004	< 0.0001	0.0004	< 0.0001

p-value testing the null hypothesis that each AUC mean change is zero.

5.2.2.2. Secondary pharmacodynamic effects

5.2.2.2.1. Thorough QTc

Study RD.06.SRE.18139 (Table 8) evaluated the effect of a single ocular administered dose of brimonidine tartrate (two drops of a 0.2% solution to each eye), on ventricular repolarisation in healthy subjects compared to placebo and/or 400 mg moxifloxacin, and to evaluate the change from baseline of QT/QTc interval corrected by QTcB, QTcF, and QTcI (subject specific) at the T_{max} using 12-lead ECGs. Moxifloxacin increased mean QTcI by 8.48 to 11.51 ms compared to placebo indicating that the assay was sensitive enough to detect changes in QTc. For brimonidine ophthalmic solution QTcI was the results indicated that the largest observed difference from placebo was 2.63 msec, three hours after the dose, and the largest upper confidence bound (UCB) was 4.58 msec at the same time interval. Therefore, brimonidine does not prolong the QTc interval compared to placebo.

Table 8: Study RD.06.SRE.18139. Treatments administered

	Brimonidine tartrate Ophthalmic Solution 0.2%	Brimonidine tartrate Placebo Advanced Eye Relief™	Moxifloxacin Oral Placebo	Moxifloxacin Oral 400 mg Tablet
Treatment A (Brimonidine tartrate Supra-Therapeutic Dose)	2 drops in each eye	None	One over-encapsulated placebo capsule	None
Treatment B (Placebo)	None	2 drops in each eye	One over-encapsulated placebo capsule	None
Treatment C (Moxifloxacin 400 mg)	None	2 drops in each eye	None	One over-encapsulated Moxifloxacin 400 mg capsule

5.2.2.2.2. Photo-toxicity and sensitisation

Three studies examined the potential for a range of concentrations of Mirvaso gel (0.07% to 0.50%) to produce photo-toxicity[2] and sensitisation when applied topically to human skin.

[2] A phototoxic substance will produce either a wheal-and-flare response immediately after exposure to UV radiation, or intense erythema and oedema 24 and 48 hours later.

Study COL-118-Phototoxicity-104 involved a one-time 24 hour occluded application of Mirvaso gel 0.2% and its vehicle to duplicate sites on the mid or lower back area followed by a single exposure to UV radiation (UVB+UVA) in 30 healthy Caucasian subjects. However under these conditions, the Mirvaso gel 0.2% and its vehicle did not possess a detectable phototoxicity potential in human skin.

In Study RD.06.SRE.18189 phototoxic reactions were graded as negative, equivocal, or positive and were assessed at 48 hours after irradiation in 35 healthy Caucasian subjects. In addition, local skin reactions were assessed at 30 minutes, 24 hours and 48 hours after irradiation. Within 30 minutes of irradiation, 51% of subjects exhibited mild erythema in at least one of the evaluated sites, including 40% at one or both of the untreated sites. The immediate responses of mild erythema appeared to be unrelated to the study drug concentration, and were consistent with normal physiologic responses to the direct UV exposure employed in the study. At the untreated and vehicle-treated sites, the incidence of erythema was higher at the irradiated sites compared with the non-irradiates sites. Conversely, for all 3 concentrations of active Mirvaso gel, the erythema incidence was lower at the irradiated sites compared with the non-irradiated sites and no increase in erythema incidence with increasing concentrations was observed suggesting that the active ingredient did not contribute to the observed responses. At 24 and 48 hours post irradiation, the observed skin responses overall were typical of expected radiation-induced erythema, with no evidence of additive effects from the study products. With one exception of one subject (hereafter in this section referred to as “that subject”), none of the subjects showed a pattern of response post-irradiation suggestive of a photo-mediated toxicity of the study products. That subject initially had moderate erythema at all irradiated sites treated with active or vehicle gel and at non-irradiated sites treated with mid-dose or high-dose gel. These reactions regressed to mild erythema by approximately 48 hours post irradiation. Non irradiated sites treated with low dose and vehicle gel in this subject initially had mild erythema, which persisted through 48 hours post irradiation. These findings were suggestive of a dose related, contact irritancy specific to this subject, rather than a true phototoxic reaction. As the response was exacerbated by 1 grade with UV exposure only in the case of the vehicle and low dose gels, any potential photo irritant would have to be an excipient in the vehicle itself, rather than the active component. However, given the relatively marginal change from a Grade 1 to Grade 2 reaction at the sites in question, and, more importantly, that there are no known phototoxic components in the vehicle gel, this specific finding is most likely due to variability in the irritation response. After a 2 week rest period, that subject underwent a 48 hour rechallenge exposure to the study drugs with no irradiation. After patch removal, all sites treated with active or vehicle gel showed mild erythema initially and at 48 hours post-exposure, with no reaction at the untreated site. These observations were consistent with a subject specific contact irritation to the test products. As reactions were noted for both the active and vehicle products, the irritation reaction was likely being driven by a vehicle gel excipient, possibly propylene glycol, rather than the active compound. It is considered highly unlikely that the reactions seen in that subject were due to phototoxic mechanism.

Study RD.06.SRE.18124 (Table 9) examined the photosensitisation potential of three concentrations of Mirvaso gel (0.07%, 0.18%, and 0.50%) and corresponding vehicle gel after repeated applications in 57 healthy, predominantly Caucasian subjects. Of the 52 subjects who completed the challenge phase, 100% had a negative photosensitisation score as determined by the investigator based on the Sensitisation Reaction Evaluation. None of the subjects showed a pattern of response suggestive of a photosensitivity to the study products. During challenge, no subject had any skin reaction greater than mild erythema (grade 1) at any of the irradiated sites: 94% of subjects had mild erythema in at least one skin site, including 92.5% of subjects who had mild erythema at the white petrolatum (negative control) site, which is consistent with normal physiologic responses to repeated MED levels of UV exposure. The mean skin reaction scores ranged from 0.48 in the Mirvaso gel 0.50% group to 0.55 in the vehicle gel group. No subject had a skin reaction at any test site (irradiated or non-irradiated) at the 1 hour observation on Day

37. On Day 39 (approximately 48 hours after patch removal), 2 subjects (3.8%) had mild erythema in at least one irradiated site treated with a study product and 3 subjects (5.8%) had mild erythema at the untreated irradiated site. No reactions occurred at any non-irradiated site. At the 72 hour (Day 40) assessment, no subject had any reaction at any test.

Table 9. Study RD.06.SRE.18124. Test materials and administration information

	CD07805/47 Gel			CD07805/47 Vehicle	White Petrolatum
	0.07%	0.18%	0.50%	0%	100%
Dose Regimen	Twice weekly for 3 weeks (Induction Phase); single application to 2 naïve skin sites (Challenge Phase)				
Study Product Dosage	0.20 mL per test patch application (using sterile syringe)				
Test Patch Site UV Irradiation Dosage	Induction Phase: 2 x MED of UVA/UVB (Week 1) and 3 X MED of UVA/UVB (Weeks 2 and 3). Challenge Phase: 0.7 x MED of UVA/UVB followed by irradiation with 10 J/cm^2 of UVA radiation.				
Route of Administration	Topically applied under an occlusive patch to a test sites on the mid-back. (Induction Phase) or upper back (Challenge Phase)				
Frequency	Two applications per week for 3 consecutive weeks; after a 2-week rest period, one application to each of 2 skin sites.				
Number of Applications	8 applications (6 applications in the Induction Phase and 2 applications in the Challenge Phase)				

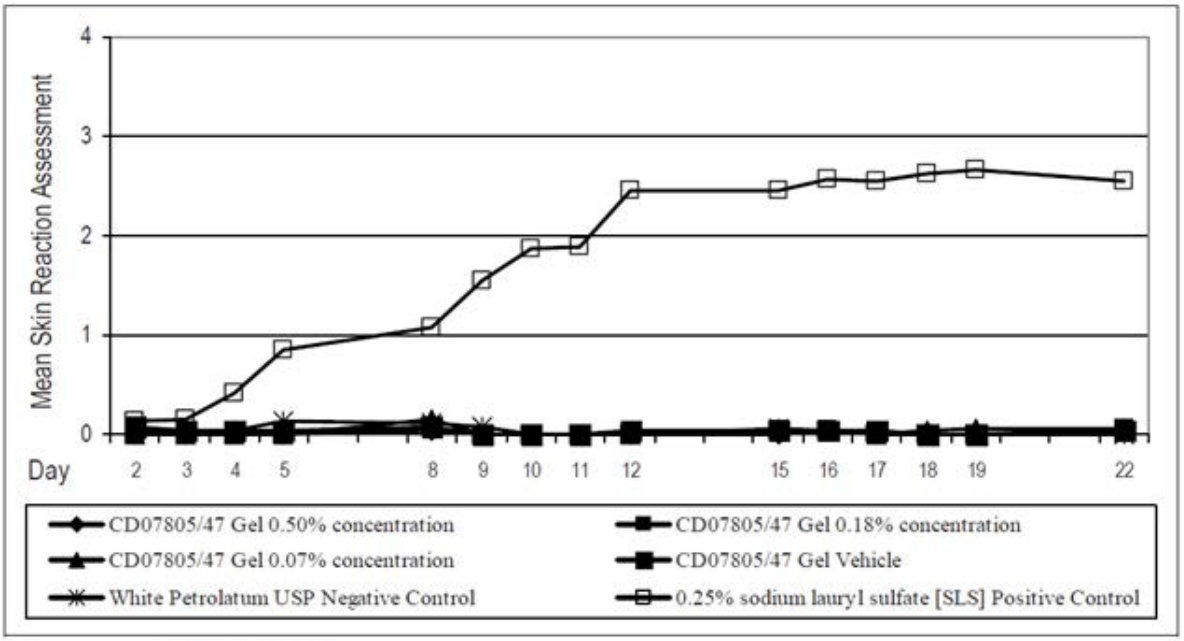
5.2.2.2.3. Tolerability and irritancy

Study RD.06.SRE.18123 examined the sensitisation potential and local tolerability of three concentrations of Mirvaso gel (0.07%, 0.18%, and 0.5%) after applications to the skin of 247 healthy, predominantly Caucasian subjects. During the challenge stage of this study, the test product was applied under occlusive patches to naïve skin. Approximately 48 hours later, the patches were removed and a Skin Reaction Assessment of the designated skin site was performed approximately 15 to 30 minutes after patch removal. Forty-eight hours following patch removal, the Skin Reaction Assessment and the Sensitisation Reaction Evaluation of the skin sites were performed. Overall, the results of this study indicated that there was no apparent correlation between the increase in the concentration of the active ingredient and the appearance or intensity of topical erythema/irritation. Each active test concentration, the gel vehicle, and the white petrolatum produced no reaction in 95% to 96% of test sites on any given evaluation day, mild erythema in 4% to 5% of test sites on any given evaluation day, and only isolated instances of moderate erythema and/or erythema with vesicles or erosion or bullae. In addition, there were no confirmed cases of contact sensitisation for any of the Mirvaso concentrations, including the vehicle gel, reported during the study. However, six subjects (2.9%) presented equivocal results at the challenge phase to one or more test compounds, where the investigator was of the opinion that there was uncertainty as to whether sensitization had occurred. Of these 6 subjects, 5 participated in a confirmatory rechallenge, where it was shown that all sites patched with the test products in question were negative for sensitisation.

Study RD.06.SRE.18125 of cumulative irritancy potential of repeated applications of three concentrations of Mirvaso gel (0.07%, 0.18%, and 0.5%) to the skin of 38 healthy, Caucasian subjects. In this study test products were applied under occlusive patches to designated skin sites on the subject's back Monday through Friday for three consecutive weeks. Patches were kept in place throughout the weekends. Overall, there was no apparent relationship between the increase in the concentration of active ingredient of Mirvaso and the appearance or intensity of topical erythema/irritation; the gel vehicle had the largest number of days/evaluations at which mild erythema was observed when compared to the gel products containing active ingredient (Figure 1). White petrolatum produced moderate erythema in one subject. The positive control, sodium lauryl sulphate produced the highest degree of erythema and the largest numbers of days/evaluations where erythema of varying intensity was observed. Based on the mean cumulative irritancy index (MCII or average of irritancy scores across all study

visits) for each product, the test articles were ranked and sites patched with the higher concentrations of Mirvaso gel (0.5% and 0.18%) exhibited slightly less irritation (MCII = 0.01) than the weakest concentration (0.07%)(MCII = 0.02) and Gel Vehicle (MCII = 0.02). The three concentrations of Mirvaso gel and the Gel Vehicle produced slightly less irritation than the negative control (MCII = 0.03) and markedly less irritation than the positive control (MCII = 1.69).

Figure 1. Study RD.06.SRE.18125. Mean irritation scores at each patch scoring.



Data Source: Section 14, Table 14.3.4.3.
Evaluation Key:
Day 2=Eval. 1 Day 5=Eval. 4 Day 10=Eval. 7 Day 15=Eval. 10 Day 18=Eval. 13
Day 3=Eval. 2 Day 8=Eval. 5 Day 11=Eval. 8 Day 16=Eval. 11 Day 19=Eval. 14
Day 4=Eval. 3 Day 9=Eval. 6 Day 12=Eval. 9 Day 17=Eval. 12 Day 22=Eval. 15

5.2.2.2.4. Effect on IOP

Comments: Although not as potent as the ophthalmic formulation, but consistent with the systemic absorption of brimonidine, all three PK studies (COL-118-BAPK-101, RD.06.SRE.18126 and RD.06.SRE.18143) indicated that following topical application of Mirvaso gel there was a reduction in IOP of between 1 and 2 mmHg.

5.2.2.2.5. Time course of pharmacodynamic effects

Study COL-118-ROSE-101, which evaluated the dose-response relationship following single administrations of placebo (diluent), 0.0125%, 0.025%, 0.10% or 0.20% Mirvaso gel identified that by 15 minutes post administration, chromameter values decreased significantly following all concentrations of Mirvaso gel ($p \leq 0.019$). By 2 hours post dose, statistically significant decreases were observed for all Mirvaso gel concentrations, with mean decreases of 1.6, 2.1, 3.0, 3.1, and 4.5 at 0.0125%, 0.025%, 0.05%, 0.1%, and 0.2%, respectively. Statistically significant decreases continued through 5 hours with all Mirvaso concentrations, and through 8 hours, the last evaluated time point, with 0.05%, 0.1%, and 0.2%.

5.2.3. Relationship between drug concentration and pharmacodynamic effects

Please Section 5.2.2.1 Primary pharmacodynamic effects of this report.

5.2.4. Genetic-, gender- and age-related differences in pharmacodynamic response

Not examined.

5.2.5. Pharmacodynamic interactions

Not examined.

5.3. Evaluator's overall conclusions on pharmacodynamics

Brimonidine tartrate is a highly selective α2-adrenergic receptor agonist with potent vasoconstrictive/vasostabilising activity.

5.3.1. Primary PD in target population

5.3.1.1. Single administration

- Fifteen minutes following administration of 0.0125%, 0.025%, 0.10% or 0.20% Mirvaso gel chromameter values had significantly decreased ($p \leq 0.019$).
- By 2 hours post dose, statistically significant decreases were observed for all Mirvaso gel concentrations, with mean decreases of 1.6, 2.1, 3.0, 3.1, and 4.5 at 0.0125%, 0.025%, 0.05%, 0.1%, and 0.2%, respectively.
- Statistically significant decreases continued through 5 hours with all Mirvaso concentrations, and through 8 hours, the last evaluated time point, with 0.05%, 0.1%, and 0.2%.
- The magnitude of the change appeared to be dose related.
- Based on the criterion of 1-grade improvement on CEA and PSA, the response rates were 83.9% (0.50% Mirvaso gel), 80.6% (0.18%), 75% (0.07%), and 28.1% (vehicle).
- The median times to onset of 1-grade improvement on CEA and PSA were 2.98 hours (0.50% Mirvaso gel), 2.08 hours (0.18%), and 2.03 hours (0.07%) post dose.
- Comparisons of the response curves were statistically significant ($p < 0.05$) for the individual CEA and PSA responses in the 0.50% and 0.18% groups. For the combined CEA and PSA, the comparisons of time to 1 grade improvement were significant ($p < 0.05$) for each active group versus vehicle.
- The median duration of effect was more than 7 hours in each of the Mirvaso gel groups and approximately 3 hours in vehicle group.
- For 2-grade improvement on combined CEA and PSA, the response rates were 54.8% (0.50% Mirvaso gel), 32.3% (0.18%), 25% (0.07%), and 12.5% (vehicle).
- The median time to onset of 2-grade improvement was 10.03 hours after dosing for the 0.50% group.
- The median duration of effect was approximately 6 hours in the 0.50% group and 3 to 4 hours in the remaining groups.
- The mean number of time points with CEA ≤ 1 ranged from 0.7 in the vehicle group to 5.0 in the 0.50% group. The mean number of time points with CEA and PSA ≤ 1 ranged from 0.5 in the vehicle group to 2.8 in the 0.50% group.
- Significant reductions in Chromameter results were identified for Mirvaso gel (0.50%, 0.18% and 0.07%) versus vehicle gel and 0.50% showed statistically significant reductions versus the 0.18% and 0.07% treatment groups.

5.3.1.2. Multiple-administrations

- Following administration of 0.18% Mirvaso gel there was a significant improvement in erythema based on the subjective scales of PSA and CEA up to 8 hours following dosing.

- Following application of 3 concentrations (0.02%, 0.07% and 0.20%) of Mirvaso gel, no more often than once every 4 hours and no more than 3 times per day for 28 days, the reduction in erythema across all time points (0 to 8 hours) and all visits (Day 0, Day 14, and Day 28), showed a clear dose response relationship as did the reduction in IGA.
- Both the 0.2% and 0.07% dose groups displayed significantly greater changes from Baseline than the vehicle group ($p < 0.001$ and $p < 0.05$, respectively).
- In the Day 28 responder analysis, with success defined as an IGA score of 0 or 1 or an improvement of at least 2 points, the differences among the treatment groups were statistically significant at Hours 1 through 4 ($p < 0.05$, Mantel-Haenszel Chi-Square statistics). At Hour 3, 37.5% of patients in the 0.2% group, 13.6% in the 0.07% group, 15.0% in the 0.02% group, and 0% in the vehicle group were successes.
- Telangiectasia and total inflammatory lesion count neither improved nor worsened following treatment.
- Peak efficacy was significantly higher in the 0.2% group than in the vehicle group on Days 0, 14, and 28 when represented by the greatest change from Baseline in CEA and on Day 28 when represented by the greatest change from Baseline in IGA.
- An onset of effect was seen as early as 15 minutes after study drug application and the duration of effect was about 5 hours.

5.3.2. Secondary pharmacodynamic effects

- Brimonidine does not prolong the QTc interval compared to placebo.
- Overall Mirvaso gel did not possess detectable phototoxicity potential in human skin.
- There was no apparent correlation between increasing concentrations of Mirvaso gel and the appearance or intensity of topical erythema/irritation.
- Each active test concentration, the gel vehicle, and the white petrolatum produced no reaction in 95% to 96% of test sites on any given evaluation day, mild erythema in 4% to 5% of test sites on any given evaluation day, and only isolated instances of moderate erythema and/or erythema with vesicles or erosion or bullae.
- There were no confirmed cases of contact sensitisation for any of the Mirvaso concentrations, including the vehicle gel.
- Based on the MCII, test sites patched with the higher concentrations of Mirvaso gel (0.5% and 0.18%) exhibited slightly less irritation (MCII = 0.01) than the weakest concentration (0.07%)(MCII = 0.02) and Gel Vehicle (MCII = 0.02).
- The three concentrations of Mirvaso gel and the gel vehicle produced slightly less irritation than the negative control (MCII = 0.03) and markedly less irritation than the positive control (MCII = 1.69).
- No studies examined race, genetic-, gender- and age-related differences in pharmacodynamic response.
- No studies examined the Pharmacodynamic interactions between Mirvaso gel and other drugs.

6. Dosage selection for the pivotal studies

6.1. Study 18144

Study 18144 was a Phase IIa, randomized, double-blind, parallel-group, vehicle-controlled, dose-finding study investigating the pharmacodynamics and safety of three concentrations of brimonidine topical gel (0.07%, 0.18%, and 0.50%), applied in subjects with moderate to severe erythematotelangiectatic rosacea.

Subjects were randomized to receive Brimonidine Tartrate Gel (0.5%, 0.18%, or 0.07%) or vehicle gel. Following application of the study drug, subjects were required to remain at the investigational centres for a mandatory 12 hour observation period.

The study endpoints included: Time to the first 1-grade improvement on the CEA, PSA, and both CEA and PSA; Time to the first 2-grade improvement on the CEA, PSA, and both CEA and PSA; Duration of effect: the interval between the first time the effect was observed and the first time the effect was lost (that is, 1-grade improvement and 2-grade improvement for CEA, PSA, and CEA and PSA); Number of time points with CEA ≤ 1, PSA ≤ 1, and with both CEA and PSA ≤ 1; Change from baseline (T0) at each post-baseline time point (30 minutes and hour 1 to hour 12), the maximum reduction and the average reduction across all post-baseline time points for CEA and PSA; Evaluation of Chromameter data (L*, a*, and b*) at each time point. Change from baseline/Pre dose (T0) at each post baseline time point, and the average change across all post baseline time points.

The intent to treat (ITT) population comprised of 122 subjects; 31, 31, 28 and 32 subjects were randomised to Brimonidine Tartrate 0.5% Gel, 0.18% Gel, 0.07% Gel and Vehicle Gel, respectively. All 122 subjects completed the study and 117 subjects were included in the per protocol (PP) population.

The majority of subjects were female (75.4%) and Caucasian (91.8%), with mean overall age of 45.7 years. There were no clinically meaningful differences in baseline or demographic characteristics. Although the difference in baseline PSA scores[3] was statistically significant, it was not clinically meaningful.

The response rate for 2-grade improvement in both CEA and PSA showed a dose ordering trend (25%, 32.3%, 54.8% and 12.5% in the Brimonidine Tartrate 0.07% Gel, 0.18% gel, 0.50 gel and vehicle groups, respectively). This dose ordering effect was also observed for 1-grade improvement in both CEA and PSA ranging from 75.0% of subjects in the Brimonidine Tartrate 0.07% Gel group to 83.9% of subjects in the Brimonidine Tartrate 0.5% Gel group, compared to 28.1% of subjects in the vehicle gel group. Thus, the response criterion of 1-grade or 2-grade improvement on the combined CEA and PSA seemed to best characterize the dose-response curves. Smaller vehicle effects were observed for the 2-grade improvements and the combined effects than the 1-grade improvement (Table 10).

[3] The differences in PSA scores were mainly due to the differences in the distribution of scores in the Brimonidine Tartrate 0.07% Gel group (approximately evenly distributed between Grades 3 and 4) compared to the other treatment groups (higher percentages of subjects with Grade 3 compared to Grade 4).

Table 10. Study RD.06.SRE.18144. Time to effect and duration of effect for CEA and PSA, ITT population

Criteria	CD07805/47 Gel			Vehicle Gel N=32
	0.50% N=31	0.18% N=31	0.07% N=28	
1-grade Improvement				
CEA				
Response Rate, n (%)	30 (96.8)	28 (90.3)	24 (85.7)	21 (65.6)
Median Time to Onset (hours)[a]	0.53	0.55	1.03	1.04
Median Duration of Effect (hours)[b]	11.53	10.27	7.18	4.00
PSA				
Response Rate, n (%)	28 (90.3)	27 (87.1)	25 (89.3)	18 (56.3)
Median Time to Onset (hours)[a]	2.00	2.00	2.00	6.50
Median Duration of Effect (hours)[b]	9.00	-	10.50	8.02
CEA and PSA				
Response Rate, n (%)	26 (83.9)	25 (80.6)	21 (75.0)	9 (28.1)
Median Time to Onset (hours)[a]	2.98	2.08	2.03	-
Median Duration of Effect (hours)[b]	7.98	7.90	7.48	2.95
2-grade Improvement				
CEA				
Response Rate, n (%)	24 (77.4)	24 (77.4)	14 (50.0)	9 (28.1)
Median Time to Onset (hours)[a]	2.02	2.07	-	-
Median Duration of Effect (hours)[b]	7.00	3.52	4.75	2.98
PSA				
Response Rate, n (%)	19 (61.3)	14 (45.2)	12 (42.9)	7 (21.9)
Median Time to Onset (hours)[a]	7.00	-	-	-
Median Duration of Effect (hours)[b]	7.00	3.00	6.50	6.02
CEA and PSA				
Response Rate, n (%)	17 (54.8)	10 (32.3)	7 (25.0)	4 (12.5)
Median Time to Onset (hours)[a]	10.03	-	-	-
Median Duration of Effect (hours)[b]	5.78	2.97	3.98	2.97

[a] Median time was not calculated when less than 50% of subjects reached the response criterion.
[b] Only subjects who responded were included in duration of effect analysis.

