19 December 2013
EMA/CHMP/115246/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mirvaso

International non-proprietary name: brimonidine

Procedure No. EMEA/H/C/002642/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Mirvaso
Applicant:	Galderma International Tour Europlaza, 20 avenue André Prothin – La Défense 4 La Défense Cedex 92927 France
Active substance:	Brimonidine tartrate
International Nonproprietary Name:	Brimonidine
Pharmaco-therapeutic group (ATC Code):	Other dermatologicals (D11AX21)
Therapeutic indication:	Mirvaso is indicated for the symptomatic treatment of facial erythema of rosacea in adult patients.
Pharmaceutical form:	Gel
Strength:	3 mg/g
Route of administration:	Cutaneous use
Packaging:	Tube
Package size:	2g, 10g, 30g

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List of abbreviations

Abbreviation	Definition
AE	Adverse event
AUC	Area under the curve
BID	Twice daily
CD07805/47	Galderma Development Code for brimonidine tartrate drug substance
CEA	Clinician Erythema Assessment
CI	Confidence interval
C_{max}	Peak serum concentration
CMH	Cochran-Mantel-Haenszel
COL-118	CollaGenex Pharmaceuticals Inc. Development Code for brimonidine tartrate
FDA	Food and Drug Administration
GEE	Generalized Estimating Equation
ICC	Intraclass correlation coefficient
IOP	Intraocular pressure
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
LOQ	Limit of quantification
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
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*)
QOL	Quality of life
SAE	Serious adverse event
SD	Standard deviation
TC	Topical corticosteroid
TEAE	Treatment-emergent adverse event
TGA	Telangiectasia Grading Assessment
UBC	United BioSource Corporation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Galderma International submitted on 30 November 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Mirvaso, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure based on demonstration of significant therapeutic innovation was agreed upon by the EMA/CHMP on 20 October 2011.

The applicant applied for the following indication: "treatment of facial erythema of rosacea in adult patients".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that brimonidine was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0281/2012 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application. In 2013, the FDA approved topical application of brimonidine 0.33% (Mirvaso) for the topical treatment of persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older.

1.2. Manufacturers

Manufacturer of the finished product

Laboratoires Galderma
Z.I. Montdésir
74450 Alby-sur-Chéran
France

Manufacturer responsible for batch release

Laboratoires Galderma
Z.I. Montdésir
74450 Alby-sur-Chéran
France

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 30 November 2012.
- The procedure started on 30 January 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 April 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 21 April 2013.
- During the meeting on 13-16 May 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan .
- During the meeting on 27-30 May 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 31 May 2013 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 September 2013 .
- During the meeting on 7-10 October 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan .
- During the CHMP meeting on 21-24 October 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant .
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 November 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 26 November 2013 .
- During the meeting on 16-19 December 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Mirvaso.

2. Scientific discussion

2.1. Introduction

Problem statement

Rosacea is defined as a chronic dermatological disease typically affecting the adult population, with prevalence between 2% and 10% in Europe (Berg 1989, Kyriakis 2005, Powell 2005, van Zuuren 2005). It affects mainly fair skinned population, with a higher occurrence in women. The course of the disease is chronic and different manifestations might occur simultaneously or separately, ranging from erythema and flushing to teleangectasia, papulo-pustular lesions, rhinophyma and ocular manifestations. Onset typically occurs between 30 to 50 years of age. Data also support that rosacea has an impact on patients' quality of life (Crawford 2004). The course of the disease and time to progression to more severe forms is unpredictable, even if usually rosacea is less severe and more prevalent in women, with the erythematotelangectasic subtype being the most frequent. In these cases, erythema is usually localised in the central area of the face and its intensity may range from mild and transient forms, to very severe forms and its intensity may worsen during the day and are influenced by many factors, such as alcohol, spicy foods, exercise and external temperature.

According to the presence of different signs and symptoms, rosacea can be classified in four different sub-types 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 (Wilkin 2002). One of 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). Erythema with or without telangectasia (TGA) is the basic manifestation that can usually be found in all rosacea subtypes. The disease may remain stable within one subtype or may have a worsening course, ranging from the basic erythematous variant to the most severe forms with high number of inflammatory lesions, rhynophyma and ocular symptoms.

Other primary symptomatology includes flushing, papules, pustules, and telangiectasias on the convex surfaces. Secondary characteristics are burning and stinging, oedema, plaques, a dry appearance, ocular manifestations, and phymatous changes. Erythematotelangiectatic rosacea (ETR), which is the most prevalent subtype, is principally characterized by the persistent central facial erythema with flushing and telangiectasia. The papulopustular subtype (PPR) is also characterized by persistent central facial erythema, but also with episodic or persistent inflammation in the form of small to medium papules and pustules in a central facial distribution (Crawford 2004, Pelle 2008).

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). 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), is commonly described as a pathogenic factor in the persistent facial erythema of rosacea. The aetiology of vasomotor instability in patients with rosacea is unknown (Crawford 2004, Kyriakis 2005, Pelle 2008, Wolf 2005).

The condition is often worsened by factors like sunlight, strong wind, alcohol, coffee, spicy food, exercise, stress and some cosmetics.

There are no approved pharmaceutical agents in Europe that directly target the persistent facial erythema of rosacea. There are several pharmaceutical treatments to the management of rosacea; they are primarily targeted towards the papulopustular rosacea subtype of the disease, reducing rosacea inflammatory lesions through anti-inflammatory mechanisms. They include local and systemic antibiotics

(metronidazole and tetracyclines), topical azelaic acid, isoflavonoid and laser and surgical treatments. Their activity on underlying erythema and flushing is based on reduction of inflammatory redness and long term action on small vessels, but they provide no immediate and evident improvement of baseline erythema that can be evident in the short term.

About the product

Brimonidine tartrate, the active substance of Mirvaso, is a relatively selective alpha-2 adrenergic agonist, with potent vasoconstrictive / vasostabilising activity is currently approved as ophthalmic solution at the concentration of 0.2%, indicated for the treatment of intraocular pressure (IOP) and glaucoma, with a posology ranging from 2 to 3 daily administrations. Erythema of rosacea is linked to permanent vasodilatation of small vessels and, therefore, treatments that might work on vasoconstriction and stabilisation of the contractile state of cutaneous small blood vessels might have a role in improving the erythematous manifestations of rosacea. Its mechanism of action includes vasoconstriction mediated by influence on postsynaptic smooth muscle alpha2-adrenergic receptors stimulation. It is extensively metabolised in humans, but absorption after ocular administration is very limited. On the basis of the known activity on ophthalmological diseases, a cutaneous formulation has been developed by the applicant, aiming at the treatment of vasodilatation of cutaneous small blood vessels that are involved in the pathophysiology of rosacea erythema. The mechanism of action should therefore imply a rapid onset and limited duration of activity, with no theoretical influence on other underlying factors involved in the pathophysiology of rosacea. The reduction of facial erythema would be of significant clinical benefit for patients who are affected by the erythematoteleangectasic variant of rosacea and would also improve the clinical manifestations of those with other types of rosacea.

The product formulated is an aqueous gel formulation at the concentration of 0.5% brimonidine tartrate (which corresponds to 0.33% brimonidine). The brimonidine development has been based on the concentrations and the posology already approved for the ophthalmic solution. The posology proposed for brimonidine tartrate gel is one daily administration, estimated to be no more than 1 g in total weight, is the maximum daily recommended dose. The to-be-marketed drug product is presented in laminated tubes with a child resistant cap to minimize the risk of accidental oral ingestion by children.

The finally approved indication is as follows: “For the symptomatic treatment of facial erythema of rosacea in adult patients”.

2.2. Quality aspects

2.2.1. Introduction

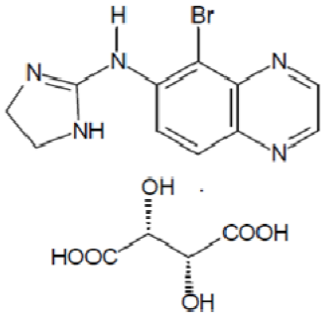
The finished product is presented as a gel containing 3 mg/g of brimonidine as active substance.

Other ingredients are: carbomer, methylparahydroxybenzoate (E218), phenoxyethanol, glycerol, titanium dioxide, propylene glycol, sodium hydroxide and purified water.

The product is available in polyethylene (PE)/Aluminium (Al)/ Polyethylene (PE) laminated plastic tubes with a high density polyethylene (HDPE) head and polypropylene (PP) child resistant closure.

2.2.2. Active Substance

The chemical name of brimonidine tartrate is 5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine L-tartrate and has the following structural formulae:



The structure of brimonidine tartrate was confirmed by elemental analysis, mass spectroscopy, 1H-NMR spectroscopy, 13C-NMR spectroscopy, IR spectroscopy and UV spectroscopy.

The active substance is a white to slightly yellowish powder, not hygroscopic, freely soluble in water and insoluble in almost all organic solvents. Therefore, it is completely dissolved in the drug product and does not form a dispersion.

Brimonidine base has no chiral centre and cannot show any optical activity. The source of optical activity is tartaric acid, which is used as natural L(+)-tartaric acid. Polymorphism has not been observed for brimonidine.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

The Active Substance Master File (ASMF) procedure was followed for the active substance. Letters of access has been received from both ASMF Holders.

Brimonidine tartrate is manufactured in two manufacturing sites.

Brimonidine tartrate is synthesized in four main steps using well defined starting materials with acceptable specifications. There are two slightly different synthetic routes with steps well defined.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMFs and it was considered satisfactory.

Specification

The active substance specification includes tests for description (visual inspection), identification (IR and identification of tartrate), pH (Eur. Ph.), melting range, loss on drying (Eur. Ph.), sulphated ash (Eur. Ph.), heavy metals (Eur. Ph.), related substances (HPLC), assay (titrimetry), specific optical rotation (Eur.

Ph.), residual solvents (Eur. Ph.) and content of tartrate (potentiometry). The absence of a test for microbiological purity has been acceptably justified.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Brimonidine tartrate is packaged by both suppliers in double polyethylene bags. The filled bags are packed inside polyethylene drums. The polyethylene bags comply with the Ph. Eur. and EU directive 2002/72.

Batch analysis data on two industrial scale batches of the active substance are provided from each manufacturer. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on eight industrial batches of active substance from the proposed manufacturers stored in the intended commercial package for 60 months under long term conditions at 25 ºC / 60% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Results on stress conditions (UV light, day light and alkaline medium) were also provide on one batch.

The following parameters were tested: appearance, clarity of solution, colour of solution, pH of solution, loss on drying, HPLC purity and assay. The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to develop an aqueous gel containing brimonidine tartrate to be used for the topical treatment of facial erythema of rosacea in adult patients. The objective was to develop a formulation with a texture adapted for application to the face that allowed the active substance to reach the site of action.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Purified water is used as a vehicle and solvent. Carbomer is used as a gelling agent. Methylparahydroxybenzoate and phenoxyethanol are included as preservatives to ensure microbiological quality of the gel. Titanium dioxide is added to ensure that a more visually appealing colour (white to off-white) is achieved since brimonidine tartrate may cause yellowing of the finished product. Propylene glycol is added as a humectant and solubiliser for both brimonidine tartrate and methylparahydroxybenzoate. Glycerol is used as humectant. Sodium hydroxide is added to the formulation in order to neutralize the acidic carbomer, essential for formation of the gelling network in order to obtain a viscous gel that is well adapted to a facial application.

The aqueous solubility of brimonidine tartrate was investigated during formulation development. The results showed that brimonidine tartrate at 3.00% w/w was dispersed in the aqueous phase and concentrations at this level were no longer pursued. But below this concentration, brimonidine tartrate was fully dissolved.

The levels of preservatives have been justified.

The performance of the finished product was also assessed through an In Vitro Release Test (IVRT). The study was conducted in accordance with the FDA SUPAC guideline for semi-solid forms by comparing an industrial registration batch with a laboratory high viscosity batch (viscosity=589, 500 mPa.s, i.e. representative of the upper limit of the specification) and a laboratory low viscosity batch (viscosity=304,500 mPa.s, i.e. representative of the lower limit of the specification). It was shown that the limits proposed for the viscosity range at release are validated. An additional IVRT was also performed with a stability batch at commercial batch size of 1,000 kg. The results showed that the release rates of the batches studied are similar, demonstrating their equivalence. These data support the consistency of the gel release performance between different batches and throughout the shelf life period.

The finished product has been developed using elements of Quality by Design such as design of experiments (DoE). In these studies, the homogeneity, colour, viscosity and pH of a prototype solution were kept constant (the concentration of brimonidine tartrate, methylparahydroxybenzoate, phenoxyethanol and NaOH solution remained constant) and excipients affecting the texture and stability of the gel (gelling agent, humectants, and opacifier) were changed. Seventeen formulations were developed and examined. Based on the results from the DoEs, three formulations were selected to be used in clinical studies. The results from the clinical studies lead to the selection of the formulation proposed for marketing.

Several manufacturing facilities have been used during development and different formulations were also developed at the different sites. However the discrepancies have been well described and the clinical batches are considered representative of the final formulation.

Brimonidine tartrate gel is packaged in polyethylene (PE)/Aluminium (Al)/ Polyethylene (PE) laminated plastic tubes with a high density polyethylene (HDPE) head and polypropylene (PP) child resistant closure. All materials in direct contact with the product comply with the Ph. Eur. requirements. The child resistant effect has been demonstrated.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process of Mirvaso comprises (1) preparation of the gel phase, (2) cooling, (3) pH adjustment and gel formation and (4) filling.

Two in-process controls are performed during manufacturing: complete dissolution of the preservatives (mixing time and temperature must be controlled to ensure that methylparahydroxybenzoate is dissolved and that a homogeneous mixture is obtained) and pH of the final formulation (the pH of the finished product after incorporation of sodium hydroxide must be controlled to ensure proper formation of the gel network).

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of pharmaceutical form.

Product specification

The finished product release specifications include tests for appearance (visual examination), identification of brimonidine (HPLC and UV), identification of methylparahydroxybenzoate and phenoxyethanol (HPLC), assay of brimonidine (HPLC), assay of methylparahydroxybenzoate and phenoxyethanol (HPLC), pH (Ph.Eur.), viscosity (viscosimetry), impurities (HPLC) and microbial purity (Ph.Eur).

Batch analysis results are provided on three industrial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The viscosity range limits are acceptable, however, based on the performed IVRT studies, to further validate the limits proposed for the viscosity range both at release and shelf life, an additional study on the *in vitro* release of brimonidine tartrate from a commercial batch should be performed. This request is included in the list of recommendations.

All methods have been satisfactorily validated. The HPLC method has been validated for specificity, linearity, range, accuracy, intermediate precision and robustness. The validation data demonstrated that the method is suitable for the identification and assay test of brimonidine, preservatives and impurities. For methods described in the Ph. Eur. validation was deemed to be unnecessary. The microbial purity of the drug product was compliant with Ph. Eur. requirements for preparations for cutaneous use.

Stability of the product

Stability data of three production scale batches of finished product stored under long term conditions for 36 months at 25 ºC / 60% RH and 30 ºC / 75% RH, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. In addition, stability data on three production scale batches stored at 25ºC/60% RH for 9 months and cycled through either cold/warm (5ºC/40ºC) or freeze/thaw (-18ºC/25ºC) conditions for two weeks were also provided. The batches of brimonidine tartrate are representative of those proposed for marketing but were packaged in a non-child resistant container closure system, i.e. different packaging material containing the same plastic polymers but with a non-child resistant cap.

The parameters tested and the test methods used were the same as those proposed for release testing. The analytical procedures used are stability indicating.

In addition, three batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of the studies showed that brimonidine tartrate gel was unstable when exposed directly to light. However, the primary packaging was found to adequately protect the finished product from exposure to light.

In use stability studies were also performed on two batches of brimonidine tartrate. The results showed no significant change in the parameters tested and remained within the proposed specification.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance and finished product have been adequately described. The excipients used in the preparation of the finished product and the manufacturing process selected are typical of a cutaneous preparation. The results of the tests indicate that the active substance and the finished product can be reproducibility manufactured and therefore the product should have a satisfactory and uniform performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The Committee recommends that the applicant performs an additional study on the *in vitro* release of brimonidine tartrate from a commercial batch to further validate the limits proposed for the viscosity range both at release and shelf life.

2.3. Non-clinical aspects

2.3.1. Introduction

Brimonidine tartrate is a well-known compound and has been extensively used in humans for more than 15 years for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

The Applicant did provide already available data from peer-reviewed literature for the pharmacology studies, safety pharmacology, and pharmacokinetics and this appear to be well justified to support the present indication.

The nonclinical toxicity studies were all conducted in compliance with Good Laboratory Practice regulations. The nonclinical toxicity studies performed with BT gel 0.5% formulation (the to be marketed formulation), were defined pivotal by the Applicant, while studies that were not performed with the to-be-marketed formulation including dose range finding (DRF) studies, are defined non-pivotal studies.

2.3.2. Pharmacology

The justification by the Applicant not to perform new pharmacodynamic interaction studies is accepted.

Primary pharmacodynamic studies

Brimonidine tartrate is a α2-adrenoreceptor agonist with approximately 1000-fold more selectivity for the α2-adrenoreceptor than for the α1-adrenoreceptor. There is no available animal model of rosacea, therefore, no primary pharmacodynamic data were submitted in support of this application which is accepted by the CHMP considering the extensive clinical experience with brimodine tartrate although at another therapeutic indication.

Secondary pharmacodynamic studies

The information on secondary pharmacodynamics is rather sparse. A Pharmacology Overview table is provided below.

Table 1. Secondary Pharmacodynamics

2.6.3.1.B Secondary pharmacodynamics

Type of Study	Test System	Method of Administration	Testing Facility	Report No.
mydriasis and miosis evaluation	Pupil size in rabbit, monkey and cats	Ocular	NA	Burke and Schwartz 1996 Gabelt et al. 1994 Burke and Potter, 1986
neuroprotection	optic nerve and retinal ganglion cells	IP	NA	Burke and Schwartz 1996
neuroprotection	Rat retinal ganglion cells	IP	NA	Ahmed et al. 2001

There is for instance no information on affinity of brimonidine tartrate to other receptors/ion channels/transporters except affinity to α-adrenoceptors. However, the clinical experience with brimonidine tartrate is extensive. Furthermore, the proposed indication with limited systemic absorption and no safety concerns due to systemic effects, overrules the lack of a complete receptor screen for brimonidine.

Mydriasis

Brimonidine tartrate can induce mydriasis in rabbits, cats and monkeys but with a less marked effect compared to clonidine and apraclonidine, due to its low affinity for the α1-adrenoceptors (Burke and Potter 1986, Gabelt et al 1994, Burke and Schwartz 1996). At ophthalmic concentrations in the clinical treatment of glaucoma, brimonidine tartrate does not induce mydriasis, thus this effect is unlikely to be relevant for the proposed indication by the dermal route.

Neuroprotection

Alpha-2 adrenoceptor agonists are neuroprotective in a variety of animal models (Burke and

Schwartz 1996). Neuroprotective effect is a general feature of α2 adrenergic receptor agonists, including brimonidine, although the underlying mechanism is unclear (Weber et al 2007).

Safety pharmacology programme

Safety pharmacology data from the literature are generally old, and the experimental designs are not in accordance with the current guidelines on safety pharmacology which can however be accepted since the clinical experience with brimonidine tartrate is extensive.