For CEA and PSA, 1-grade improvement was observed earlier than 2-grade improvement and CEA response was observed earlier than PSA response. The CEA and PSA were to be completed at 13 time points post dose, over a 12 hour observation period. For the mean number of time points with CEA ≤ 1 and both CEA and PSA ≤ 1, the largest effects were seen in the Brimonidine Tartrate 0.5% Gel group and were statistically significant ($p < 0.05$) versus each of the other active groups as well as versus vehicle gel. The mean number of time points with CEA ≤ 1 ranged from 0.7 in the vehicle group to 5.0 in the Brimonidine Tartrate 0.5% Gel group. The mean number of time points with CEA and PSA ≤ 1 ranged from 0.5 in the Vehicle group to 2.8 in the Brimonidine Tartrate 0.5% Gel group.

No clinically relevant deterioration of telangiectasia or worsening of inflammatory lesions was observed in any treatment group.

> **Comments:** Following a single application of Brimonidine Tartrate Gel, a dose-response relationship was observed. All three potencies were shown to be more effective than Vehicle Gel at reducing facial erythema, with the largest effect observed with the 0.5% concentration, followed by the 0.18% and 0.07% concentrations. The treatment effect cycle for Brimonidine Tartrate Gel was observable over the course of 1 treatment day, with fast onset of effect, 1 grade improvement, maximum effect, and gradual recurrence, but without complete return to baseline over an observation period of 12 hours. This study was designed in accordance with ICH Guideline E4, titled "Dose-Response Information to Support Drug Registration," to provide data that would guide the safe and effective use of Brimonidine Tartrate Gel in subsequent studies. Based on the results

of this study, both the 0.18%, and 0.5% concentrations of Brimonidine Tartrate Gel were selected for evaluation in the Phase IIb efficacy and safety study18161.

6.2. Study 18161

Study 18161 was a Phase IIb, 4 week, randomized, double blind, parallel group, vehicle controlled, multicentre study. The main objectives were to evaluate the efficacy and safety of two concentrations of brimonidine gel, 0.5% and 0.18%, applied topically in subjects with moderate to severe facial erythema associated with rosacea. Using corresponding vehicle controls, the 0.5% concentration was to be tested using a once daily qd regimen for 4 weeks, and the 0.18% concentration was to be tested using qd or twice daily (bid) regimens for 4 weeks.

Key inclusion criteria were: A clinical diagnosis of rosacea; A Clinician's Erythema Assessment (CEA) and Patient Self-Assessment-5 (PSA-5) score of ≥ 3 at Screening and at pre dose (T0) on Baseline/Day 1; A Patient Self-Assessment-11 (PSA-11) score of ≥ 5 at Screening and at pre dose (T0) on Baseline/Day 1. Key exclusion criteria were: Three (3) or more facial inflammatory lesions; Diagnosis (at the Screening visit) of Raynaud's Syndrome, thromboangitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or depression; Prior clinical diagnosis or the hallmark signs and symptoms of phymatous rosacea; Known allergies or sensitivities to any components of the study drugs, including the active gel ingredient, brimonidine tartrate; Intraocular pressure (IOP) less than 10 mmHg at the Screening visit.

Subjects were to be randomized in a 1:1:1:1:1 ratio to one of the following treatment arms:

- CD07805/47 gel 0.5% applied topically qd
- CD07805/47 gel 0.18% applied topically bid
- CD07805/47 gel 0.18% applied topically qd
- Vehicle gel applied bid
- Vehicle gel applied qd

The main efficacy variables were CEA, PSA-5, PSA-11, Patient Assessment of Appearance (PAA), Patient Assessment of Whitening (PAW), Overall Treatment Effect (OTE) (Tables 11-14), and Dermatology Life Quality Index (DQLI). Other measurements were IGA of lesions, facial inflammatory lesion count, and Telangiectasia Grading Assessment (Tables 15 and 16).

Table 11: Phase IIb study 18161 CEA scales; Studies ROSE-201, 18144, 18161, 18140, 18141, 18142

Grade	Description (Initial Version)[a]	Description (Final Version)[b]
0	Clear skin with no signs of erythema	Clear skin with no signs of erythema
1	Almost clear; slight pinkness	Almost clear; slight redness
2	Mild erythema; definite redness	Mild erythema; definite redness
3	Moderate erythema; marked redness, greater than Grade 2	Moderate erythema; marked redness
4	Severe erythema; fiery redness, greater than Grade 3	Severe erythema; fiery redness

[a] Called the Clinician's Erythema Assessment. Version used in Study ROSE-201.

[b] Version used in Studies 18140, 18141, 18142, 18144, and 18161.

Table 12. Phase IIb study 18161. PSA scales; Studies 18144, 18161, 18140, 18141, 18142

Grade	Description (Version for Phase 2a)	Description (Final Version for Phase 2b and Phase 3)
0	Clear of unwanted redness	No redness
1	Nearly clear of unwanted redness	Very mild redness
2	Somewhat more redness than I prefer	Mild redness
3	More redness than I prefer	Moderate redness
4	Completely unacceptable redness	Severe redness

The PSA version for the Phase 2b study that is described in this table was called the PSA-5 in that study.

Table 13. Phase IIb study 18161. PAA scale; studies 18161, 18140, 18141, 18142

Circle the number that best describes how satisfied you are with the overall appearance of your skin **RIGHT NOW**.	
0	Very satisfied
1	Satisfied
2	Neither satisfied nor dissatisfied
3	Dissatisfied
4	Very dissatisfied

Table 14. Phase IIb study 18161. OTE; studies 18161, 18140, 18141, 18142

Since starting this study, the management of my rosacea-related facial redness is: *(Circle one number)*	
1	Very much worse
2	Moderately worse
3	A little worse
4	About the same
5	A little better
6	Moderately better
7	Very much better

Table 15: Investigator's global assessment (IGA) and facial inflammatory lesion count

Grade	Score	Clinical Description
Clear	0	No Papules/Pustules; No Nodules
Almost Clear	1	Few Small Papules/Pustules; No Nodules
Mild	2	Some Small Papules/Pustules; No Nodules
Moderate	3	Several Small and Medium Sized Papules/Pustules; One Nodule May Be Present
Severe	4	Numerous Small, Medium, and Large Sized Papules/Pustules; Two or More Nodules Present

Inflammatory lesions were defined as Papule – a small, red, solid elevation less than 1.0 cm in diameter.
Pustule – a small, circumscribed elevation of skin that sontained yeelow-white exudates.
Papules and pustules were to be counted separately on eahc of the five facila regions (forehead, chin, nose, right cheek, and left cheek.

Table 16: Telangiectasia Grading Assessment

Grade	Description
0	Clear; with no signs of telangiectasia
1	Almost clear; with scarce, barely visible telangiectasia
2	Mild; with few visible telangiectasia
3	Moderate; with the presence of clearly visible telangiectasia
4	Severe; with the presence of many clearly visible telangiectasia

The primary efficacy endpoint was 2 grade Composite Success at Hours 3, 6, 9, and 12 on Day 29, then on Day 15, and lastly on Day 1; 2-grade Composite Success was defined as a 2 grade

improvement from baseline (T0 at Day 1) on both CEA and PSA-5 at each time point. Secondary and other efficacy endpoints were provided.

The primary analyses were to test treatment differences between each active treatment (0.5% qd, 0.18% bid, and 0.18% qd) versus the corresponding vehicle gel on the correlated repeated measurements for Composite Success at Hours 3, 6, 9 and 12 on Day 29 using the Generalized Estimating Equation (GEE) methodology in the ITT population. When the data were missing at all four time points (that is, Hours 3, 6, 9, and 12), the last observation carried forward (LOCF) method was applied by using the data from the previous visit. Three sensitivity analyses[4] were performed. The testing for Composite Success at Hours 3, 6, 9, and 12 on Day 15 and Day 1 was performed to evaluate the early efficacy profile. The primary analyses were performed based on the ITT population, and were repeated based on the PP population to confirm the results. Both the Hochberg procedure and gate keeping methods were considered to handle the multiple arms and clinic visits.

For completeness, three statistical analyses were added after unblinding of the study:

1. 1 grade Composite Success at Hours 3, 6, 9, and 12 on Day 29, Day 15, and Day 1: 1 grade Composite Success was defined as 1 grade improvement from Baseline (T0 at Day 1) on both CEA and PSA-5 at each time point.
2. 1 grade CEA Success at Hours 3, 6, 9, and 12 on Day 1, Day 15, and Day 29: 1 grade CEA Success was defined as 1 grade improvement from Baseline (T0 at Day 1) on CEA.
3. 1 grade PSA-5 Success at Hours 3, 6, 9, and 12 on Day 1, Day 15, and Day 29: 1 grade PSA-5 Success was defined as 1 grade improvement from Baseline (T0 at Day 1) on PSA-5.

The sample size was calculated based on results from similar study 18144. Assuming the correlation between the repeated measures analysis is 0.6, the Composite Success rate for vehicle is 5%, and the minimum treatment difference is 20% (that is, 25% versus 5%), a sample size of 260 (that is, 52 per arm) was required to detect a treatment difference of 20% with an 80% power when conducted as a two-sided test at the 2.5% significance level, and adjusting for a 10% dropout rate.

Of the 352 enrolled patients, 269 were randomised to treatment (ITT population); 32 subjects were excluded from the PP population due to protocol violations; non-compliance[5], assessment/ dosing deviations and entrance criteria deviations were most common.

Majority of subjects were female (80.7%) and Caucasian (96.7%) with mean age of 44.3 years. All Skin Phototypes ranged from I to IV. For the CEA, all Baseline scores were in the Moderate (CEA=3) to Severe (CEA=4) range. For the PSA-5, all Baseline scores were in the Moderate (PSA-5=3) to Severe (PSA-5=4) range, and for PSA-11, all Baseline scores were in the Moderate (PSA-11=4) to Very Severe (PSA-11=10) range. The baseline demographics and disease characteristics were similar across treatment groups.

On days 1, 15 and 29, a statistically significant ($p < 0.001$) greater proportion of subjects treated with brimonidine gel 0.5% qd achieved 2 grade Composite Success compared to vehicle gel qd . A statistically significant difference between CD07805/47 gel 0.18% qd and vehicle gel qd was observed on Day 29 ($p = 0.027$), however, no significant difference was observed on Day 15 ($p = 0.126$) or Day 1 ($p = 0.071$). No statistically significant differences were observed for

[4] Three sensitivity analyses were performed by (a) imputing 'Failure' for the missing data; (b) imputing 'success' as meeting the criteria for composite success at each of the repeated measurements at Hours 3, 6, 9, and 12; and (c) imputing 'success' as at least 2-grade reduction on CEA and PSA-5 using the average score of the repeated measurements at Hours 3, 6, 9, and 12.

[5] Treatment compliance was assessed on day 15 and 29, subjects were required to return study drug tubes which were then weighed; subjects were also questioned regarding study drug application technique and use of any additional topical or systemic medications (including OTC products).

CD07805/47 gel 0.18% bid versus vehicle gel bid. The primary efficacy results were confirmed in the PP and sensitivity analysis (Tables 17 and 18).

Table 17. Summary of 2 Grade composite success, LCOF, PP population

Composite Success[a] n/N (%)	CD07805/47 Gel			Vehicle Gel	
	0.5% QD	0.18% BID	0.18% QD	BID	QD
Day 1					
Hour 3	10/47 (21.3)	2/43 (4.7)	3/50 (6.0)	1/47 (2.1)	1/50 (2.0)
Hour 6	13/47 (27.7)	4/43 (9.3)	5/50 (10.0)	4/47 (8.5)	1/50 (2.0)
Hour 9	8/47 (17.0)	6/43 (14.0)	4/50 (8.0)	5/47 (10.6)	1/50 (2.0)
Hour 12	9/47 (19.1)	6/43 (14.0)	3/50 (6.0)	4/47 (8.5)	2/50 (4.0)
p-value[b]	**<0.001**	0.423	0.138	NA	NA
Day 15					
Hour 3	12/47 (25.5)	1/43 (2.3)	4/50 (8.0)	2/47 (4.3)	2/50 (4.0)
Hour 6	11/47 (23.4)	3/43 (7.0)	6/50 (12.0)	5/47 (10.6)	1/50 (2.0)
Hour 9	12/47 (25.5)	5/43 (11.6)	4/50 (8.0)	6/47 (12.8)	4/50 (8.0)
Hour 12	7/47 (14.9)	5/ 43 (11.6)	6/50 (12.0)	6/47 (12.8)	3/50 (6.0)
p-value[b]	**0.001**	0.579	0.145	NA	NA
Day 29					
Hour 3	14/47 (29.8)	8/43 (18.6)	9/50 (18.0)	3/47 (6.4)	2/50 (4.0)
Hour 6	13/47 (27.7)	8/43 (18.6)	10/50 (20.0)	6/47 (12.8)	4/50 (8.0)
Hour 9	15/ 47 (31.9)	9/43 (20.9)	6/50 (12.0)	8/47 (17.0)	2/50 (4.0)
Hour 12	9/47 (19.1)	6/43 (14.0)	5/50 (10.0)	7/47 (14.9)	2/50 (4.0)
p-value[b]	**<0.001**	0.531	**0.047**	NA	NA

Table 18. Summary of 2-Grade composite success on day 29, sensitivity analyses, ITT population

Composite Success[a] n/N (%)	CD07805/47 Gel			Vehicle Gel	
	0.5% QD	0.18% BID	0.18% QD	BID	QD
Sensitivity - Failure					
Hour 3	16/53 (30.2)	10/54 (18.5)	10/54 (18.5)	4/53 (7.5)	2/55 (3.6)
Hour 6	15/53 (28.3)	8/54 (14.8)	10/54 (18.5)	7/53 (13.2)	4/55 (7.3)
Hour 9	17/53 (32.1)	11/54 (20.4)	7/54 (13.0)	10/53 (18.9)	2/55 (3.6)
Hour 12	10/53 (18.9)	7/54 (13.0)	5/54 (9.3)	9/53 (17.0)	2/55 (3.6)
p-value[b]	**<0.001**	0.680	**0.027**	NA	NA
Sensitivity - Success					
Hour 3	18/53 (34.0)	12/54 (22.2)	12/54 (22.2)	5/53 (9.4)	4/55 (7.3)
Hour 6	17/53 (32.1)	10/54 (18.5)	12/54 (22.2)	8/53 (15.1)	6/55 (10.9)
Hour 9	19/53 (35.8)	13/54 (24.1)	9/54 (16.7)	11/53 (20.8)	4/55 (7.3)
Hour 12	12/53 (22.6)	9/54 (16.7)	7/54 (13.0)	10/53 (18.9)	4/55 (7.3)
p-value[b]	**<0.001**	0.446	0.069	NA	NA
Sensitivity - Average Score					
Hour 3	16/51 (31.4)	10/52 (19.2)	10/52 (19.2)	4/52 (7.7)	2/53 (3.8)
Hour 6	15/51 (29.4)	8/52 (15.4)	10/52 (19.2)	7/52 (13.5)	4/53 (7.5)
Hour 9	17/51 (33.3)	11/52 (21.2)	7/52 (13.5)	10/52 (19.2)	2/53 (3.8)
Hour 12	10/51 (19.6)	7/52 (13.5)	5/52 (9.6)	9/52 (17.3)	2/53 (3.8)
p-value[b]	**<0.001**	0.662	**0.026**	NA	NA

NA=Not applicable

Generalized Estimating Equation (GEE) methodology was used to test Success Profile.

[a] Composite Success was defined as 2-grade improvement on CEA and 2-grade improvement on PSA-5.

[b] p-value was based on the testing between each CD07805/47 active treatment and the corresponding vehicle gel control.

On days 1, 15 and 29, a statistically significant ($p < 0.001$) greater proportion of subjects treated with brimonidine gel 0.5% qd achieved 1 grade Composite Success compared to vehicle gel qd. A statistically significant difference between CD07805/47 gel 0.18% qd and vehicle gel qd was observed on Day 1 ($p = 0.009$), but not on Day 29 ($p = 0.396$) or Day 15 ($p = 0.099$). A statistically significant difference between brimonidine gel 0.18% bid and vehicle gel bid was observed on Day 29 ($p = 0.043$) and Day 1 ($p < 0.001$), but not on Day 15 ($p = 0.096$).

On days 1, 15 and 29, a statistically significant ($p < 0.003$) greater proportion of subjects treated with brimonidine gel 0.5% qd achieved CEA success[6] compared to vehicle gel qd. Statistically significant differences between brimonidine gel 0.18% bid versus vehicle gel bid ($p = 0.006$), and 0.18% qd versus vehicle gel qd ($p = 0.002$) were observed on Day 1, but not on days 15 and 29. Similar results were observed for mean change from baseline in CEA. The mean changes in CEA following the 4 week treatment period[7] were similar across all treatment groups. Only a few subjects showed CEA scores increased from Baseline in both the active treatment groups and the vehicle gel controls. No aggravation of CEA, or rebound of facial erythema, was observed during the Follow-up period.

On days 1, 15 and 29, a statistically significant ($p < 0.001$) greater proportion of subjects treated with brimonidine gel 0.5% qd achieved PSA success[8] compared to vehicle gel qd. No statistically significant differences were observed for PSA-5 in other treatment groups, on any day. The brimonidine gel 0.5% qd group showed statistically significant reductions ($p < 0.001$) in PSA-5 from Baseline (T0 on Day 1) on all days (Day 29, Day 15, and Day 1). The 0.18% gel bid group showed statistically significant reductions in PSA-5 on Day 29 ($p = 0.049$), and Day 1 ($p =0.011$). No significant reductions in PSA-5 were observed for the 0.18% gel qd group on any day.

The mean changes in PSA-5 following the 4 week treatment period were similar across all treatment groups. Only a few subjects showed PSA-5 scores increased from Baseline in both the active treatment groups and the vehicle gel controls. No aggravation of PSA-5, or rebound of facial erythema, was observed during the follow up period.

The brimonidine gel 0.5% qd group showed statistically significant reductions ($p < 0.001$) in PSA-11 from Baseline (T0 on Day 1) on all days (Day 1, Day 15, and Day 29); the brimonidine gel 0.18% bid group also showed significant reductions in PSA-11 from baseline on all days ($p < 0.001$); however, the 0.18% gel qd group did not show any significant reduction in PSA-11 on any day. The mean changes in PSA-11 following the 4 week treatment period were similar across all treatment groups. No aggravation of PSA-11, or rebound of facial erythema, was observed during the Follow up period. The mean changes from baseline in IGA of lesions were small and not clinically meaningful and there did not appear to be any aggravation of IGA beyond what is expected to occur following the natural course of the disease during the study treatment phase or the follow up period. Overall, the 4 week treatment of facial erythema with brimonidine gel did not result in clinically meaningful increases of facial inflammatory lesions in study subjects. For the proposed brimonidine gel 0.5% qd group, the mean change in facial inflammatory lesion counts from baseline was lower than the vehicle gel control. Furthermore, there was no worsening of facial inflammatory lesion counts beyond what is expected to occur following the natural course of the disease during the study treatment phase or the Follow-up period. No effect on telangiectasia was observed for any treatment group, at any time point.

[6] CEA success defined as 2-grade improvement from Baseline (T0 at Day 1) at each time point (Hours 3, 6, 9, and 12) on Day 29, then on Day 15, and lastly on Day 1.

[7] Subjects were monitored by the Investigators/evaluators at pre-specified time points following the 4-week treatment period, which included performing CEA evaluations at each Follow up/Early Termination visit (Day 30, Week 5, Week 6, and Week 8).

[8] Patient Self Assessment (PSA-5) Success was defined as 2-grade improvement from Baseline (T0 at Day 1) at each time point (Hours 3, 6, 9, and 12) on Day 29, then on Day 15, and lastly on Day 1.

The brimonidine gel 0.5% qd group showed the most favourable outcome for PAA compared to the brimonidine gel 0.18% bid, brimonidine gel 0.18% qd, vehicle gel bid, and vehicle gel qd groups. Early satisfaction was observed based on the PAA data starting at Hour 3 on Day 1 and 15 subjects (28.3%) in the CD07805/47 gel 0.5% qd group rated their overall appearance as 'satisfied' or 'very satisfied' and the ratings increased over the duration of the study. At Hour 12 on Day 29, 37.3% of subjects in the CD07805/47 gel 0.5% qd group rated their overall appearance as 'satisfied' or 'very satisfied'. On all non-clinic days (Days 2 to 14, and Days 16 to 28) the CD07805/47 gel 0.5% gel group had the highest mean percentage of days overall with a rating of 'satisfied' or 'very satisfied' (31.12% and 36.09% for Days 2 to 14, and Days 16 to 28, respectively). In addition, the mean percentage of days with a rating of 'satisfied' or 'very satisfied' in the CD07805/47 gel 0.5% qd group was at least twice the amount observed in the vehicle gel qd group (11.89% and 16.52% for Days 2 to 14, and Days 16 to 28, respectively).

The number of subjects who reported unwanted over whitening (for example, an unwanted over extended pharmacodynamic effect) was relatively higher in the active treatment groups than in the vehicle treatment groups. After the first treatment on Day 1 (at Hour 3), more subjects in the brimonidine gel 0.5% qd group (13.2%) experienced unwanted over whitening than in the 0.18% bid and qd groups (5.6% and 5.6%, respectively), and the vehicle gel bid or qd groups (0% and 1.8%, respectively). However, the number of reports of unwanted over whitening decreased over the course of the study and no subject discontinued the study due to the effect of over whitening. By Day 29, there were notably fewer reports of unwanted over whitening in the brimonidine gel 0.5% qd group at all time points when compared with Day 1. Analysis of OTE showed that the brimonidine gel 0.5% qd group had the greatest number of subjects with a score of "very much better" (13.7%). The number of subjects with a score of "moderately better", or "a little better" was similar across all treatment groups, with no obvious trends observed. The overall mean scores for DLQI were low and similar in all treatment groups. No dose dependent effect was observed. No clinically relevant worsening of telangiectasia or exacerbation of inflammatory lesions was observed in any treatment group. Rebound evaluation: After treatment had ceased, no aggravation effect (rebound) of subject's facial erythema was observed during the 4 week Follow up/Early Termination period for any treatment group. In addition, no worsening of IGA, facial inflammatory lesion counts, or Telangiectasia Grading Assessment was observed during the 4 week Follow up/Early Termination period for any treatment group.

One additional Phase II, 29-day dose-finding Study (COL-118-ROSE-201) that was conducted by the previous sponsor was summarized as it provided supportive data on the efficacy of Brimonidine Tartrate Gel in the treatment of erythema of rosacea. However, interpretation was limited as the proposed to be marketed dose (Brimonidine Tartrate 0.5% Gel) was not evaluated and different endpoints were evaluated relative to the current sponsor studies.

> **Comments:** Since this was a Phase 2 study, multiplicity adjustment to control type I error was not performed. This study was designed in accordance with the guidance provided in ICH E4 to provide data that would determine the most safe and effective dose of CD07805/47 gel in subsequent Phase III studies. The study provided evidence that the CD07805/47 gel 0.5% qd dosing regimen was significantly more effective in the treatment of facial erythema than the vehicle gel qd control, and also the CD07805/47 gel 0.18% bid, or CD07805/47 gel 0.18% qd dosing regimens. Both the CD07805/47 gel 0.18% bid and CD07805/47 gel 0.18% qd groups showed numerical effectiveness against their respective vehicle gel controls, however the results were not statistically significant and superiority over the vehicle gel control was not observed in most instances. CD07805/47 gel 0.5% qd was therefore shown to be the most effective concentration and dosing regimen among the three active treatment groups.
>
> Two (2) grade Composite Success on Day 29 ranged from 18.9% to 32.1% with the proposed brimonidine 0.5% gel compared to the vehicle gel control (3.6% to 7.3%). The

outcome of the study is robust as results were confirmed in the PP population and in sensitivity analyses. For a 1 grade improvement, which was still noticeable and clinically meaningful, Composite Success for CD07805/47 gel 0.5% qd ranged from 60.4% to 75.5% on Day 29 compared to vehicle gel control (30.9% to 41.8%). The difference between CD07805/47 gel 0.5% qd and the corresponding vehicle gel control was statistically significant on Day 29, as well as on Day 15, and Day 1.

A rapid onset of treatment effect for CD07805/47 gel 0.5% qd was observed in several subjects with improvement occurring by hour 3 of day 1. The positive treatment effect of CD07805/47 gel 0.5% qd continued over the course of the 4 week treatment period with statistically significant improvement of facial erythema observed at Day 15 and Day 29. No evidence of tachyphylaxis was observed over the duration of the treatment phase.

The CD07805/47 gel 0.5% qd treatment group also showed the most favourable outcome with respect to PSA-11, PAA, and OTE, compared to either the CD07805/47 gel 0.18% bid group, or the CD07805/47 gel 0.18% qd group, and the corresponding vehicle controls. Unwanted over-whitening was highest in the CD07805/47 gel 0.5% qd group on day 1. The trend for unwanted over-whitening in the CD07805/47 gel 0.5% qd group decreased over time and by day 29, the number of subjects reporting unwanted over-whitening was modest and similar across all active treatment groups, suggesting a positive acclimation to an unwanted over extended treatment effect. There was no clinically relevant worsening of telangiectasia or exacerbation of inflammatory lesions was observed in any treatment group. After treatment had ceased, no aggravation effect (rebound) of subject's facial erythema was observed during the 4 week Follow-up/Early Termination period for any treatment group.

Based on the Phase IIb study results and additional data from previous studies, CD07805/47 0.5% applied once daily was an appropriate concentration and dose regimen selected for the Phase III program.

7. Clinical efficacy

7.1. Treatment of facial erythema of rosacea

7.1.1. Pivotal efficacy studies

7.1.1.1. Study 18140

7.1.1.1.1. Study design, objectives, locations and dates

This was a Phase III, multicentre, randomized, double blind, parallel group, vehicle controlled pivotal study. The main objective of the study was to demonstrate the efficacy of CD07805/47 gel 0.5%, applied topically once daily for 4 weeks versus vehicle control, in the treatment of moderate to severe facial erythema associated with rosacea.

7.1.1.1.2. Inclusion and exclusion criteria

The main inclusion criteria were : Male or female at least 18 years of age or older with a clinical diagnosis of facial rosacea; CEA score and Patient Self-Assessment (PSA) score of ≥ 3 at Screening and at Baseline/Day 1 (prior to the T0 study drug application).

The main exclusion criteria were :Particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other concomitant facial dermatoses that are similar to rosacea such as peri oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, or actinic telangiectasia; Presence of three (3) or more facial inflammatory lesions of rosacea; Current treatment with

monoamine oxidase (MAO) inhibitors, barbiturates, opiates, sedatives, systemic anesthetics, or alpha-agonists.; Less than 3 months stable dose treatment with tricyclic anti-depressants, cardiac glycosides, beta blockers or other antihypertensive agents; Current diagnosis of Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or depression; Any uncontrolled chronic or serious disease or medical condition that would have normally prevented participation in a clinical trial; Known allergies or sensitivities to any component of the study drugs, including the active ingredient brimonidine tartrate. The study also excluded patients who had received, applied or taken topical facial treatments or systemic treatment within the specified time frame prior to baseline.

7.1.1.1.3. Study treatments

Subjects who met the inclusion/exclusion criteria at screening and continued to meet the criteria prior to study drug application at the Baseline/Day 1 clinic visit were to be randomized (in 1:1 ratio) to receive study drug (CD07805/47 gel 0.5% and vehicle gel) for a period of 4 weeks. Following the 4 week dosing period, subjects were to return to the investigational centres on Week 6 and Week 8/Early Termination (ET) for follow up evaluations.

For each clinic visit, subjects were to be instructed not to apply study drug prior to arriving at the investigational centre. At each clinic visit, efficacy and safety assessments were to be performed prior to T0. Subjects were then to apply the study drug under investigational centre personnel supervision. On non-clinic days (Days 2-14 and 16-28), subjects were to apply approximately one small pea size amount of gel on each of the following facial regions qd in the morning after washing the entire face: right cheek, left cheek, forehead, chin, and nose. Application to the following areas was to be avoided: eyes, eyelids, inner nose, mouth, and lips. Furthermore, application of study drug to severely irritated skin or open lesions was to be avoided. The amount of study drug to be applied was approximately 1 gram. No dose modification was allowed during the course of the study.

For assessment of treatment compliance, subjects were to be instructed to bring back the study drug tubes and dosing calendar to the investigational centre on Days 15 and 29 for drug application and accountability assessment. On Days 15 and 29, subjects were to be questioned regarding the study drug application technique and use of any additional topical or systemic medications (including over the counter (OTC) products). Subjects were also to be questioned regarding the frequency of application and missed doses. Compliance was to be documented in the eCRF.

7.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables were: CEA [9], Patient Self-Assessment (PSA), PAA, and OTE. Other efficacy measurements included IGA of lesions, facial inflammatory lesion count, Telangiectasia Grading Assessment, PAW, SF-12v2 Acute Health Survey, Productivity and Social Life Questionnaire, and facial photographs.

Subject assessments were to be performed at the investigational centre during a 12-hour post-dose evaluation period on Day 1, Day 15, and Day 29. On non-clinic days (Days 2 to14 and 16 to 28) subjects were to apply study drug as directed and to complete daily subject assessments. Subjects were required to complete various self-assessments during the study. Subjects were to complete the PSA at each study visit, including on non-clinic days (Days 2-14 and 16-28) and during the follow-up period. The PAA and the PAW assessments were to be completed on Days 1, 15, and 29, and on non-clinic days (Days 2-14 and 16-28). Subjects were to complete the SF-12v2 Acute Health Survey on Days 1, 15, 29, and at each follow-up visit. Subjects were to

[9] The version of the this investigator-assessed scale that was used in the Phase 2a, Phase 2b, and Phase 3 studies was intended to be a static assessment, meaning that the Investigator was not to consider the level of erythema observed during previous assessments or visits.

complete the Productivity and Social Life Questionnaire on Days 1 and 29 and at the Week 8/ET Follow up visit. The OTE assessment was to be completed on Day 29.

The investigator/evaluator (a board certified dermatologist) was to complete the CEA at each clinic visit, including during the screening and follow up periods; the Telangiectasia Grading Assessment on Day 1, Day 29, and each follow-up visit; a facial inflammatory lesion count at each clinic visit (except Day 15); and the IGA of Lesions on Day 1, Day 29, and each follow-up visit.

The subject self-assessment instruments (PSA, PAA, PAW, and OTE) that were used in the Phase IIb and Phase III studies were developed using rigorous scientific methodology and tested in the target patient population. The PSA-11 was not used in the Phase III program because the FDA subsequently expressed to the applicant that study results would be difficult to interpret based on a composite endpoint that used scales with different numbers of categories. Thus, because the CEA consisted of 5 categories, the PSA scale version that also consisted of 5 categories was included in the primary endpoint (composite endpoint) for the Phase III program.

Subject self-assessments of satisfaction with the overall appearance of their facial skin were based on the PAA scale[10]. Subjects completed self-assessments of the overall impact of therapy on the management of their facial erythema relative to the beginning of the study, which were based on the OTE scale. The purpose of the OTE was to provide data regarding whether a clinically important change in erythema had occurred based on subject perceptions.

The primary endpoint to compare the active treatment arm with the vehicle control arm was Composite Success at Hours 3, 6, 9 and 12 first on Day 29, then on Day 15 and lastly Day 1. Composite Success was defined as 2 grade improvement on both CEA and PSA at each time point.

A secondary endpoint, the 30 minute Effect, was used to evaluate and compare the active treatment arm to the vehicle control for onset of initial clinical effect. The 30 minute Effect was defined as 1 grade improvement on CEA and PSA at 30 minutes on Day 1.

Tertiary Endpoints included: 1 grade and 2 grade Composite Success at Hour 3, 6, 9, 12 on Day 29, Day 15, and Day 1; 2 grade PSA Success at Hours 3, 6, 9, and 12 on Day 29, Day 15 and Day 1; Percentage of Days with PSA scored '0' or '1' between visits; Change in pre dose CEA and PSA from Baseline (T0 on Day 1) at each post Baseline visit during treatment and follow up phases.

The other variables were: Change in PAA from Baseline (T0 at Day 1) at Hours 3, 6, 9, 12 on Day 29, Day 15, and Day 1; Percentage of Days with PAA scored '0' or '1' between visits; OTE on Day 29; Change in IGA of Lesions from Baseline (T0 at Day 1) on Day 29, and at follow-up; Change from Baseline in facial inflammatory lesion counts[11] on Day 29 and at Follow up visit; Change in Telangiectasia Grading Assessment from Baseline (T0 at Day 1) on Day 29, and at Follow-up visit; PAW at Hours 3, 6, 9, and 12 on Day 29, Day 15, and Day 1; Percentage of Days with PAW scored 'yes' for Whitening, and scored 'yes' for bothered by the whitening between visits; Change from Baseline in SF-12v2 Acute Health Survey[12] data on Day 15, Day 29 and follow up

[10] In Studies 18161, 18140, and 18141, subjects were also required to complete the PAA daily, just before bedtime, on non-clinic days (Days 2-14 and Days 16-28). The same grading criteria were used for non-clinic days; however, because the PAA was intended as an overall assessment of the entire day ("daily recall") rather than a static evaluation, the PAA instructions for non-clinic days were worded accordingly.
[11] A facial inflammatory lesion count was to be performed by the Investigator/evaluator (a board-certified dermatologist). Inflammatory lesions were defined as papules and pustules and were to be counted separately on each of the 5 facial regions (forehead, chin, nose, right cheek, left cheek).
[12] The SF-12v Acute Health Survey was summarized according to 2 components (Physical Health Component and Mental Health Component) and 8 scales (Physical Functioning, Role- Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health). The Change from Baseline on Day 15, Day 29, and the Follow-up visit was summarized descriptively.

visit; Change from Baseline in Productivity and Social Life Questionnaire on Day 29 and follow up visit. Facial photographs were to be obtained by the Investigator/evaluator at selected investigational centres for subjects who had signed the photo consent form. No analyses of the photographs were performed for this study, as the photographs were not obtained to support the efficacy endpoints for this study.

7.1.1.1.5. Randomisation and blinding methods

Treatments were to be balanced into consecutive blocks for CD07805/47 gel and vehicle gel (1:1 randomization). Complete blocks of treatment materials were to be sent to the investigational centres. At the Screening visit, designated study personnel at each investigational centre were to call the IVRS to obtain an SIN[13] upon signature of the Informed Consent Form. The study was double-blind as both investigators and subjects were blind to the study treatment; Active CD07805/47 gel and vehicle gel were identical in appearance and were packaged in identical tubes.

7.1.1.1.6. Analysis populations

The ITT population was defined as comprising all subjects who were randomized and to whom study drug was administered. All efficacy and "other" variables were to be analysed based on the ITT population. The PP population was defined as comprising the ITT subjects who met all major protocol criteria and subjects who had any major protocol deviations were to be excluded from the PP population.

7.1.1.1.7. Sample size

Based on the results from the Phase IIb study 18161, the treatment differences between 0.5% qd and Vehicle qd in the average Composite Success rates across Hours 3, 6, 9 and 12 were 19.9%, 17.6%, and 22.9% for Day 1, Day 15, and Day 29, respectively. The corresponding average vehicle effect was 2.3%, 4.6%, and 4.5%. Considering the possibility that the variability and vehicle effect could have been higher in the present study, it was assumed that the treatment difference in Composite Success rate between 0.5% qd and Vehicle qd would be 15%, the vehicle effect would be 10%, the correlation between repeated measurements would be 0.7, and the dropout rate would be 10%. A sample size of 260 (130 per arm) was estimated to be sufficient to detect the specified treatment difference of 15% (25% vs. 10%) in Composite Success with a statistical power of 90% when conducted as a two sided test at the 5% significance level.

7.1.1.1.8. Statistical methods

The primary analyses were to test treatment differences between active treatment and vehicle treatment on the correlated repeated measurements for Composite Success at Hours 3, 6, 9 and 12 on Day 29 using the Generalized Estimating Equation (GEE)[14] methodology in the ITT population. The dependent variable in the model was Composite Success at Hours 3, 6, 9, and 12 on Day 29 and the independent variables were treatment, analysis centre, time points (Hours 3, 6, 9, and 12) and treatment analysis centre. The treatment by centre interaction for Composite Success on Day 29 was assessed at an alpha level of 0.10 by testing treatment by centre effect in the GEE model.

To handle missing data at any time points (Hours 3, 6, 9, or 12), the Multiple Imputation (MI) procedure was used as the primary imputation method. Multiple imputed datasets were created

[13] A SIN was to be allocated by the IVRS in ascending order to each subject and no number was to be omitted. During the whole study, the subject was to be identified using the SIN for all documentation and discussion.

[14] The logit link function was used to model the marginal expectation. The GEE method requires specification of the structure for the underlying correlation matrix, and the m-dependent (m=3) matrix was used due to lack of convergence using the unstructured correlation matrix.

by the MI procedure. In addition to the MI procedure, three sensitivity analyses[15] were performed.

The conditional stepwise testing for 2 grade Composite Success at Hours 3, 6, 9, and 12 on Day 15 and Day 1 was performed to evaluate the early efficacy profile. The testing on Day 29 was performed first as the primary analysis. If the result was statistically significant, the testing was to continue to Day 15 and Day 1 accordingly. The 30-minute Effect was analysed by the CMH test stratified by analysis centre, with the general association statistic, as a single secondary efficacy endpoint. All variables designated as "Tertiary Endpoints" or "Other Endpoint were summarized descriptively.

7.1.1.1.9. Participant flow

Of the 325 enrolled subjects, 260 were randomised and included in the ITT and safety populations (CD07805/47 0.5% gel = 129; vehicle = 131). Majority of subjects completed the study (98.4% and 96.9% in the CD07805/47 Gel 0.5% and vehicle gel groups, respectively).

7.1.1.1.10. Major protocol violations/deviations

A total of 29 subjects (11.2%) had major protocol deviations: 16 (12.4%) in the CD07805/47 Gel 0.5% group and 13 (9.9%) in the Vehicle Gel group. Administrative error[16] was the most common deviation, which was reported for 18 subjects: 10 in the CD07805/47 Gel 0.5% group and 8 in the Vehicle Gel group.

7.1.1.1.11. Baseline data

Majority of patients were females (79.2%), White (98.5%) had moderate erythema based on CEA score of 3 (86%) and PSA score of 3 (85%). The mean age was 48.8 years and skin prototype II (54%) or III (29%) was most common. There were no significant differences in demographic and baseline disease characteristics between the treatment groups. Overall, 6.2% of subjects took previous therapies (for rosacea or any other therapies during 6 months prior to screening) and the only previous therapies taken by more than 1 subject overall were metronidazole (5 subjects, 1.9%), azelaic acid (2 subjects, 0.8%), and other emollients and protectives (2 subjects, 0.8%).

Concomitant therapies were taken by 76.9% of subjects, with the most common (> 10% of total subjects) comprising other emollients and protectives (43 subjects, 16.5%), multivitamins (42 subjects, 16.2%), and acetylsalicylic acid (28 subjects, 10.8%).

7.1.1.1.12. Results for the primary efficacy outcome

The Composite Success profile for subjects who received CD07805/47 Gel 0.5% was statistically significantly ($p < 0.001$) greater compared to subjects who received Vehicle Gel on Days 1 (Brim 0.5% vs vehicle: 13-24% vs 3-4%) , day 15 (16-27% vs 3-6%) and day 29 (22-32% vs 8-11%). The differences between the Composite Success profiles in the CD07805/47 Gel 0.5% and Vehicle Gel groups were observed across all time points within each assessment day. This same trend was observed for the PP population. The summaries of 2 grade Composite Success using LOCF and the sensitivity analyses, showed the same trends as those with the observed data (Table 19).

[15] Three sensitivity analyses were performed by (a) imputing 'Failure' in the case of missing data; (b) imputing 'Success' in the case of missing data; and (c) imputing 'Success' if at least a 2-grade reduction was observed on CEA and PSA using the average score of the repeated measurements at Hours 3, 6, 9, and 12.

[16] For all 18 of these subjects, a sub-Investigator at a single investigative centre had not completed the CEA harmonization training prior to conducting the CEA evaluation on those subjects.

Table 19. Study 18140. Summary of 2 grade composite success, observed data, ITT Population

Success	CD07805/47 Gel 0.5% (N=129) n/N (%)	Vehicle Gel (N=131) n/N (%)
Day 1		
Hour 3	21/129 (16.3%)	4/131 (3.1%)
Hour 6	30/129 (23.3%)	3/131 (2.3%)
Hour 9	25/129 (19.4%)	5/131 (3.8%)
Hour 12	17/129 (13.2%)	4/130 (3.1%)
Day 15		
Hour 3	32/128 (25.0%)	4/128 (3.1%)
Hour 6	35/128 (27.3%)	8/128 (6.3%)
Hour 9	25/128 (19.5%)	7/128 (5.5%)
Hour 12	21/128 (16.4%)	3/128 (2.3%)
Day 29		
Hour 3	40/127 (31.5%)	14/128 (10.9%)
Hour 6	39/127 (30.7%)	12/128 (9.4%)
Hour 9	33/127 (26.0%)	13/128 (10.2%)
Hour 12	29/127 (22.8%)	11/128 (8.6%)

2-grade Composite Success: 2-grade improvement on CEA and 2-grade improvement on PSA.

7.1.1.1.13. Results for other efficacy outcomes

7.1.1.1.13.1. Secondary endpoint

For analysis of the 30-minute Effect, the observed data were statistically significant ($p < 0.001$) for the CD07805/47 Gel 0.5% group compared to the Vehicle Gel group in both the ITT and PP population. In the ITT population, 27.9% of subjects in the CD07805/47 Gel 0.5% group demonstrated 1 grade improvement on both CEA and PSA at the 30 minute time point on Day 1 compared to 6.9% in the Vehicle Gel group, which was the time point for which inferential analyses were performed.

7.1.1.1.13.2. Tertiary endpoints

At each time point, a significantly greater percentage of subjects in the CD07805/47 Gel 0.5% group showed 1-grade Composite Success for both CEA and PSA compared to the Vehicle Gel group, ranging from 46.5% at Day 1/Hour 12 to 70.9% at Day 29/Hour 3. Similar trends were observed with the LOCF method for the ITT population.

At each time point, higher percentages of subjects in the CD07805/47 Gel 0.5% group showed 2-grade improvement in CEA scores relative to the Vehicle Gel group (Table 20).

Table 20: Study 18140. Summary of 2 grade success, observed data, ITT population

Success	CD07805/47 Gel 0.5% (N=129) n/N (%)	Vehicle Gel (N=131) n/N (%)
Day 1		
Hour 3	59/129 (45.7%)	8/131 (6.1%)
Hour 6	65/129 (50.4%)	9/131 (6.9%)
Hour 9	52/129 (40.3%)	13/131 (9.9%)
Hour 12	30/129 (23.3%)	9/131 (6.9%)
Day 15		
Hour 3	54/128 (42.2%)	15/128 (11.7%)
Hour 6	50/128 (39.1%)	17/128 (13.3%)
Hour 9	43/128 (33.6%)	18/128 (14.1%)
Hour 12	31/128 (24.2%)	14/128 (10.9%)
Day 29		
Hour 3	61/127 (48.0%)	22/128 (17.2%)
Hour 6	54/127 (42.5%)	23/128 (18.0%)
Hour 9	46/127 (36.2%)	22/128 (17.2%)
Hour 12	36/127 (28.3%)	15/128 (11.7%)

2-grade CEA Success: 2-grade improvement on CEA.

The differences between the active and vehicle group for the mean change in CEA scores relative to day 1/ hour 0 were largest at Hour 3 on Days 1, 15, and 29, with some tapering off by Hour 12; although the data at Hour 12 showed approximately 1 grade improvement in mean scores relative to Hour 0. In the CD07805/47 Gel 0.5% group, the mean changes in CEA scores at Weeks 6 and 8 each showed reductions of 0.3 points, with few subjects showing worsening during the follow up period relative to Baseline (5/126 subjects at Week 6 and 6/127 subjects at Week 8). In the vehicle group, the mean reduction in CEA scores was 0.3 to 0.4 point.

The 2-grade PSA Success, change in PSA score from pre dose (Day 1/Hour 0) and the percentage of days that subjects had PSA scores of 0 (no redness) or 1 (very mild redness) were analysed as tertiary endpoints, without inferential statistics. At each time point, higher percentages of subjects in the CD07805/47 Gel 0.5% group showed 2 grade improvement in PSA scores relative to the Vehicle Gel group (Table 21). The differences between the active and vehicle group for the mean change in PSA scores relative to day 1/ hour 0 were generally largest at Hours 3 and/or 6 on Days 1, 15, and 29, and with Hour 12 showing that the scores in the active group remained approximately 1 grade lower than Hour 0. In the CD07805/47 Gel 0.5% group, the mean changes in PSA scores at Weeks 6 and 8 each showed reductions of 0.7 to 0.8 points, with few subjects showing worsening during the follow up period relative to Baseline (3/125 subjects at Week 6 and 2/127 subjects at Week 8). On Days 2 to 14 (between study visits), subjects reported PSA scores of 0 or 1 for 27.94% of those days in the CD07805/47 Gel 0.5% group, compared to 10.53% of those days in the Vehicle Gel group. On Days 16 to 28, subjects reported PSA scores of 0 or 1 for 30.69% of those days in the CD07805/47 Gel 0.5% group, compared to 16.70% of those days in the Vehicle Gel group. The average PSA scores on Days 2 to 14 and Days 16 to 28 were also lower in the CD07805/47 Gel 0.5% group compared to the Vehicle Gel group.

Table 21. Study 18140. Summary of 2 grade PSA success, observed data, ITT population

Success	CD07805/47 Gel 0.5% (N=129) n/N (%)	Vehicle Gel (N=131) n/N (%)
Day 1		
Hour 3	33/129 (25.6%)	6/131 (4.6%)
Hour 6	41/129 (31.8%)	6/131 (4.6%)
Hour 9	37/129 (28.7%)	7/131 (5.3%)
Hour 12	31/129 (24.0%)	6/130 (4.6%)
Day 15		
Hour 3	51/128 (39.8%)	12/128 (9.4%)
Hour 6	50/128 (39.1%)	18/128 (14.1%)
Hour 9	42/128 (32.8%)	12/128 (9.4%)
Hour 12	42/128 (32.8%)	11/128 (8.6%)
Day 29		
Hour 3	61/127 (48.0%)	28/128 (21.9%)
Hour 6	54/127 (42.5%)	23/128 (18.0%)
Hour 9	50/127 (39.4%)	26/128 (20.3%)
Hour 12	48/127 (37.8%)	25/128 (19.5%)

2-grade PSA Success: 2-grade improvement on PSA.

7.1.1.1.13.3. Patient Assessment of Appearance (PAA) and OTE

Very few subjects were either satisfied or very satisfied with their appearance on Day 1/Hour 0. At each post baseline time point, greater numbers of subjects in the CD07805/47 Gel 0.5% group reported being satisfied or very satisfied with their appearance compared to subjects in the Vehicle Gel group. The greatest proportion of subjects who reported being satisfied with their appearance was 46.5% at Hour 3 on Day 29 in the Brimonidine 0.5% gel group compared with 22.7% at Hour 6 on Day 29 in the vehicle gel group. On Days 2 to 14, subjects reported PAA scores of 0 or 1 for 39.39% of those days in the CD07805/47 Gel 0.5% group, compared to 13.87% of those days in the Vehicle Gel group. On Days 16 to 28, subjects reported PAA scores of 0 or 1 for 42.65% of those days in the CD07805/47 Gel 0.5% group, compared to 18.94% of those days in the Vehicle Gel group. The average PAA scores on Days 2 to 14 and Days 16 to 28 were also lower in the CD07805/47 Gel 0.5% group compared to the Vehicle Gel group.

The data for OTE, as assessed by subjects at Hour 12 on Day 29 showed that a greater percentage of subjects in the CD07805/47 Gel 0.5% group assessed the overall treatment effect as "moderately better" or "very much better" compared to subjects in the Vehicle Gel group.

The SF-12v2 Acute Health Survey Scale/Component Scores showed no notable differences in the mean scores on the various domains between subjects in the CD07805/47 Gel 0.5% and Vehicle Gel groups on Days 1, 15, or 29.

7.1.1.1.13.4. Other efficacy results

The Baseline assessments were similar between the treatment groups and no significant worsening in mean IGA[17] scores was observed in either group at any post baseline time point, including the post treatment follow up period. The baseline assessments of facial inflammatory count were similar between the treatment groups and no significant worsening in mean lesion counts was observed in either group on Day 29 or during the post treatment follow up period. The Baseline assessments were similar between the treatment groups and no significant

[17] The Investigator/evaluator (a board-certified dermatologist) was to assess the subject's overall severity of rosacea-related facial lesions by performing a static ("snap-shot") evaluation using the IGA of Lesions, and to report the one integer that best described the overall severity.

worsening in mean Telangiectasia Grading Assessment[18] scores was observed in either group on Day 29 or during the post-treatment follow up period.

Subjects were to evaluate potential over extended pharmacological effect of the study drug (for example over-whitening, or blanching, or blotching of the skin) at the clinic and on non-clinic days by using the PAW[19]. As expected, a higher percentage of subjects in the CD07805/47 Gel 0.5% group reported too much whitening compared to the Vehicle Gel group. The proportions of subjects in the CD07805/47 Gel 0.5% group who reported too much whitening and being bothered by too much whitening tended to decrease throughout the course of the study. The PAW scores between clinic visits are summarized in Table 22. Similar to the observed data for clinic visits, subjects in the CD07805/47 Gel 0.5% group tended to report a higher percentage of days with too much whitening and being bothered by too much whitening compared to subjects in the Vehicle Gel group.