Table 2. Effects on Central Nervous System

Species	Type of study	Route	Results	references
Rabbit	Sedation	Ocular	one drop (35 µL) of brimonidine ophthalmic solutions at 0.5 and 0.8% in one eye induce sedation	Angelov et al. 1996 p21
Monkey	Sedation	Oral (gavage)	0.5 and 2.5 mg/kg/day treatments induce sedation	Angelov et al. 1996 p21

Table 3. Effects on cardiovascular system

Species	Type of study	Route	Results	references
Rat	Measurement of BP & HR in conscious and pithed rats	IV	Increased BP & HR in conscious rats; in pithed rats increased MAP to a greater extend, no effect on HR	Bayorh et al. 1997
Dog	Measurement of BP, HR, ECG	PO	Significant reduction of BP and HR; ECG: increased PR interval	Suwanwipat et al. 2007
Monkey	Measurement of BP, HR, ECG	PO	Slight hypotension, sinus bradycardia and occasionally sinus arrhythmia	Angelov et al. 1996 p21
Monkey	Measurement of BP	Ocular	Reduction 4 hours following administration	Serle et al. 1991
Monkey	Measurement of BP, HR	Ocular	Reduction within 25µg to 250µg/animal	Gabelt et al. 1994

Abbreviations: ECG: electrocardiogram, MAP: Mean arterial pressure, HR: Heart rate, BP: blood pressure

Effects were characterized on the following organ systems; CNS, CV, respiratory, renal and pancreatic functions, and is overall associated with the primary pharmacology activity of brimonidine tartrate being a potent α2A-adrenoceptor agonist (exaggerated pharmacodynamic effects). Furthermore, the proposed indication with low systemic absorption, which is similar to that observed with ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution, and no safety concerns due to systemic effects noted in clinical trials, overrules the lack of a "modern" set of safety pharmacology studier. No exposure data are available in these animal species or routes of administration therefore no extrapolation can be made to human exposures. This is acceptable since exposure data from repeat dose toxicity studies are available.

Pharmacodynamic drug interactions

The justification by the Applicant not to perform new pharmacodynamic interaction studies is accepted as brimonidine tartrate is a well-known active substance and has been extensively used in humans for more than 15 years. Possible pharmacodynamics drug interactions in humans are already well characterized and identified. It has been demonstrated in a human 4-week pharmacokinetic bridging study (Clinical study RD.06.SPR.18143) that brimonidine tartrate 5 mg/g Gel cutaneous treatments of rosacea patients with facial erythema resulted in systemic exposure which is in the same range as the systemic exposure after ophthalmic instillation of the eye drops when applied three times per day as recommended in the prescribing information for the ophthalmic product.

2.3.3. Pharmacokinetics

No pharmacokinetic studies have been performed in animals with the finished product brimonidine tartrate 0.5% Gel. A summary of published data on pharmacokinetic properties was provided by the Applicant. To bridge the dermal application of brimonidine tartrate gel in the proposed therapeutic indication, toxicokinetic data obtained in repeat-dose dermal toxicity studies conducted with the finished product are presented below.

No tissue distribution study in animals or plasma protein binding study is available which is accepted considering the proposed topical use of the product.

The Applicant has presented data on *in vitro* and *in vivo* metabolism in the rat. Metabolism is extensive both *in vitro* and *in vivo* in liver in man, monkey, rat and dog (Acheampong 1996). This information is considered of limited value for the dermal route of administration since the systemic absorption of

brimonidine is limited and the efficacy is mediated in the vessels of the skin. *In vitro*, at least 8 major drug metabolites (I, IIc, IIIa, IIIb, IV, V, VI, and VII) were detected in all species. The liver metabolite pattern for rats, rabbits and monkeys was qualitatively quite similar to that for humans. Conversely, the prominent metabolites in the dog were VI and VII. Metabolite IIc was only detected in rats and dogs, while IIIb was present only in monkeys and humans. After a 4-hour incubation of brimonidine tartrate, the highest metabolite fraction was noted in humans (88%), followed by monkeys (70%), rats (65%) and dogs (20%).

Data indicated an extensive hepatic metabolism of brimonidine tartrate and provided evidence for an involvement of aldehyde oxidase (Acheampong et al 1996).

The principal metabolism pathways of brimonidine tartrate in rats, rabbits, monkeys and humans are α(N)-oxidation to the 2,3-dioxobrimonidine, and oxidative cleavage of the imidazoline ring to 5-bromo-6-guanidinoquinoxaline (Acheampong et al 1996). In contrary, the dog major metabolites were 4',5'-dehydrobrimonidine (IIc) and 5-bromo-6-guanidinoquinoxaline (VI). The species differences in hepatic brimonidine tartrate metabolism were likely related to the low activity of dog-liver aldehyde oxidase.

There is only limited information available on excretion of radiolabelled brimonidine after ocular administration, indicating both rapid absorption and elimination. No information is available regarding excretion following dermal application. This is considered acceptable by the CHMP.

2.3.4. Toxicology

Original and published data provided by the Applicant

Original studies

The original nonclinical studies performed by the Applicant with brimonidine tartrate gel formulation to support the present MAH are listed in the table 4 below.

Table 4. The original nonclinical studies performed by the Applicant with brimonidine tartrate gel formulation

Study Type, and duration	Pivotal/ non-pivotal status	Formulation (% brimonidine tartrate)	Route of Administration	Species	Study No.
Repeat-Dose toxicity					
13 week photo(co)-carcinogenicity range finding	non-pivotal	Gel: 0.18%, 1%, 2%	Dermal	Albino hairless mouse	RDS.03.SRE.12627
13 weeks tolerance	non-pivotal	Gel: 0.2%, 1%, 2% Cream: 0.2%, 1%, 2%	Dermal	Wistar rat	MB 07-15233.03
13 week carcinogenicity range finding	pivotal	Gel: 0.18%, 1%, 2%	Dermal	Wistar Han rat	RDS.03.SRE.12648
13 weeks tolerance	non-pivotal	Gel: 0.2%, 1%, 2% Cream: 0.2%, 1%, 2%	Dermal	Göttingen minipig	IYA00006
39 weeks	pivotal	Gel: 0.06%, 0.18%, 1%	Dermal	Göttingen minipig	RDS.03.SRE.12694
57 weeks	pivotal	Gel: 0.18%, 1%, 2%	Dermal	Wistar Han rat	RDS.03.SRE.12626
Carcinogenicity					
Carcinogenicity study	pivotal	Gel: 0.03%, 0.06%, 0.18%, 0.36%, 0.72%, 1%, 2%	Dermal	Wistar Han rat	RDS.03.SRE.12667
Photo(co)carcinogenicity					
Photo(co)-carcinogenicity	pivotal	Gel: 0.18%, 1%, 2%	Dermal	Hairless mouse	RDS.03.SRE.12629
Local Tolerance					
Skin irritation and phototoxicity	pivotal	Gel: 0.2%, 1%, 2%	Dermal	Hairless mouse	IYA00013
Eye irritation	pivotal	Gel: 0.5%	Ocular	New Zealand white rabbit	RDS.03.SRE.12734
Skin sensitization	pivotal	Gel: 2%	Dermal	Hartley guinea pig	MB 07-15969.06

Published paper

The toxicological aspects documented by the Applicant based on published data are

- Genotoxicity: "A review of the genotoxicity of marketed pharmaceuticals (Snyder and Green 2001, Mutation Research 488: 151-169)
- Carcinogenicity after systemic administration: "Preclinical safety profile of brimonidine" (Angelov et al 1996, European Journal of Ophthalmology,6:21-26)
- Fertility and early development and Pre- and post-natal toxicity "Reproductive and developmental safety studies with brimonidine, Alphagan. (Angelov et al 1996, abstract of a non identified Congress)
- Teratogenicity (Razeghinejad et al.2011 "Pregnancy and Glaucoma "Survey of ophthalmology, 56:324-335).

Relevance of animal versus human skin – importance of vehicle

Concerning local skin reactions and the value of animal species as predictors for these types of effects, it is well-known that mouse/rat/rabbit skin is more sensitive to local adverse events than the skin of mini-pigs and humans. Moreover, percutaneous absorption is several times higher in rodents than in mini-pigs and humans which leave the mini-pig as the animal species with highest relevance to humans.

The vehicle in dermal products can have large influence on development of adverse local reactions. In many cases, it is not the active compound that causes adverse local reactions but the vehicle, also noted in the present set of dermal repeat-dose studies. The effect of a gel versus a cream formulation containing brimonidine tartrate were investigated in the rat and the minipig, and the cream formulation showed

slightly worse histopathological changes than the gel formulation. The gel formulation is proposed for marketing, and the pivotal non-clinical studies have been performed with this formulation, which therefore has been adequately toxicologically tested.

Single dose toxicity

No single-dose dermal toxicity studies are available and also no data on single dose toxicity after other modes of administration. This is considered acceptable considering that brimonidine tartrate is a well-known active substance with more than 15 years clinical experience. Toxicity following repeated dermal dosing has been sufficiently addressed.

Repeat dose toxicity

The Applicant has performed repeat-dose dermal studies in hairless mice, rats and minipigs. Oral toxicity studies selected from the literature provides supplementary data at systemic exposure to brimonidine tartrate. Since brimonidine tartrate is a well-known active substance, focus will be on the proposed dermal route of administration.

Only dedicated validated analytical methods used to analyse brimonidine plasma concentrations in GLP dermal toxicity studies in rats and minipigs performed by the Applicant to provide toxicology information are summarized in this section, since the old additional bioanalytical methods available in the literature are considered scarcely suitable and relevant for the present Assessment.

On overview of the developed methods is given in the table 5 below.

Table 5 Overview of the analytical methods applied in the analysis of toxicokinetic samples.

Study number/ GLP status	**Analyte(s)**	**Species/ Matrix**	**Method**	**Range (ng/mL)**	**Enzym. Hydrol**	**Lower LoQ (ng/mL)**
Parent drug						
RDS.03.VRE.34198	Brimonidine	Rat/plasma	LC-MS/MS	0.025-25	NO	0.025
RDS.03.VRE.34213	Brimonidine	Minipig/plasma	HPLC-ESI MS/MS	0.025-2.0	NO	0.025

Oral route of administration

Toxicity of brimonidine tartrate was evaluated following repeated oral administration in mice (21 months), rats (24 months) and monkeys (1 year) (Angelov et al 1996 p21).

In chronic/carcinogenicity dietary toxicity studies in both rats (at 0.25 and 1 mg/kg/day) and mice (at 2.5 mg/kg/day), hypertrophy of the tunica muscularis and epithelial hyperplasia of the mucosa of the small and large intestine were by the authors evaluated as exaggerated pharmacological effects which generally reverted after treatment removal (Angelov et al 1996 p21).

In monkeys (at 2.5 mg/kg/day), sedation, bradycardia, sinus arrhythmias, and hypotensive effects were noted, which by the authors were considered as exaggerated pharmacological effects and which were reversed during the recovery period (Angelov et al 1996 p21).

Exposure margins based on Cmax at NOAEL in oral repeat-dose toxicity studies is 19 in mice, 22 in rats and 146 in monkeys. The margins are considered sufficiently large. Furthermore, brimonidine tartrate is a marketed compound with systemic exposure at approved ophthalmic use at similar levels than those obtained at the proposed dermal use in the treatment of rosacea.

Dermal route of administration

Mice (13 weeks), rats (13 and 57 weeks) and mini-pigs (13 and 39 weeks) have been treated topically with brimonidine tartrate. A summary of performed studies can be seen below.

Mice (13 weeks), rats (13 and 57 weeks) and mini-pigs (13 and 39 weeks) have been treated topically with brimonidine tartrate. Concerning local reactions and the value of animal species as predictors for these types of effects, mouse/rat/rabbit skin is more sensitive than the skin of minipig and humans. The cream formulation showed slightly worse microscopic properties than the gel formulation that is proposed for marketing. The non-clinical studies with the longest duration were performed with the final gel formulation proposed for marketing, which therefore has been adequately toxicologically qualified.

The mouse 13 week study was performed as a dose-range finding study to the photo(co)carcinogenicity study and demonstrated various clinical signs and also a few deaths, where the cause of death could not be determined. No significant skin reaction was noted either with or without UVR exposure. In rats, adverse effects on body weight gain and food consumption were noted in both the 13 and 57 weeks studies. Female animals dosed with high dose (2% gel) in the 57 week study showed treatment related mortality. The cause of death was only determined in one animal. However, the clinical signs are considered severe enough to cause death of the animals. No signs of local adverse reactions or histopathological signs of toxicity were noted in either rat study. The exposure margin (calculated on AUC values) at NOAEL in male animals is approximately 100 while it is 2000 in female animals.

Due to skin similarities the studies in the minipig (13 weeks, 39 weeks) are considered the most important for non-clinical evaluation of safety of brimonidine tartrate. In the 13 week study, a comparison between gel and cream formulations was performed, and similarly as in the rat, the cream induced slightly worse microscopic findings. The microscopic findings were noted in all dosage groups, including vehicle, and may thus be related to the vehicle and not induced by brimonidine tartrate.

In the 39 week pivotal minipig study, the animals were treated daily with 0.06, 0.18 and 1% brimonidine tartrate in a gel formulation. No treatment-related systemic clinical signs were observed. Furthermore, no ocular findings were seen and cardiovascular parameters were not affected. There were no differences in body weight, body weight gain or food consumption. There were no relevant treatment-related effects on haematology, coagulation, serum clinical chemistry, urinary parameters or organ weights and no treatment-related macroscopic or microscopic pathological findings. To conclude, brimonidine tartrate was well tolerated following topical administration in the minipig as might be expected considered the higher susceptibility of mouse and rat skin. Toxicokinetic data obtained in minipig (see above) demonstrated a dose related systemic exposure to brimonidine tartrate in both male and female animals with no sex related differences. The exposure margin (calculated on AUC values) at NOAEL in male animals is 12 while it is 14 in female animals.

Genotoxicity

Literature data has demonstrated that brimonidine tartrate has no genotoxic potential. The absence of new genotoxicity data is considered acceptable since brimonidine tartrate is a well-known active substance with more than 15 years clinical experience in treatment of ocular hypertension and open-angle glaucoma.

Carcinogenicity study

No carcinogenic potential of brimonidine tartrate has been demonstrated in published dietary studies in mice and rats. No toxicokinetic data are available from these studies. However, extrapolation of plasma drug concentrations at the highest dose level in mice resulted in large exposure margins (4.53 ng/mL in mice /46 pg/ml in humans) in both sexes. In rats, a similar large exposure margin was obtained (6.90 ng/mL in rats /46 pg/ml in humans).

In support of the application, a dermal photo (co)carcinogenicity study (RDS.03.SRE.12629) in mice and a 2-year dermal carcinogenicity study (RDS.03.SRE.12667) in rats supported by toxicokinetic data have been performed. Hairless mice were treated dermally with brimonidine tartrate gel 0.18, 1.0, 2.0% (100 µL/mouse) 5 times/week for 40 weeks. In addition, the animals were exposed to ultraviolet radiation exposure, 600 RBU/week in all groups except one control group which received 1200 RBS/week. The high UVR calibration group was terminated earlier in week 41 due to an UVR dose-dependent tumour response. Brimonidine tartrate did not enhance photocarcinogenesis in the hairless mouse. In contrast, a brimonidine tartrate induced and dose-dependent delay in UVR-induced skin tumour development, compared with only UVR exposure, was observed.

In the dermal carcinogenicity study, rats were treated with; 0.03, 0.06, 0.18% male animals and 0.18, 1, 2% in females for 24 months. Dosing of mid and high dose females were reduced to 0.36% and 0.72% after 49 weeks due to decreased survival. Survival rate at the end of the study was acceptable for study interpretation. Before death, behavioural (decreased activity, clonic convulsions, hypersensitivity to touch, vocalization) and gastrointestinal (distended abdomens and low carriage) clinical signs were observed which are assessed as exaggerated pharmacological response to alpha2-receptor stimulation. The most common cause of death was pituitary tumour in all dose groups including control groups which is a common cause of death in aged rats. No treatment-related clinical signs of systemic toxicity were noted. No treatment-related local effects, only slight occurrence of erythema was observe and no treatment-related neoplastic or non-neoplastic findings. Toxicokinetic data demonstrates that the animals were exposed to brimonidine tartrate in a dose-related manner.

To conclude, brimonodine tartrate is not genotoxic and not carcinogenic in a photo (co)carcinogenicity study in hairless mice and in a conventional dermal carcinogenicity studies in rats.

Reproduction Toxicity

The Applicant has not performed any studies to evaluate the reproductive and developmental toxicity of brimonidine tartrate gel. This section is documented by literature data with brimonidine tartrate given orally. No adverse findings on reproductive function have been noted in oral studies with brimonidine tartrate. Since the systemic exposure of brimonidine tartrate is similar following dermal administration compared to the approved ocular route of administration, there are no concerns for human safety. The SmPC section 4.6 is worded in a similar way as for the approved ocular product which is accepted.

No studies in juvenile animals has been performed which is acceptable since rosacea does not occur in children.

Toxicokinetic data

The NOAELs obtained in dermal repeat-dose chronic studies are presented below.

Table 6. NOAELs obtained in dermal repeat-dose chronic studies

Species	Duration	Concentrations, volumes and Dose levels (mg/kg)*	NOAEL mg/kg/day	AUC_{0-24h} (ng.h/mL)	Safety margin (human AUC_{0-24h} =417 pg.h/mL)**
Rat/ Wistar	57 weeks	0.18, 1, 2% Male: 0.6 mL/kg (1.08, 6, 12) Female: 3mL/kg (5.4, 30, 60)	 Male: 1.08 Female: 30	 Male: 43 Female: 964	 Male: 103 Female: 2312
Minipigs/ Göttingen	39 weeks	0.06, 0.18, 1% 2 mL/kg (1.2, 3.6, 20)	Male: 20 Female: 20	Male: 4.8 Female: 6.0	Male: 12 Female: 14

* Expressed as mg/kg brimonidine tartrate
** Systemic exposure data from clinical study RD.06.SRE.18143 (highest mean value obtained after 15 daily cutaneous applications of Brimonidine tartrate 0.5% Gel)

The NOAELs obtained in oral repeat-dose chronic studies are presented below.

Table 7. NOAELs obtained in oral repeat-dose chronic studies

Species/ strain	Duration	Dose levels (mg/kg/day)	NOAEL* (mg/kg/day)	Corresponding mean C_{max} (ng/mL)	Safety margin ** (Human C_{max} =46 pg/mL)
Mice/CD1	21 months	0.1, 0.5, 2.5	0.5	0.860	19
Rat/SD	24 months	0.05, 0.25, 1	0.05	1.02	22
Monkey/cynomolgus	12 months	0.1, 0.5, 2.5	2.5	6.73	146

*: NOAEL not reported in Angelov et al 1996 p21. Applicant's interpretation of the data
** C_{max} from clinical study RD.06.SRE.18143 (highest mean value obtained after 15 daily cutaneous applications of Brimonidine tartrate 0.5% Gel)

Local Tolerance

Three local tolerance studies have been performed investigating primary skin irritation and phototoxicity, eye irritation and skin sensitization. Brimonidine tartrate gel formulation did not cause primary irritation to the skin and was not phototoxic at concentrations up to 2%. It was not irritating to the eye at 0.5% and did not produce skin sensitization at 2%.

Other toxicity studies

Impurities

The impurity profile of Mirvaso has been qualified. The pivotal dermal chronic toxicity studies (rat/minipig) and the rat dermal carcinogenicity study were performed with batches having identical impurity profiles and specifications compared to those used in the clinical pivotal studies representing the drug product proposed for marketing. With regards to impurities, it seems reasonable to conclude that no toxicological concern is raised.