Table 22: Summary of patient assessment of whitening (PAW) between visits, ITT population

Patient Assessment of Whitening (PAW) Between Visits	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)
Days 2 to 14		
Percent Days with Too Much Whitening (%)		
N	129	131
Mean	7.62	1.17
SD	19.959	9.076
Median	0.00	0.00
Minimum, Maximum	0.0, 100.0	0.0, 100.0
Percent Days with Bothered by Too Much Whitening (%)		
N	129	131
Mean	4.29	0.88
SD	14.175	8.778
Median	0.00	0.00
Minimum, Maximum	0.0, 100.0	0.0, 100.0
Days 16 to 28		
Percent Days with Too Much Whitening (%)		
N	128	128
Mean	7.57	1.08
SD	21.414	8.511
Median	0.00	0.00
Minimum, Maximum	0.0, 100.0	0.0, 92.3
Percent Days with Bothered by Too Much Whitening (%)		
N	128	128
Mean	5.53	1.02
SD	17.907	8.491
Median	0.00	0.00
Minimum, Maximum	0.0, 100.0	0.0, 92.3

[18] The Investigator/evaluator (a board-certified dermatologist) was to evaluate the subject's rosacea-associated facial telangiectasia severity by performing a static ("snap-shot") evaluation using the TeGA, and to report the one integer that best described the overall severity. When evaluating the subject's telangiectasia, the Investigator/evaluator was to make no reference to previous assessment.

[19] The PAW is a questionnaire with 2 yes/no questions. In Part A, the subject was to answer the first yes/no question, which was to ask if the subject felt he/she had too much whitening. The subject was only to complete Part B (answer yes or no about being bothered by too much whitening) if the subject answered yes to Part A. On clinic visit days, subjects were to perform static ("snap-shot") evaluations. On non-clinic days, the same PAW grading scale was used; however, it was intended as an overall assessment of the entire day (or "daily recall") rather than a static evaluation. Thus, the wording in the subject instructions for completing the assessment on non-clinic days was different from the instructions for clinic days. Assessment completion guidelines for non-clinic days were to be provided to all subjects.

7.1.1.1.13.5. Rebound evaluation

After cessation of a 4 week continuous treatment period, no aggravation effect on facial erythema was observed during the follow up period, in comparison to Baseline/Day 1 (T0) assessments. In the CD07805/47 Gel 0.5% group, the mean changes in CEA and PSA scores at Weeks 6 and 8 each showed reductions of 0.3 points for the CEA and 0.7 to 0.8 points for the PSA. Few subjects in the active treatment group showed worsening in scores during the follow-up period relative to Baseline: 5/126 subjects (4.0%) for CEA and 3/125 subjects (2.4%) for PSA at Week 6, and 6/127 subjects (4.7%) for CEA and 2/127 subjects (1.6%) for PSA at Week 8. A similar incidence was observed in the Vehicle Gel group, suggesting that this response was indicative of the natural course of the disease.

7.1.1.1.13.6. Global disease assessments

No effect on telangiectasia (Telangiectasia Grading Assessment) was observed. There was no aggravation of IGA or increasing facial lesion counts with CD07805/47 Gel 0.5% beyond what is expected to occur following the natural course of the disease as observed in the Vehicle Gel group during the treatment phase or the follow up phase of the study. Consequently, the 4 week treatment of facial erythema did not result in exacerbation of other common manifestations of rosacea.

Comments: CD07805/47 Gel 0.5% was significantly superior ($p < 0.001$) compared to Vehicle Gel for the primary endpoint (2 grade Composite Success for CEA and PSA at Hours 3, 6, 9, and 12 on Day 29). Using the observed case data, 2 grade Composite Success ranged from 22.8% to 31.5% on Day 29 compared to the Vehicle Gel control (8.6% to 10.9%). The outcome of the study is robust as the results were confirmed in the ITT population using the LOCF method, and the PP population, and in the sensitivity analyses.

The secondary endpoint, 30 minute Effect (defined as 1 grade improvement on both CEA and PSA at 30 minutes on Day 1) was statistically significantly better than Vehicle Gel ($p < 0.001$) in both the ITT and PP populations. The grade 1 Composite Success rates with CD07805/47 Gel 0.5% observed data was statistically significantly greater ($p < 0.001$) and ranged from 56.7% to 70.9% on Day 29 compared to Vehicle Gel, which ranged from 29.7% to 32.8%.

PAA and OTE: CD07805/47 Gel 0.5% consistently showed a more favourable outcome in PAA and OTE compared to Vehicle Gel. The PAW): As expected, slightly more subjects in the CD07805/47 Gel 0.5% group reported unwanted over whitening compared to subjects in the Vehicle Gel group. Overall, subjects in the active group adapted to the over whitening effect (that is, the incidence decreased from Day 1 to Day 29) and no subjects discontinued from the study due to the effect of over whitening.

Global disease assessments: No effect on telangiectasia was observed. There was no aggravation of IGA or increasing facial lesion counts with CD07805/47 Gel 0.5% beyond what is expected to occur following the natural course of the disease as observed in the Vehicle Gel group during the treatment phase or the follow-up phase of the study. Consequently, the 4 week treatment of facial erythema did not result in exacerbation of other common manifestations of rosacea.

There was no evidence of tachyphylaxis was observed. Efficacy profiles for Day 29 were generally comparable to or better than Day 1 profiles, indicating no reduction in effectiveness over the course of the treatment phase of the study.

Rebound evaluation: After cessation of a 4 week continuous treatment period, no aggravation effect on facial erythema was observed during the follow-up period, in comparison to Baseline/Day 1 (T0) assessments. In the CD07805/47 Gel 0.5% group, the mean changes in CEA and PSA scores at Weeks 6 and 8 each showed reductions of

0.3 points for the CEA and 0.7 to 0.8 points for the PSA. Few subjects in the active treatment group showed worsening in scores during the follow-up period relative to Baseline: 5/126 subjects (4.0%) for CEA and 3/125 subjects (2.4%) for PSA at Week 6, and 6/127 subjects (4.7%) for CEA and 2/127 subjects (1.6%) for PSA at Week 8. A similar incidence was observed in the Vehicle Gel group, suggesting that this response was indicative of the natural course of the disease.

Overall, this well conducted study provided compelling evidence that the CD07805/47 Gel 0.5% qd dosing regimen showed statistically significant and clinically relevant improvements in reduction of facial erythema than the Vehicle Gel control.

7.1.1.2. Study 18141

7.1.1.2.1. Study design, objectives, locations and dates

The study was conducted at 15 centres in USA and Canada from 16 May 2011 to 22 Nov 2011. The study design and objectives were identical to those discussed for study 18140 above.

7.1.1.2.2. Inclusion and exclusion criteria

These were identical to those discussed for study 18140 above.

7.1.1.2.3. Study treatments

These were identical to those discussed for study 18140 above.

7.1.1.2.4. Efficacy variables and outcomes

These were identical to those discussed for study 18140 above.

7.1.1.2.5. Randomisation and blinding methods

These were identical to those discussed for study 18140 above.

7.1.1.2.6. Analysis populations, sample size, statistical methods

These were identical to those discussed for study 18140 above.

7.1.1.2.7. Participant flow

Of the 346 enrolled patients, 293 were randomised and included in the safety and ITT populations (CD07805/47 gel 0.5%=148; vehicle gel=145). The modified intent to treat (MITT) Population comprised 260 subjects, excluding 33 subjects from a single investigational centre for which a data validity concern had been identified prior to database lock Within each treatment group, a majority of subjects completed the study, which was comparable between the 2 groups: 95.3% of subjects in the CD07805/47 Gel 0.5% group and 97.9% in the CD07805/47 Vehicle Gel group.

7.1.1.2.8. Major protocol violations/deviations

A total of 54 subjects (18.4%) had major protocol deviations: 29 (19.6%) in the CD07805/47 Gel 0.5% group and 25 (17.2%) in the Vehicle Gel group Site-specific data validity concern was the most common deviation, which was reported for 33 subjects: 17 in the CD07805/47 Gel 0.5% group and 16 in the Vehicle Gel group. The specific concern was raised for the data from a single investigational centre.

7.1.1.2.9. Baseline data

Majority of patients were females (72.72%), White (98.6%) had moderate erythema based on CEA score of 3 (76%) and PSA score of 3 (86%). The mean age was 47.5 years and skin prototype II (59%) or III (25%) was most common. There were no significant differences in demographic and baseline disease characteristics between the treatment groups. Overall, 7.8% of subjects took previous therapies (for rosacea or any other therapies during 6 months prior to screening) and the only previous therapies taken by more than 1 subject overall were

metronidazole (15 subjects, 5.1%), doxycycline (3 subjects, 1%) and azelaic acid (2 subjects, 0.7%).

Concomitant therapies were taken by 76.9% of subjects, with the most common being multivitamins (9.9%), other emollients and protectives (9.6%) and cholesterol-lowering agents (12.3%).

7.1.1.2.10. Results for the primary efficacy outcome

CD07805/47 Gel 0.5% was significantly superior ($p < 0.001$) compared to Vehicle Gel for the primary endpoint: 2-grade Composite Success for CEA and PSA at Hours 3, 6, 9, and 12 on Day 29. Using the observed case data, 2-grade Composite Success ranged from 17.6% to 25.4% on Day 29 compared to the Vehicle Gel control (9.2% to 10.6%). Consistently, statistical superiority of CD07805/47 Gel 0.5% versus Vehicle Gel was demonstrated on Day 15 ($p<0.001$) and Day 1 ($p<0.001$). Results were confirmed in the ITT population using the LOCF method, in the MITT population, in the PP population, and in the sensitivity analyses.

7.1.1.2.11. Results for other efficacy outcomes

7.1.1.2.11.1. Secondary endpoint

The secondary endpoint, 30-minute Effect (defined as 1 grade improvement on both CEA and PSA at 30 minutes on Day 1) was statistically significant ($p < 0.001$) in the ITT, MITT, and PP populations, indicating that CD07805/47 Gel 0.5% is significantly better than Vehicle Gel at initiating the onset of a meaningful clinical effect within 30 minutes after the first application of study drug.

7.1.1.2.11.2. Tertiary endpoints

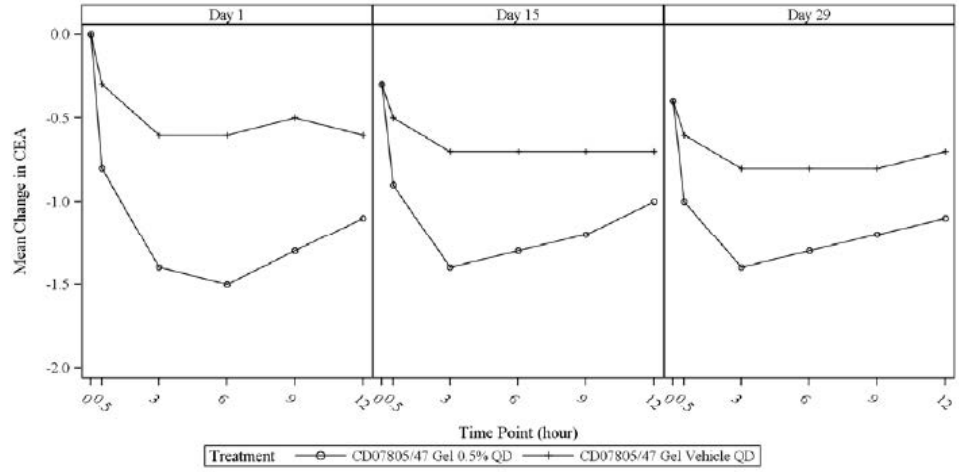
For 1 grade Composite Success, which is noticeable and clinically meaningful, as the endpoint represented Investigator and subject (independent) concurrence that a 1 grade improvement had occurred, the Composite Success rates for CD07805/47 Gel 0.5% ranged from 53.5% to 71.1% on Day 29 compared to Vehicle Gel (39.4% to 43.0%). This effect was also statistically significant on Days 1, 15, and 29 ($p<0.001$ 7).

For the other CEA tertiary endpoints, the observed data at each time point showed higher percentages of subjects in the CD07805/47 Gel 0.5% group with 2-grade improvement in CEA scores relative to the Vehicle Gel group (Table 23). For mean change in CEA score from Pre-dose at Hour 12, the scores in the CD07805/47 Gel 0.5% group were approximately 1 grade lower than Day 1/Hour 0 on Days 1, 15, and 29 (Figure 2).

Table 23: Summary of 2 grade CEA success, observed data, ITT population

Success	CD07805/47 Gel 0.5% (N=148) n/N (%)	Vehicle Gel (N=145) n/N (%)
Day 1		
Hour 3	71/148 (48.0%)	16/145 (11.0%)
Hour 6	76/148 (51.4%)	26/145 (17.9%)
Hour 9	61/148 (41.2%)	14/144 (9.7%)
Hour 12	46/148 (31.1%)	20/144 (13.9%)
Day 15		
Hour 3	66/143 (46.2%)	19/141 (13.5%)
Hour 6	58/143 (40.6%)	26/141 (18.4%)
Hour 9	51/143 (35.7%)	29/141 (20.6%)
Hour 12	44/143 (30.8%)	27/141 (19.1%)
Day 29		
Hour 3	60/142 (42.3%)	33/142 (23.2%)
Hour 6	55/142 (38.7%)	28/142 (19.7%)
Hour 9	44/142 (31.0%)	29/142 (20.4%)
Hour 12	48/142 (33.8%)	33/142 (23.2%)

Figure 2. Mean change in CEA on day1, day 15 and day 29, ITT population



Clinician Erythema Assessment (CEA) Score: 0=Clear skin with no signs of erythema; 1=Almost clear; slight redness; 2=Mild erythema; definite redness; 3=Moderate erythema; marked redness; 4=Severe erythema; fiery redness.

For Change in CEA from Baseline: 0=no change, -1=1-grade reduction, -2=2-grade reduction.

The 2 grade PSA Success, mean change in PSA score from pre dose (Day 1/Hour 0) and the percentage of days that subjects had PSA scores of 0 (no redness) or 1 (very mild redness) between visits were analysed as tertiary endpoints. For 2 grade PSA success, more subjects in the CD07805/47 Gel 0.5% group showed 2 grade PSA success relative to the Vehicle Gel group. For mean change in PSA score from Pre-dose at Hour 12, the scores in the CD07805/ 47 Gel 0.5% group were approximately 1 grade lower than Day 1/Hour 0 on Days 1, 15, and 29. For PSA scores between visits, subjects reported PSA scores of 0 or 1 for 31.70% of Days 2 to 14 in the CD07805/47 Gel 0.5% group, compared to 13.35% of those days in the Vehicle Gel group. On Days 16 to 28, subjects reported PSA scores of 0 or 1 for 36.09% of the days in the CD07805/47 Gel 0.5% group, compared to 19.49% of the days in the Vehicle Gel group.

7.1.1.2.11.3. Patient Assessment of Appearance (PAA) and OTE

Very few subjects were either satisfied or very satisfied with their appearance at Baseline on Day 1/Hour 0. At each post Baseline time point, greater numbers of subjects in the CD07805/47 Gel 0.5% group reported being satisfied or very satisfied with their appearance compared to subjects in the Vehicle Gel group. The greatest proportion of subjects who reported being satisfied with their appearance was 36.4% at Hour 3 and Hour 6 on Day 15 in the brimonidine 0.5% gel group compared with 20.4% at Hour 3 on Day 29 in the vehicle gel group. On Days 2 to 14, subjects reported PAA scores of 0 or 1 for 41.39% of those days in the CD07805/47 Gel 0.5% group, compared to 18.52% of those days in the Vehicle Gel group. On Days 16 to 28, subjects reported PAA scores of 0 or 1 for 43.79% of those days in the CD07805/47 Gel 0.5% group, compared to 21.04% of those days in the Vehicle Gel group. The average PAA scores on Days 2 to 14 and Days 16 to 28 were also lower in the CD07805/47 Gel 0.5% group compared to the Vehicle Gel group.

The data for OTE, as assessed by subjects at Hour 12 on Day 29 are summarized in Table 24. Greater percentages of subjects in the CD07805/47 Gel 0.5% group assessed the overall treatment effect as “moderately better” or “very much better” compared to subjects in the Vehicle Gel group.

Table 24: Summary of overall treatment effect (OTE) at day 29/ hour 12, ITT population

Overall Treatment Effect (OTE)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
1=Very much worse	1 (0.7%)	1 (0.7%)
2=Moderately worse	4 (2.8%)	1 (0.7%)
3=A little worse	10 (7.0%)	3 (2.1%)
4=About the same	37 (26.1%)	80 (56.3%)
5=A little better	25 (17.6%)	29 (20.4%)
6=Moderately better	39 (27.5%)	19 (13.4%)
7=Very much better	26 (18.3%)	9 (6.3%)
Total	142 (100.0%)	142 (100.0%)
N	142	142
Mean	5.1	4.6
SD	1.38	1.03
Median	5.0	4.0
Minimum, Maximum	1, 7	1, 7

7.1.1.2.11.4. Other efficacy results

The Baseline assessments were similar between the treatment groups and no significant worsening in mean IGA scores was observed in either group at any post-baseline time point, including the post-treatment follow-up period. The baseline assessments of facial inflammatory count were similar between the treatment groups and clinically meaningful increases in lesion counts were observed in either group on Day 29 or during the post-treatment follow-up period. The Baseline assessments were similar between the treatment groups and no significant worsening in mean Telangiectasia Grading Assessment (TeGA)[20] scores was observed in either group on Day 29 or during the post-treatment follow-up period.

As expected, a higher percentage of subjects in the CD07805/47 Gel 0.5% group reported too much whitening compared to the Vehicle Gel group. The proportions of subjects in the CD07805/47 Gel 0.5% group who reported too much whitening and being bothered by too much whitening tended to decrease throughout the course of the study. The PAW scores between clinic visits are summarized in Table 25. Similar to the observed data for clinic visits, subjects in the CD07805/47 Gel 0.5% group tended to report a higher percentage of days with too much whitening and being bothered by too much whitening compared to subjects in the Vehicle Gel group. For SF-12v2 Acute Health survey scale/ component scores, no notable differences were observed in the mean scores on the various domains between subjects in the CD07805/47 Gel 0.5% and Vehicle Gel groups on Days 1, 15, or 29.

[20] The investigator/evaluator (a board-certified dermatologist) was to evaluate the subject's rosacea-associated facial telangiectasia severity by performing a static ("snap-shot") evaluation using the TeGA, and to report the one integer that best described the overall severity. When evaluating the subject's telangiectasia, the Investigator/evaluator was to make no reference to previous assessment.

Table 25: Summary of patient assessment of whitening (PAW) between visits, ITT population

Patient Assessment of Whitening (PAW) Between Visits	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Days 2 to 14		
Percent Days with Too Much Whitening (%)		
N	148	145
Mean	5.52	2.86
SD	16.773	15.381
Median	0.00	0.00
Minimum, Maximum	0.0, 100.0	0.0, 100.0
Percent Days with Bothered by Too Much Whitening (%)		
N	148	145
Mean	3.10	1.33
SD	13.421	9.903
Median	0.00	0.00
Minimum, Maximum	0.0, 100.0	0.0, 100.0
Days 16 to 28		
Percent Days with Too Much Whitening (%)		
N	144	142
Mean	3.93	2.71
SD	14.967	15.141
Median	0.00	0.00
Minimum, Maximum	0.0, 100.0	0.0, 100.0
Percent Days with Bothered by Too Much Whitening (%)		
N	144	142
Mean	1.84	1.30
SD	9.715	10.954
Median	0.00	0.00
Minimum, Maximum	0.0, 76.9	0.0, 100.0

No effect on telangiectasia was observed. There was no aggravation of IGA or increasing facial lesion counts with CD07805/47 Gel 0.5% beyond what is expected to occur following the natural course of the disease as observed in the Vehicle Gel group during the treatment phase or the follow-up phase of the study. Consequently, the 4-week treatment of facial erythema did not result in exacerbation of other common manifestations of rosacea.

Overall, no evidence of tachyphylaxis was observed. Efficacy profiles for Day 29 were generally comparable to or better than Day 1 profiles, indicating no reduction in effectiveness over the course of the treatment phase of the study.

7.1.1.2.11.5. Rebound evaluation

In the CD07805/47 Gel 0.5% group, the mean changes in CEA and PSA scores at Weeks 6 and 8 each showed reductions of 0.5 points for the CEA and 0.7 points for the PSA. Few subjects in the active treatment group showed worsening in scores during the follow up period relative to Baseline: 5/140 subjects (3.6%) for CEA and 6/139 subjects (4.3%) for PSA at Week 6, and 3/141 subjects (2.1%) each for CEA and for PSA at Week 8. A similar incidence was observed in the Vehicle Gel group, suggesting that this response was indicative of the natural course of the disease.

Comments: CD07805/47 Gel 0.5% was significantly more effective ($p < 0.001$) for reduction of facial erythema of rosacea than Vehicle Gel when applied once daily for 29 days based on the inferential analyses of the primary endpoint of 2 grade Composite Success and the secondary endpoint for rapid onset of effect (30-minute Effect). These results were robust and clinically meaningful as analyses in the MITT and PP populations showed similar results to those observed in the ITT analysis.

CD07805/47 Gel 0.5% was significantly superior ($p<0.001$) compared to Vehicle Gel for the primary endpoint (2 grade Composite Success for CEA and PSA at Hours 3, 6, 9, and

12 on Day 29). Using the observed case data, 2 grade Composite Success ranged from 17.6% to 25.4% on Day 29 compared to the Vehicle Gel control, which ranged from 9.2% to 10.6%.

For the secondary endpoint, the observed data were statistically significant ($p<0.001$) in the ITT, MITT, and PP populations, indicating that CD07805/47 Gel 0.5% is significantly better than Vehicle Gel at initiating the onset of a meaningful clinical effect within 30 minutes after the first application of study drug.

CD07805/47 Gel 0.5% consistently showed a more favourable outcome in PAA and OTE compared to Vehicle Gel. As expected, slightly more subjects in the CD07805/47 Gel 0.5% group reported unwanted over whitening compared to subjects in the Vehicle Gel group. Overall, subjects in the active group adapted to the over whitening effect (that is, the incidence decreased from Day 1 to Day 29) and no subjects discontinued from the study due to the effect of over whitening.

Results from this second pivotal study confirmed the efficacy and safety of brimonidine 0.5% gel in the treatment of facial erythema of rosacea in adult patients.

7.1.2. Other efficacy studies

7.1.2.1. Study 18194

The CEA scale, single-centre study 18194 was an independent study conducted by the Sponsors to evaluate the inter rater and intra rater reliability of the final version of the CEA scale for assessment of the severity of persistent facial erythema in subjects with rosacea. Study subjects were not treated with Brimonidine Tartrate Gel in this study. Adult subjects with a clinical diagnosis of rosacea and fewer than 3 facial inflammatory lesions were eligible for study participation. At the Screening visit, the principal investigator performed a CEA assessment on each subject to ensure appropriate representation of each of the 5 CEA categories (Grades 0-4) within the study population. The raters who participated in CEA evaluations were required to be board certified dermatologists.

Training and consensus harmonization[21] in the use of the CEA scale was provided to the raters on Day 1 of the study, prior to evaluating study subjects. A total of 12 board-certified dermatologists participated as raters in this study which enrolled 28 subjects. Following completion of the aforementioned training and consensus harmonization, the raters determined the CEA scores for subjects by using a photo-numeric guide that showed facial photographs with the associated grades according to the CEA scale criteria. Each rater evaluated every subject twice, at least 2 hours apart (Session 1 and Session 2).

For inter-rater reliability, the overall weighted Kappa statistic for Sessions 1 and 2 were 0.740 and 0.673, respectively, which is considered "substantial" agreement for both Sessions by the Landis and Koch (1977) criteria. The overall intra class correlation coefficient (ICC) values for Sessions 1 and 2 were 0.601 and 0.576, respectively, which is considered "fair to good reproducibility" for both Sessions by the Fleiss (1981 and 1986) criteria. Taken together these results indicate substantial inter rater reliability with use of the CEA scale and the photo numeric guide.

[21] During this session, the Principal Investigator discussed the proper use of the scale, detailing each grade of the scale, and the rationale for the descriptors used. Representative patient photographs were used to highlight the key morphological characteristics of each grade. Raters were then shown a series of sample patient photographs (previously selected and graded by an expert consensus panel) and asked to grade each one independently, using the CEA. The Principal Investigator then led an open group discussion, during which the Raters discussed their selection of CEA grade for each sample photograph, with the goal of reaching a consensus harmonization for all Raters on CEA grade selection.

For intra rater reliability, the overall weighted Kappa statistic for reproducibility between Session 1 and Session 2 was 0.692. The mean ICC value was 0.658, with a median of 0.666 and an overall range of 0.378 to 0.833. As with the inter rater results, applying the same criteria, the intra rater results indicate "substantial" agreement and "good reproducibility" for test-retest reliability of the CEA scale with the photo numeric guide.

7.1.2.2. Long-term study 18142

Study 18142 was a Phase III, multicentre, open label, non-comparative 52 week study which evaluated the long-term safety and efficacy of CD07805/47 gel 0.5% applied qd in 449 patients with moderate to severe facial erythema of rosacea. Efficacy assessment was a secondary objective of this study. The efficacy measurements included the PSA, CEA, PAA, and OTE.

The mean change of -1.0 observed at the Baseline (Day 1) Hour 3 assessment improved over the course of the study reaching a level of improvement of -1.6 at the Month 3 visit. For the remaining clinic visits, a mean change in PSA of -1.5 or -1.7 was maintained until the end of the study, which suggested that no tachyphylaxis of treatment effect occurred over time.

The mean change in CEA score of -1.5 observed at the Baseline (Day 1) hour 3 assessment improved over the course of the study reaching the greatest level of improvement (-1.8) at the month 6 visit. For the remaining clinic visits, a mean change in CEA of -1.7 or -1.8 was maintained until the end of the study, which suggested that no tachyphylaxis of treatment effect occurred over time.

The possibility of survivor bias contributing to the positive trend in PSA and CEA improvement over time was also evaluated The results showed that the trends in PSA and CEA improvement over the course of the study were similar between subjects who completed the study (that is, completed the month 12 visit) and subjects who prematurely discontinued the study (non-completers), thus demonstrating that survivor bias is an unlikely cause of the improvement observed in PSA and CEA scores.

The mean change in PAA score of -1.3 observed at the Baseline (Day 1) Hour 3 assessment improved over the course of the study reaching a level of improvement of -1.7 at the Month 3 Hour 3 assessment. At the Month 3 Hour 3 assessment, 14.8% of subjects had a PAA score of "Very Satisfied" and 41.7% of subjects had a score of "Satisfied". For the remaining clinic visits, a mean change in PAA of -1.6 to -1.8 was maintained until the end of the study. At the Month 12 Hour 3 assessment, 17.5% of subjects had a PAA score of "Very Satisfied" and 39.3% of subjects had a score of "Satisfied".

At Week 1, the mean OTE score was 4.8, with the majority of subjects (approximately 86%) scoring the OTE as "About the same" (24.9%), "A little better" (41.6%), or "Moderately better" (19.8%). Very few subjects at Week 1 perceived that the OTE made management of their facial erythema worse (grades 1 to 3; approximately 8%). The percentage of subjects who scored the OTE as "Very much better" was 5.6%. The mean OTE had improved to 5.1 by the Month 3 visit and was maintained until the end of the study. The percentage of subjects who perceived the two highest levels of improvement ("Moderately better" and "Very much better") increased over the course of the study, with 25.6% and 21.7% of subjects scoring the OTE as "Moderately better" and "Very much better", respectively, at the Month 12 visit. For subjects who scored the OTE as "Very much better", this was a 4 fold increase from Week 1 to Month 12. The percentage of subjects who perceived the OTE as making management of their facial erythema worse (grades 1 to 3) remained similar, and relatively low, over the course of the study.

At the Baseline visit, the mean IGA score was 1.1. At all subsequent clinic visits there was no noticeable change in IGA score with the mean change in IGA ranging between -0.0 and -0.2 for all clinic visits. At the Baseline (Day 1) visit, the mean number of inflammatory lesions was 5.4. Over the course of the study, there was a slight decrease in the mean number of inflammatory lesions, indicating that chronic long-term use of the study drug did not exacerbate subjects' inflammatory lesions.

The mean Telangiectasia Grading Assessment score at Baseline was 2.3, with most subjects (approximately 73%) being scored either Mild or Moderate for telangiectasias. There was a slight improvement in telangiectasia grading assessment scores over the duration of the study with mean change in telangiectasia grading assessment from Baseline ranging from -0.1 at the Week 1 clinic visit to -0.5 at the Month 12 and End of Treatment clinic visits. Forty-three (43) subjects overall (9.6%) had worsening of their telangiectasias, while all other subjects' telangiectasias either remained unchanged (212 subjects, 47.5%) or improved (191 subjects, 42.8%) from Baseline to End of Treatment.

At the Baseline visit, 61 subjects (13.6%) reported that they had too much whitening, and 29 of these subjects (6.5%) reported that they were bothered by too much whitening. The proportions of subjects who reported too much whitening and being bothered by too much whitening were low and tended to decrease throughout the course of the study, a trend that is consistent with previous Phase III studies. At the Month 12 visit, 15 subjects (5.3%) reported that they had too much whitening and 8 of those subjects (2.8%) reported that they were bothered by too much whitening. No subjects discontinued the study due to over whitening or blanching of the skin.

Subjects were to complete the Productivity and Social Life Questionnaire (Table 26) at the Baseline (Day 1) visit, at the Month 3, 6, 9, and 12 visits, and at the End of Treatment/ET visit to assess the impact of rosacea on their productivity and social life. Overall, the results indicated that there were limited changes over time for the first three questions regarding productivity; however, noticeable changes over time for the last three questions (questions 4 to 6) regarding social function were observed. A post-hoc McNemar analysis showed that a statistically significant reduction was observed at all post baseline visits for subjects answering yes to questions 4, 5, and 6. These results suggest that long term use of the study drug tended to have a positive impact on the psychosocial function of the subjects.

Table 26: Productivity and social life questionnaire

In the last month,
1. How many days have you missed from work because of your rosacea? Number of days:_____ ❒ None ❒ Not Applicable (if you do not work)
2. How much did your rosacea affect your productivity while at work? ❒ Significantly affected productivity ❒ Somewhat affected productivity ❒ No effect on productivity ❒ Not Applicable (if you do not work)
3. How much did your rosacea affect your ability to do your normal daily activities such as shopping, exercising, running errands, home projects, childcare, etc? ❒ Significantly affected ability to do normal daily activities ❒ Somewhat affected ability to do normal daily activities ❒ No effect on ability to do normal daily activities
4. Have you avoided public contact or canceled a social engagement because of your rosacea? ❒ Yes ❒ No
5. Has it been difficult to establish new relationships because of your rosacea? ❒ Yes ❒ No
6. Has your rosacea inhibited your social life? ❒ Yes ❒ No

Comments: The observed efficacy data confirmed the known short term effectiveness of CD07805/47 gel 0.5% and revealed no tachyphylaxis of treatment effect with long-term, chronic use. The results also indicated that long-term use of CD07805/47 gel 0.5% had a positive impact on the long term psychosocial function of rosacea subjects.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

None[22].

7.1.4. Evaluator's conclusions on clinical efficacy for treatment of facial erythema of rosacea

Brimonidine Tartrate 0.5% Gel, applied topically qd, was selected as the optimal concentration and dose regimen for Phase III because the single (18144) and multiple (18161) dose finding studies had demonstrated that Brimonidine Tartrate 0.5% Gel showed the best potential for achieving the desired treatment objectives of reducing facial erythema in the greatest number of subjects. That is, Brimonidine Tartrate 0.5% Gel qd provides significant effectiveness without significant over extended effects, while maintaining a high safety margin with respect to systemic exposure. The treatment objective for the product was to maintain, on a daily basis, at least a 1 grade improvement (that is, a noticeable effect) in CEA and/or PSA for a maximal

[22] Because the two confirmatory trials (18140 and 18141) were adequate and well controlled trials designed as independent demonstrations of the efficacy of brimonidine tartrate 0.5% Gel, the Applicant did not pool the results from these trials. The data from the Phase 2 trials (ROSE-201, 18144, and 18161) that were conducted to establish the dose for the confirmatory trials were not pooled due to the differences in trial design and doses evaluated.

amount of time (target of 12 hours after dosing), while being able to achieve daily 2 grade improvement in both assessments for a sustained period (Table 27).

Table 27: Summary of relevant clinical studies contributing to dose selection

Study Number	Study Design	Number of subjects Gender Mean Age	Doses and Treatment Duration	Results
Subjects with Rosacea				
RD.06.SRE.18144	Randomized, double-blind, parallel-group, vehicle-controlled, multicenter, dose-finding study	122 subjects 30M, 92F 45.7 years	Brimonidine Tartrate Gel (0.5%, 0.18%, 0.07%) Gel or Vehicle Gel Single dose	Brimonidine Tartrate Gel was found to be effective in the treatment of facial erythema of rosacea. The effect was superior to Vehicle Gel and consistently dose-dependent with the highest concentration (0.5%) being the most effective. Safety and tolerability were good and comparable between the groups treated with Brimonidine Tartrate Gel and Vehicle Gel.
RD.06.SRE.18161	Randomized, double-blind, parallel-group, vehicle-controlled, multicenter, efficacy and safety study	269 subjects 52M, 217F 44.3 years	Brimonidine Tartrate Gel (0.5%, 0.18% QD or BID) Gel or Vehicle Gel (QD or BID) 29 days	Brimonidine Tartrate 0.5% gel was statistically superior to Vehicle Gel for the primary endpoint. No evidence of tachyphylaxis was observed. All Brimonidine Tartrate Gel concentrations/regimens were well-tolerated with an acceptable safety profile during the treatment and follow-up phases.
RD.06.SRE.18143	Intra-individual, double-blind, randomized, multicenter, comparative, maximal use PK study	102 subjects 40M, 62F 41.6 years	Day 1: 1 drop of brimonidine tartrate 0.2% ophthalmic solution instilled in each eye every 8 hours over a 24-hour period Days 2-3: washout Days 4 to 32 (29 days): Topical administration of Brimonidine Tartrate Gel (0.07% BID, 0.18% QD or BID, and 0.5% QD). For the BID groups, the second application of Brimonidine Tartrate Gel was 6 hours after the first dose	Systemic bioavailability of Brimonidine Tartrate 0.5% Gel administered topically QD for 29 days was lower in comparison to ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution administered for a single day (3 times at 8 hour intervals over a 24-hour period)

Data Source: COI-118-BAPK-101, RD.06.SRE.18139, RD.06.SRE.18126, RD.06.SRE.18143

The two Phase III pivotal studies (18140 and 18141) were designed and conducted as adequate and well controlled trials that satisfied the criteria outlined in ICH Guideline E5(R1) and US Title 21 Code of Federal Regulations Part 314.126. The Phase III pivotal studies were designed in consideration of input from both US and EU Regulatory Authorities.

The patients included in these pivotal studies were representative of the target patient population for the proposed brimonidine 0.5% gel topical treatment; majority of the patients were female (75 to79%), White (98%) with moderate facial erythema (85 to 88% had CEA and PSA scores > 3 at baseline).

The primary endpoint of 2 grade Composite Success was a composite endpoint based on analyses of independent static evaluations of erythema by the investigators, CEA and the subjects, PSA. The final version of the PSA that was used in the Phase IIb and Phase III studies was developed and validated in accordance with the 2009 FDA Guidance titled “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims.” The Phase IIb study (18161) provided evidence of the appropriateness and sensitivity of the primary endpoint within a 29 day treatment period, in consideration of the anticipated design of the subsequent Phase III pivotal studies, and evaluated the same primary endpoint as the subsequent Phase III pivotal studies.

The 2 grade Composite Success rate for the Brimonidine Tartrate 0.5% Gel group was statistically significant and clinically meaningful compared to the Vehicle Gel group at each time point (Days 1, 15, and 29). Two (2) grade Composite Success ranged from 18.9% to 32.1% on Day 29 compared to the Vehicle Gel control (3.6% to 7.3%) at Hours 3, 6, 9, and 12. The Phase III pivotal studies met the predefined primary endpoint of 2 grade Composite Success, demonstrating the superiority of Brimonidine Tartrate 0.5% Gel compared to Vehicle Gel in reduction of facial erythema in subjects with rosacea. The Brimonidine Tartrate 0.5% Gel qd dose regimen showed robust efficacy when compared to the Vehicle qd regimen, as demonstrated by the analyses of 2-grade Composite Success over Hours 3, 6, 9, and 12. Because the treatment effect was significant at Day 29 ($p < 0.001$), the successive earlier time points were tested (Day 15 and Day 1), which also showed statistically significant and clinically relevant improvement in erythema of rosacea starting from the first day of treatment.

A statistically significant ($p < 0.001$) rapid onset of action was also demonstrated for the secondary endpoint (30-minute Effect) in the Phase III pivotal studies, which was 1 grade improvement on both the CEA and PSA 30 minutes after the first dose on Day 1. Brimonidine Tartrate 0.5% Gel was superior to Vehicle Gel at initiating the onset of a meaningful clinical effect on erythema as assessed independently by the investigator and by the subject within 30 minutes after the very first dose. In each study, approximately 28% of subjects in the Brimonidine Tartrate 0.5% Gel group showed 1 grade improvement on both the CEA and PSA at 30 minutes post dosing on Day 1, compared to 6.9% of Vehicle Gel subjects in Study 18140 and 4.8% of Vehicle Gel subjects in Study 18141. The odds of achieving 1 grade Composite Success on both the CEA and PSA 30 minutes after the first dose on Day 1 were 5 times higher in Study 18140 and 7 times higher in Study 18141 in the Brimonidine Tartrate 0.5% Gel groups relative to the Vehicle Gel groups.

Both the 2 grade Composite Success and 30 minute Effect in the ITT populations for the Phase III pivotal studies were confirmed by PP population analyses and sensitivity analyses of success and failure for both studies.

The endpoint of 1 grade Composite Success (1 grade improvement on both CEA and PSA) was a secondary endpoint in Study 18161 and a tertiary endpoint in the Phase III pivotal studies (18140 and 18141). The endpoint of 1 grade Composite Success is an apparent and distinguishable improvement from the baseline condition as assessed independently by the investigator and by the subject within the 12 hour post dosing period. Given that each scale is a 5 point scale, a 1 grade change can be considered relevant (for example, severe to moderate or moderate to mild).

The odds of achieving 2 grade and 1 grade Composite Success in the Brimonidine Tartrate 0.5% group on Day 29 were 3 to 4 times higher compared to the Vehicle Gel groups in the pivotal studies (18140 and 18141).

Each of the Phase III pivotal studies demonstrated that the positive effect of Brimonidine Tartrate 0.5% Gel on reducing facial erythema was sustained during the treatment day. On Days 1, 15, and 29, at each of the 4 time points in Studies 18140 and 18141, Brimonidine Tartrate 0.5% Gel showed a consistent and clinically meaningful reduction in erythema. The observed effect tended to be strongest at Hours 3 and 6, and although smaller at Hour 12, was still present. Over the course of each 12 hour measurement period, a single dose of Brimonidine Tartrate 0.5% Gel generally provided at least a 1 grade improvement, as measured by Composite Success (CEA and PSA combined), CEA Success, and PSA Success; this effect was maintained for a maximal amount of time (12 hours) in a majority of subjects.

The use of Brimonidine Tartrate Gel in the treatment of erythema of rosacea did not result in exacerbation of other signs of rosacea (inflammatory lesions and telangiectasia) or unintended effects such as subjects perceiving an overextended PD effect due to the vasoconstrictive effect of the drug (over whitening). In addition, QOL assessments were included No worsening of lesions was observed in the Phase IIb or Phase III pivotal studies in the Brimonidine Tartrate 0.5% Gel groups relative to the corresponding Vehicle Gel groups in any of the studies. In addition, no worsening of mean Telangiectasia Grading Assessment scores was observed Brimonidine Tartrate 0.5% Gel groups during the studies. As reduction in vascular erythema is the primary effect of Brimonidine Tartrate 0.5% Gel, the drug is not expected to reduce the incidence or severity of inflammatory lesions of rosacea. Although the drug could potentially reduce the transient perilesional erythema of papulopustular lesions of rosacea, thus making them temporarily less visible, this was not specifically investigated by the applicant.

The Phase IIb and the Phase III pivotal studies demonstrated that subjects perceived improvements on both clinic and non clinic days in their erythema and overall facial appearance, and showed minimal unwanted over whitening effects, as measured by the PSA, PAA, and PAW, respectively. Some subjects in the Brimonidine Tartrate 0.5% Gel qd group

reported being bothered by unwanted over whitening in each study. There is evidence to suggest that skill in treatment application technique (smooth, even application across all facial surfaces), which generally improves over time in subjects, may reduce any noticeable contrast between treated and untreated areas, and thus may contribute to the reductions in reports of unwanted over whitening from Day 1 to Day 29 in the Brimonidine Tartrate 0.5% Gel groups in each study. The incidence of unwanted over whitening was similar in the Brimonidine Tartrate 0.5% and Vehicle Gel groups by Day 29. Furthermore, no subjects discontinued any of the studies due to any effects of over whitening.

The long term, open label, uncontrolled study 18142 demonstrated that treatment with Brimonidine Tartrate 0.5% Gel for up to 1 year resulted in reduction in facial erythema in the target patient population, which was clinically meaningful in terms of investigator and subject assessments. The observed efficacy data confirmed the known short term effectiveness of Brimonidine Tartrate 0.5% Gel and also suggested a positive impact on the long term psychosocial function of rosacea. However, interpretation was limited by the open label, uncontrolled nature of the study.

No evidence of tachyphylaxis of the treatment effect was observed in the 29 day vehicle controlled studies or in the 1 year, long term study. Furthermore, during the follow up period in the 4 vehicle controlled studies that evaluated potential erythema rebound effect (Studies ROSE-201, 18161, 18140, and 18141), no rebound effect was observed.

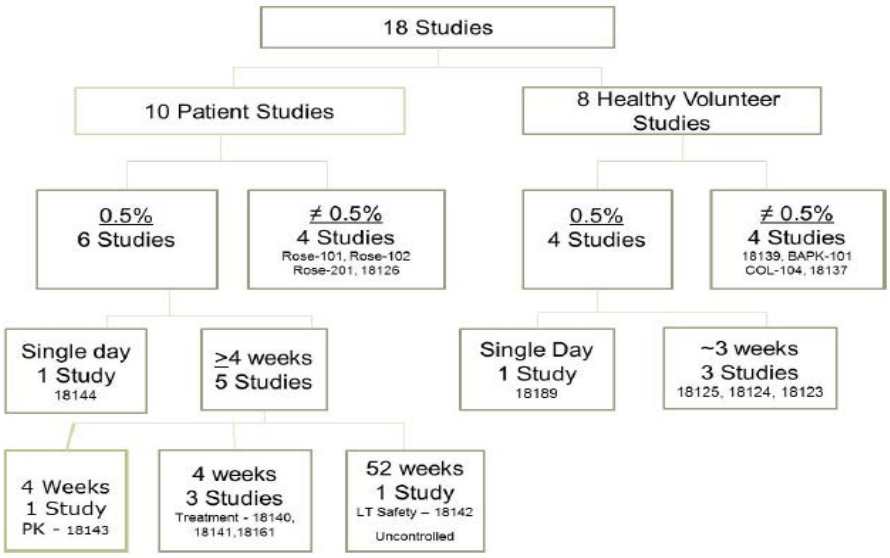
The main limitations of the submission regarding demonstration of efficacy were lack of evaluation in patients aged < 18 years of age and lack of a long term, controlled, double blind study (to provide evidence of efficacy beyond 29 days).

8. Clinical safety

8.1. Studies providing evaluable safety data

Overall, 18 clinical studies were performed in the program and the safety of Brimonidine Tartrate Gel was assessed in each of the studies; 10 of the 18 studies were conducted in subjects with rosacea and 8 studies were conducted in healthy subjects (Figure 3). Five (5) clinical trials were conducted by the previous sponsor and 13 clinical trials were conducted by Galderma R&D (the current sponsors).

Figure 3: Schematic of clinical studies for brimonidine tartrate gel



Five safety populations were defined for analysis of safety.

1. Core Studies: Four studies in subjects with rosacea including 2 identically designed double blind, randomised pivotal clinical trials (18140 and 18141), the 4 week randomised double blind, randomised study 18161 and the 52 week open label, uncontrolled study 18142.
2. Dose ranging studies population: This included 5 studies in rosacea subjects with each study analysed separately (COL-118-ROSE-101, COL-118-ROSE-102, COL-118-ROSE-201,18144 and18161).
3. Dermal safety studies population: This included 6 studies in healthy subjects with each study analysed separately (COL-118-104, 18189, 18123, 18124, 18125 and 18137).
4. PK studies population included 4 studies with each study analysed separately (COL-118-BAPK-101, 18126, 18143 and 18139).
5. Open label long-term safety and efficacy study 18142 (this has been discussed in detail in section 8.2 below).

The safety monitoring of Brimonidine Tartrate Gel for each study was performed by collecting treatment-emergent adverse events (TEAEs) and routine laboratory data, physical examination, and vital signs and, in some studies, intraocular pressure (IOP) measurements (Table 28). The MedDRA (Medical Dictionary for Regulatory Activities) classification system by SOC (System Organ Class) and PT (Preferred Term) was employed where appropriate. Regardless of the dictionary version used to code AEs at the study level, all AEs in the pooled SCS (ISS) database were coded/re-coded using the MedDRA version 11.0 to ensure consistency.

Table 28: Safety assessments in applicant studies for brimonidine tartrate 0.5% gel

Study Category	Study Number	AEs	Laboratory Measurements	Vital Signs	IOP
Well controlled	RD.06.SRE.18140	XX	XX	XX	--
	RD.06.SRE.18141	XX	XX	XX	--
Long term safety	RD.06.SRE.18142	XX	XX	XX	XX
Dose Finding	RD.06.SRE.18161	XX	--	XX	XX
	ROSE-101	XX	X	X	--
	ROSE-102	XX	X	X	--
	ROSE-201	XX	X	X	--
	RD.06.SRE.18144	XX	--	XX	XX
PK	BAPK-101	XX	--	X	X
	RD.06.SRE.18139	XX	X	X	X
	RD.06.SRE.18126	XX	X	X	X
	RD.06.SRE.18143	XX	XX	XX	XX
Dermal Safety	Phototoxicity-104	XX	--	--	--
	RD.06.SRE.18123	XX	--	--	--
	RD.06.SRE.18124	XX	--	--	--
	RD.06.SRE.18125	XX	--	--	--
	RD.06.SRE.18137	XX	--	--	--
	RD.06.SRE.18189	XX	--	--	--

AE = adverse event, not necessarily TEAE

IOP = Intraocular pressure

XX Summary in SCS (i.e., ISS) Tables

X Data available but not summarized in ISS Tables

8.2. Pivotal studies that assessed safety as a primary outcome

8.2.1. Study 18142

8.2.1.1. Study design, objectives, locations and dates

This was a Phase III, multicentre, open label, non-comparative 52 week study which evaluated the long term safety and efficacy of CD07805/47 gel 0.5% applied qd in patients with moderate

to severe facial erythema of rosacea. The primary objective of this study was to evaluate and document the long-term safety of CD07805/47 gel 0.5% applied qd for up to 52 weeks. Documentation of long term efficacy was the secondary objective of this study.

8.2.1.2. Inclusion and exclusion criteria

The main inclusion criteria were: Male or female who was at least 18 years of age or older with a clinical diagnosis of facial rosacea; CEA and PSA score of > 3 at Screening and at Baseline (prior to study drug application). The key exclusion criteria were: Particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other concomitant facial dermatoses that are similar to rosacea such as peri oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, or actinic telangiectasia; Current diagnosis of Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or depression; current treatment with monoamine oxidase inhibitors, barbiturates, opiates, sedatives, systemic anaesthetics, or alpha-agonists; less than 3 months stable dose treatment with tricyclic antidepressants, cardiac glycosides, beta blockers or other antihypertensive agents.

8.2.1.3. Study treatments

In this open label study, all subjects were to receive treatment with CD07805/47 gel 0.5% applied once daily, for up to 12 months. Concomitant standard of care treatments (for example, doxycycline or metronidazole) for subjects with inflammatory lesions of rosacea were allowed in all phases of the study. Subjects on active treatments for lesions at the time of enrolment were permitted to continue their current regimen for the duration of the study and if necessary, the regimen could have been modified by the investigator during the course of the study. Subjects requiring new therapy for the presence of inflammatory lesions at the time of enrolment or during the course of the study could have been prescribed the standard of care treatment at the investigator's discretion.

8.2.1.4. Safety variables and outcomes

The main safety assessments included AEs, SAEs, discontinuations due to AEs, physical examinations, vital signs, intraocular pressure (IOP) measurements and laboratory safety tests.

8.2.1.5. Randomisation and blinding methods

Not applicable.

8.2.1.6. Analysis populations

All data were summarized for the Safety Population defined as all subjects enrolled and who applied study drug at least once. As this was a safety study, an ITT population and a PP population were not defined.

8.2.1.7. Sample size, statistical methods

The sample size of 450 was chosen based on the ICH E1A Guideline: Extent of Population Exposure to Assess Clinical Safety. It was estimated with 450 subjects enrolled and receiving study drug, at least 300 subjects would be exposed for 6 months and at least 100 subjects would be exposed for 12 months. Both summary statistics and frequency distributions for the PSA, CEA, and PAA assessments were to be presented for the Baseline visit and all post Baseline visits (Week 1, Month 1, Month 3, Month 6, Month 9, Month 12, and End of Treatment).

8.2.1.8. Participant flow

Of the 586 subjects screened, 137 subjects were screen failures and 449 subjects were enrolled and included in the Safety Population. A total of 279 subjects (62.1%) completed the study (up to the Month 12 visit) and 170 subjects (37.9%) prematurely discontinued the study. A total of 335 subjects (74.6%) completed at least 6 months of treatment.