2.3.5. Ecotoxicity/environmental risk assessment

The Applicant conducted a valid Early Life Stage (ELS) Toxicity test with *Danio rerio*, in compliance to OECD 210 guideline; the study report (Study Report N0.714A-101) and the updated Environmental Risk

Assessment for the active substance Brimonidine tartrate, were submitted. The test was conducted with test concentrations of 0.1, 0.32, 1.0, 3.2, and 10 mg brimonidine tartrate/L. A NOEC of 0.32 mg/L was obtained, based on survival. Growth, measured as total length, wet and dry weight, was the most sensitive biological endpoint measured in this study.

The LOEC for growth was 0.1 mg/L; an EC10 of 0.019 mg/L based on the wet weight, 0.063 mg/L based on the dry weight and 0.11 mg/L based on the length were calculated as recommended in the OECD 210 guideline. The Applicant acknowledges that the calculated values of the EC10 based on the weights do not fully comply with specific recommendation of OECD 210, revision July 2013, i.e. the test concentrations should bracket the EC10 so that it comes from interpolation rather than extrapolation; and, as a general guide, EC10 might be not more than about 25% below the lowest tested concentration (0.1 mg/L). The Applicant is recommended to repeat the Early Life Stage (ELS) Toxicity test with *Danio rerio*, and to provide the Agency with the test results at a post-approval stage.

Nevertheless, the Applicant highlighted that a large safety margin is obtained with the current EC10 value of 19 µg/L for the effects of brimonidine tartrate on aquatic environment: the current calculation of PEC/PNEC ratio is based on the PEC surface water of 0.025 µg/L and the PNEC surface water of 1.9 µg/L, determined from the EC10 in *Danio rerio*. The resulting PEC/PNEC ratio is 13.2.10-3. It is unlikely that a refined NOEC value as low as 0.25 µg/L (76 times lower than the current EC10) will be obtained with the new run of experiment, resulting in a PEC/PNEC ratio higher than the threshold value of 1, which would trigger further testing in the aquatic compartment.

The current estimate of PEC/PNEC ratio (0.025/1.9 = 0.013) is below the threshold but CHMP does not know the response in the full range due to the extrapolation and therefore cannot endorse the comment of the Applicant stating that "is unlikely that a refined NOEC value as low as 0.25 µg/L (76 times lower than the current EC10) will be obtained with the new run of experiment".

The CHMP recommends therefore the Applicant to repeat the Early Life Stage (ELS) Toxicity test with *Danio rerio*, and to provide the Agency with the test results in the context of a recommendation.

Table 8. Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Pow ≤ -1.0 at pH 4 log Pow = -0.2 at pH 7 log Pow = 0.6 at pH 9	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.025	µg/L	> 0.01 threshold (Y/N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =610 - 5024 - 1464 - 23771 -1811 mL/g	Mean Koc = 6536 mL/g Median Koc = 1811 mL/g

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Water phase: DT50 = 1.1 and 1.7 day			Low degradation in sediment, 50% of applied radioactivity in the sediment after 97 days
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	72 h-NOEC	1.0	1.0 mg/L	Test species: *Pseudokirchneriella subcapitata*, Strain No. 61.81 SAG
Daphnia sp. Reproduction Test	OECD 211	21 day-NOEC	20	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	32 day-EC10	0.019	mg/L based on mean wet weight	Test species: Zebrafish *Danio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	>100	mg/L	

2.3.6. Discussion on non-clinical aspects

Pharmacology

There is no *in vivo* animal model of rosacea available and therefore primary pharmacodynamics of brimonidine tartrate is not included in this application. This is accepted, since there is extensive clinical experience of brimonidine tartrate at another therapeutic indication (treatment of open angle glaucoma and elevated intraocular pressure). The data submitted for this application fulfil the requirements.

Pharmacokinetics

No pharmacokinetic studies in animals were performed using the finished product brimonidine tartrate 0.5% gel for topical administration. Instead a summary of published data on pharmacokinetic properties was provided by the Applicant. The metabolism data provided was also based on the literature. No animal data on excretion of brimonidine tartrate was provided, which is accepted considering the proposed topical use of the product.

Toxicology

The Applicant has focused on the dermal safety and local tolerance of the product. All other aspects of the nonclinical toxicology are based on published data. Neither dermal toxicity studies nor local tolerance studies showed any adverse effects related to brimonidine tartrate. The CHMP recommends the Applicant who is recommended to repeat the Early Life Stage (ELS) Toxicity test with *Danio rerio*, and to provide the Agency with the test results in the context of a recommendation.

2.3.7. Conclusion on the non-clinical aspects

All toxicity studies have been performed in compliance with GLP. Overall the non-clinical program conducted by the Applicant meets the requirements and the data are acceptable from the pharmacodynamic and pharmacokinetic point of view; brimonidine tartrate is well characterized.

Overall, the majority of the non-clinical issues have been satisfactorily addressed in the SmPC. There is no potential safety issue, the product is deemed to be well tolerated when used in the proposed dosage. The CHMP recommends the Applicant to repeat the Early Life Stage (ELS) Toxicity test with *Danio rerio*, and to provide the test results.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 9 overview of clinical studies

Study Number	Study Design	Number of subjects Gender Mean Age	Doses and Treatment Duration
Healthy Subjects			
COL-118-BAPK-101	Open-label, randomized, 2-way crossover PK study LOQ=25 pg/mL	16 subjects 12M, 4F 35 years	Treatment A: COL-118 0.2% gel Treatment B: Brimonidine tartrate 0.2% ophthalmic solution A single topical 1 g application of gel and 1 drop of ophthalmic solution instilled in each eye, with a washout of at least 1 day between the 1-day treatment periods.
RD.06.SRE.18139	Positive- and placebo-controlled, double-blind, single-dose, 3-way crossover thorough QTc study LOQ=10 pg/mL (brimonidine tartrate) and 40.00 ng/mL (moxifloxacin)	60 subjects 27M, 33F 32.9 years	Treatment A: Brimonidine tartrate 0.2% ophthalmic solution and over-encapsulated placebo capsule Treatment B: Advanced Eye Relief™ (placebo ophthalmic solution) and over-encapsulated placebo capsule Treatment C: : Advanced Eye Relief (placebo ophthalmic solution) and over-encapsulated moxifloxacin 400 mg capsule Two drops (dosing interval: 3 minutes) of ophthalmic solution were instilled in each eye and 1 capsule was orally administered during each 1-day treatment period, with a washout of 6 days between treatment periods.
Subjects with Rosacea			
RD.06.SRE.18126	Double-blind, randomized, vehicle-controlled, 2-way crossover PK study LOQ=25 pg/mL	20 female subjects 45.1 years	Treatment A: COL-118 0.18% gel and Advanced Eye Relief (placebo ophthalmic solution). Treatment B: Brimonidine tartrate 0.2% ophthalmic solution and Vehicle Gel Two topical 1 g applications of gel on the face and 1 drop of ophthalmic solution instilled in each eye during each 1-day treatment period. The second application of gel was 4 hours after the first dose.
RD.06.SRE.18143	Intra-individual, double-blind, randomized, multicenter, comparative, maximal use PK study LOQ=10 pg/mL	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

Brimonidine tartrate 0.2% ophthalmic solution and Advanced Eye Relief were manufactured by Bausch & Lomb.

BID=Twice daily

Table 10 Summary of efficacy and safety studies

Study Number	Study Objectives	Number of Subjects	Primary Efficacy Endpoint
Phase 2 Studies			
COL-118-ROSE-201	Evaluation of dose-response relationship and pharmacodynamic profile	110 ITT	Combined magnitude of the clinical effect measured by the CEA score and the duration of the effect over time using a composite CEA area under the curve (AUC) score
RD.06.SRE.18144	Evaluation of dose-response relationship and safety	122 ITT 117 PP 122 SAF	Not applicable, as efficacy was not a study objective
RD.06.SRE.18161	Assessment of efficacy and safety	269 ITT 237 PP 269 SAF	Composite Success at Hours 3, 6, 9, 12 on Day 29, then on Day 15 and lastly on Day 1, with Composite Success defined as 2-grade improvement from Baseline (T0 at Day 1) on both CEA and PSA-5 at each time point
Phase 3 Pivotal Studies			
RD.06.SRE.18140	Assessment of efficacy and safety	260 ITT 231 PP 260 SAF	2-grade Composite Success at Hours 3, 6, 9, and 12 on Day 29, then on Day 15, and lastly on Day 1, with 2-grade Composite Success defined as a 2-grade improvement on both CEA and PSA at each time point
RD.06.SRE.18141	Assessment of efficacy and safety	293 ITT 260 MITT 239 PP 293 SAF	2-grade Composite Success at Hours 3, 6, 9, and 12 on Day 29, then on Day 15, and lastly on Day 1, with 2-grade Composite Success defined as a 2-grade improvement on both CEA and PSA at each time point
Phase 3 Long-term Efficacy Study			
RD.06.SRE.18142	Assessment of long-term safety and efficacy	449 SAF	Not applicable

Modified Intent-to-Treat (MITT): ITT Population excluding all 33 subjects from a single investigational center (8283) due to site-specific data validity concerns.

ITT=Intent-to-treat Population, MITT=Modified Intent-to-treat Population, PP=Per-protocol Population; SAF=Safety Population

Table 11 Summary safety studies (local tolerance)

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
COL-118-Phototoxicity-104	Assessment of phototoxic potential	Randomized, intra-individual comparison, evaluator-blind, single-center, vehicle-control and no-treatment control	Test Products Brimonidine Tartrate 0.2% Gel Vehicle Gel Dosage Regimen 40 mg of each product applied to the back under occlusion for 24 hours, and one untreated area occluded for 24 hours Route Topical	30	Healthy subjects	1 day	Complete; Full (Legacy)
RD.06.SRE.18123	Assessment of sensitization potential	Randomized, intra-individual comparison, evaluator-blind, single-center, vehicle-control and negative-control	Test Products Brimonidine Tartrate 0.07% Gel Brimonidine Tartrate 0.18% Gel Brimonidine Tartrate 0.5% Gel Vehicle Gel White petrolatum USP Dosage Regimen Induction Phase (Days 1-21): 0.1 mL of each product applied to the back under occlusion; 3 times per week for 21 days Rest Phase (Days 22-35): No product application Challenge Phase(Days 36-40): Single dose of 0.1 mL of each product applied to the back under occlusion Re-challenge Phase (at least 2 weeks after Day 40, if applicable): Single dose of 0.1 mL of each product (and, if appropriate, 0.1 mL of individual ingredients with known sensitization potential) applied to the back under occlusion Route Topical	247	Healthy subjects	Refer to Dosage Regimen section	Complete; Full

RD.06.SRE.18124	Assessment of photosensitization/ photoallergic potential	Randomized, intra-individual comparison, evaluator-blind, single-center; vehicle-control, negative-control, and non-irradiated control	Test Products Brimonidine Tartrate 0.07% Gel Brimonidine Tartrate 0.18% Gel Brimonidine Tartrate 0.5% Gel Vehicle Gel White petrolatum USP Dosage Regimen Induction Phase (Days 1-21): 0.2 mL of each product applied to the back under occlusion twice weekly for 3 weeks Rest Phase (Days 22-35): No product application Challenge Phase (Days 36-40): Single dose of 0.2 mL of each product applied to the back under occlusion to 2 naïve skin sites Re-challenge Phase (at least 2 weeks after Day 40, if applicable): Single dose of 0.2 mL of each product (and, if appropriate, 0.2 mL of individual ingredients with known sensitization potential) applied to the back under occlusion Route Topical	57	Healthy subjects	Refer to Dosage Regimen section	Complete; Full
RD.06.SRE.18125	Assessment of cumulative irritancy potential	Randomized, intra-individual comparison, evaluator-blind, single-center; vehicle-control and negative-control	Test Products Brimonidine Tartrate 0.07% Gel Brimonidine Tartrate 0.18% Gel Brimonidine Tartrate 0.5% Gel Vehicle Gel White petrolatum USP Dosage Regimen 0.1 mL of each product applied to the back under occlusion once daily for 5 days for 3 consecutive weeks Route Topical	38	Healthy Subjects	Refer to Dosage Regimen section	Complete; Full
RD.06.SRE.18189	Assessment of phototoxic (photoirritation) potential	Randomized, intra-individual comparison, evaluator-blind, single-center; vehicle-control and non-irradiated control	Test Products Brimonidine Tartrate 0.07% Gel Brimonidine Tartrate 0.18% Gel Brimonidine Tartrate 0.5% Gel Vehicle Gel Dosage Regimen Single application of 200 µL of each product applied to the back under occlusion Route Topical	35	Healthy subjects	1 day	Complete; Full

Table 12 Summary safety studies (QT study)

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
RD.06.SRE.18139	Assessment of effect on ventricular repolarization, PD relationship between QT/QTc interval duration and plasma concentration, and safety	Randomized, double-blind, 3-way crossover, single-center; positive-control and placebo-control	Test Products Treatment A: brimonidine tartrate 0.2% ophthalmic solution and over-encapsulated placebo capsule Treatment B: Placebo ophthalmic solution (Advanced Eye Relief, Bausch and Lomb) and over-encapsulated placebo capsule Treatment C: Placebo ophthalmic solution (Advanced Eye Relief, Bausch and Lomb) and over-encapsulated moxifloxacin 400 mg capsule Dosage Regimen Dosing Periods 1, 2, and 3: Single dose of each product consisting of 2 drops of ophthalmic solution instilled in each eye (3-minute dosing interval included occlusion of both nasolacrimal ducts for 60 seconds) and oral administration of capsule with 240 mL of room temperature water Washout: 6 days between periods Route Ophthalmic (solution) Oral (capsule)	60	Healthy subjects	Refer to Dosage Regimen section	Complete; Full

2.4.2. Pharmacokinetics

Three clinical pharmacokinetic studies have been conducted with the aim to explore the systemic exposure following topical administration of brimonidine tartrate gel compared to ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution (Table 1). The comparison enables to bridge with non-clinical systemic safety data for brimonidine tartrate by referring to the safety data for the 0.2% ophthalmic solution.

Among the three relative bioavailability studies, only Study RD.06.SRE.18143 is regarded as definitive because the study was conducted in subjects with rosacea, included the intended to-be-marketed formulation, used the more sensitive analytical method (LOQ=10 pg/ml), and evaluated repeated dosing of Brimonidine tartrate gel (29 days).

In addition, plasma exposure following supra-therapeutic dosing of brimonidine tartrate 0.2% ophthalmic solution was evaluated in a QTc study.

The substance codes COL-118 or CD07805/47 have been used for brimonidine tartrate gel in some of the clinical pharmacology studies.

Analytical methods

The bioanalytical method for the determination of brimonidine in human plasma were adequately validated through a HPLC method with tandem mass spectrometry detection (MS/MS).

The method used in studies COL-118-BAPK-101 and RD.06.SRE.18126 was developed at Covance and was successfully validated over a concentration range of 0.025 to 5.00 ng/ml. Sodium heparin, K_2EDTA or K_3EDTA was used as anticoagulant (cross-validated).

In order to decrease the limit of quantitation, a new HPLC method with MS/MS detection was developed at York Bioanalytical Solutions and used in the clinical study RD.06.SRE.18139 for the determination of brimonidine in human plasma. The method was successfully validated over a concentration range of 0.01 to 25.00 ng/ml.

The lower LOQ was also applied in the bioanalytical method used in study RD.06.SRE.18143. The method was developed and used at Galderma R&D and was successfully validated over a concentration range of 0.010 to 5.00 ng/ml. Brimonidine and the internal standard, brimonidine-d4, were extracted from human plasma by liquid phase extraction. After evaporation under nitrogen, the residue was reconstituted and analysed. Results were calculated using peak area ratios, and calibration curves were generated using a weighted (1/x2) linear least-squares regression. Satisfactory between- and within-run accuracy and precision was shown for low, medium and high QC sample concentrations.

Satisfactory method performance during study sample analysis was demonstrated, including acceptable overall (mean) accuracy and precision of the QC samples of all accepted runs. Appropriate batch acceptance criteria were used.

Pharmacokinetic data analysis

Standard methods were used in the non-compartmental analysis.

Pharmacokinetic variables were calculated using conventional non-compartmental methods.

Relative bioavailability was calculated by the following parameters for each subject:
AUC ratio: Ratio of AUC_{0-24h} of topical gel to ophthalmic solution corrected by the dose ratio.
C_{max} ratio: Ratio of C_{max} of topical gel to ophthalmic solution corrected by the dose ratio.

Daily applied doses:
-The daily applied dose for the brimonidine ophthalmic solution was determined in a mock dose experiment and the results were: Assuming that the weight of 1 eye drop was 30.7 mg, the daily applied dose of brimonidine tartrate was 0.37 mg (0.061 mg of brimonidine tartrate per drop of ophthalmic solution x 3 doses per day x 2 eyes).
-Taking into account that 1 g of gel was applied, the daily topical applied doses of brimonidine tartrate in the treatment groups were 1.4 mg (0.07% BID), 1.8 mg (0.18% QD), 3.6 mg (0.18% BID) and 5 mg (0.5% QD).

Plasma levels that were below LOQ were replaced by LOQ (10 pg/ml) for mean C_{max} calculation and if AUC_{0-24h} was not reportable and the corresponding C_{max} was <10 pg/ml, the AUC_{0-24h} were replaced by 10 pg·h/ml for statistical analysis.

Statistical analysis

Pharmacokinetic parameters were summarised using descriptive statistics.

The PK parameters from topical treatment (AUC_{0-24h} and C_{max}) were examined for treatment effect and time effect by analysis of covariance (ANCOVA) using PROC MIXED procedure in SAS including the corresponding PK value from the ophthalmic solution as a covariate, and subject, time, treatment and time*treatment as factors in the model. The AUC_{0-24h} and C_{max} data were transformed into natural logarithms (ln) prior to analysis.

Absorption

Bioavailability

No studies were performed to evaluate the absolute bioavailability of brimonidine tartrate 0.5% gel. The relative bioavailability was investigated in three studies comparing topical application of brimonidine tartrate gel with ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution.

Plasma concentrations of brimonidine following topical application of the gel could not be detected in studies COL-118-BAPK-101 and RD.06.SRE.18126 since all samples was below the lower limit of quantitation (LOQ) of the bioanalytical method. In study RD.06.SRE.18143, the LOQ was decreased to 10 pg/ml and the plasma exposure was evaluable.

The plasma exposure was also evaluated in a QTc-study (Study RD.06.SRE.18139) following ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution.

Study COL-118-BAPK-101 was a single-dose relative bioavailability study comparing topical application of brimonidine tartrate 0.2% gel with ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution in healthy subjects. This was an open-label, randomised, 2-way, crossover study conducted in 16 healthy subjects. The study consisted of two treatment periods, with a wash-out of at least 1 day between periods. The brimonidine tartrate 0.2% gel was applied as 1 g applied to the entire face and the brimonidine tartrate 0.2% ophthalmic solution was administered as 1 drop in each eye. Blood samples were collected pre-dose and up to 8 hours after administration.

Results: Following treatment with brimonidine tartrate 0.2% gel, all plasma concentrations of brimonidine were below the LOQ of 25 pg/ml and consequently no pharmacokinetic parameters could be calculated and the relative bioavailability could not be evaluated. However the plasma concentrations following treatment with brimonidine tartrate 0.2% ophthalmic solution could be detected in 14 of the 16 subjects and the pharmacokinetic evaluation resulted in the following plasma exposure: mean C_{max} was 51±16 pg/ml (range: <25-76 pg/ml), AUC_{0-t} was 152±75 pg*h/ml (range: <25-313 pg*h/ml) and median t_{max} was 2 hours.