8.2.1.9. Major protocol violations/deviations

A total of 28 subjects (6.2%) had significant protocol deviations. The most common significant deviation (18 of 28 subjects) was subjects missing greater than 30% of doses between the start date at Baseline and the last post Baseline visit. Other significant protocol deviations included: missed scheduled visit (5 subjects); PSA score less than 3 at Baseline (2 subjects); CEA assessment completed by unauthorized individual (2 subjects) and prior treatment with CD07805/47 gel (1 subject).

8.2.1.10. Baseline data

The majority of subjects were female (74.8%), White (97.6%), and Not Hispanic or Latino (92.9%). Mean age was 50.9 years and most subjects were in the 18 to 64 years age group (88.0%); Skin Phototypes ranged from I to VI, with the majority of subjects (approximately 80%) having Skin Phototype II or III (Table 29). A total of 13.4% of subjects received previous therapies[23].

Table 29: Summary of subject baseline characteristics, safety population

Variable	CD07805/47 Gel 0.5% (N=449)
Skin Phototype, n (%)	
I	34 (7.6)
II	179 (39.9)
III	179 (39.9)
IV	50 (11.1)
V	6 (1.3)
VI	1 (0.2)
Total	449 (100)
Patient Self-Assessment (PSA) at Baseline (Day 1, Hour 0), n (%)	
2=Mild redness	2 (0.4)
3=Moderate redness	379 (84.4)
4=Severe redness	68 (15.1)
Total	449 (100)
Clinician's Erythema Assessment (CEA) at Baseline (Day 1, Hour 0), n (%)	
3=Moderate erythema, marked redness	394 (87.8)
4=Severe erythema, fiery redness	55 (12.2)
Total	449 (100)

The previous therapies taken by more than 2 subjects overall were Metronidazole (10 subjects, 2.2%), doxycycline (5 subjects, 1.1%), Vicodin (3 subjects, 0.7%), and other emollients and protectives (3 subjects, 0.7%). Concomitant therapies were taken by 84.9% of subjects, with the most common (> 10% of total subjects) comprising Metronidazole (70 subjects, 15.6%), ibuprofen (58 subjects, 12.9%), and multivitamins (56 subjects, 12.5%). A total of 131 subjects (29.2%) were taking concomitant therapies for inflammatory lesions associated with their rosacea. Over the course of the study, the mean subject compliance was 95.18% and the mean number of missed applications of study drug was 9.49. Overall, 276 subjects (61.5%) had a treatment duration of ≥ 365 days.

8.2.1.11. Safety results

A summary of the main safety results are provided in Table 30.

[23] Previous therapies were defined as products used for the treatment of rosacea and any other therapies received during the previous 6 months prior to Screening

Table 30: Summary of overall adverse events, safety population

Category	Entire Study N=449 n (%)	Day 29 N=449 n (%)	1st Quarter N=449 n (%)	2nd Quarter N=382 n (%)	3rd Quarter N=337 n (%)	4th Quarter N=308 n (%)
Subjects With At Least One Adverse Event	275 (61.2)	133 (29.6)	188 (41.9)	94 (24.6)	82 (24.3)	60 (19.5)
Related AE	139 (31.0)	75 (16.7)	96 (21.4)	29 (7.6)	26 (7.7)	13 (4.2)
Unrelated AE	213 (47.4)	78 (17.4)	130 (29.0)	73 (19.1)	63 (18.7)	50 (16.2)
Subjects With At Least One Serious Adverse Event	12 (2.7)	1 (0.2)	6 (1.3)	2 (0.5)	2 (0.6)	2 (0.6)
Unrelated AE	12 (2.7)	1 (0.2)	6 (1.3)	2 (0.5)	2 (0.6)	2 (0.6)
Subjects With At Least One Adverse Event Leading to Discontinuation	75 (16.7)	22 (4.9)	36 (8.0)	17 (4.5)	13 (3.9)	9 (2.9)
Related AE	67 (14.9)	20 (4.5)	32 (7.1)	16 (4.2)	12 (3.6)	7 (2.3)
Unrelated AE	8 (1.8)	2 (0.4)	4 (0.9)	1 (0.3)	1 (0.3)	2 (0.6)
Subjects With At Least One Mild Adverse Event	187 (41.6)	90 (20.0)	117 (26.1)	50 (13.1)	44 (13.1)	39 (12.7)
Related AE	63 (14.0)	46 (10.2)	52 (11.6)	7 (1.8)	7 (2.1)	4 (1.3)
Unrelated AE	152 (33.9)	52 (11.8)	81 (18.0)	45 (11.8)	38 (11.3)	35 (11.4)
Subjects With At Least One Moderate Adverse Event	153 (34.1)	51 (11.4)	87 (19.4)	51 (13.4)	41 (12.2)	23 (7.5)
Related AE	82 (18.3)	27 (6.0)	41 (9.1)	20 (5.2)	18 (5.3)	10 (3.2)
Unrelated AE	99 (22.0)	28 (6.2)	56 (12.5)	35 (9.2)	26 (7.7)	14 (4.5)
Subjects With At Least One Severe Adverse Event	40 (8.9)	12 (2.7)	26 (5.8)	4 (1.0)	7 (2.1)	4 (1.3)
Related AE	16 (3.6)	8 (1.8)	13 (2.9)	2 (0.5)	1 (0.3)	0
Unrelated AE	26 (5.8)	4 (0.9)	13 (2.9)	3 (0.8)	6 (1.8)	4 (1.3)
Subjects With At Least One Adverse Event of Special Interest	82 (18.3)	34 (7.6)	47 (10.5)	17 (4.5)	12 (3.6)	9 (2.9)
Related AE	82 (18.3)	34 (7.6)	47 (10.5)	17 (4.5)	12 (3.6)	9 (2.9)

Subjects may be counted twice, once in Related AE category and once in Unrelated AE category for having more than one AE. N is the number of subjects at the beginning of each period.

MedDRA dictionary version 11.0.

1st Quarter: Study days 1 to 90; 2nd Quarter: Study days 91 to 180; 3rd Quarter: Study days 181 to 270; 4th Quarter: Study days ≥271.

8.2.1.11.1. Adverse events

A total of 749 AEs were reported for 275 subjects (61.2%). The incidence of AEs was highest during the first quarter of the study with 41.9% of subjects reporting AEs, while 24.6%, 24.3%, and 19.5% of subjects reported AEs for the second, third, and fourth quarters of the study, respectively. The most common AEs (≥ 4% of subjects) for the entire study were flushing (10.2%), erythema (7.8%), rosacea (5.3%), nasopharyngitis (4.9%), skin burning sensation (4.2%), increased IOP (4.2%), and headache (4.0%) (Table 31). Overall, 6 subjects (1.3%) reported systemic cardiac disorders, with 2 subjects (0.4%) reporting palpitations, and 4 subjects reporting one incidence each (0.2%) of unstable angina, atrial fibrillation, tachycardia, and ventricular tachycardia. All systemic cardiac AEs were assessed by the investigators as unrelated to the study drug. Most AEs that occurred in the study were assessed by the investigators as mild (392 AEs in 187 subjects, 41.6%) or moderate (294 AEs in 153 subjects, 34.1%) in severity. A total of 55 severe AEs were reported in 40 subjects (8.9%) and of these severe AEs, 26 were considered to be related to the study drug. All severe related AEs were dermatological in nature.

Table 31: Summary of adverse events in > 1% of subjects for the entire study by system organ class and preferred term, safety population

Therapy Category Preferred Term	CD07805/47 Gel 0.5% (N=449)
Number (%) of Subjects who Took Concomitant Therapies	381 (84.9)
Ace Inhibitors, Plain	35 (7.8)
Lisinopril	28 (6.2)
Aminoalkyl Ethers	15 (3.3)
Diphenhydramine Hydrochloride	14 (3.1)
Anilides	50 (11.1)
Paracetamol	34 (7.6)
Biguanides	20 (4.5)
Metformin	19 (4.2)
Calcium	35 (7.8)
Calcium	32 (7.1)
Corticosteroids, Moderately Potent (Group II)	17 (3.8)
Desonide	15 (3.3)
Hmg Coa Reductase Inhibitors	64 (14.3)
Rosuvastatin	14 (3.1)
Simvastatin	28 (6.2)
Multivitamins, Other Combinations	56 (12.5)
Multivitamins (Ascorbic Acid, Ergocalciferol, Folic Acid, Nicotinamide, Panthenol, Retinol, Riboflavin, Thiamine Hydrochloride)	56 (12.5)
Multivitamins, Plain	31 (6.9)
Multi-Vit (Vitamins Nos)	27 (6.0)
Other Anti-Acne Preparations For Topical Use	28 (6.2)
Azelaic Acid	27 (6.0)
Other Antihistamines For Systemic Use	41 (9.1)
Loratadine	22 (4.9)
Other Chemotherapeutics	70 (15.6)
Metronidazole	70 (15.6)
Other Emollients and Protectives	28 (6.2)
Other Emollients and Protectives	21 (4.7)
Other Lipid Modifying Agents	41 (9.1)
Fish Oil	35 (7.8)
Piperazine Derivatives	20 (4.5)
Cetirizine Hydrochloride	16 (3.6)
Platelet Aggregation Inhibitors Excluding Heparin	39 (8.7)
Acetylsalicylic Acid	39 (8.7)
Propionic Acid Derivatives	79 (17.6)
Ibuprofen	58 (12.9)
Naproxen Sodium	19 (4.2)
Proton Pump Inhibitors	48 (10.7)
Omeprazole	30 (6.7)
Tetracyclines	75 (16.7)
Doxycycline	45 (10.0)
Tetracycline	18 (4.0)
Thiazides, Plain	18 (4.0)
Hydrochlorothiazide	18 (4.0)
Thyroid Hormones	45 (10.0)
Levothyroxine Sodium	31 (6.9)
Vitamin D and Analogues	43 (9.6)
Ergocalciferol	36 (8.0)

8.2.1.11.2. Treatment-related AEs:

Overall, 238 AEs were assessed by investigators as related to the study drug and were reported for 139 subjects (31.0%) over the entire study. Related AEs were reported for 31.0% of subjects and the most common AEs (≥ 3% of subjects) were flushing (9.1%), erythema (6.5%), rosacea (3.6%), skin burning sensation (3.3%), and skin irritation (3.1%). Most related AEs were in the Skin and Subcutaneous Tissue Disorders System Organ Class. The only systemic related AEs reported were headache (8 subjects, 1.8%), dizziness (3 subjects, 0.7%), balance disorders (1 subject, 0.2%), and decreased white blood cell count (1 subject, 0.2%). Of the 238 related AEs, 90 were assessed by the investigators as mild in severity and 122 were assessed by the investigators as moderate in severity. Twenty six (26) related AEs were assessed as severe by the investigators and all severe related AEs were dermatological in nature. There were no related systemic cardiovascular AEs. The majority of related AEs were dermatological in nature and could be categorized as either AEs reflecting an "exacerbation" of the existing rosacea disease pathology (flushing, worsening erythema, worsening rosacea, and skin warm), or other cutaneous related AEs which are not specific to rosacea; majority of these AEs were mild to moderate in severity. Given that the effect of CD07805/47 gel 0.5% diminishes several hours after daily application, thus allowing for progression back to Baseline erythema levels late in the day, the subjects' perception of this loss of effect could also have contributed to the frequency in reporting of these "exacerbation" AEs. In many cases, the investigator did not witness the AE in person and relied on the subject's assessment of symptoms and severity for reporting of the AE. Many of these "exacerbation" AEs also occurred later in the day, which would be consistent with the effect of the study drug wearing off.

8.2.1.11.3. Deaths, SAEs

One death occurred in the study due to an SAE of advanced squamous cell carcinoma of the lung which was considered unrelated to study drug. Sixteen (16) SAEs were reported in 12 subjects (3%). All SAEs reported during the study were assessed by the investigators as unrelated to the study drug.

8.2.1.11.4. Discontinuations due to AEs

A total of 75 subjects (16.7%) discontinued the study due to 92 AEs. Of these 92 AEs, 82 were considered related to the study drug, and therefore, AEs of special interest (AESIs). Of the 75 subjects who discontinued the study due to AEs, 67 (14.9%) discontinued due to AEs that were related to the study drug. The majority of related AEs that led to study discontinuation were in the Skin and Subcutaneous Tissue Disorders System Organ Class and were mild or moderate in severity. Most AEs that led to study discontinuation occurred in the first quarter of the study and 36 subjects (8.0%) discontinued due to AEs during this time, compared with 9 subjects (2.9%) who discontinued the study due to AEs in the fourth quarter.

8.2.1.11.5. AESIs

A total of 82 subjects (18.3%) reported 113 AESIs, the majority of which were in the Skin and Subcutaneous Tissue Disorders System Organ Class. Twenty four (24) subjects (5.3%) required patch testing in order to rule out suspected allergic sensitization reactions to the study drug. Of these 24 subjects, 17 agreed to undergo patch testing and 3 positive cases were identified. Of these 3 subjects, 2 agreed to additional testing with individual study product ingredients; 1 subject was allergic to brimonidine tartrate and 1 subject was allergic to phenoxyethanol, a preservative excipient. A sensitization rate of approximately 1% was conservatively estimated for this one year study, based on the incidence ratio of positive versus negative sensitization cases. This observed rate of sensitization can be considered acceptable when compared to other available topical products, such as Benzoyl Peroxide containing compounds and topical corticosteroids.

There were no clinically meaningful trends observed in mean change from baseline in haematology, clinical chemistry and urinalysis laboratory parameters. Most of the clinically

significant haematology abnormalities occurred in 1 subject and this subject was reported as having an AE of anaemia that was considered by the investigator as unrelated to the study drug. Most of the clinically significant chemistry abnormalities were for high triglycerides. No clinically meaningful differences in mean blood pressure and heart rate were observed over time. No clinically meaningful changes in mean IOP were observed over the course of the study. Three subjects (0.7%) reported transient decreased IOP measurements that were assessed by investigators as related to the study drug. Two pregnancies were reported during the study and both subjects were terminated early from the study. One pregnancy went to full term and at the expected date the subject gave birth to a normal baby boy by caesarean section. No foetal distress or safety issues were reported and no hospitalizations occurred during the pregnancy. The other pregnancy was ongoing at the conclusion of the clinical study.

> **Comments:** No new major safety signals were revealed after long-term, chronic exposure to the study drug and the safety profile was consistent with the existing safety profile determined throughout development of CD07805/47 gel 0.5% (that is, that CD07805/47 gel 0.5%.is safe and well tolerated) with an acceptable allergic sensitization rate of approximately 1%.

8.3. Patient exposure

There were 1619 subjects who were exposed to Brimonidine Tartrate active gels out of 2174 participants in the 18 studies in the clinical development program. Of the 1619 subjects, 1210 subjects were exposed to Brimonidine Tartrate 0.5% Gel qd.

Eight studies of the gel formulation were conducted in healthy subjects; 423 healthy subjects were exposed to active gel formulations (0.07% gel, 0.18% gel, 0.20% gel or 0.50% gel) and 432 subjects received vehicle gel applications.

Nine clinical studies, excluding the LTS study, were conducted in subjects with rosacea; 747 rosacea subjects were exposed to active gel formulations (0.02% gel, 0.07% gel, 0.1% gel, 0.18% gel, 0.20% gel, and 0.50% gel) and 462 rosacea subjects received vehicle gel applications. In addition, 120 subjects in Studies 18126 and 18143 were treated with the 0.2% ophthalmic solution.

In the 2 Phase III, well-controlled, efficacy and safety studies (18140 and 18141), 277 subjects were exposed to 0.50% gel qd. If the 53 subjects from the Phase IIb, vehicle-controlled, efficacy and safety study 18161 treated with the 0.50% gel are included in this sum, a total of 330 rosacea subjects received 0.50% gel qd under controlled conditions for a 29-day treatment period, which is the concentration and regimen selected for the proposed marketed product.

In the long-term safety and efficacy 18142, a total of 449 subjects were to be exposed to 0.50% gel qd up to 365 days; 276 of these subjects were exposed for ≥ 365 days. Exposure to brimonidine tartrate gel in all clinical studies has been provided and summarised (Table 32).

Table 32. Subjects exposed to brimonidine tartrate. All studies

Population/Study Type/Study	Brimonidine Tartrate Active Treatment				Other Treatment		Total
	Brimonidine Tartrate Gel 0.50%	Brimonidine Tartrate Gel 0.49%-0.08%	Brimonidine Tartrate Gel ≤0.07%	Total	Vehicle[a] Gel	Brimonidine Tartrate Ophthalmic Solution 0.20%	
Healthy Subjects	**377**	**423**	**377**	**423**	**432**	**76**	**508**
Dermal Safety							
COL-118-Photoxicity-104 (Intra-individual 4-zone)	0	30	0	30	30	0	30
RD.06.SRE.18123 (Intra-individual 5-zone)	247	247	247	247	247	0	247
RD.06.SRE.18124 (Intra-individual 5-zone)	57	57	57	57	57	0	57
RD.06.SRE.18125 (Intra-individual 6-zone)	38	38	38	38	38	0	38
RD.06.SRE.18137 (Intra-individual 3-zone)	0	0	0	0	25	0	25
RD.06.SRE.18189 (Intra-individual 10-zone)	35	35	35	35	35	0	35
PK in Healthy Subjects							
COL-118-BAPK-101 (2-way crossover)	0	16	0	16	0	16	16
RD.06.SRE.18139 (TQT 3-way crossover with Moxifloxacin)	0	0	0	0	0	60	60
Subjects with Rosacea	**833**	**254**	**109**	**1196**	**462**	**141**	**1666**
PK in Subjects With Rosacea							
RD.06.SRE.18126 (2-way crossover)	0	19	0	19	18	18	20
RD.06.SRE.18143 (2-phase)	23	49	26	98	0	102	102
Dose Finding							
COL-118-ROSE-101 (Intra-individual 6-zone)	0	0	0	0	0	21	21
COL-118-ROSE-102 (Intra-individual 6-zone)	0	20	0	20	0	0	20
COL-118-ROSE-201 (Randomized, Double-blind, 4-arm parallel)	0	27	55	82	28	0	110
RD.06.SRE.18144 (Randomized, Double-blind, 4-arm parallel)	31	31	28	90	32	0	122
RD.06.SRE.18161 (Randomized, Double-blind, 5-arm parallel)	53	108	0	161	108	0	269
Phase 3 Well-Controlled							
RD.06.SRE.18140 (Randomized, Double-blind, 2-arm parallel)	129	0	0	129	131	0	260
RD.06.SRE.18141 (Randomized, Double-blind, 2-arm parallel)	148	0	0	148	145	0	293
Long-Term							
RD.06.SRE.18142 (Open label)	449	0	0	449	0	0	449
Total	**1210**	**677**	**486**	**1619**	**894**	**217**	**2174**

[a] Vehicle ophthalmic solution is not included in statistical analysis.

In the short-term studies in rosacea subjects, the average number of treatment days for subjects treated with the 0.50% gel or the vehicle was approximately 26 days. The mean number of treatment days for subjects who received 0.50% gel or vehicle in the Controlled Core Studies was approximately 29 days (that is 28.6 days),while the mean treatment duration of the LTS study was approximately 278 days. The mean daily treatment use for subjects who received 0.50% gel qd in Studies.18161, 18140, and 18141 was 0.8 g. In the LTS study, the mean daily treatment use was 0.5 g.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

Approximately one-third of all subjects in the Controlled Core Studies, both in the 0.50% gel group (33%) and in the vehicle group (27.5%), reported at least 1 TEAE. For every TEAE related to study drug in either controlled Core study group, there were 2 TEAEs not related to study drug. Most TEAEs in the Controlled Core Studies were mild to moderate in intensity. During the first 29 days of the LTS study, 30% of subjects reported TEAEs which was similar to that for the Controlled Core Studies, most were mild or moderate in intensity (17% unrelated and 17% related)[24]. Concerning TEAEs categorized by SOC/PT that occurred in > 1% of all subjects during the Controlled Core Studies, Skin and Subcutaneous Tissue Disorders predominated (brimonidine versus vehicle: 13.0% versus 9.4%). Within this SOC. erythema (3.6% versus 0.9%) and pruritus (2.4% versus 2.4%) were the predominant PTs. Flushing (SOC: Vascular Disorders) was reported in 6 subjects (1.8%) in the active gel group and in no subjects in the vehicle gel group. In the 3 pooled Controlled Core Studies, the top 4 most frequently reported SOCs (as numbers of subjects experiencing) were, in order of decreasing overall frequency: headache, erythema, pruritus, and nasopharyngitis.

The incidence of severe TEAEs reported in the Core Studies was low and was reported mainly in the Skin and Subcutaneous Tissue Disorder SOC (also including flushing in the Vascular Disorders SOC). These severe Skin and Subcutaneous Tissue Disorders occurred most frequently in the LTS study group (first 29 days), with 1 subject in the controlled active treatment group and 6 subjects in the LTS group who reported TEAEs.

Of the 18 studies comprising the clinical development program, only 2 studies (18140 and18142) had severe TEAEs related to treatment with Brimonidine Tartrate Gel. In study18140, there was only 1 severe TEAE attributed to treatment with the 0.50% gel: dermatitis contact.

8.4.1.2. Other studies

8.4.1.2.1. Dose-ranging studies

No TEAEs were reported in Study COL-118-ROSE-101, a single application study of serial dilutions of 0.2% ophthalmic solution to the skin of 21 subjects. In Study COL-118-ROSE-102, cream and gel formulations containing 0.1% brimonidine tartrate were applied once in an intra-individual comparison; 1 TEAE of mild nausea (unrelated) was reported. In Study COL-118-ROSE-201, vehicle gel and 0.02%, 0.07%, and 0.20% gels were applied by the subject up to 3 times daily for 29 days in 110 subjects. TEAEs were reported by 63%, 48%, 50% and 43% of subjects in the 0.20%, 0.07%, 0.02% and vehicle groups, respectively. All TEAEs were mild or moderate intensity. Across treatment groups, Skin and Subcutaneous Tissue Disorders predominated over all other SOCs (erythema most common especially in early stages of study and diminished over time). TEAEs other than erythema that were reported in a higher proportion of subjects in the 0.20% group than in other groups were dry skin, pain of skin, skin burning sensation, and urticaria. All TEAEs were mild or moderate in intensity. None was considered to be severe. Two (2) Cardiac Disorder TEAEs[25] were observed and both were considered related to the study drug: Three (3) treatment-related Nervous System Disorder TEAEs were reported: 1 subject (3.4%) with headache in the 0.07% gel group and 1 subject (3.6%) in the vehicle group, 1 subject (3.8%) with paresthesia in the 0.02% group, and 1 subject

[24] A pool of all TEAEs was prepared for the 3 individual Controlled Core Studies (RD.06.SRE.18161 [only the 0.50% gel and vehicle gel qd groups], RD.06.SRE.18140, and RD.06.SRE.18141) and compared to all TEAEs in in the first 29 days in the LTS Study RD.06.SRE.18142.

[25] One male subject (3.4%) with arrhythmia in the 0.07% gel treatment group and one female subject (3.8%) with bradycardia in the 0.02% gel group.

(3.7%) with somnolence in the 0.20% group. In study 18144, the 0.07%, 0.18%, or 0.50% gel was applied by the site personnel once to the faces of 122 subjects. Overall, the percentages of subjects with TEAEs were similar in each treatment group, ranging from 12.9% (4 subjects) in the Brimonidine Tartrate Gel 0.18% group to 19.4% (6 subjects) in the Brimonidine Tartrate 0.5% Gel group. No severe TEAEs, SAEs, or AEs leading to study discontinuation were reported. There is no relationship between concentration of active substance and frequency of TEAEs in any category. The percentages of subjects with drug-related TEAEs ranged from 6.5% (2 subjects) in the Brimonidine Tartrate Gel 0.50% group to 14.3% (4 subjects) in the Brimonidine Tartrate Gel 0.07% group. Most AE were mild in severity and no dose-dependent trend was observed and most of these resolved < 24 hours after onset. Decreased IOP was reported at Hour 12 for 1 subject each in the Brimonidine Tartrate Gel 0.50% and 0.18% groups. The decreases in IOP were mild, transient, and reversible, most likely caused by inadvertent contact of the eye with study drug.

In Study 18161, 269 subjects with rosacea applied 0.50% gel once daily, or 0.18% gel or vehicle gel versus applied once or twice daily for 4 weeks (29 days). Overall, the percentages of subjects with TEAEs were similar in each of the active treatment groups and were comparable to the vehicle gel treatment groups. Most TEAEs that occurred during the study were assessed by investigators as mild or moderate in severity, with only 3 severe TEAEs (of which 2 were SAEs). There was 1 TEAE unrelated to study drug that led to discontinuation. The most frequent TEAEs occurred in the SOCs of Skin and Subcutaneous Tissue Disorders (PTs: pruritus, skin burning sensation, and skin warm), Nervous System Disorders (PT: headache), Vascular Disorders (PT: flushing), and Investigations (PT: intraocular pressure increased). No sensitization reactions were observed. The number of subjects with treatment related TEAEs was comparable among the active treatment groups, as well as the vehicle gel qd group. The most common treatment-related TEAEs (more than 1 subject in a treatment group) were pruritus, skin burning, skin warm, flushing.