Study RD.06.SRE.18126 was a single-day relative bioavailability study comparing topical application of brimonidine tartrate 0.18% gel with ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution in subjects with rosacea. This was a double-blind, randomised, vehicle-controlled, 2-way, crossover study conducted in 20 subjects with moderate to severe rosacea. The study consisted of two treatment periods, with a wash-out of at least 1 day between periods. The brimonidine tartrate 0.18% gel was applied as two doses (1 g per application) with a 4-hour interval between doses and the brimonidine tartrate 0.2% ophthalmic solution was administered once as 1 drop in each eye. Blood samples were collected pre-dose and at 1, 2, 3, 4 (prior to second dose of brimonidine tartrate gel), 5, 6, 7 and 8 hours after administration.

Results: Following treatment with brimonidine tartrate 0.18% gel, no pharmacokinetic parameters could be calculated since all plasma concentrations of brimonidine were below the LOQ of 25 pg/ml except one single value of 60 pg/ml detected 1 hour after the second application. The value was inconsistent with the flat pharmacokinetic profile expected after topical application and was considered as an outlier value.

Following treatment with brimonidine tartrate 0.2% ophthalmic solution plasma concentrations could be detected in 11 of the 18 subjects who received the ophthalmic solution. Mean C_{max} and AUC was not calculated but the C_{max} ranged from <25-100 pg/ml, the AUC_{0-t} from <25-471 pg*h/ml and t_{max} ranged from 0.9-4.1 hours.

The relative bioavailability was calculated using the LOQ (25 pg/ml) as C_{max} for brimonidine tartrate 0.18% gel and the highest C_{max} (100 pg/ml) obtained with the brimonidine tartrate 0.2% ophthalmic

solution. Based on this calculation, the relative bioavailability comparing topical route to the ophthalmic route was less than 3%.

In both Studies COL-118-BAPK-101and RD.06.SRE.18126 plasma concentrations of brimonidine following topical application of the gel could not be detected since all samples was below the lower limit of quantitation (LOQ) of the bioanalytical method and consequently the relative bioavailability could not be calculated. The plasma concentrations of brimonidine following ophthalmic administration of the 0.2% solution (single dose, one drop in each eye) could be detected in some of the subjects and resulted in a C_{max} that ranged from <25-100 pg/ml and AUC_{0-t} from <25-471 pg*h/ml. Therefore the results from the two studies are considered as non-conclusive and are not discussed further.

Study RD.06.SRE.18143 was a phase I, multi-centre, randomised, evaluator-blinded, intra-individual comparative pharmacokinetic study of brimonidine tartrate ophthalmic solution 0.2% and brimonidine tartrate topical gel (CD07805/47) (0.07%, 0.18% and 0.50%) applied under maximal use conditions in subjects with moderate to severe facial erythema associated with rosacea. On day 1, all subjects received 3 doses of brimonidine tartrate 0.2% ophthalmic solution (1 drop in each eye every 8 hours over a 24-hour period). After a 2-day washout period, subjects were distributed among 4 treatment groups (randomised on day 1) to receive brimonidine tartrate 0.07% gel BID, 0.18% gel QD, 0.18% gel BID or 0.5% gel QD during days 4 to 32. To ensure maximal use conditions of brimonidine tartrate gel, 1 g of gel QD or BID was applied to the entire face (3% of body surface area) for 4 weeks (total daily dose of gel: 1 g or 2 g). Subjects in the BID dosing groups received the second dose 6 hours after the first application. The blood sampling schedule is described in table 13.

Table 13. Pharmacokinetic blood sampling schedule in Study RD.06.SRE.18143.

PK Sampling Day	Day 1	Day 2	Day 4/Baseline	Day 5	Day 10	Day 18	Day 19	Day 24	Day 32/ET	Day 33	Day 34	Day 35
Treatment	Ophthalmic Solution	-	CD07805/47 Gel							-	-	-
Time Points	40 minutes, 1, 2, 3, 4, 8, 10, 11, 14, and 16 and 18 hours after the initial dose	24 hours after the initial dose on Day 1	Predose, 2, 3, 5, 6, 8, 9, 10, 11, 12, and 16 hours after the initial dose	Predose	Predose	Predose, 2, 3, 5, 6, 8, 9, 10, 11, 12, and 16 hours after the initial dose	Predose	Predose	Predose, 2, 3, 5, 6, 8, 9, 10, 11, 12, and 16 hours after the initial dose	24 hours after initial dose on Day 32	48 hours after initial dose on Day 32	72 hours after initial dose on Day 32

ET=Early Termination

Results: Daily topical application for 29 days demonstrated quantifiable plasma concentrations (≥10 pg/ml) in 22%, 48%, 71% and 79% of subjects receiving brimonidine tartrate 0.07% gel BID, 0.18% gel QD, 0.18% gel BID and 0.5% gel QD, respectively. Ophthalmic instillation of brimonidine tartrate 0.2% solution resulted in quantifiable plasma concentrations in all 96 subjects who received all three doses.

Plasma sample concentrations from 5 subjects following topical application were excluded from the pharmacokinetic analysis due to abnormally high plasma concentrations in comparison to the overall concentration data and within-subject individual plasma concentration profiles. These plasma samples were reassayed using back-up aliquots (if available) and all the values were confirmed. The outlier values were excluded since the abnormal plasma concentrations might be due to sample contamination. Three individuals in dose group 0.07% BID (#8319-027, #8319-074, #8319-086) had all plasma concentrations below LOQ except one concentration with values that ranged from 324.61 to 686.11 pg/ml. One individual in dose group 0.5% QD (#8319-031) had one plasma concentration of 6265.92 pg/ml, which is 100-fold higher than C_{max}. In one of the individuals in dose group 0.18% BID, outlier data points were detected at all three days (days 4, 18 and 32) but since one application was missed at day 18 the subject was excluded from further pharmacokinetic analysis.

Mean pharmacokinetic parameters of brimonidine following ocular administration of 0.2% solution and topical administration of 0.5% gel are summarised in Table 3. Following TID dosing of brimonidine

tartrate 0.2% ophthalmic solution the time-concentration profiles were characterized by three distinct peaks and the observed mean C_{max} (±SD) was 54±28 pg/ml, mean AUC_{0-24h} (±SD) was 568±277 pg·h/ml and t_{max} ranged from 0.65-18.02 hours. Following repeated administration of the 0.5% gel, the highest mean exposures were observed after 15 days of topical application (C_{max} = 46±62 pg/ml, AUC_{0-24h} = 417±264 pg·h/ml). 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. Following the other three topical dose groups (0.07% BID, 0.18% QD, 0.18% BID), the highest plasma exposure were observed at the end of the treatment period (after 29 days of topical application). The observed mean C_{max} (±SD) were 13 ± 9 pg/ml, 17± 20 pg/ml, 18 ± 10 pg/ml, 26 ± 24 pg/ml and mean AUC_{0-24h} were 42 ± 74 pg·h/ml, 93 ± 117 pg·h/ml, 193 ± 155 pg·h/ml, 290 ± 242 pg·h/ml following 29 days of topical application of brimonidine tartrate gel 0.07% BID, 0.18% QD, 0.18% BID or 0.5% QD, respectively.

Table 14. Mean pharmacokinetic parameters (C_{max} and AUC_{0-24h}) of brimonidine following ophthalmic (single-day TID dose) and dermal route (repeated-dose, once daily administration of 0.5% gel)

Day	**Statistics**	**C_{max} [(a)] (pg/ml)**	**AUC_{0-24h} [(a)] (pg*h/ml)**
Brimonidine tartrate 0.2% ophthalmic solution			
Day 1 TID application	N (quantifiable)	96 (96)	96 (96)
	Mean ± SD (CV%)	54 ± 28 (52)	568 ± 277 (49)
	Min, Max	16, 134	124, 1490
Brimonidine tartrate gel 0.5% QD			
Day 4 First application	N (quantifiable)	23 (17)	23 (17)
	Mean ± SD (CV%)	19 ± 12 (60)	262 ± 209 (80)
	Min, Max	10, 52	10, 733
Day 18 15th application	N (quantifiable)	21 (20)	21 (20)
	Mean ± SD (CV%)	46 ± 62 (133)	417 ± 264 (63)
	Min, Max	10, 255	10, 1077
Day 32 29th application	N (quantifiable)	19 (15)	19 (15)
	Mean ± SD (CV%)	26 ± 24 (95)	290 ± 242 (83)
	Min, Max	10, 118	10, 949

(a) Note: BLQ data value replaced by LOQ (10 pg/ml) for mean C_{max} calculation; AUC_{0-24h} were calculated only if there is at least one quantifiable time point. However, for statistical analysis not reportable AUC_{0-24h} were replaced by the lowest AUC_{0-24h} calculated in this study (i.e. 10 pg*h/ml).

The study design allowed for intra-subject comparisons of the systemic exposure (expressed as C_{max} or AUC_{0-24h}) following the topical administered gel formulation compared to the ophthalmic solution and irrespective of the concentration and dose regimen, the topical/ocular ratios calculated over the entire brimonidine tartrate gel treatment period were significantly lower than 1.

The relative bioavailability was calculated comparing plasma exposure (using C_{max} or AUC_{0-24h}) following topical application of brimonidine tartrate gel with ophthalmic instillation and corrected by the daily applied dose. The daily applied dose for brimonidine tartrate ophthalmic solution was determined in a mock dose experiment. The relative bioavailability (±SD) comparing topical route to the ophthalmic route was low ranging from 5% (±3%) to 9% (±6%) using AUC_{0-24h} and from 4% (±2%) to 9% (±12%) using C_{max}.

Intra-subject comparison of topical/ocular exposure ratio were significantly lower than 1 over the entire brimonidine tartrate gel treatment period. However comparison of the mean values results in similar plasma exposures regarding both AUC and Cmax. The highest exposure following topical administration

was observed after 15 days with the C_{max} of 46±62 pg/ml and AUC_{0-24h} of 417±264 pg·h/ml and following ocular administration TID C_{max} was 54±28 pg/ml and AUC_{0-24h} was 568±277 pg·h/ml. Hence, the brimonidine mean systemic exposure (C_{max}) following ocular route is 1.2 times higher than the highest mean C_{max} obtained following topical route. Considering TID ophthalmic dosing instead of the recommended BID dosing, the systemic exposure of brimonidine following ocular administration might be overestimated. As discussed by the applicant considering the short terminal half-life of brimonidine via the ophthalmic route, the C_{max} would be unchanged with a BID or TID dosing regimen, but AUC will be probably be higher after TID dosing.

Relative bioavailability of topical administration compared to ocular administration was calculated by the ratio of Cmax or AUC (taking into account that different doses were administered). Mean Relative bioavailability were similar among the treatment groups and ranged from 5 to 9% when calculated using AUC0-24hr, and from 4 to 9% when calculated using Cmax.

Despite the appropriate written instructions provided to sites in the study protocol, abnormally high plasma concentrations were specifically observed in 1 investigational site. Furthermore, the PK profile observed in Study 18143 demonstrated that there was no drug accumulation over the treatment period that could have accounted for these high values. There is no apparent physiological explanation for the outlier values considering the route of administration because these plasma fluctuations (i.e. 32- to 100-fold higher than the baseline levels in a short time period) were rapid with short spikes.

Therefore, the Applicant's original explanation that these abnormally high values are likely due to *ex vivo* sample contamination is upheld. The explanation regarding the excluded outlier data is acceptable.

Study RD.06.SRE.18139 was a QTc study in healthy subjects with the objective to evaluate the effect on ventricular repolarisation following a single ocular dose of brimonidine tartrate 0.2% ophthalmic solution (supra-therapeutic dose of 2 drops instilled in each eye, with a 3-minute dosing interval). The rationale for using the ophthalmic solution instead of brimonidine tartrate gel was to allow a higher exposure than would have been achievable with topical application of brimonidine tartrate gel. This was a positive- and placebo-controlled, double-blind, randomised, single-dose, 3-way crossover study conducted in 60 healthy subjects. Moxifloxacin was used as an active control. Subjects were randomised to 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, BAC or CBA) with a 6-day washout period between periods. The 3 study treatments are described in the table 15 below.

Table 15. Study treatments. Study RD.06.SRE.18139.

Treatment	Brimonidine Tartrate 0.2% Ophthalmic Solution	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[a]	None	1 over-encapsulated placebo capsule	None
Treatment B (Placebo)	None	2 drops in each eye[a]	1 over-encapsulated placebo capsule	None
Treatment C (Moxifloxacin)	None	2 drops in each eye[a]	None	1 over-encapsulated moxifloxacin 400 mg capsule

[a] The 3-minute ophthalmic dosing interval included occlusion of both nasolacrimal ducts for 60 seconds.

Blood samples for the determination of brimonidine were collected pre-dose and at 42 min, 1.2, 2.2, 3.2, 4.2, 6.2, 8.2, 10.2, 12.2 and 23.2 hours after administration.

The C_{max} achieved following the claimed supra-therapeutic ophthalmic dose was 54±24 pg/ml (range 22-156 pg/ml, CV=44%). The mean C_{max} is similar as in the study RD.06.SRE.18143 where C_{max} following ophthalmic dose TID (1 drop in each eye every 8 hours over a 24-hour period) was 54±28 pg/ml (range 16-134 pg/ml, CV=52%). These values are in the same range as following repeated administration of 0.5% brimonidine tartrate gel where the highest exposure was obtained after 15 days of topical application with a C_{max} value of 46±62 pg/ml (range 10-255 pg/ml, CV=133%). The inter-individual variability following topical administration is higher compared to the supra-therapeutic ophthalmic administration and the individual with the highest plasma exposure following topical administration of the gel (C_{max}=255 pg/ml) is above the highest plasma exposure following the claimed supra-therapeutic ophthalmic dose (C_{max}=156 pg/ml).

In conclusion, the ophthalmic dose of 2 drops in each eye is not considered to generate supra-therapeutic conditions since the mean C_{max} in the QTc study is similar to the C_{max} following therapeutic ocular dosing and in the same range as the highest mean C_{max} following topical administration.

Distribution

The protein binding of brimonidine has not been studied which is accepted considering the proposed topical use of the product

Elimination

Brimonidine is extensively metabolised in the liver. Urinary excretion is the route of elimination of brimonidine and its metabolites. This is reflected in section 5.2 in the SmPC.

Dose proportionality and time dependencies

Dose proportionality

For topical application of brimonidine tartrate gel, systemic exposure increased with applied dose and statistical analysis showed that the increase in exposure (C_{max}) was slightly less than dose proportional. After 29 days of brimonidine tartrate gel application, the C_{max} high dose (0.5% QD, 5 mg applied daily) to low dose (0.07% BID, 1.4 mg applied daily) ratio was 1.5 (90% CI 121 to 197%) in comparison with the 3.6-fold increase in daily dose and C_{max} high dose (0.5% QD, 5 mg applied daily) to mid dose (0.18% QD, 1.8 mg applied daily) ratio was 1.4 (90% CI 107 to 171%) in comparison with the 2.8-fold increase in daily dose. Following topical administration C_{max} tended to increase slightly less than proportional to dose. However, due to limited number of subjects with quantifiable plasma concentrations at the end of the brimonidine tartrate gel treatment period for the two lowest doses (22% for 0.07% BID and 48% for 0.18% QD), the dose proportionality data should be interpreted with caution.

Time dependency

The systemic exposure following one day of topical application was comparable with the exposure following 29 days of topical application in all treatment groups with Day 32/ Day 4 ratios for C_{max} of 110-124%. The Day 32/Day 18 ratio for the 0.5% group was 61% and the Day 18/Day 4 ratio was 180%, which could be attributed to high isolated plasma levels observed at day 18. Day 32/Day 4 ratios for AUC_{0-24h} ranged from 113-145%. Of note, due to the limited number of quantifiable plasma concentrations (especially in the two lowest dose groups) and the imputation method for AUC_{0-24h}, the statistical analysis should be interpreted with caution for AUC_{0-24h}. In conclusion, the statistical analysis suggested no drug accumulation throughout the treatment duration (4 weeks) irrespective of the concentration and dose regimen.

Residual concentrations ($C_{through}$) were analysed on day 4, 5, 10, 18, 19, 24 and 32. At day 4 all $C_{through}$ (pre-dose, before the first topical application of gel) were below the LOQ confirming that the wash-out

period following ocular administration on day 1 was long enough. Mean $C_{through}$ values remain stable during the 4 weeks of topical treatment ranging from <10 to 12.0 pg/ml for the 0.07% BID group, from <10 to 14.7 pg/ml for the 0.18% QD group, from 10.3 to 13.3 for the 0.18% BID group and from 12.0 to 15.1 pg/ml for the 0.5% QD group.

Overall a time stationarity of the PK parameters (C_{max}, $C_{through}$, AUC_{0-24h}) was observed after repeated topical application of brimonidine tartrate gel (0.07% QD, 0.18% QD, 0.18% BID and 0.5% QD) and thus no further accumulation would be expected with a longer treatment period. No evidence of time-dependent pharmacokinetics was seen.

Special populations

No studies have been performed in special populations. This is also reflected in the SmPC section 4.4 whereby it is mentioned that Mirvaso has not been studied in patients with renal or hepatic impairment; caution should be used in treating such patients.

Pharmacokinetic interaction studies

No drug interaction studies have been performed. This is mentioned in the SmPC section 4.5. Concomitant treatment with other rosacea products is addressed in the clinical part of the assessment report.

2.4.3. Pharmacodynamics

Mechanism of action

Brimonidine tartrate is a selective alpha$_2$-adrenergic receptor agonist that is approximately 1000-fold more selective for the alpha$_2$-adrenoreceptor than the alpha$_1$-adrenoreceptor. It is expected to offer a positive effect on reducing cutaneous erythema caused by vasomotor instability through direct cutaneous vasoconstriction.

Natural or synthetic alpha-adrenergic receptor agonists can initiate physiological responses such as vasoconstriction, leading to a reduction in blood flow to associated tissues. There are two different subtypes of alpha-adrenergic receptors: alpha$_1$ and alpha$_2$. In general, alpha$_1$-adrenergic receptors have a wider systemic distribution, and mediate effects on vascular smooth muscle, myocardium, eye, gastrointestinal and genitourinary contractility, whereas alpha$_2$-adrenergic receptors affect gastrointestinal smooth muscle wall relaxation, fat cell lipolysis and, pertinently, peripheral arterial and venous vasoconstriction. The classical model of vascular alpha-adrenergic receptors anatomically divided alpha$_1$ and alpha$_2$ subtypes based on postsynaptic (alpha$_1$) and presynaptic (alpha$_2$) locations. Although this model appears to hold true for larger muscular arteries (internal diameter >1 mm), later research indicates that in subcutaneous tissue, vasoconstriction of small, distal resistance arteries depends mainly on postjunctional (postsynaptic) smooth muscle alpha$_2$-adrenergic receptor stimulation. This observation is based on studies using isolated mouse tail vessels and human subcutaneous resistance arteries in an *in vitro* organ bath. This research also found that the influence of the postsynaptic alpha$_2$ component on vascular contractile state increases with decreasing vessel diameter and that these small vessels exhibited a significant lack of response to alpha$_1$-adrenergic agonists. Additionally, research indicating a selective increase in reactivity of postjunctional vascular smooth muscle alpha$_2$-adrenergic receptors in the skin of patients with scleroderma, a disease in which abnormal vasospasm and ischemic organ damage are important in the pathogenesis, provides further evidence that alpha$_2$-receptors play a major role in the regulation of cutaneous vascular tone.

Primary and Secondary pharmacology

The Applicant has not submitted any new primary pharmacology data, which is acceptable considering that brimonidine tartrate is a well-known compound with 15 years of clinical experience in the treatment of ocular hypertension and open-angle glaucoma. In subcutaneous tissue, vasoconstriction of small, distal resistance arteries depends mainly on postjunctional (postsynaptic) smooth muscle alpha$_2$-adrenergic receptor stimulation. It is, thus, possible that the ability of brimonidine tartrate to reduce erythema is via direct vasoconstriction in the skin.

No specific studies on secondary pharmacological effects have been performed, which is acceptable considering that brimonidine tartrate is a well-known compound with previous clinical experience from ocular use. The systemic exposure to brimonidine tartrate is in a similar range with the gel formulation proposed for marketing compared with the approved ocular solution (Alphagan®). The proposed mechanism of action of brimonidine tartrate in reducing erythema is direct vasoconstriction in the skin by action on smooth muscle alpha$_2$-adrenergic receptor stimulation. The systemic exposure after ocular administration if the authorised Alphagan ® SPC in EU were followed may be lower than the systemic exposure reached if the recommendations of the USA Product Information were followed. USA Product Information recommendations were applied in the studies submitted for the present MA.

The reasons of a lower systemic exposure could be: 1) in EU the authorised posology for Alphagan® is twice daily; 2) the Alphagan® EU SPC recommends that systemic absorption should be minimized by compressing the lachrymal sac at the medial canthus (punctual occlusion) for one minute immediately following the instillation of each drop.

According to the Protocols and Study Reports of the submitted studies the manoeuvre has not been performed. However, it is unlikely that rather small differences in the exposure could have a significant influence on systemic safety.

With the dermal application there is some systemic exposure of brimonidine tartrate and due to the alpha$_2$-adrenergic agonist properties it would be plausible to have adverse effect due to gastrointestinal smooth muscle wall relaxation, fat cell lipolysis and peripheral arterial and venous vasoconstriction

Pharmacodynamic interactions with other topical or systemic products for the treatment of rosacea or with cosmetics have not been formally studied. This is further discussed in the sections below.

2.4.4. Discussion on clinical pharmacology

A plausible mechanism of action for the pharmacological effect of brimonidine tartrate in the treatment of facial erythema due to rosacea has been proposed and no further data are requested.

Pharmacokinetic data showed that the highest mean systemic plasma exposure (in terms of C_{max}) following once daily topical application of 0.5% gel was in the same range as the plasma exposure following ocular single day TID administration of 0.2% solution.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology program was well designed in order to collect exposure data allowing to bridge to the safety database of ophthalmic brimonidine. Systemic exposure after cutaneous gel application, as compared to the exposure after ocular administration, both in healthy subjects and target population. The PK after 1 month of daily administrations was investigated in the target population. All data indicate that with the intended commercial 0.5% formulation, and with the proposed once daily administration, systemic exposure to brimonidine is similar or lower than the TID ocular administration, both in terms of

Cmax and AUC. After one month of daily cutaneous administration there was no systemic accumulation of brimonidine.

The low bioavailability after cutaneous administration is consistent with the physico-chemical properties of the drug, which is freely soluble in water and insoluble in organic solvents. The lack of accumulation is consistent with the reported half-life of brimonidine, which is approximately 3 h after ocular administration (Alphagan® SPC).

The CHMP agrees that the data that have been presented for the evaluation of the medicinal product are sufficient, and have no more outstanding issues.

2.5. Clinical efficacy

2.5.1. Dose response studies

The efficacy claims for Mirvaso are based mainly upon six clinical studies; three phase 2 studies, two pivotal phase 3 studies and one open-label, long-term phase 3 study.

Study COL-118-ROSE-201

This early study evaluated the dose-response relationship and pharmacodynamic profile of three concentrations of Brimonidine tartrate gel (0.02%, 0.07%, and 0.2%) and vehicle gel applied to the face of subjects with rosacea. The treatment duration was 29 days. Subjects with moderate to severe categories of rosacea based on CEA, IGA, and CTG scores were eligible for the study. The intended to-be-marketed concentration of Brimonidine tartrate gel (0.5%) was not evaluated and the study used different endpoints and different versions of efficacy assessments compared to subsequent studies.

The primary endpoint, reduction in erythema using the CEA score, across all time points (0 to 8 hours) and all visits (Day 0, Day 14, and Day 28) showed a dose-response relationship. Both the 0.2% and 0.07% groups had significantly greater changes from Baseline than the vehicle group ($p<0.0001$ and $p<0.05$, respectively).

Although, the results showed a dose-response relationship for the CEA score for the studied concentrations. This study did not include the final, commercial 0.5% concentration of Brimonidine Tartrate Gel and is thus, of limited interest for the assessment.

Study RD.06.SRE.18144

Study RD.06.SRE.18144 was a Phase 2a single-dose, randomized, double-blind, parallel-group, vehicle-controlled, dose-response study in subjects with moderate to severe facial erythema of rosacea. Subjects were randomized to receive Brimonidine Tartrate Gel (0.5%, 0.18%, or 0.07%) or Vehicle Gel. Subjects were observed for a 12-hour period following application of the study drug. Study endpoints included time to the first 1-grade and 2-grade improvements on the CEA and PSA and evaluation of chromameter data at each time point.

A total of 122 subjects, comprising the ITT Population, were randomized to the following treatment groups: Brimonidine Tartrate 0.5% Gel (31 subjects), Brimonidine Tartrate 0.18% Gel (31 subjects), Brimonidine Tartrate 0.07% Gel (28 subjects), and Vehicle Gel (32 subjects). All 122 subjects completed the study. A total of 117 subjects were included in the PP Population. The majority of subjects were female (75.4%) and Caucasian (91.8%) and the mean age was 45.7 years. There were no clinically meaningful differences in baseline or demographic characteristics. A statistically significant difference in baseline PSA scores was observed; however, the difference is not likely to be clinically meaningful.

The response rate for 2-grade improvement in both CEA and PSA showed a dose-related trend ranging from 25.0% of subjects in the Brimonidine Tartrate 0.07% Gel group to 54.8% of subjects in the Brimonidine Tartrate 0.5% Gel group, compared to 12.5% of subjects in the Vehicle Gel group. The results showed a dose-response relationship for the CEA and PSA scores.

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.

Assessment of erythema was also made with a chromameter, which provides an objective measure of skin redness and these results were in agreement with the CEA and PSA results.

A dose-response relationship in reduction of erythema (redness), as measured by chromameter was shown during the 12-hour treatment interval between the Brimonidine Tartrate 0.5% Gel and Vehicle Gel groups.

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

Based on these study results, both the 0.18%, and 0.5% concentrations of Brimonidine Tartrate Gel were selected for evaluation in the Phase 2b efficacy and safety study (18161).

Study RD.06.SRE.18161

Study RD.06.SRE.18161 was a randomized, double-blind, parallel-group, vehicle-controlled, multi-center study investigating the efficacy and safety of CD07805/47 gel in concentrations of 0.5% applied topically once daily (QD), and 0.18% applied topically once daily (QD) or twice daily (BID), in subjects with moderate to severe facial erythema associated with rosacea. The treatment period was 29 days, followed by 4 weeks of additional treatment-free follow-up. The study was conducted in the US in 2010.

Subjects were randomized to receive Brimonidine tartrate 0.5% gel QD, 0.18% Gel BID, 0.18% Gel QD, Vehicle Gel BID or Vehicle Gel QD. Subjects were assessed during a 12-hour post-dose observation and evaluation period on Baseline/Day 1, Day 15, and Day 29. On non-clinic days (Days 2-14 and 16-28) subjects were to apply study drug as directed and to complete daily self-assessments. Subjects were to return to the investigational centres during the post-treatment follow-up period at Day 30, Week 5, Week 6, and Week 8.

The sample size determination for this study was based on the results from Study 18144. A sample size of 260 (52 per arm) was estimated to be sufficient to detect the specified treatment difference of 25% (35% vs. 10%) in Composite Success with a statistical power of 90% when conducted as a two-sided test at the 5% significance level.

The primary analyses were to test 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 GEE methodology in the ITT Population. The logit link function was used to model the marginal expectation. The LOCF method was used to handle missing data and three different sensitivity analyses were performed.

The primary efficacy endpoints were 2-grade Composite Success at Hours 3, 6, 9, and 12 on Day 29, then on Day 15 and lastly on Day 1, where a 2-grade Composite Success was defined as 2-grade improvement from Baseline (T0 at Day 1) on both CEA and PSA-5 at each time point.

Several secondary end-points were included, e.g. 1-grade Composite Success for CEA and PSA-5; CEA Success (defined as 2-grade improvement from Baseline on CEA), 1-grade CEA Success; PSA-5 Success

(defined as 2-grade improvement from Baseline on PSA-5); 1-grade PSA-5 Success, all assessed at Hours 3, 6, 9, and 12 on Day 1, Day 15, and Day 29. Other end-points were assessments of PAA and OTE.

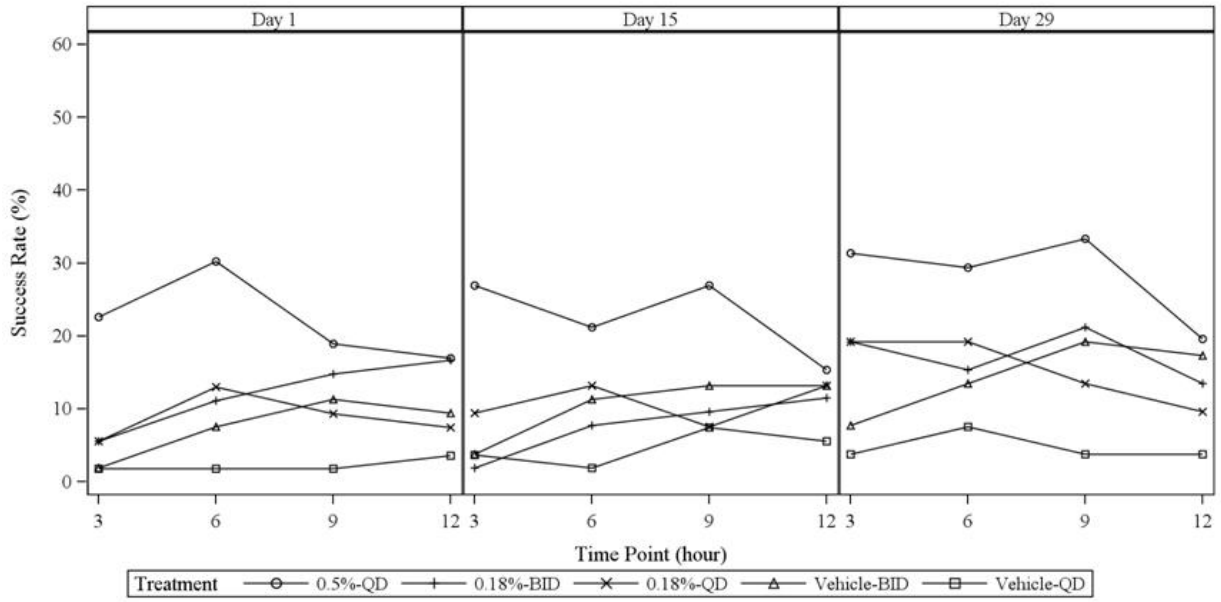
Adverse events (AEs) were monitored throughout the course of the study and assessments of vital signs and physical examinations were performed. Intraocular pressure (IOP) measurements were performed to control for possible occurrence of ocular hypotension, defined as IOP less than 10 mmHg (normal range 10 to 21 mmHg).

Results

A total of 269 subjects, comprising the ITT Population, were randomized to the treatment groups: Brimonidine Tartrate 0.5% Gel QD (53 subjects), Brimonidine tartrate 0.18% Gel BID (54 subjects), Brimonidine tartrate 0.18% Gel QD (54 subjects), Vehicle gel BID (53 subjects), and Vehicle gel QD (55 subjects). A total of 237 subjects were included in the PP Population. There were no clinically meaningful or statistically significant differences in baseline or demographic characteristics among the treatment groups. The study population comprised mainly female subjects (>80%), aged about 45 years and >96% were Caucasians.

Both the Brimonidine tartrate 0.18% gel BID and Brimonidine tartrate 0.18% gel QD groups showed numerical effectiveness against their respective vehicle gel controls, however, the results were not statistically significant and superiority over the corresponding Vehicle gel controls (BID or QD) was not observed in most instances. Brimonidine tartrate 0.5% Gel QD was therefore shown to be the most effective concentration and dosing regimen among the 3 Brimonidine tartrate gel treatment groups.

Figure 1. 2-grade Composite Success during treatment, Study 18161, LOCF, ITT Population



Study SRE.18161 showed a statistically significant treatment effect for Brimonidine Tartrate 0.5% Gel on the reduction of facial erythema of rosacea as assessed by the investigators and by the subjects (CEA and PSA) within a 29-day treatment period. Brimonidine Tartrate 0.5% Gel QD was the most effective concentration and dosing regimen among the three Brimonidine Tartrate Gel treatment groups.

Brimonidine tartrate 0.5% gel QD was significantly superior ($p<0.001$) compared to vehicle gel QD by the primary analysis (2-grade Composite Success for CEA and PSA-5 at Hours 3, 6, 9, and 12 on Day 29). Two (2)-grade Composite Success ranged from 18.9% to 32.1% on Day 29 compared to the Vehicle Gel control, which ranged from 3.6% to 7.3%. Statistical superiority of Brimonidine tartrate 0.5% Gel QD versus Vehicle gel QD was also demonstrated on Days 15 and Day 1 ($p<0.001$). Results for the primary endpoint were confirmed in the PP Population and in sensitivity analyses. The 2-grade Composite Success rate for the 0.5% gel ranged from 19% to 32% on Day 29, which are quite modest numbers, although significantly higher compared to the Vehicle Gel control ranging from 3.6% to 7.3%.

Composite Success assessed as 1-grade improvement on both CEA and PSA for Brimonidine tartrate 0.5% Gel QD ranged from 60.4% to 75.5% on Day 29 compared to Vehicle Gel control, which ranged from 30.9% to 41.8%. As with the primary endpoint, the difference between Brimonidine tartrate 0.5% gel QD and the corresponding Vehicle Gel control for this endpoint was statistically significant on Day 29 (Hours 3, 6, 9, and 12), as well as on Day 15, and Day 1 ($p<0.001$ for all days).

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

After cessation of treatment, no aggravation (rebound) of subject's facial erythema (based on the CEA or PSA) was observed in any Brimonidine tartrate gel group compared to Baseline/Day 1 (T0) erythema levels. In the Brimonidine tartrate 0.5% gel group, the mean reductions in CEA scores ranged from 0.6 to 0.7 points and the mean reductions in PSA scores ranged from 0.8 to 0.9 points relative to Day 1/Hour 0 across the 4 follow-up visits. In addition, no worsening of the IGA of Lesions, increasing facial inflammatory lesion counts, or worsening of the TGA was observed during the 4-week follow-up period in the Brimonidine tartrate 0.5% gel group.

The brimonidine tartrate 0.5% gel QD treatment group also showed the most favourable outcome with respect to PAA and OTE, compared to either the Brimonidine tartrate 0.18% Gel BID group or the Brimonidine tartrate 0.18% gel QD group, and the corresponding vehicle controls.

In the brimonidine tartrate 0.5% gel QD group, unwanted over-whitening (based on the PAW) was highest on Day 1 (up to 19% bothered by over-whitening at some time point) and the trend for unwanted over-whitening in the Brimonidine tartrate 0.5% gel QD group decreased over time. By Day 29, the number of subjects reporting unwanted over-whitening was lower (<10% bothered by over-whitening for the 0.5% gel at all time-points).

Based on the results of the studies described above, the 0.5% concentration of Brimonidine Tartrate Gel administered once daily was selected for the Phase 3 studies. Concentrations higher than 0.5% or BID application of the 0.5% gel have not been studied. The decision to go for the 0.5% QD posology was also based on pharmacokinetic results, since a higher gel concentration or BID application may result in too high systemic exposure to brimonidine. The rationale for not selecting the concentrations and/or dose regimens that would achieve a maximal effect (2-grade improvement) for the maximum daily duration (up to 12 hours) was to maintain an optimized benefit/risk ratio for the product and to avoid excessive unwanted pharmacodynamic effects (such as “over-whitening”).

2.5.2. Main studies

The two pivotal studies in the application are 18140 and 18141, with an identical design. These studies were conducted in parallel (the first subject in each study was enrolled on 16 May 2011).

The studies were of multicentre, randomized double-blind, vehicle-controlled, parallel group design with the aim to demonstrate the efficacy and assess the safety of CD07805/47 Gel 0.5% applied topically once daily in subjects with moderate to severe facial erythema associated with rosacea.

Since the pivotal studies had an identical design, the methods are not described for each study separately. The efficacy results were not pooled and therefore the results of the studies are presented for each study separately.

Methods

RD.06.SRE.18140 and RD.06.SRE.18141

Randomized, double-blind, parallel-group, multicentre, vehicle-controlled

Study Participants

The phase 3 studies were performed in the US and Canada. Subjects with a clinical diagnosis of facial rosacea with moderate or severe erythema (CEA and PSA scores ≥3) were included. Exclusion of subjects with three or more facial inflammatory lesions of rosacea was made in order to exclude a population with a dominance of inflammatory rosacea lesions.

Main inclusion criteria:

- Male or female at least 18 years of age or older
- A clinical diagnosis of facial rosacea
- A CEA score of ≥3 at Screening and on Baseline/Day 1 (prior to the T0 study drug application)
- A PSA score of ≥3 at Screening and on Baseline/Day 1 (prior to the T0 study drug application)

- Females of childbearing potential with a negative UPT at Screening and Baseline/Day 1 (prior to the T0 study drug application), or females of non-childbearing potential (post-menopausal, documented hysterectomy, or bilateral oophorectomy)

Main Exclusion Criteria

- 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 3 or more facial inflammatory lesions of rosacea.
- Treatment at the time of eligibility assessment (Screening/Day 1) with monoamine oxidase (MAO) inhibitors, barbiturates, opiates, sedatives, systemic anaesthetics, or alpha-agonists.
- Less than 3 months stable dose treatment with tricyclic anti-depressants, cardiac glycosides, beta blockers or other antihypertensive agents.
- Diagnosis at the time of eligibility assessment (Screening/Day 1) 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.
- Exposed to excessive ultraviolet (UV) radiation within 1 week prior to Baseline and/or subject was unwilling to refrain from excessive exposure to UV radiation during the course of the study.
- Presence of beard or excessive facial hair at screening which would interfere with the study treatments or study assessments and refusal to remove for duration of study.
- Treatment at the time of eligibility assessment (Screening/Day 1) with brimonidine tartrate ophthalmic solution or with any topical facial formulation containing brimonidine tartrate or oxymetazoline.
- The subject had received, applied, or taken the following treatments within the specified time frame prior to the Baseline/Day 1 clinic visit:

Topical facial treatments: Laser, Photodynamic Therapy or intense pulsed light (IPL) treatment, electrocoagulation, dermabrasion, facial peels, any other dermatologic/surgical procedure on the face within 4 weeks; prescription medications for the treatment of rosacea (e.g., azelaic acid, metronidazole) or for treatment of acne, immunomodulator or corticosteroids within 4 weeks; antibiotics within 2 weeks; Over-the-counter (OTC) medications for treatment of acne within 1 week or astringents or abrasives within 2 days.