8.4.1.2.2. Dermal safety studies:

No TEAEs were reported in study COL-118-Phototoxicity-104.

In Study 18189, 3 subjects (8.6%) reported TEAEs and 1 subject had TEAEs considered to be treatment related (moderate erythema).

In study 18123, 20 of 247 subjects (8.1%) reported TEAEs during the sensitization study; 3 TEAEs (increase in blood pressure, influenza, and hypertension) resulted in discontinuation from the study; none were considered related to the study drug. No SAEs were reported during the study. Two subjects had severe unrelated adverse reactions (mouth injury; skin laceration). There is no apparent correlation between the increase in the concentration of the active ingredient and the appearance or intensity of topical erythema/ irritation. Each Brimonidine Tartrate gel concentration, the Vehicle gel, and white petrolatum produced no reaction in most observations (minimum of 95% to 96% of test sites on each evaluation day). There were few observations of mild erythema (minimum of 4% to 5% of test sites on each evaluation day) and few isolated observations of moderate erythema and/or erythema with vesicles or erosion or bullae.

In study18124, no skin reaction worse than mild erythema occurred at any test site. There were 7 subjects out of 57 subjects (12.3%) who reported TEAEs during the photosensitization study none were considered related to the study treatment.

In the cumulative irritancy Study RD.06.SRE.18125, 7 of 38 (18.4%) of subjects reported TEAEs during this study and these included 1 serious (and severe) TEAE, gastroenteritis, which resulted in study discontinuation. The SAE plus all of the other 6 TEAEs were unrelated to the study treatment. These TEAEs were gastroenteritis (2 subjects), nasopharyngitis, venomous bite, arthralgia, headache, and dysmenorrhoea.

In Study 18137, 25 subjects received single applications of Vehicle Gel and of active control, homosalate 8% lotion (sunscreen) versus an untreated site in an intra-individual comparison. As no applications were done under patch occlusion, this study was not designed to assess dermal toxicity. No deaths, SAEs, severe or significant AEs, TEAEs, or AESIs were reported. No subject discontinued the study due to TEAE.

8.4.1.2.3. PK studies

In Study18126, 3 subjects treated with 0.18% facial gel plus placebo ophthalmic solution reported headaches lasting 1 to 2 days that were deemed possibly related to the study treatment.

In Study.18143, no correlation could be made between dose strength, dosing regimen, or plasma concentration and number or intensity of TEAEs. The most common treatment-related AEs (more than 1 subject in a treatment group) were: pruritus in 3 subjects (0.18% bid), headache in 3 subjects (0.07% bid) and 2 subjects (0.18% qd), orthostatic hypotension[26] in 2 subjects (0.18% qd), and flushing in 2 subjects (0.07% bid). There were only 3 subjects out of 24 who reported a total of 6 AEs during the gel treatment period related to the study treatment.

In PK Study RD.06.SRE.18139, only the 0.2% ophthalmic solution of brimonidine tartrate (supra-therapeutic dose) was assessed versus placebos and a positive control.

8.4.2. Treatment-related adverse events (adverse drug reactions)

In the Controlled Core Studies, the percentage of subjects who received 0.50% gel in the Controlled Core Studies (11.8%) and the first month of the LTS study reporting treatment-related TEAEs (16.7%) was higher than that for subjects treated with vehicle (8.8%). The incidences of Skin and Subcutaneous Tissue Disorders, predominant both for subjects in the 0.50% gel group (9.7%) and in the first month of the open label study (11.1%), are similar to each other and higher than that in the vehicle group (6.6%). The most commonly reported (> 1% of subjects) related TEAEs in subjects treated with Brimonidine Tartrate 0.5% Gel were erythema, pruritus, flushing, and skin burning sensation. In general, the overall incidence of related TEAEs in the Brimonidine Tartrate 0.5% Gel group in the Controlled Core Studies and in LTS study 18142 was low and few of the related TEAEs showed a difference in incidence between the active groups compared to the Vehicle Group. No related TEAEs were observed in the SOCs of Respiratory, Infections/Infestations, Cardiac, or Metabolic Disorders.

8.4.3. Deaths and other serious adverse events

There was 1 death reported in 1 of the 18 clinical studies performed during this development program for Brimonidine Tartrate Gel. In the LTS open label study.18142, one subject had an SAE of lung cancer that led to death (unrelated to the study drug).

Of the 18 studies in the Brimonidine Tartrate Gel development program, 7 studies reported 1 or more SAEs (18140, 18141, 18142, 18161,18124, 18125, and 18143). There were no SAEs reported in the SOCs of Skin and Subcutaneous Tissue Disorders, Cardiac Disorders, or Nervous System Disorders, the SOCs with the highest frequencies of TEAEs, in the clinical studies of Brimonidine Tartrate 0.5% Gel. Furthermore, no SAE was found to be related to Brimonidine Tartrate Gel in any study subject in any SOC in any of the 18 studies comprising the clinical development program. Two children accidentally ingested the 0.50% gel assigned to their mother in study18140. SAEs for the controlled core studies are summarised in Table 33. In

[26] Of the 3 subjects (2 subjects, 0.18% qd; 1 subject, 0.07% bid) who experienced mild to moderate and transient orthostatic hypotension related to study drug in RD.06.SRE.18143, none was observed in the 0.50% gel qd group. Of these 3 subjects, 2 subjects experienced isolated occurrences of orthostatic hypotension after consecutive multiple blood draws for PK sampling. The third subject was reported with orthostatic hypotension prior to study drug application (0.07% gel bid) that never occurred again in subsequent visits where vital signs were measured.

Study 18142, 16 SAEs occurred in 12 subjects (3%) and all were assessed as unrelated to study drug.

Table 33: Summary of serious adverse events by system organ class and preferred term, safety population, core studies

	Controlled Studies		LTS Study (first 29 Days)
SYSTEM ORGAN CLASS Preferred Term	Brimonidine Tartrate 0.50% (N = 330)	Vehicle (N = 331)	Brimonidine Tartrate 0.50% (N = 449)
SUBJECTS REPORTING ANY SERIOUS ADVERSE EVENT, N(%)	**2 (0.6)**	**1 (0.3)**	**1 (0.2)**
INFECTIONS AND INFESTATIONS	**1 (0.3)**	**0**	**1 (0.2)**
Appendicitis	1 (0.3)	0	0
Pneumonia primary atypical	0	0	1 (0.2)
Sepsis	0	0	1 (0.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**1 (0.3)**	**0**	**0**
Accidental drug intake by child	1 (0.3) [a]	0	0
INVESTIGATIONS	**1 (0.3) [a]**	**0**	**0**
Heart rate irregular	1 (0.3) [a]	0	0
NERVOUS SYSTEM DISORDERS	**1 (0.3) [a]**	**0**	**0**
Lethargy	1 (0.3) [a]	0	0
Psychomotor hyperactivity	1 (0.3) [a]	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**1 (0.3) [a]**	**0**	**1 (0.2)**
Hypoxia	0	0	1 (0.2)
Respiratory distress	1 (0.3) [a]	0	0
VASCULAR DISORDERS	**0**	**1 (0.3)**	**0**
Deep vein thrombosis	0	1 (0.3)	0

8.4.4. Discontinuation due to adverse events

TEAEs resulting in discontinuation in the Core Studies were infrequent, predominantly in the SOC Skin and Subcutaneous Tissue Disorders and were typically reports of events common to rosacea which were mild to moderate in intensity and eventually resolved. Majority of these discontinuations due to TEAEs occurred in the LTS study (study 18142, first 29 days), and were usually mild or moderate in severity. The 15 severe, treatment-related TEAEs in 13 subjects that resulted in premature discontinuation were provided. All were cutaneous TEAEs and all but 1 occurred in the LTS study. Rosacea and flushing were responsible for discontinuation of 3 subjects each. Skin burning sensation, erythema, contact dermatitis, and allergic dermatitis were the causes of discontinuation of 2 subjects each.

8.5. Laboratory tests

8.5.1. Liver function

There were no clinically relevant changes in liver function tests.

8.5.2. Kidney function

Urinalysis data from the 2 well-controlled Phase III studies (18140 and 18141) were pooled and did not show any clinically meaningful changes between treatment groups. There were no critically clinically significant urinalysis values for individual subjects.

8.5.3. Other clinical chemistry

Integrated summary of laboratory parameters for clinical chemistry were prepared based on the following Core Studies (18140, 18141 and 18142). The other Core Study18161 did not have laboratory assessments. Laboratory parameters in study18143 are summarized separately as supportive laboratory data, given that the study was primarily PK Study.

Analysis of the pooled individual subject chemistry data revealed 2 subjects, both in Study 18141 who had critically clinically significant chemistry laboratory values (1 in the 0.50% gel group high non fasting blood glucose and 1 in the vehicle gel group high potassium levels). In addition, there were 2 subjects in study 18142 (one had low and the other had high non fasting blood glucose) and 1 subject in study 18143 (high potassium levels) who had critically clinically significant chemistry laboratory values.

Occasional shifts of some parameters from normal to outside of the normal range were seen at similar magnitudes in the 0.50% gel group and the vehicle group and were not accompanied by any clinical manifestations, thus implying that such shifts are part of the normal variability of these values in the target population and are not indicative of a safety trend of concern. Those occasional shifts of glucose or triglycerides outside of the normal range (Normal to High) in the pooled Controlled Core Studies could be attributed to the non-fasting state of the subjects. Such fluctuations are to be expected, and were particularly seen in subjects with diabetes.

8.5.4. Haematology

The studies in which changes in haematology values were analysed were 18140,18141, 18142, and 18143.When the data are reviewed across these studies, any mean changes from Screening at Day 29 (or Day 32 in the case of study 18143) were small and generally similar between treatment groups for all variables. Subjects whose normal values at screening shifted high or low at Day 29/ET did not show any abnormal trends.

8.5.5. Vital signs

There were no observable differences in mean blood pressures and heart rate between the 0.50% gel and vehicle treatment groups at any measurement time in the pooled controlled study analysis and in Studies.18161, 18140 and 18141 taken individually. No trend was seen between mean measurements for sitting versus standing blood pressures across the studies indicating a lack of any orthostatic effect caused by the active substance. Furthermore, there was no trend with respect to increasing concentration of active substance upon changes in mean blood pressure as measured in the dose range-finding studies.18161 and.18144 and in the PK single day Study 18143.

8.5.6. Electrocardiograph

ECG was not assessed in the core studies. Results from the QT study 18139 showed that single ocular administration of brimonidine tartrate (2 drops of a 0.2% solution to each eye) did not increase QTc.

8.5.7. Other safety parameter- IOP

There were no IOP data collected in the 2 well-controlled Phase III studies (18140 and 18141). Complete IOP data were collected in the 4 week dose-finding study 18161 and the 4 week PK study18143. Additional IOP data were obtained in the 1 day dose finding study18144. Long term safety in the LTS study 18142 provided long-term IOP data.

In LTS study 18142, few subjects showed IOPs that shifted above or below the normal range suggesting lack of any trends of concern or safety signals associated with Brimonidine Tartrate 0.5% Gel when applied once daily for short term or long term use.

In study 18143, during the Brimonidine Tartrate gel treatment period, no clinically meaningful reductions in mean IOP were observed after Days 1, 15, or 29 applications in any of the gel

treatment groups (0.07% bid, 0.18% qd or bid, and 0.50% qd). There were no TEAEs reported, either overall or related to study drug, in the PT Intraocular pressure decreased, in this study. Increasing drug concentration or regimen up to 0.50% qd had no effect on the incidence of isolated IOP decreases, and there were no reported AEs of clinically significant low or decreased IOP during the study.

In the single-day study 18144, the mean reductions in IOP of 1 to 2 mm Hg at Hour 12 were small, similar across treatment groups, and similar in each eye.

In study 18161, there were no clinically meaningful differences in mean IOP between any of the active treatment groups versus the corresponding vehicle gel controls.

Results of the analysis of data from the studies in which IOP changes were reported as TEAEs indicate that decreases in IOP were minimal, infrequent, and of short duration. In no instance was a change in IOP a reason for discontinuation from any study. It is likely that the IOP decreases resulted from inadvertent contamination of the eye with the topical gel. Such inadvertent contaminations should be of low clinical relevance, given that such contaminations are not associated with any known adverse clinical outcomes. Brimonidine tartrate, when administered daily as a topical gel, can be concluded to have little or no effect on IOP by the systemic route in the target population under short-term or long-term use conditions.

8.6. Post-marketing experience

Not applicable as Brimonidine Tartrate 0.5% Gel is not marketed in any country to date.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Liver toxicity

None.

8.7.2. Haematological toxicity

None.

8.7.3. Serious skin reactions

There were no SAEs related to skin and subcutaneous tissue, although they were the most commonly reported TEAEs (most of these were mild to moderate in severity).

8.7.4. Cardiovascular safety

None.

8.7.5. Unwanted immunological events

Sensitization to any of the components of the Brimonidine Tartrate Gel was assessed in all studies with the exception of the 6 studies performed by the previous Sponsor.. Possible sensitization reactions were reported by only 2 of the remaining 12 studies conducted in the clinical development program for Brimonidine Tartrate Gel (18123 and 18142). For identification of sensitization reactions, no specific clinical threshold criteria were predefined.

Sensitization responses could only be determined by an experienced evaluator who was a board certified dermatologist.

In study 18123, the sensitization potential of various concentrations of the study drug and vehicle showed no evidence of sensitization except in 1 subject who exhibited positive sensitization results at challenge with the 0.07% gel and the gel vehicle. Response was equivocal at re challenge and the subject was unavailable for a second re challenge.

In the long term study 18142, 24 subjects (5.3%) developed adverse reactions that the investigators considered suspicious enough to require patch testing in order to rule out an allergic sensitization to the study product (allergic dermatitis). Of these 24 subjects, 17 agreed to undergo diagnostic patch testing and 14 of these subjects had a negative patch test result suggesting no allergy to the study drug and 3 subjects had a positive patch test result. Of the three positive cases, 1 was confirmed as a reaction to brimonidine tartrate, a second was confirmed as a reaction to the phenoxyethanol preservative, and the third was not conclusively confirmed (subject refused further patch testing).

No phototoxicity was observed in Study COL-118-Phototoxicity-104. In Study18189, 1 subject exhibited contact irritation, not photosensitization. In photosensitization Study 18124, no photosensitivity or photo irritancy was observed. A suspected, related, mild "photosensitization" was reported in 1 subject in Study COL-118-ROSE-201.

> **Comments:** The rate of sensitization for the 1619 subjects exposed to Brimonidine Tartrate Gel is estimated at < 1% across the entire clinical development program. This estimate is based upon a conservative calculation, including the 3 subjects with initially positive patch tests in study 18142, the 7 subjects who refused rechallenge/patch testing in study 18142, and the 1 subject with suspected but unconfirmed sensitization in study 18123.

8.8. Other safety issues

8.8.1. Safety in special populations

8.8.1.1. Gender

The TEAEs reported overall in the Controlled Core Studies and in the first month of LTS study 18142 are compiled by gender. No clear difference was seen between genders with respect to TEAEs, related or unrelated to Brimonidine Tartrate 0.5% Gel. The ratio of females (506 subjects) to males (155 subjects) participating overall in the Controlled Core Studies (approximately 3.3 females: 1.0 male) parallels the ratio of females (168 subjects) to males (32 subjects) with TEAEs independent of causation (approximately 5.3 females:1.0 male).

8.8.1.2. Race

The incidences of TEAEs overall by race were provided. The preponderance of TEAEs that were not related to study drug was greater than those TEAEs related to study drug (1:2 approximate ratio) for Caucasians in the Controlled Core Studies but the ratio of related to unrelated TEAEs for Caucasians in the LTS study was 1:1. There were similar proportions of Caucasian (33.1% active gel, 27.6% vehicle) and Non Caucasian (28.6% active gel, 20% vehicle) subjects reporting TEAEs overall in the Controlled Core Studies.

8.8.1.3. Age

The incidence of TEAEs in the controlled active group was 33% for the younger age group and 32% for the older age group. In the first 29 days of the LTS study, the incidence of TEAEs was 30% in the younger age group and 25.9% in the older age group. Therefore, the incidence of TEAEs overall for adult subjects on active therapy was slightly higher than that for geriatric subjects on active therapy across the Core Studies. Similarly, the incidences for related TEAEs in the adult subjects were either the same (17%, LTS group) or higher (13%, active controlled group) than incidences for related TEAEs in the geriatric group (17%, LTS group; 0%, active controlled group).

These findings indicate that subjects 65 years of age and older are not at increased risk of TEAEs with use of the study product compared to younger subjects.

8.8.1.4. Other select populations

Brimonidine Tartrate Gel has not been studied in subjects with renal or hepatic impairment; caution should be exercised when treating such patients.

Specific evaluations of extrinsic factors such as food, alcohol, or tobacco consumption was not done during the clinical development program for Brimonidine Tartrate Gel.

8.8.2. Safety related to drug-drug interactions and other interactions

In the pivotal vehicle controlled studies, participants with more than 2 inflammatory lesions were not permitted to use concomitant anti acne/anti rosacea medications in order not to confound the efficacy results. However, in the open label, LTS Study18142, the use of concomitant, standard of care, anti-acne/anti rosacea medications was permitted.

Concomitant anti acne/anti rosacea medications used by subjects in the LTS study were metronidazole, azelaic acid, and tetracyclines (that is tetracycline, minocycline, and doxycycline). These medications are prescribed to treat inflammatory lesions associated with rosacea.

There was no indication of interaction between rosacea medications taken concomitantly with Brimonidine Tartrate 0.5% Gel that could lead to increased risk of AEs. Specifically, there does not appear to be a potentiation or additive effect with respect to AEs above the normal AE profiles anticipated for each drug individually. Of those AEs in the SOC Skin and Subcutaneous Tissue Disorders (that is local tolerability), no clinically meaningful differences were seen with respect to concomitant treatment with rosacea medications. Severe AEs were reported in 10.7% of subjects who took concomitant medications compared to 8.2% of subjects who did not take them. Most of these severe AEs occurred in SOCs with no known relationship of AE to study drug. Incidence of SAEs was 3.1% and 2.5% in rosacea subjects taking and not taking concomitant medications. The differences in frequencies of discontinuations due to AEs for subjects taking concomitant rosacea medications and those subjects who did not were not clinically meaningful.

8.8.3. Use in pregnancy and lactation

Pregnant or lactating women with erythema of rosacea have been excluded from participation in studies with Brimonidine Tartrate Gel. Subjects who became pregnant during the studies were required to withdraw immediately and the pregnancy was to be followed up to the final outcome.

The safety of use of Brimonidine Tartrate Gel during pregnancy has not been established. It has not demonstrated teratogenicity after oral administration to pregnant rats and pregnant rabbits. It has been shown to increase pre implantation loss in rabbits. In animal studies, brimonidine crossed the placenta and entered into the foetal circulation to a limited extent. It is not known if the drug is excreted in human milk, although it was detected in the milk of the lactating rat.

There were 4 pregnancies reported during the clinical development program, 1 in Study 18123, 1 in Study COL-118-ROSE-201, and 2 in Study 18142.

8.8.4. Overdose, drug abuse, withdrawal and rebound

Brimonidine Tartrate 0.5% Gel is for topical application once daily. In case of accidental ingestion, appropriate supportive and symptomatic therapy is advised. A patent airway should be maintained. An accidental ingestion of Brimonidine Tartrate 0.5% Gel occurred in 2 children of a subject who was assigned 0.50% gel in 1 of the well-controlled Phase III studies. The children experienced lethargy, low level of consciousness, confusion, bradycardia, and respiratory distress. One (1) of the children required admission to the intensive care unit of a hospital with intubation. Both children were reported to have made a full recovery within 24 hours.

No investigations of the dependency potential of Brimonidine Tartrate 0.5% Gel have been performed. Given the limited systemic bioavailability following topical administration, it is unlikely that dependency or addiction would occur.

No evidence of tachyphylaxis was seen in the Phase IIb (18161) and 2 Phase III studies (18140, 18141) in which it was assessed over the course of a 12-hour observation period at 3 separate clinic visits on Days 1, 15, and 29. For the assessment of potential for rebound erythema, a 4 week, no treatment follow-up period was included in COL-118-ROSE-201, 18161, 18140, and 18141, which included assessments of erythema by the investigators and subjects based on the CEA and PSA. In COL-118-ROSE-201, there was no indication of a rebound effect 4 weeks after treatment with 3 concentrations of brimonidine tartrate (the highest concentration being 0.20%) administered up to 3 times daily. In the Phase IIb study and 2 Phase III studies, the assessment of potential rebound effect was performed at weeks 6 and 8 (and additionally at day 30 and week 5 in RD.06.SRE.18161). In each of the studies, even after the subjects had discontinued treatment with Brimonidine Tartrate 0.5% Gel, the subjects continued to show reductions in mean CEA and PSA scores relative to Baseline. In the Phase III controlled studies, only a small minority of subjects showed worsening in CEA and PSA scores relative to Baseline during the follow-up period; however, a similar incidence was observed in the corresponding vehicle gel groups, which suggested that this response was indicative of variability in the natural course of the disease.

In clinical trials, Brimonidine Tartrate 0.5% Gel has no or negligible influence on ability to drive or operate machinery. Cases of fatigue and/or drowsiness were rarely reported during the clinical trials with Brimonidine Tartrate Gel.

8.9. Evaluator's overall conclusions on clinical safety

A total of 1619 of the 2174 subjects in the clinical development program were exposed to Brimonidine Tartrate Gel. Of these, 1210 subjects were exposed to the proposed marketing formulation (Brimonidine Tartrate 0.5% Gel) in 10 studies: 377 healthy subjects in 4 studies and 833 subjects with rosacea in 6 studies.

Analysis of TEAEs both overall and those considered related to study drug by the investigator in the dose-range finding studies exhibited no dose relationship, were infrequent, mild or moderate in severity, and did not result in discontinuation. Analysis of TEAEs in the dermal safety studies confirmed the safety and local tolerability of brimonidine tartrate topical gels: no phototoxicity, photosensitivity, or irritancy potential and low sensitization potential were seen in healthy subjects. There was no clear dose relationship and no correlation between TEAEs and plasma concentrations seen in the PK studies performed under maximized conditions of clinical use. The incidences of TEAEs in the Controlled Core Studies were generally equivalent between active gel and vehicle groups (approximately 30% in each group).

The TEAEs considered related to the study drug predominated in the Skin and Subcutaneous Tissue Disorders System Organ Class (SOC) in the Controlled Core Studies, as expected for a topical gel. Flushing, in the SOC Vascular Disorders, was also more frequently reported in the active gel group. These treatment-related, local TEAEs were mostly mild to moderate in severity and transient in duration. Many of these local, rosacea-related TEAEs were reported later in the day, consistent with the effect of the study drug wearing off. The vasoconstriction effect of Brimonidine Tartrate 0.5% Gel does diminish several hours after daily application, allowing for progression back towards Baseline erythema levels late in the day.

With respect to the LTS study, TEAEs occurred at similar frequencies during the first 29 days when compared to both active and vehicle controlled Core Study groups. Most TEAEs occurred during that first month, and markedly decreased at the second quarter (that is 90 days to 180 days after the first dose). Systemic TEAEs were infrequent and rarely related to study treatment. In particular, treatment related Cardiac, Metabolic, Respiratory, or Gastrointestinal

Disorders were not reported during the first 29 days of the LTS study. As with the controlled Core Study subjects who received active medication, Skin and Subcutaneous Tissue Disorders predominated in the LTS study. Headache incidence was low (3.3%, overall; 1.8%, treatment-related) and did not increase over time. In the LTS study, a minimal, acceptable sensitization rate (1% to 2.2%) was observed in rosacea subjects exposed to the active gel over 1 year. The presence of inflammatory lesions and the use of concomitant rosacea medications in LTS study subjects did not have a clinically relevant relationship to the incidence of AEs or the seriousness/severity of AEs, overall or related to the study drug. In addition, there were no signals observed from the vital signs or laboratory data collected in this study. The incidence of related AEs and premature discontinuations due to AEs did not increase over time with long-term use of the study drug and there was no evidence that long-term use of the study drug conveyed an increased risk of occurrence of any specific type of AE.

Across the 18 studies in the development program, serious adverse events (SAEs) were few and not related to Brimonidine Tartrate 0.5% Gel. One (1) SAE related to study drug, hypotension, was reported in a subject who received 0.2% brimonidine tartrate ophthalmic solution prior to topical treatment (RD.06.SRE.18143). Seven (7) SAEs related to the study drug were reported in 2 children who ingested the 0.50% gel assigned to their mother. The remaining SAEs were systemic events.

Discontinuations due to treatment-related TEAE were rare, mostly associated with rosacea pathophysiology, and mainly mild to moderate in severity. Severe TEAEs were also infrequent, and often not related to study drug.