Systemic treatments: Isotretinoin within 6 months; immunomodulators within 12 weeks; prescription medications for the treatment of rosacea (e.g., doxycycline, tetracycline, macrolides) or for treatment of acne, oral or injectable corticosteroids within 4 weeks; phototherapy within 4 weeks; antibiotics within 4 weeks; prescription anti-inflammatory medications within 2 weeks; chronic, daily use of OTC anti-inflammatory medications (e.g., ibuprofen, naproxen) for more than 1 week (not including low-dose aspirin for cardiac prophylaxis) or niacin ≥500 mg per day within 1 week.

Treatments

The subjects were randomized to receive either CD07805/47 gel 0.5% or vehicle gel administered topically once daily for 29 days on the face. Other rosacea treatments were not allowed. The vehicle gel

has a composition identical to the active CD07805/47 0.5% gel, without the active substance brimonidine tartrate. All other components of the formulation remained the same.

Subjects were instructed not to apply study drug prior to arriving at the investigational center on assessment days. 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 center 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 once daily in the morning after washing the entire face: right cheek, left cheek, forehead, chin, and nose. Application on the eyes, eyelids, inner nose, mouth, and lips was to be avoided and so was application of study drug to severely irritated skin or open lesions. The amount of study drug to be applied was approximately 1 gram. No dose modification was allowed during the course of the study.

Study procedures:

Subjects who met the Inclusion/Exclusion criteria at Screening and at the Baseline/Day 1 clinic visit were randomized to receive study drug for a period of 4 weeks. Following the 4-week dosing period, subjects returned to the investigational centres on Week 6 and Week 8/Early Termination (ET) for follow-up evaluations.

Subject assessments were performed at the investigational center during a 12-hour post-dose evaluation period on Day 1, Day 15, and Day 29. On non-clinic days (Days 2-14 and 16-28) 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 the non-clinic days (Days 2-14 and 16-28) and during the follow-up period. The Patient Assessment of Appearance (PAA) and the Patient Assessment of Whitening (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 complete the Productivity and Social Life Questionnaire on Days 1 and 29 and at the Week 8/ET Follow-up visit. The Overall Treatment Effect (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 (TGA) on Day 1, Day 29, and each follow-up visit; a facial inflammatory lesion count at each clinic visit (except Day 15); and the Investigator's Global Assessment (IGA) of Lesions on Day 1, Day 29, and each follow-up visit. Whenever possible, the same Investigator/evaluator who performed the initial assessments was to perform the assessments for each individual subject for the entire duration of the study.

The patients arrived at the investigational center 1 hour prior to study drug application to allow for proper acclimation to the investigational center environment. Efficacy and safety assessments were to be completed within 10 minutes of the scheduled time point.

In the protocol, it is stated that on clinic visit days, subjects were to wash their face with water and their routine mild facial cleanser. After washing, subjects should follow instructions for study drug application and not apply anything else to their face that day. On non-clinic days, subjects could use facial products such as lotions, creams, ointments, cosmetics, and sunscreens, unless specifically excluded. Study drug should be applied prior to any other facial product.

Objectives

The objectives of the pivotal phase 3 studies were to demonstrate the efficacy and to assess safety 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.

Outcomes/endpoints

The end-points in studies 18140 and 18141 were the following:

Table 16. End-points in studies 18140 and 18141

Primary Efficacy Endpoints
2-grade Composite Success at Hours 3, 6, 9, 12 on Day 29, then on Day 15 and lastly on Day 1, with 2-grade Composite Success defined as a 2-grade improvement on both CEA and PSA at each time point.
Secondary Efficacy Endpoints
30-minute Effect, defined as 1-grade Composite Success (1-grade improvement on both CEA and PSA) at 30 minutes on Day 1.
Tertiary Efficacy Endpoints
1-grade Composite Success at Hour 3, 6, 9, 12 on Day 29, Day 15, and Day 1; 1-grade Composite Success was defined as 1-grade improvement on CEA and PSA.
2-grade CEA Success at Hours 3, 6, 9, and 12 on Day 29, Day 15 and Day 1; 2-grade CEA Success was defined as 2-grade improvement on CEA.
2-grade PSA Success at Hours 3, 6, 9, and 12 on Day 29, Day 15 and Day 1; 2-grade PSA Success was defined as 2-grade improvement on PSA.
Percentage of Days with PSA scored '0' or '1' between visits.
Change in Pre-dose CEA from Baseline (T0 on Day 1) at each post-Baseline visit during treatment and follow-up phases.
Change in Pre-dose PSA from Baseline (T0 on Day 1) at each post-Baseline visit during treatment and follow-up phases.
Other Endpoints
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 on Day 29 and at Follow-up visit
Change in TGA 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 data on Day 15, Day 29 and Follow-up visit
Change from Baseline in Productivity and Social Life Questionnaire on Day 29 and Follow-up visit.

Safety assessments included recording of AEs, laboratory safety tests (blood chemistry, haematology, urinalysis) vital signs (systolic and diastolic blood pressure and heart rate) and physical examinations. Intra-ocular pressure (IOP) was not measured in the pivotal studies.

The primary efficacy end-point was a composite end-point including both the clinicians and the patient's assessments of erythema (CEA and PSA, respectively). A 2-grade improvement on both the CEA and PSA scales was required for success to be concluded at each time point. Thus, the criteria for meeting the primary end-point were set quite high.

The secondary efficacy end-point aimed to assess the onset of efficacy, by assessing a 1-grade Composite Success (1-grade improvement on both CEA and PSA) at 30 minutes on Day 1.

A large number of tertiary and other end-points were also included.

Sample size

The sample size determinations for the Phase 3 pivotal studies were based on the results from the phase 2b Study (RD.06.SRE.18161). Considering the variability and vehicle effect could have potentially been higher in the Phase 3 studies, it was assumed that the underlying treatment difference in Composite Success rate between brimonidine tartrate 0.5% Gel and Vehicle Gel was 15%, the vehicle effect was 10%, the correlation between repeated measurements was 0.7, and the expected dropout rate was 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.

Randomisation

Approximately 260 subjects for each study were to be randomized in a 1:1 ratio to receive either CD07805/47 gel 0.5% or vehicle gel for once daily application. The randomisation was stratified by centre.

Blinding (masking)

The randomization list was to be secured in a locked cabinet and/or an electronic file with restricted access until the database was locked. Investigators and/or subject evaluators were not to be permitted access to the randomization list.

Active CD07805/47 gel and vehicle gel were identical in appearance to each other and no visible differences could be observed between the study drugs. Active CD07805/47 gel and vehicle gel were packed in identical tubes. The procedures used to ensure blinding seem acceptable. It should be borne in mind that due to the pharmacodynamic effect of CD07805/47 gel, the vasoconstriction results in blanching effect of the skin, which is visibly detected by the patients. Thus, maintaining blinding can obviously be difficult for this kind of product due to the desired clinical effect. The PSA and other end-points are rated by the patients themselves whereas other end-points such as CEA are rated by the clinician, who is blinded to treatment. If un-blinding due to observation of the effect by the patient was obvious, larger effects on PSA vs. the CEA scales over time could be expected. No un-blinding took place.

Statistical methods

The statistical methods are overall acceptable.

Endpoints

Using only one time-point for the baseline assessments of CEA and PSA and 4 time-points at follow-up assessments (Hours 3, 6, 9, and 12 after treatment) makes it difficult to assess the time course of effect during the day. A baseline curve covering the same time points of the day without treatment would have been of interest in order to evaluate whether the degree of erythema shows a diurnal variation, e.g. an increased intensity at later time points of the day. However, the vehicle arm may to some extent account for this.

Analysis of Primary Variable

The primary analyses tested the hypothesis of no treatment difference between active treatment and vehicle 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. Tests of treatment effects were also performed on Day 15 and Day 1 using GEE methodology. 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 for the data

in the Phase 3 pivotal studies due to lack of convergence using the unstructured correlation matrix. The dependent variable in the model was Composite Success at Hours 3, 6, 9, and 12 and the independent variables were treatment, analysis centre, and time points (Hours 3, 6, 9, and 12).

The primary analyses were performed based on the ITT Population, and were repeated based on the PP Population and the MITT population in the 18141 study to confirm the ITT results.

Subgroup summaries for 2-grade Composite Success by gender, age group (18-64 vs. 65 and above) and race (Caucasian vs. non-Caucasian) were provided by descriptive statistics.

Handling of Missing Data

The multiple imputation (MI) procedure was the primary imputation method to handle missing CEA or PSA data at any time point (Hours 3, 6, 9, or 12) for the primary endpoint. Instead of filling in a single value for each missing value, the MI procedure replaced each missing CEA and PSA value with a set of plausible values that represented the uncertainty about the value to impute.

In addition to the MI procedure, 3 sensitivity analyses were applied to 2-grade Composite Success at 4 time points (Hours 3, 6, 9, and 12) as follows: (a) imputing 'Failure' for any missing data, (b) imputing 'Success' for any missing data, and (c) using the average score of the available data at Hours 3, 6, 9, and 12 on CEA and PSA to impute 'Success' or 'Failure' accordingly. In addition, last observation carried forward (LOCF) methodology was used as a sensitivity analysis.

Because observed data were used for the secondary endpoint, tertiary endpoints, and other assessments, missing data were not imputed.

Analysis of Secondary Variable

The secondary endpoint of 30-minute Effect was analysed by the Cochran-Mantel-Haenszel (CMH) test stratified by analysis centre, with the general association statistic.

Control of Type I Error

In the Phase 3 pivotal studies, Type I error (alpha) was strictly controlled by clearly pre-specifying the primary variable, primary time point, primary analysis methodology, and primary population (2-grade Composite Success, Day 29, GEE with MI, and ITT). The experiment-wise alpha was further controlled by the pre-specification of hierarchical testing of earlier time points: Day 15 and then Day 1. Following the testing of the primary variable the test of hypotheses was limited to the testing of only one secondary variable: 30-minute Effect.

Results

Participant flow

The subject enrolment and disposition in the pivotal studies are outlined in the tables below.

Table 17. Summary of Subject Enrolment (Study 18140)

Population	CD07805/47 Gel 0.5%	Vehicle Gel	Total
Screen Failure (Not Randomized)	-	-	65
Inclusion/Exclusion criteria not fulfilled	-	-	50
Subject's request	-	-	1
Other	-	-	12
Adverse event	-	-	2
Intent-to-treat (ITT)	129	131	260
Per-protocol (PP)	113	118	231
Safety (SAF)	129	131	260

Intent-to-treat (ITT): Subjects who were randomized and to whom study drug was administered.

Per-protocol (PP): ITT subjects who met all major protocol criteria.

Safety (SAF): Subjects who were randomized and applied study drug at least once.

Table 18. Summary of Subject Disposition, ITT Population Study (18140)

Completion Status	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	Total (N=260)
Normal Completion	127 (98.4%)	127 (96.9%)	254 (97.7%)
Premature Discontinuation	2 (1.6%)	4 (3.1%)	6 (2.3%)
Lack of Efficacy	0	0	0
Adverse Event	2 (1.6%)	1 (0.8%)	3 (1.2%)
Subject's Request	0	1 (0.8%)	1 (0.4%)
Protocol Violation	0	1 (0.8%)	1 (0.4%)
Lost to Follow-up	0	1 (0.8%)	1 (0.4%)

To address a concern about data validity at a single investigational center (8283) in study 18141, the MITT Population was defined as the ITT Population excluding all subjects from that investigational center. All efficacy analyses were to be performed for the MITT Population to validate the results.

Table 19. Summary of Subject Enrolment (Study 18141)

Population	CD07805/47 Gel 0.5%	Vehicle Gel	Total
Screen Failure (Not Randomized)	-	-	53
Inclusion/Exclusion criteria not fulfilled	-	-	36
Subject's request	-	-	8
Other	-	-	8
Adverse event	-	-	1
Intent-to-treat (ITT)	148	145	293
Modified Intent-to-treat (MITT)	131	129	260
Per-protocol (PP)	119	120	239
Safety (SAF)	148	145	293

Intent-to-treat (ITT): Subjects who were randomized and to whom study drug was administered.

Modified Intent-to-Treat (MITT): ITT Population excluding all 33 subjects from a single investigational center (8283) due to site-specific data validity concerns.

Per-protocol (PP): ITT subjects who met all major protocol criteria.

Safety (SAF): Subjects who were randomized and applied study drug at least once.

Table 20. Summary of Subject Disposition, ITT Population (Study 18141)

Completion Status	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)	Total (N=293)
Normal Completion	141 (95.3%)	142 (97.9%)	283 (96.6%)
Premature Discontinuation	7 (4.7%)	3 (2.1%)	10 (3.4%)
Adverse Event	1 (0.7%)	1 (0.7%)	2 (0.7%)
Subject's Request	2 (1.4%)	0	2 (0.7%)
Protocol Violation	3 (2.0%)	2 (1.4%)	5 (1.7%)
Other	1 (0.7%)	0	1 (0.3%)

The number of subjects completing the studies was high (>96%) in both pivotal studies.

Recruitment

Both studies were initiated the 16 May 2011 and study 18140 was completed on 23 September 2011 and study 18141 on 22 November 2011.

Conduct of the study

A total of 15 investigational centres located in the US and Canada enrolled subjects in both studies.

Two amendments to the study protocol were prepared for study 18140, related to for instance the exclusion criteria, previous and concomitant therapies and vital signs and safety laboratory testing. The same amendments were made for study 18141.

One amendment to the SAP, dated 16 January 2012, was prepared for study 18141 prior to unblinding. The changes included definition of a modified ITT Population (MITT), defined as the ITT Population excluding all subjects of the investigational center 8283 for which data validity concerns were discovered. The ITT analyses remained primary, though. Furthermore, changes in the primary efficacy analyses model without treatment-by-center interaction term were made.

The amendments to the protocol are not considered to have an impact on the evaluation of the results.

Baseline data

There were no major differences between the active treatment and the vehicle groups in baseline characteristics in the two pivotal studies.

The majority of included subjects were females (>70%) with a mean age in the range 45-50 years. Almost only Caucasian or white subjects were included. Most subjects had a Fitzpatrick skin phototype of II or III, but some subjects in the categories with lighter or darker skin types were included as well. It is not unexpected that mainly fair-skinned subjects are those mainly affected by rosacea with facial erythema.

The subjects included had PSA and CEA scores of 3 or 4, in accordance with the inclusion criteria (with one exception in study 18140 due to a protocol violation). Thus, subjects with moderate to severe facial erythema were included although the majority (generally >80%) had moderate erythema.

Numbers analysed

Major protocol deviations that resulted in subjects being excluded from the PP Population are summarized in Table 21 and Table 22.

Table 21. Summary of Subjects Excluded from the Per-protocol Population, ITT Population (Study 18140)

	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	Total (N=260)
Number of Subjects with Major Protocol Deviation(s)[a]	16 (12.4%)	13 (9.9%)	29 (11.2%)
Administrative Error	10 (7.8%)	8 (6.1%)	18 (6.9%)
Non-Compliance	3 (2.3%)	3 (2.3%)	6 (2.3%)
Incomplete Primary Endpoint	2 (1.6%)	3 (2.3%)	5 (1.9%)
Prohibited Medication	3 (2.3%)	1 (0.8%)	4 (1.5%)
Entrance Criteria Deviation	2 (1.6%)	1 (0.8%)	3 (1.2%)

a: Subjects with major protocol deviations were excluded from the PP Population.
A subject was counted once even if the subject had more than one major protocol deviation.

In study 18140, administrative error was the most common deviation, which was reported for 18 subjects, and was due to a sub-Investigator at a single investigative center who had not completed the CEA harmonization training prior to conducting the CEA evaluation on those subjects. Non-compliance, defined as a dosing deviation of more than 30% of planned doses, was also common, mainly due to subjects who prematurely discontinued from the study.

Table 22. Summary of Subjects Excluded from the Per-protocol Population, ITT Population (Study 18141)

	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)	Total (N=293)
Number of Subjects with Major Protocol Deviation(s)[a]	29 (19.6%)	25 (17.2%)	54 (18.4%)
Site Specific Data Validity Concern	17 (11.5%)	16 (11.0%)	33 (11.3%)
Non-Compliance	6 (4.1%)	6 (4.1%)	12 (4.1%)
Prohibited Medication	5 (3.4%)	5 (3.4%)	10 (3.4%)
Incomplete Primary Endpoint	6 (4.1%)	3 (2.1%)	9 (3.1%)
Entrance Criteria Deviation	2 (1.4%)	3 (2.1%)	5 (1.7%)

A subject was counted once even if the subject had more than one major protocol deviation.
All 33 subjects from a single investigational center (8283) were excluded from the PP Population due to site-specific data validity concerns.
a: Subjects with major protocol deviations were excluded from the PP Population.

In study 18141, 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 center (8283).

A total of 12 subjects, 6 in each treatment group, were excluded from the PP Population due to non-compliance, which included dosing deviations of more than 30% of planned doses, mainly due to premature discontinuation from the study. A total of 5 subjects were excluded from the PP Population due to entrance criteria deviations, all of which were due to insufficient washout periods.

No major concerns arise, except for the issue related to data validity concerns for one center in study 18141. The reason for the “site-specific data validity concern” in study 18141 was study coordinator admission of falsification of vital sign data for one subject. Conservatively, all subjects at this site were being classified as major deviators and excluded from the PP population.

Outcomes and estimation

Primary end-point

The results for the primary end-point, a 2-grade Composite Success for CEA and PSA, are given in the table and figures below.

Table 23. 2-grade Composite Success; Studies 18140, 18141; Observed Data; ITT Population

Success, n/N (%)	18140				18141			
	CD07805/47 0.5% Gel (N=129)	Vehicle Gel (N=131)	p-value	Odds Ratio (95% CI)	CD07805/47 0.5% Gel (N=148)	Vehicle Gel (N=145)	p-value	Odds Ratio (95% CI)
Day 1								
Hour 3	21/129 (16.3)	4/131 (3.1)	<0.001	NC	29/148 (19.6)	0/145 (0)	<0.001	NC
Hour 6	30/129 (23.3)	3/131 (2.3)			44/148 (29.7)	3/145 (2.1)		
Hour 9	25/129 (19.4)	5/131 (3.8)			27/148 (18.2)	1/144 (0.7)		
Hour 12	17/129 (13.2)	4/130 (3.1)			20/148 (13.5)	2/144 (1.4)		
Day 15								
Hour 3	32/128 (25.0)	4/128 (3.1)	<0.001	NC	36/143 (25.2)	5/141 (3.5)	<0.001	NC
Hour 6	35/128 (27.3)	8/128 (6.3)			37/143 (25.9)	6/141 (4.3)		
Hour 9	25/128 (19.5)	7/128 (5.5)			31/143 (21.7)	7/141 (5.0)		
Hour 12	21/128 (16.4)	3/128 (2.3)			22/143 (15.4)	10/141 (7.1)		
Day 29								
Hour 3	40/127 (31.5)	14/128 (10.9)	<0.001	3.750 (2.100, 6.696)	36/142 (25.4)	13/142 (9.2)	<0.001	2.947 (1.687, 5.148)
Hour 6	39/127 (30.7)	12/128 (9.4)			36/142 (25.4)	13/142 (9.2)		
Hour 9	33/127 (26.0)	13/128 (10.2)			25/142 (17.6)	15/142 (10.6)		
Hour 12	29/127 (22.8)	11/128 (8.6)			30/142 (21.1)	14/142 (9.9)		

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. Composite Success was defined as 2-grade improvement from Baseline (T0 at Day 1) on both CEA and PSA at each time point.

Generalized Estimating Equation (GEE) methods with Logit link function and marginal expectation model was used for analyses. The m-dependent (m=3) correlation matrix was used in the GEE model.
NC=Not calculated.

Figure 2. 2-grade Composite Success during treatment, Study 18140, Observed Data, ITT Population

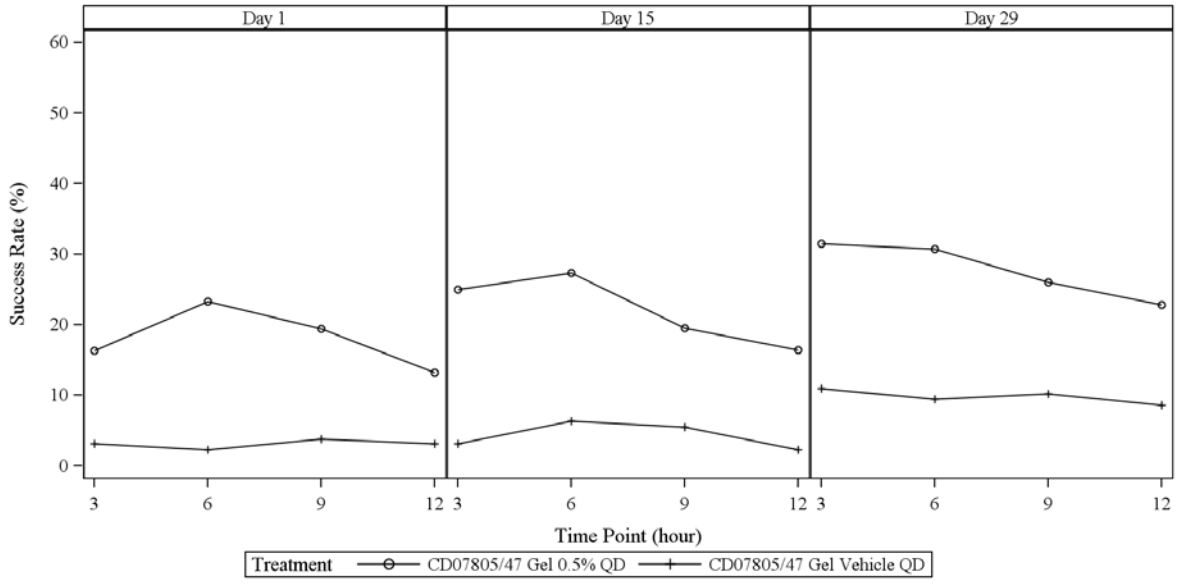
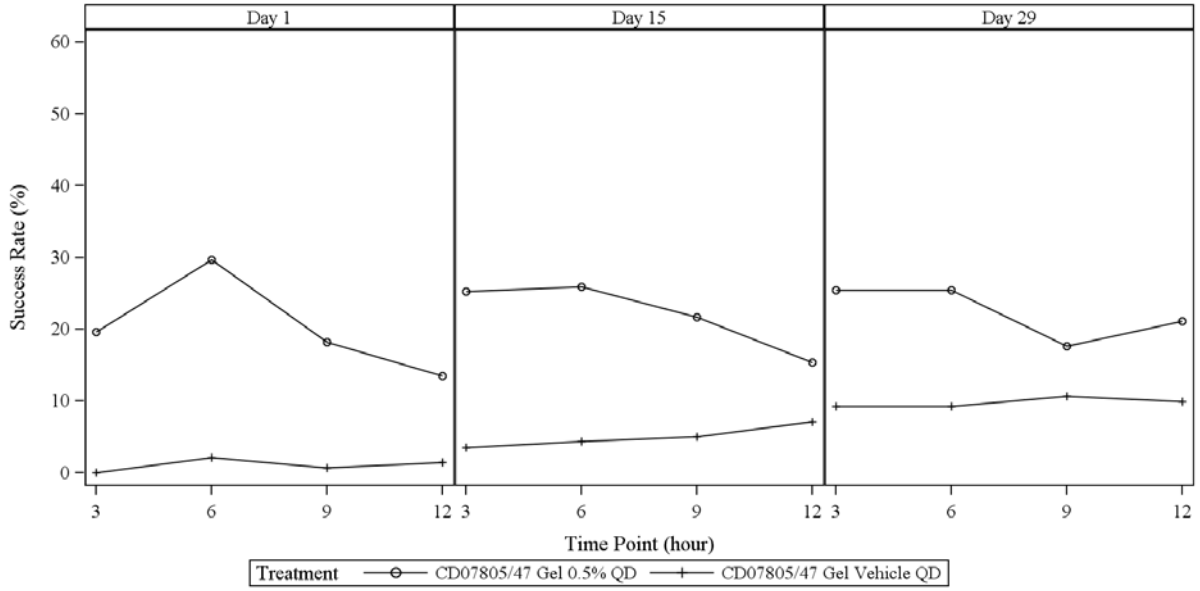


Figure 3. 2-grade Composite Success during treatment, Study 18141, Observed Data, ITT Population



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

In both pivotal studies, 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). Statistical superiority of CD07805/47 Gel 0.5% versus Vehicle Gel was also demonstrated on Day 15 ($p<0.001$) and Day 1 ($p<0.001$).

The results were confirmed in the ITT Population using the LOCF method, in the MITT population (in Study 18141) and the PP Population, and in the sensitivity analyses.

There was a tendency to an increased response across days 1, 15 and 29 both in the active and vehicle gel treated groups. On day 29, the vehicle response was approximately 10% and for brimonidine tartrate 0.5% Gel, the response at different time points ranged between 17.6% and 31.5%. The highest response was observed at the 3 and 6 hour time points and the effect tended to wear off at the later time points.

For completeness, results for the MITT population (excluding center 8283) for study 18141 are presented below.

Table 24. Summary of 2-grade Composite Success, Observed Data, MITT Population, study 18141

Success n/N (%)	CD07805/47 Gel 0.5% QD	CD07805/47 Gel Vehicle QD
Day 1 /Hour 3	23/131 (17.6%)	0/129 (0.0%)
Day 1 /Hour 6	36/131 (27.5%)	3/129 (2.3%)
Day 1 /Hour 9	24/131 (18.3%)	1/128 (0.8%)
Day 1 /Hour 12	15/131 (11.5%)	2/128 (1.6%)
Day 15 /Hour 3	30/126 (23.8%)	5/126 (4.0%)
Day 15 /Hour 6	30/126 (23.8%)	6/126 (4.8%)
Day 15 /Hour 9	28/126 (22.2%)	7/126 (5.6%)
Day 15 /Hour 12	19/126 (15.1%)	10/126 (7.9%)
Day 29 /Hour 3	27/125 (21.6%)	13/127 (10.2%)
Day 29 /Hour 6	29/125 (23.2%)	13/127 (10.2%)
Day 29 /Hour 9	23/125 (18.4%)	15/127 (11.8%)
Day 29 /Hour 12	24/125 (19.2%)	14/127 (11.0%)

As described above, a data validity concern was raised for the data from a single investigational center (8283), and a modified ITT population was defined. A clear statistically significant difference between

CD07805/47 0.5% Gel and Vehicle gel is observed irrespective of analysis population (ITT, MITT, and PP). Looking at efficacy results for the primary end-point from this center, it can be noted that the 2-grade success rate in the vehicle group was 0% at all days and time points. The response rate in the CD07805/47 0.5% Gel group tended to be somewhat higher at several time points than in the overall population, with success rates ranging from 12 up to 53%. The complete lack of response in the vehicle group is somewhat remarkable. Complete lack of response at all-time points for the Vehicle Gel group was in fact also observed at 2 additional centres in study 18141 and also in 3 centres in study 18140. Although this could be due to normal variation, it could also indicate problems related to blinding. The applicant was asked to discuss this finding and analyse the efficacy data from both studies without these centres.

The requested analyses were provided with exclusion of sites for which none of the vehicle subjects achieved 2-grade Composite Success on Day 29. This concerned a fairly large number of sites (a total of 12 out of 30). Still, statistical significance vs. vehicle was maintained for all comparisons, except for the Day 29 results in study 18141. It is agreed that with an anticipated 10% incidence of 2-grade Composite Success in the vehicle group it is not unlikely that there would be several sites without any vehicle subjects achieving 2-grade Composite Success.

Secondary end-point

The secondary endpoint evaluated the early effect of treatment (30-minute Effect) assessed as a 1-grade improvement on CEA and 1-grade improvement on PSA at 30 minutes post dosing.

Table 25. 30-minute CEA and PSA Effect; Studies 18140, 18141; Observed Data; ITT Population

Success, n/N (%)	18140				18141			
	CD07805/47 0.5% Gel (N=129)	Vehicle Gel (N=131)	p-value	Odds Ratio (95% CI)	CD07805/47 0.5% Gel (N=148)	Vehicle Gel (N=145)	p-value	Odds Ratio (95% CI)
30-minute Effect	36/129 (27.9)	9/131 (6.9)	<0.001	4.751 (2.220, 10.168)	42/148 (28.4)	7/145 (4.8)	<0.001	7.448 (3.256, 17.037)

30-minute CEA and PSA Effect: 1-grade improvement on CEA and 1-grade improvement on PSA at 30 minutes post dosing.

30-minutes Effect was analysed by the Cochran-Mantel-Haenszel test stratified by analysis center, with general association statistics.

brimonidine tartrate 0.5% Gel produced a statistically significant (p<0.001) earlier effect compared to the Vehicle Gel groups in Studies 18140 and 18141 based on the definition used. 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 5-7% of Vehicle Gel subjects.

Tertiary end-points

1-grade Composite Success

Table 26. 1-grade Composite Success; Studies 18140, 18141; Observed Data; ITT Population

Success n/N (%)	18140				18141			
	CD07805/47 0.5% Gel (N=129)	Vehicle Gel (N=131) n/N (%)	p-value	Odds Ratio (95% CI)	CD07805/47 0.5% Gel (N=148)	Vehicle Gel (N=145)	p-value	Odds Ratio (95% CI)
Day 1								
Hour 3	76/129 (58.9)	23/131 (17.6)	<0.001	NC	82/148 (55.4)	24/145 (16.6)	<0.001	NC
Hour 6	89/129 (69.0)	31/131 (23.7)			98/148 (66.2)	33/145 (22.8)		
Hour 9	80/129 (62.0)	27/131 (20.6)			98/148 (66.2)	36/144 (25.0)		
Hour 12	60/129 (46.5)	26/130 (20.0)			85/148 (57.4)	42/144 (29.2)		
Day 15								
Hour 3	81/128 (63.3)	34/128 (26.6)	<0.001	NC	91/143 (63.6)	50/141 (35.5)	<0.001	NC
Hour 6	83/128 (64.8)	36/128 (28.1)			89/143 (62.2)	56/141 (39.7)		
Hour 9	84/128 (65.6)	33/128 (25.8)			87/143 (60.8)	55/141 (39.0)		
Hour 12	61/128 (47.7)	33/128 (25.8)			80/143 (55.9)	51/141 (36.2)		
Day 29								
Hour 3	90/127 (70.9)	42/128 (32.8)	<0.001	4.373 (2.783, 6.872)	101/142 (71.1)	57/142 (40.1)	<0.001	2.772 (1.835, 4.187)
Hour 6	88/127 (69.3)	41/128 (32.0)			92/142 (64.8)	61/142 (43.0)		
Hour 9	81/127 (63.8)	38/128 (29.7)			95/142 (66.9)	56/142 (39.4)		
Hour 12	72/127 (56.7)	39/128 (30.5)			76/142 (53.5)	57/142 (40.1)		

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. Composite Success was defined as 2-grade improvement from Baseline (T0 at Day 1) on both CEA and PSA at each time point.

Generalized Estimating Equation (GEE) methods with Logit link function and marginal expectation model was used for analyses. The m-dependent (m=3) correlation matrix was used in the GEE model.

Figure 4. 1-grade Composite Success, Study 18140, Observed Data, ITT Population

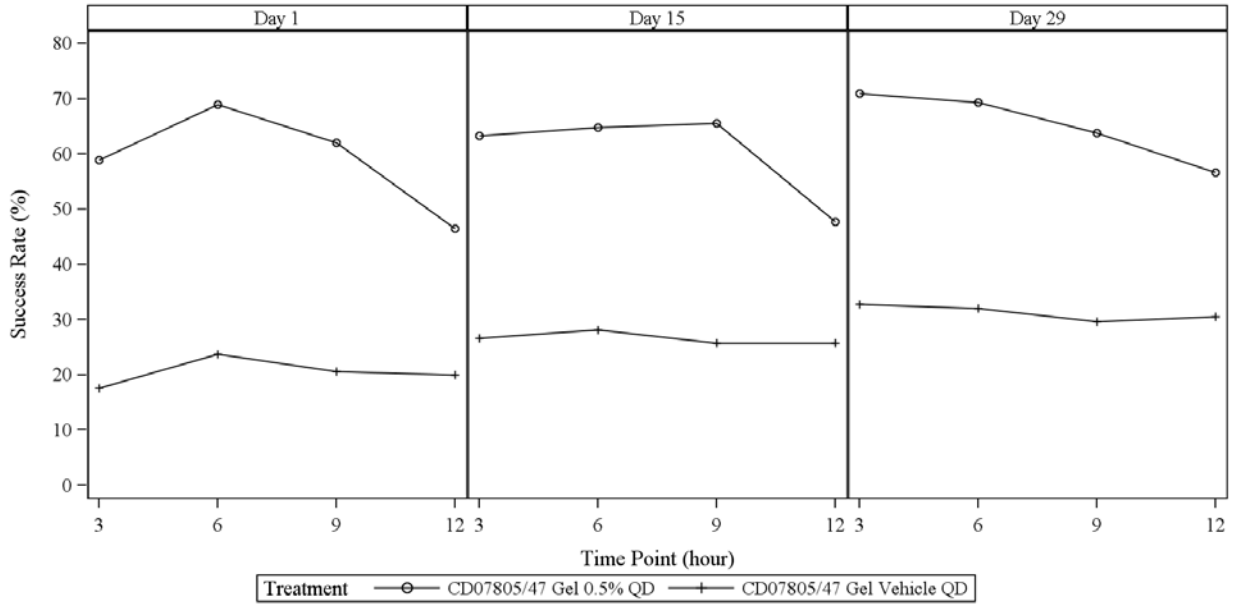
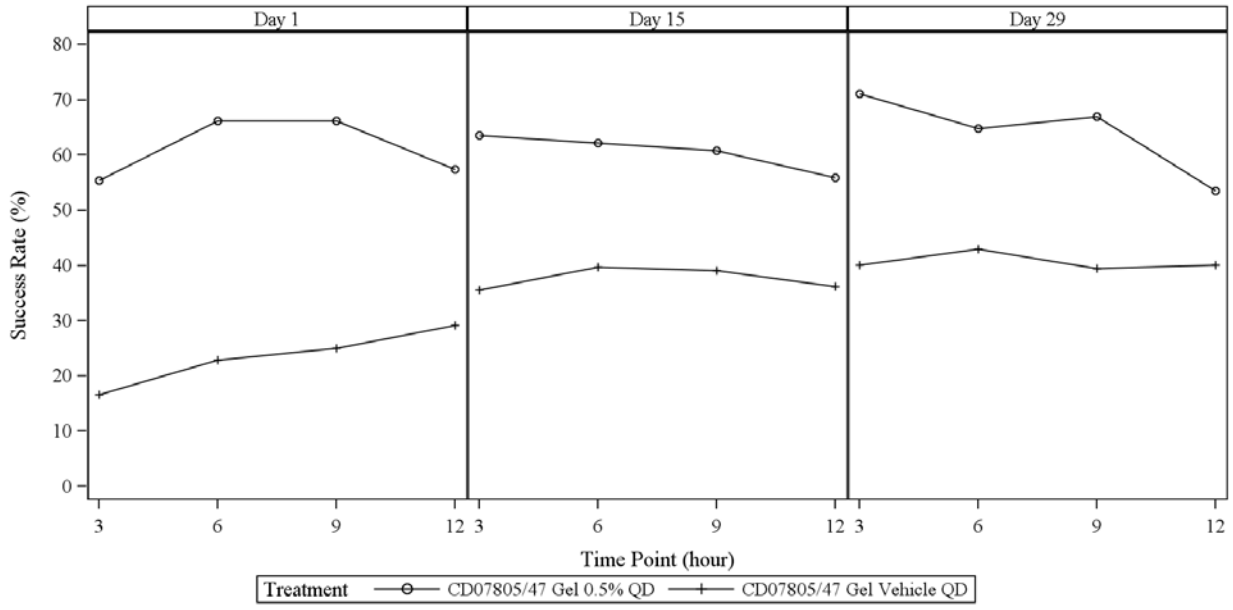


Figure 5. 1-grade Composite Success, Study 18141, Observed Data, ITT Population



1-grade Composite Success: 1-grade improvement on CEA and 1-grade improvement on PSA.

The 1-grade Composite Success profile was statistically significant ($p<0.001$) on Days 1, 15, and 29 in the brimonidine tartrate 0.5% Gel group compared to subjects who received Vehicle Gel. The results for 1-grade Composite Success on Day 29 ranged from 53.5% to 71% and the vehicle effect was around 30% in study 18140 and 40% in study 18141 at Day 29. Thus, the percentage of patients reaching 1-grade Composite Success was clearly higher than those reaching 2-grade Composite Success. As for the 2-grade Composite Success, the vehicle effect and to some extent also the brimonidine tartrate 0.5% Gel effect tended to increase somewhat over time.

CEA success

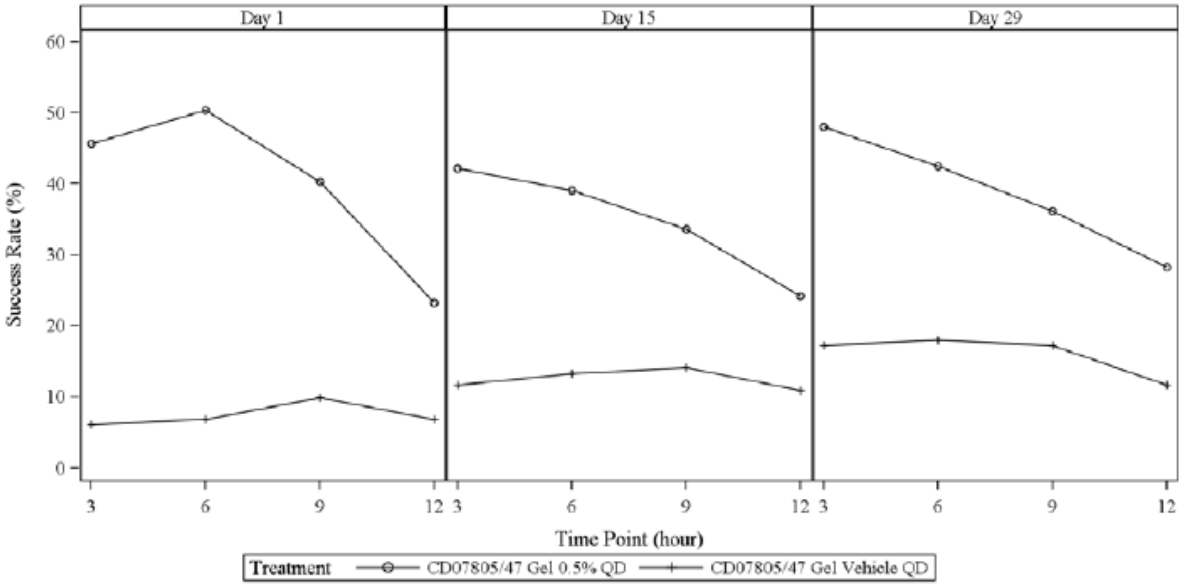
Results for CEA success (2-grade improvement on CEA), i.e. based solely on the clinician´s erythema rating, and are provided below, for Study 18140.