There were no notable, clinically meaningful differences in TEAE incidences with respect to gender, age, or race in the context of subgroup analyses performed on data from the Core Studies and the full duration of the LTS study. When stratified by age, according to the Applicant's data, subjects 65 years of age and older had a similar or lower incidence of TEAEs when compared to those seen in the 18 to 64 years of age group. Those subjects in the older age group reporting TEAEs considered related to the study drug were few. No TEAEs in the geriatric age group were serious, severe, or resulted in study discontinuation.

There were no clinically important effects on laboratory parameters, IOP or vital signs and physical findings seen in any of the 18 studies in the clinical development program. The minor shifts of laboratory parameters or vital signs outside the normal ranges were rare and did not present a safety signal.

Brimonidine Tartrate Gel showed a good safety profile in the subjects with moderate to severe facial erythema of rosacea enrolled in the dose-finding studies. Overall TEAEs and those related to study drug exhibited no dose relationship, were infrequent, generally mild and of short duration, not severe, and did not result in discontinuation. The most common treatment-related TEAEs included pruritus, flushing, skin burning sensation, and skin warm. , there is no clear dose relationship and no correlation between TEAEs and plasma concentrations in these PK studies, as seen in Study 18143.

In the dermal safety studies, Brimonidine Tartrate Gel is well tolerated locally, with little incidence of application site irritation or treatment-related TEAEs observed following application under patch occlusion. There was only 1 unconfirmed allergic sensitization in 1 subject out of a total of 407 subjects who were tested under patch occlusion in the dermal safety studies (that is excluding subjects from RD.06.SRE.18137, who were not tested under occlusion).

There was only one death reported in the clinical studies (lung cancer in LT study18142). There were no SAEs reported in the SOCs of Skin and Subcutaneous Tissue Disorders, Cardiac Disorders, or Nervous System Disorders, the SOCs with the highest frequencies of TEAEs, in the clinical studies of Brimonidine Tartrate 0.5% Gel. Furthermore, no SAE was found to be related to Brimonidine Tartrate Gel in any study subject in any SOC in any of the 18 studies comprising

the clinical development program. Two (2) children accidentally ingested the 0.50% gel assigned to their mother in RD.06.SRE.18140.

TEAEs resulting in discontinuation from any study that were related to treatment with Brimonidine Tartrate 0.5% Gel were typically reports of events common to rosacea (for example erythema, flushing), which were mild or moderate in intensity and eventually resolved. Other TEAEs that resulted in discontinuation included skin burning sensation, skin irritation, contact dermatitis, and allergic dermatitis. All of these TEAEs occurred at less than 2% in the LTS study and rarely in the other studies.

In the pivotal short-term studies (18140 and 18141), Concomitant use of other treatments for rosacea was not permitted (the only topical medications used were emollients and protective). However, concomitant medications for rosacea were permitted in the LT, open-label study 18142. In this LTS study, subjects using Brimonidine Tartrate 0.50% Gel concomitantly with other medications for the treatment of rosacea do not appear to be at increased risk for serious, severe, or systemic AEs. There does not appear to be a potentiation or additive effect with respect to AEs above the normal AE profiles anticipated for each drug individually.

Although specific drug interaction studies have not been conducted with Brimonidine Tartrate Gel, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered. No data on the level of circulating catecholamines after Brimonidine Tartrate Gel administration are available. However, caution is advised in patients taking medications that can affect the metabolism and uptake of circulating amines (for example chlorpromazine, methylphenidate, and reserpine). Alpha-adrenergic receptor agonists should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of brimonidine 0.5% gel in the proposed usage are:

- Statistically significant and clinically relevant improvements in facial erythema in adult patients with rosacea confirmed by the primary endpoint of 2-grade Composite Success which was a composite endpoint based on analyses of independent static evaluations of erythema by the investigators (CEA) and the subjects (PSA).
- Brimonidine Gel 0.5% was significantly better than Vehicle Gel at initiating the onset of a meaningful clinical effect within 30 minutes after the very first application of study drug and this effect was sustained for up to 12 hours post-dose.
- No evidence of tachyphylaxis of the treatment effect was observed in the 29-day vehicle-controlled studies or in the 1-year, long-term study.
- No rebound effect was observed.
- Brimonidine 0.5% gel consistently showed a more favourable outcome in PAA and OTE compared to vehicle gel.
- The low incidence of severe local TEAEs confirms that Brimonidine Tartrate 0.50% Gel is safe and well tolerated in the target population.
- Long-term treatment (for up to 52 weeks) of subjects with once daily application of CD07805/47 gel 0.5% resulted in no new major safety findings or signals and the safety

profile determined during shorter pivotal studies was confirmed. However, interpretation was limited by the open-label, uncontrolled study design.

9.2. First round assessment of risks

The risks of brimonidine 0.5% gel in the proposed usage are:

- Rosacea-related AEs such as erythema, flushing were most common following treatment with brimonidine 0.5% gel; however, most of these AEs were mild to moderate in severity and were usually reported later in the day consistent with the effect of the drug wearing off.
- unwanted over-whitening effects although there was a reduction in reports of over whitening with continued use with similar incidence between brimonidine 0.5% gel and vehicle gel treatment groups by day 29.
- Lack of any drug interaction studies with other medications used in treatment of rosacea in the pivotal short-term studies. However, data from the LT, open-label, uncontrolled study 18142 showed that Subjects using Brimonidine Tartrate 0.50% Gel concomitantly with other medications for the treatment of rosacea does not appear to be at increased risk for serious, severe, or systemic AEs.
- Lack of controlled efficacy and safety data beyond 4 weeks.

9.3. First round assessment of benefit-risk balance

The PK, efficacy, and safety profile of Brimonidine Tartrate 0.5% Gel was adequately evaluated in adult subjects with erythema of rosacea in a total of 18 clinical trials, including two adequate and well controlled Phase III studies. A total of 1619 of the 2174 subjects in the clinical development program were exposed to Brimonidine Tartrate Gel, with 1210 of the 1619 subjects exposed to proposed marketing formulation of Brimonidine Tartrate 0.5% Gel qd.

Treatment with Brimonidine Tartrate 0.5% Gel qd in vehicle-controlled studies for 29 days resulted in statistically significant and clinically meaningful reductions in facial erythema of rosacea, as independently observed by the investigators and the subjects. Furthermore, this onset of effect was rapid (30 minutes after the first dose of study drug on Day 1 in many cases) and was observable and statistically significant relative to subjects who received Vehicle Gel. This rapid onset of action provides an advantage for proposed brimonidine gel as the other marketed pharmaceutical treatments for rosacea that target inflammatory lesions require 8 weeks or more of continuous therapy to achieve significant effectiveness on reduction of lesions. Thus, Brimonidine Tartrate 0.5% Gel offers a direct effect on facial erythema of rosacea that is not provided by current pharmaceutical treatments for rosacea and also offers fast onset of effect on reduction in facial erythema of rosacea.

Brimonidine Tartrate 0.5% Gel was able to maintain, on a daily basis, at least a 1-grade improvement (that is, noticeable effect) in CEA and/or PSA for a maximal amount of time (target of 12 hours after dosing), while being able to achieve daily 2 grade improvement in both assessments for a sustained period.

The Phase IIb and the Phase III pivotal studies demonstrated that subjects perceived improvements on both clinic and non-clinic days in their erythema and overall facial appearance, as measured by the PSA and PAA. The PAW subject self-assessment also showed that few subjects with over whitening were bothered by the effect, and additionally that the percentage of subjects who were bothered by over-whitening decreased over time which may be due to better application technique with time. Brimonidine Tartrate Gel should be applied smoothly and evenly across all application areas. A small pea-size amount (estimated to be no more than 1 g in total weight) of Brimonidine Tartrate Gel should be applied to each of the five

areas of the face (that is, forehead, chin, nose, each cheek) and these facts have been adequately covered in the proposed PI.

No clinically meaningful worsening of lesions was observed in the Phase IIb or Phase III pivotal studies in the Brimonidine Tartrate 0.5% Gel groups relative to the corresponding Vehicle Gel groups in any of the studies. In addition, no worsening of mean Telangiectasia Grading Assessment scores was observed during the studies. As, reduction in vascular erythema (that is, vasoconstriction) is the primary target of Brimonidine Tartrate 0.5% Gel, the drug is not expected to reduce the incidence or severity of inflammatory lesions of rosacea.

No clinically meaningful trends with respect to tachyphylaxis or rebound effects (worsening of baseline erythema after cessation of treatment) were observed with use of Brimonidine Tartrate 0.5% Gel for 29 days.

In the long-term, open-label, 1 year safety and efficacy study, reductions in facial erythema were maintained over the study duration, showing durability of treatment effect with chronic use and a potential for positive impact on the long term psychosocial function of rosacea subjects; however, interpretation was limited by the open label, uncontrolled study design.

The safety of Brimonidine Tartrate Gel in humans was evaluated in 1210 subjects who were exposed to Brimonidine Tartrate 0.5% Gel. The 1-year open-label study (18142) provided approximately 345 subject years of exposure. The subject populations in the Applicant's studies were representative of target patient population.

The most commonly reported related TEAEs in subjects treated with Brimonidine Tartrate 0.5% Gel in the Controlled Core Studies were erythema, pruritus, skin burning sensation, and flushing which occurred in 1.2% to 3.3% of subjects. They are usually transient, mild to moderate in severity, and usually do not require discontinuation of treatment. Furthermore, most of these AEs were mild to moderate in severity and were usually reported later in the day consistent with the effect of the drug wearing off.

Clinical local tolerance studies that evaluated Brimonidine Tartrate 0.5% Gel showed; no detectable phototoxicity or photosensitization potential, low contact sensitization potential, and low cumulative irritancy potential for the active formulations and for the vehicle. This was consistent with the results of the nonclinical local tolerance studies. Furthermore, no cases of allergic dermatitis were reported in rosacea subjects with up to 4 weeks of treatment across all Phase II and Phase III clinical studies, In the 1-year open label study in 449 subjects with rosacea, 17 subjects were patch tested for possible allergic dermatitis. Of these, 3 were confirmed positive and 14 were negative. Seven additional cases of possible allergic dermatitis were reported, but no patch testing was performed for confirmation. All of these events occurred after 4 weeks of exposure, with the onset between 3 and 6 months in the majority of these subjects.

Routine blood chemistry, haematology, and urinalysis were performed in Studies 18143, 18140, 18141, and 18142. No clinically relevant changes in blood chemistry, haematology, or urinalysis were observed for subjects who received Brimonidine Tartrate Gel.

Overall, treatment with Brimonidine Tartrate 0.5% Gel showed reductions in facial erythema that were both statistically significant and clinically meaningful, with a rapid onset of effect in many cases (30 minutes after the first dose on Day 1). Brimonidine Tartrate 0.5% Gel has been shown to be safe and well-tolerated, as evidenced in the data from the development program for Brimonidine Tartrate 0.5% Gel. Furthermore, the long-term, open-label study showed no attenuation of treatment effect with long-term, chronic use in addition to a positive effect on the social impact of treatment for facial erythema of rosacea with Brimonidine Tartrate 0.5% Gel.

Rosacea is one of the most common chronic dermatological diseases; the prevalence statistics published in Europe and the United States are highly variable, ranging from less than 1% to more than 20% of the adult population. Rosacea substantially impacts quality of life and can be

associated with depressive symptoms. The psychological and social consequences of rosacea are often underestimated, as they are not consistently commensurate with the quantitative severity of the facial lesions. Rosacea is significantly associated with depression (Chosidow and Cribier 2011).

Currently, there are no approved pharmaceutical agents that directly target the persistent facial erythema of rosacea. Current pharmaceutical treatments available for rosacea primarily target the papulopustular rosacea subtype of the disease, reducing rosacea inflammatory lesions through anti-inflammatory/antiparasitic mechanisms.

Topical treatment with brimonidine 0.5% gel applied once daily provides a rapid, effective and safe treatment option with potential positive social impact for adult patients with facial erythema of rosacea. However, there are certain limitations of the submission which need to be addressed before recommending authorisation for marketing.

The benefit-risk balance of Mirvaso given the proposed usage (for the treatment of facial erythema of rosacea) is unfavourable, but would become favourable if changes recommended in section 10 (see below) are accepted.

10. First round recommendation regarding authorisation

It is recommended that approval of the submission be granted subject to the following conditions:

Approval is granted for the modified indication of: "Mirvaso is indicated for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients."

11. Clinical questions

11.1. Pharmacokinetics

1. Why was the less sensitive analytical method, which had a LLQ of 25 pg/mL, rather than the method from study RD.06.SRE.18143, which had a LLQ of 10 pg/mL, used to determine plasma concentrations of brimonidine in the 2 initial BA studies?
2. Why was 0.5% Mirvaso gel not examined in the BA studies in healthy subjects, that is the to-be-marketed concentration, as the higher dose may have been easier to detect in plasma?
3. Have the sponsors conducted a population pharmacokinetic analysis on pooled data which examines the effects of race, age, gender and Fitzgerald's skin types on the PK, PD and safety of Mirvaso Gel?
4. Can the sponsor please justify why drug-drug interaction studies with other pharmaceutical agents used in the treatment of facial rosacea, such as low-dose clonidine, long acting beta-blockers, antibiotics or retinoids have not been conducted?

11.2. Pharmacodynamics

None.

11.3. Efficacy

None.

11.4. Safety

None.

11.5. PI (Indications)

The proposed indications are:

Mirvaso is indicated for the treatment of facial erythema of rosacea.

Mirvaso was only evaluated in adult patients aged > 18 years. Furthermore, It should be specified that it is only a topical symptomatic treatment. Hence, it is recommended that the proposed indication be changed to the following:- "Mirvaso is indicated for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients."

12. Second round evaluation of clinical data submitted in response to questions

12.1. Pharmacokinetics questions

Question 1: *Why was the less sensitive analytical method, which had a LLQ of 25 pg/mL, rather than the method from study RD.06.SRE.18143, which had a LLQ of 10 pg/mL, used to determine plasma concentrations of brimonidine in the 2 initial BA studies?*

Applicant's response: Brimonidine Tartrate Gel was originally developed by the previous sponsor. The PK profile of Brimonidine Tartrate Gel was initially evaluated by the previous sponsor in two single-day crossover studies (COL-118-BAPK-101 [healthy subjects] and RD.06.SRE.18126 [subjects with rosacea]. At that time, the previous sponsor contracted a clinical research organisation to develop the bioanalytical method. The validated HPLC-MS/MS method used in the previous PK studies conducted by the sponsor (Bioanalytical Report: Study 6438-622) has a minimum brimonidine quantifiable concentration of 25 pg/mL. All the collected plasma samples from these 2 initial BA studies were below the LoQ (< 25 pg/mL) for Brimonidine Tartrate Gel. Furthermore 7 subjects out of the 18 receiving the ophthalmic solution in the second BA study presented non -quantifiable plasma concentrations.

In 2008, the Applicant (GALDERMA R&D) acquired the previous sponsor and completed the PK clinical program with a multiple-dose PK maximal-use study in subjects with moderate to severe erythematous rosacea. This maximal use PK study RD.06.SRE.18143 was designed to obtain a complete PK profile at steady state on the target patient population and to provide an intra-individual comparison of the PK profile obtained after topical and ophthalmic administrations. Considering the initial PK profile of brimonidine topical gel or ophthalmic solution, the Applicant considered that the initial method was not sensitive enough for brimonidine determination in human plasma. Consequently the Applicant developed a more sensitive analytical method than had been used in the 2 previous PK studies, with the limit of quantification (LOQ) lowered from 25 pg/mL to 10 pg/mL.

In conclusion, among these three studies, only Study RD.06.SRE.18143 conducted in 2010 is regarded as definitive by the Applicant because this study used the more sensitive analytical method (LOQ = 10 pg/mL).

Evaluator's comments: The sponsor's response is acceptable.

Question 2: *Why was 0.5% MIRVASO gel not examined in the BA studies in healthy subjects, i.e. the to-be-marketed concentration, as the higher dose may have been easier to detect in plasma?*

Applicant's response: Brimonidine Tartrate Gel was originally developed by the previous sponsor. Based on their clinical development plan, the to-be marketed concentration anticipated by the sponsor was 0.18%. Subsequently, the PK profile of Brimonidine Tartrate Gel 0.18% and 0.2% was initially evaluated by the sponsor in two single-day crossover studies (COL-118-BAPK-101 [healthy subjects] and RD.06.SRE.18126 [subjects with rosacea].

In 2008, the applicant acquired the previous sponsor and pursued the development program with two clinical Phase II studies to determine an optimal formulation, concentration, and dose regimen. The pharmacodynamic profile of Brimonidine Tartrate gel has been categorized for concentrations ranging from 0.07% to 0.5% Brimonidine Tartrate gel in a Phase IIa study (RD.06.SRE.18144, study date: 2009). Based on this study, both the 0.18%, and 0.5% concentrations were selected for evaluation in a subsequent Phase IIb efficacy and safety study (study RD.06.SRE.18161, study date: 2009). In 2010, based on the Phase II clinical results, Brimonidine Tartrate 0.5% Gel was selected as the to-be-marketed formulation and used in the Phase III program.

In parallel to this Phase IIb study, the Applicant conducted a maximal use PK study in order to assess the safe use of the proposed to-be-marketed concentrations in the upcoming Phase III program. Taking into account that erythema associated with rosacea may lead to increased systemic absorption of brimonidine compared to healthy skin, the Applicant considered that one study in healthy volunteers was not adequate to support the safe use of the 0.5% gel formulation at that stage of development.

Therefore MIRVASO gel 0.5% was directly evaluated in subjects with moderate to severe erythematous rosacea.

Evaluator's comments: The sponsor's response is acceptable.

Question 3: *Have the sponsors conducted a population pharmacokinetic analysis on pooled data which examines the effects of race, age, gender and Fitzgerald's skin types on the PK, PD and safety of MIRVASO Gel?*

Applicant's response: The Applicant did not conduct a population pharmacokinetic analysis on pooled data for discriminating among the different sources of variability (patient covariate) on the pharmacokinetic parameters. In lieu, the applicant conducted subgroup analyses to explore the potential differences of common TEAEs within a subgroup (gender, age, race and ethnicity) compared with the entire study population.

Regarding PK of MIRVASO gel, a total of 3 PK, relative bioavailability studies were conducted during the development of Brimonidine Tartrate Gel: 2 single-day crossover studies (COL-118-BAPK-101 [healthy subjects] and RD.06.SRE.18126 [subjects with rosacea]) and 1 multiple-dose study under maximal use conditions in subjects with rosacea (RD.06.SRE.18143). Among these three studies, only Study RD.06.SRE.18143 is regarded as definitive by the Applicant because the study was in subjects with rosacea, used the more sensitive analytical method (LOQ = 10 pg/mL), and evaluated repeated dosing of the to-be-marketed formulation under maximal use conditions (1 g of Brimonidine Tartrate Gel applied to the entire face under controlled conditions by a nurse).

Of note, among these 3 relative bioavailability studies quantifiable PK profiles after topical application of Brimonidine Tartrate Gel were observed only in study 18143. In this study, daily topical application for 29 days under maximal use conditions resulted in quantifiable plasma concentrations in samples from 15 out of 19 subjects who received Brimonidine Tartrate Gel 0.5% QD, (i.e. 79% of subjects). The time-concentration profiles for Brimonidine Tartrate 0.5% Gel were flat, with T_{max} values ranging from pre-dose to 24 hours post-dose.

Considering this limited number of PK profiles (i.e. 15 subjects) and the variability associated with Tmax due to the flat PK profile, the Applicant considered that sparse sampling in Phase 3 studies would have led to a majority of non-quantifiable plasma concentrations. Indeed, the flat

PK profile of MIRVASO 0.5% gel was not appropriate to build robust pharmacokinetic models for a population PK analysis and therefore the sparse data collected may not provide adequate information for discriminating among the different sources of variability on the pharmacokinetic parameters. Nevertheless, because of these very low systemic exposures, no new safety issues would be anticipated for Brimonidine Tartrate Gel in special patient populations.

Regarding the safety of MIRVASO gel, subgroup analyses were conducted to explore the potential differences of common TEAEs within a subgroup (gender, age, race, ethnicity) compared with the entire study population. With respect to gender, women were observed to report more TEAEs than men, both in the active treatment groups and in the vehicle group. Male representation in studies was low relative to females, consistent with the incidence of rosacea in the general population. Noted differences in specific TEAE incidences between the genders are likely due to normal variability and not indicative of a gender-specific risk.

Available data do not indicate that subjects ≥65 years of age have an increased risk of adverse events when compared to subjects 18 to 64 years of age.

Based on the very low number of Non-Caucasian participants, conclusions on AEs based on race are difficult to make.

Subjects with rosacea and a preponderance of inflammatory lesions (>10) do not seem at increased risk for AEs compared to subjects with few or no concomitant inflammatory lesions.

Evaluator's comments: The evaluator accepts that the MIRVASO may have been difficult to detect in plasma. However, due to the small number of participants enrolled in the definitive study, i.e. Study RD.06.SRE.18143, it is impossible, based on the PK data available, to determine whether gender and age related differences or factors such as hepatic or renal impairment affect the PKs of MIRVASO. The current PI already states that the effects of hepatic and renal impairment have not been studied and that the data relating to subjects older than 65 is limited; however, no statement is included in the PI, which identifies the fact that the effects of gender on the PKs of MIRVASO are unknown and a statement to this effect should be included in the revised.

Question 4*: Can the sponsor please justify why drug-drug interaction studies with other pharmaceutical agents used in the treatment of facial rosacea, such as low-dose clonidine, long acting beta-blockers, antibiotics or retinoids have not been conducted?*

Applicant's response: PK studies to assess the drug-drug interaction potential of Brimonidine Tartrate Gel were not conducted by the Applicant. Because of the very low systemic exposure observed in clinical studies, no new safety issues would be anticipated for MIRVASO 0.5% Gel applied concomitantly with other topical or systemic products for the treatment of rosacea. Indeed, PK data showed that the highest mean systemic peak plasma exposure (C_{max}) following once daily topical application of MIRVASO 0.5% gel was 2- to 3-times lower in comparison to a single day TID administration of 0.2% ophthalmic solution. The Applicant defers to the Agency's previous findings of safety in special populations for brimonidine tartrate 0.2% ophthalmic solution as reflected in the approved prescribing information.

In the pivotal, controlled Phase III studies, use of other topical or systemic products for the treatment of rosacea was not permitted, whereas in the open-label, long-term Phase III study, other rosacea treatments were allowed.

In the LTS study, concomitant medications were taken by 85% of subjects, with the most common (>10% of total subjects) being metronidazole (70 subjects, 16%), ibuprofen (58 subjects, 13%), multivitamins, other combinations (56 subjects, 12%), and doxycycline (45 subjects, 10%). These concomitant medications were permitted during the LTS study and were sometimes prescribed for the treatment of acne and/or rosacea, specifically metronidazole and doxycycline/minocycline/tetracycline. Other anti-acne and anti-rosacea preparations taken

were azelaic acid (27 subjects, 6%), tetracycline (18 subjects, 4%), benzoyl peroxide with clindamycin (1 subject, <1%), tretinoin (3 subjects, 1%), and adapalene (1 subject, <1%).

Other agents used for treatment of acne and/or rosacea were allowed and were taken by about 30% of the subjects. Analyses of adverse events in patients treated with other rosacea medications vs. those who were not were made and there does not appear to be a potentiation or additive effect with respect to AEs above the normal AE profiles anticipated for each drug individually, including local tolerability.

It is likely that MIRVASO 3.3 mg/g Gel will be combined with other topical treatments (for example topical antibiotics), in subjects having not only erythema, but also inflammatory lesions of rosacea. Based on the LTS data, no new safety issues would be anticipated for MIRVASO 3.3 mg/g Gel applied concomitantly with other topical or systemic products for the treatment of rosacea.

Evaluator's comments: The sponsor's response is acceptable.

12.1. Questions on the clinical aspects of the draft product information (indications)

The proposed INDICATIONS are:

> *MIRVASO is indicated for the treatment of facial erythema of rosacea.*

MIRVASO was only evaluated in adult patients aged > 18 years. Furthermore, It should be specified that it is only a topical symptomatic treatment. Hence, it is recommended that the proposed indication be changed to the following:

> *"MIRVASO is indicated for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients."*

Applicant's response: The applicant agrees with the proposed indication and has updated the PI accordingly.

Evaluator's comments: The sponsor's response is acceptable.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of response to clinical questions, the benefits of Mirvaso in the proposed usage are unchanged from those identified in section 9.1.

13.2. Second round assessment of risks

After consideration of response to clinical questions, the risks of Mirvaso in the proposed usage are unchanged from those identified in section 9.2.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Mirvaso given the proposed usage for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients is favourable.

14. Second round recommendation regarding authorisation

It is recommended that approval of the submission be granted for the indication of:

> *"Mirvaso is indicated for the cutaneous symptomatic treatment of facial erythema of rosacea in adult patients."*

Approval is subject to incorporation of a minor change to the proposed PI.

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