Table 27. Summary of 2-grade CEA Success, Observed Data, ITT Population, study 18140

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%)

The results for CEA success were similar in study 18141 (data not shown), with success rates ranging between 30 and 51% for the active treatment, across all days and time points (ITT).

Figure 6. Two-Grade CEA Success on Day 1, Day 15, and Day 29, Observed Data, ITT Population



PSA Success

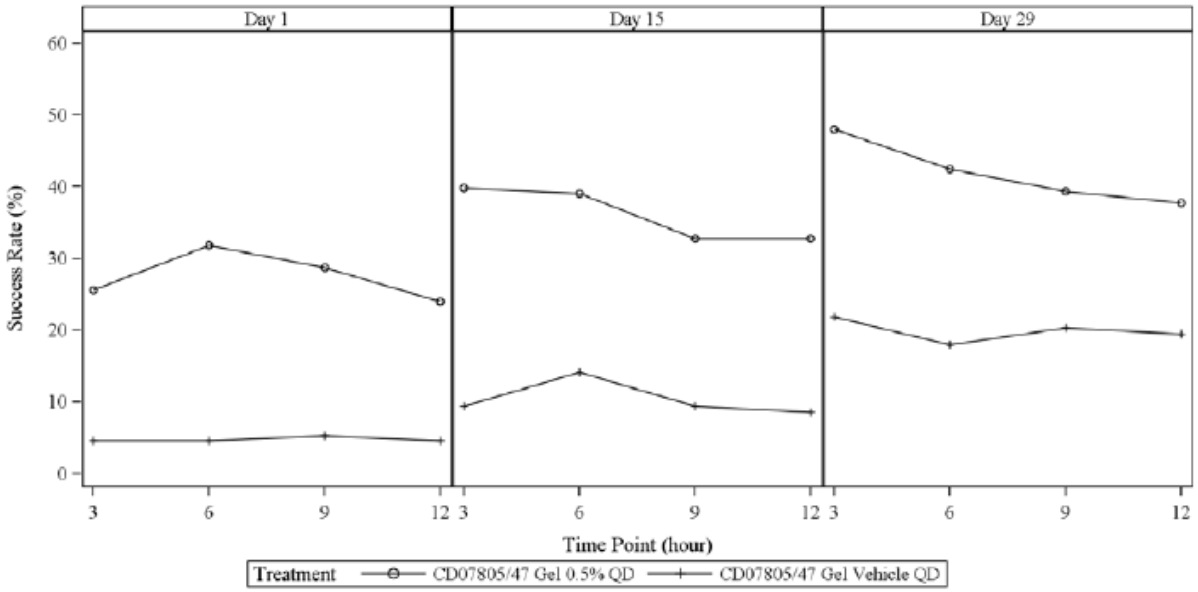
Results for PSA success (2-grade improvement on PSA), i.e. success based solely on the patient´s erythema rating, are provided below, for Study 18140.

Table 28. Summary of 2-grade PSA Success, Observed Data, ITT Population, study 18140

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.

Figure 7. Two-Grade PSA Success on Day 1, Day 15, and Day 29, Observed Data, ITT Population, study 18140



The results for PSA success were similar in study 18141 (data not shown), with success rates ranging between 22 and 39% for the active treatment, across all days and time points (ITT).

Mean changes in CEA scores

The mean changes in CEA scores on Days 1, 15, and 29 are graphically depicted in Figures 8. The differences between the active and vehicle group mean responses 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.

Figure 8. Mean Change in CEA on Day 1, Day 15 and Day 29, ITT Population, Study 18140

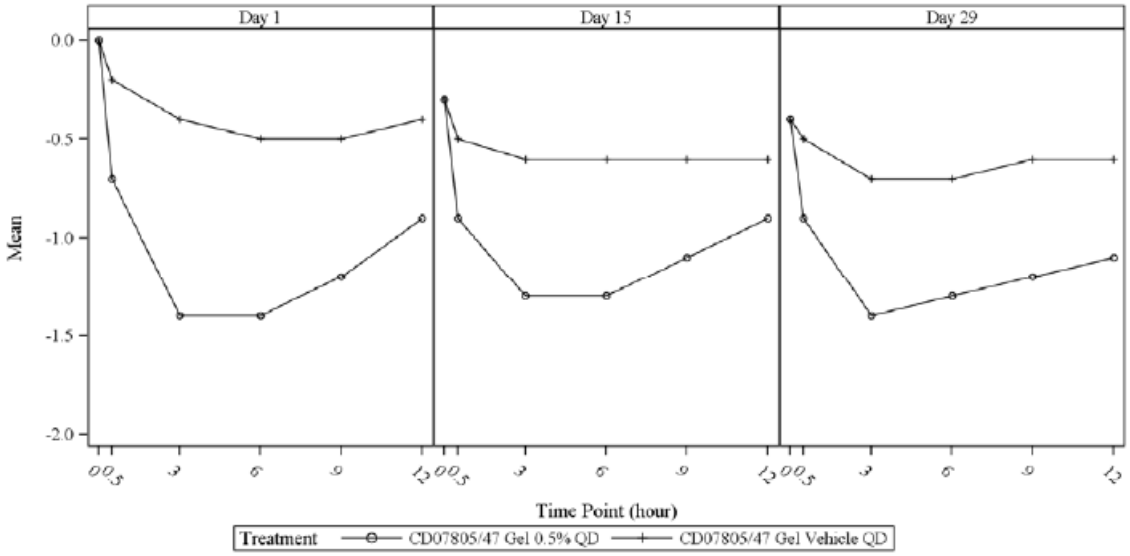
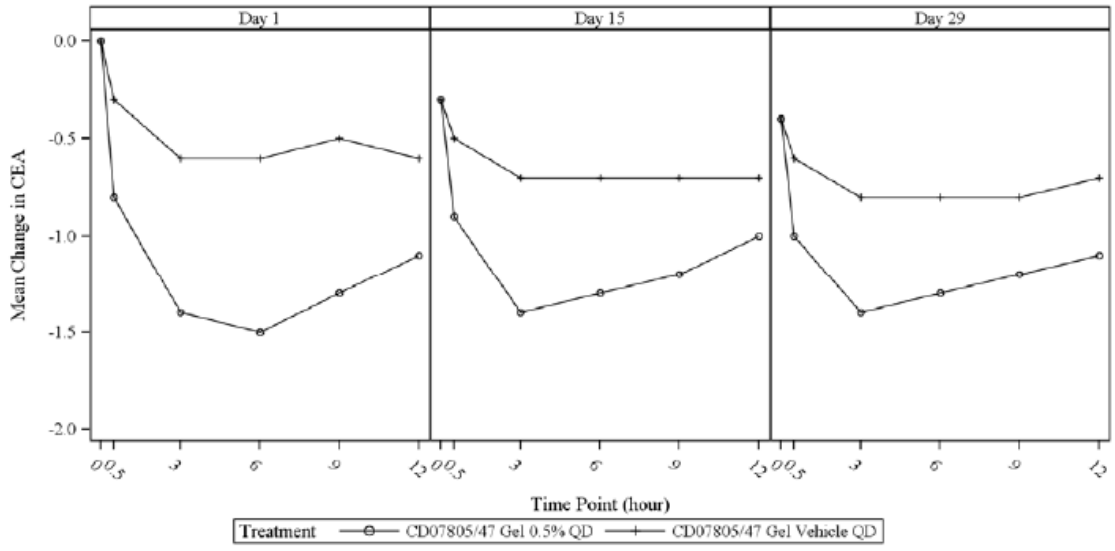


Figure 9. Mean Change in CEA on Day 1, Day 15 and Day 29, ITT Population, Study 18141



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.

Mean changes in PSA scores

The mean changes in PSA scores on Days 1, 15, and 29 are graphically depicted in the figures below. The differences between the active and vehicle group mean responses 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.

Figure 10. Mean Change in PSA on Day 1, Day 15 and Day 29, ITT Population, Study 18140

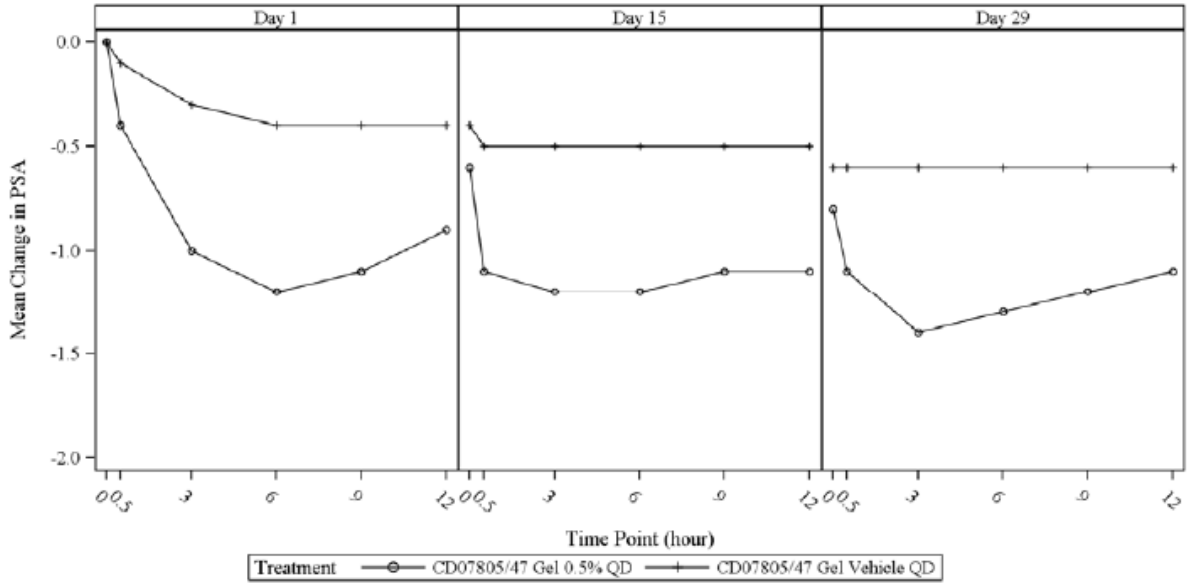
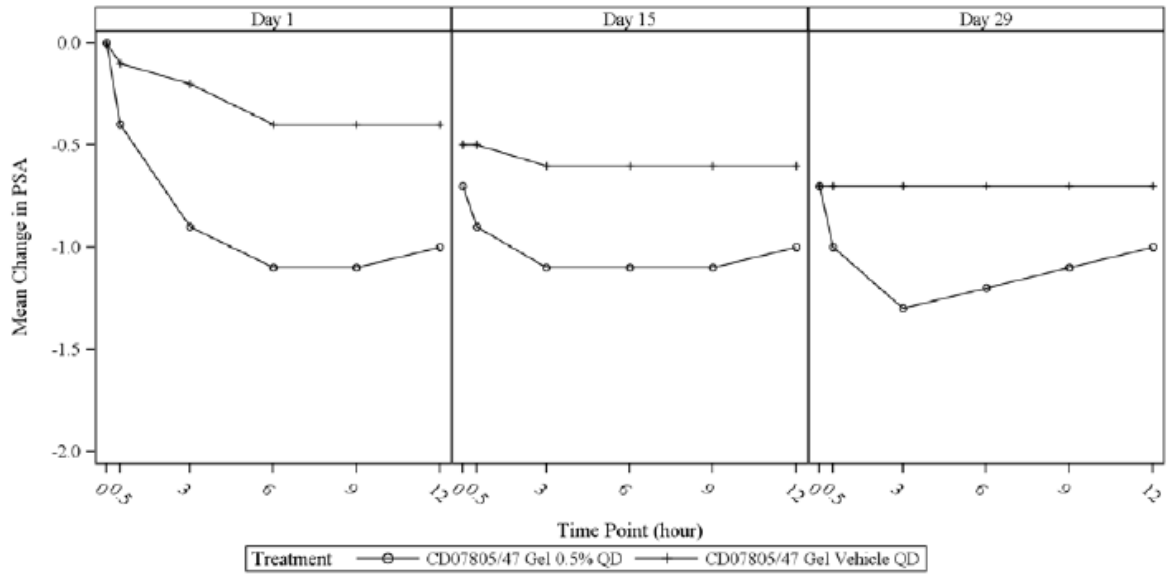


Figure 11. Mean Change in PSA on Day 1, Day 15 and Day 29, ITT Population, Study 18141



Patient Self Assessment (PSA) score: 0=No redness, 1=Very mild redness, 2=Mild redness, 3=Moderate redness, 4=Severe redness.
For Change in PSA from Baseline: 0=no change, -1=1-grade reduction, -2=2-grade reduction.

Patient Assessment of Appearance (PAA)

The subject's self-assessments of satisfaction with the overall appearance of their facial skin were based on the 5-grade PAA scale. At the end of the treatment period (Day 29/Hour 12), greater proportions of subjects in the brimonidine tartrate 0.5% Gel group in each study reported being satisfied or very satisfied with their appearance compared to subjects in the corresponding Vehicle Gel groups.

Table 29. PAA on Days 1 and 29; Studies 18140, 18141; ITT Population

PAA[a]	18140		18141	
	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Day 1: Hour 0				
0=Very satisfied	0	0	0	0
1=Satisfied	6 (4.7)	1 (0.8)	1 (0.7)	3 (2.1)
Day 29: Hour 12				
0=Very satisfied	10 (7.9)	1 (0.8)	13 (9.2)	3 (2.1)
1=Satisfied	45 (35.4)	25 (19.5)	38 (26.8)	24 (16.9)

[a] PAA Scores: 0=Very satisfied, 1=Satisfied, 2=Neither satisfied or dissatisfied, 3=Dissatisfied, 4=Very dissatisfied

Corresponding rates for categories 3 and 4 combined (dissatisfied and very dissatisfied) at day 29, Hour 12 were 27.6% for brimonidine tartrate 0.5% Gel and 43.7% for the Vehicle gel in Study 18140 and 24.6% and 42.2%, respectively, in study 18141.

The percentage of days that subjects had PAA scores of 0 (very satisfied) or 1 (satisfied) and the average PAA scores between visits (Days 2 to 14 and Days 16 to 28) are summarized below. Greater proportions of subjects reported scores or 0 or 1 and lower mean PAA scores were reported in the brimonidine tartrate 0.5% Gel groups compared to the Vehicle Gel groups.

Table 30. PAA between visits; 18140, 18141; ITT Population

PAA	18140		18141	
	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Days 2 to 14				
Average Score				
Mean	1.89	2.37	1.81	2.31
SD	0.855	0.710	0.831	0.792
Percent Days with Score 0 or 1 (%)				
Mean	39.39	13.87	41.39	18.52
SD	40.874	27.447	40.982	31.951
Days 16 to 28				
Average Score				
Mean	1.84	2.26	1.75	2.23
SD	0.867	0.773	0.842	0.834
Percent Days with Score 0 or 1 (%)				
Mean	42.65	18.94	43.79	21.04
SD	42.444	32.846	42.306	35.720

PAA Scores:: 0=Very satisfied, 1=Satisfied, 2=Neither satisfied nor dissatisfied, 3=Dissatisfied, 4=Very dissatisfied.

In Study 18140, the Day 15 visit for Subject 8026-002 was on Day 17; therefore, the Day 2-16 and Day 18-28 diary data were summarized in Day 2-14 (between Day 1 and Day 15) and Day 16-28 (between Day 15 and Day 29) instead.

Overall Treatment Effect (OTE)

Subject self-assessments of the overall impact of therapy on the management of their facial erythema relative to the beginning of the study were based on the OTE. The OTE assessments were completed on Day 29 at 12 hours after the first application of study drug. The data for the OTE, as assessed by subjects at Hour 12 on Day 29, are summarized below.

Table 31. OTE at Day 29/Hour 12; Study 18140; ITT Population

Overall Treatment Effect (OTE)	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)
1 = Very much worse	1 (0.8%)	1 (0.8%)
2 = Moderately worse	6 (4.8%)	3 (2.3%)
3 = A little worse	6 (4.8%)	3 (2.3%)
4 = About the same	30 (23.8%)	72 (56.3%)
5 = A little better	33 (26.2%)	32 (25.0%)
6 = Moderately better	33 (26.2%)	11 (8.6%)
7 = Very much better	17 (13.5%)	6 (4.7%)
Total	126 (100.0%)	128 (100.0%)
N	126	128
Mean	5.0	4.5
SD	1.34	1.00
Median	5.0	4.0
Minimum, Maximum	1, 7	1, 7

Table 32. OTE at Day 29/Hour 12; Study 18141; 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

Quality of life assessment results

The Phase 3 pivotal studies included QOL assessments based on the SF-12v2™ Acute Health Survey and the Productivity and Social Life Questionnaire.

The SF-12v2™ Acute Health Survey Scale/Component Score assessment was completed at predose (Hour 0) on Days 1, 15, 29 and during the Week 6 and Week 8 follow-up visits. No notable differences were observed in the mean scores on the various domains in either study between subjects in the brimonidine tartrate 0.5% Gel and Vehicle Gel groups on Days 1, 15, or 29.

The Productivity and Social Life Questionnaire assessment was completed at Hour 12 on Days 1 and 29 and during the Week 8 follow-up visit. As for the SF-12v2™ Acute Health Survey, no notable differences were observed between subjects in the brimonidine tartrate 0.5% Gel and Vehicle Gel groups in either study at any time point.

The Patient Assessment of Appearance (PAA), Overall Treatment Effect (OTE) and Quality of life assessments are different subject self-assessments of the treatment results.

For the PAA, less than 10% of the Brimonidine Tartrate 0.5% Gel treated subjects were very satisfied with their appearance at Day 29/Hour 12, while 30-35% were satisfied with their appearance. In the corresponding Vehicle Gel groups, a total of about 20% were satisfied or very satisfied with their appearance. The number of subjects being dissatisfied or very dissatisfied at Day 29/Hour 12 were higher for the vehicle gel, however, quite large numbers of subjects in the Brimonidine Tartrate 0.5% Gel groups were also dissatisfied or very dissatisfied with their appearance on the last treatment day.

For the OTE, higher percentages of subjects in the Brimonidine Tartrate 0.5% Gel group assessed the management of their facial erythema since starting the study as “Moderately better” or “Very much better” (40-45%) as a result of the treatment compared to subjects in the respective Vehicle Gel groups (less than 20%). The mean OTE scores were similar between treatment groups, though.

Of note is that for the three categories indicating worsening, about 10% of subjects in the brimonidine tartrate 0.5% Gel group assessed, the management of their facial erythema as worse compared to subjects in the respective Vehicle Gel groups (3-5%). Thus, twice as many subjects in the active treatment group considered that their condition had worsened as a result of treatment. This was, however, not reflected in the CEA and PSA results, since the number of patients experiencing a 1-grade impairment was lower in the active vs. the vehicle group

For the Quality of life assessments, no notable differences could be observed between the Brimonidine Tartrate 0.5% Gel and Vehicle Gel groups in either of the two scales at any time point. These scales do not seem to be of particular relevance for the assessment of QOL in a condition like rosacea. For instance for the Productivity and Social Life Questionnaire, the majority of subjects responded at baseline that their rosacea did not affect their productivity at work or daily activities, or that they avoided public contact or cancelled social engagement because of rosacea. Thus, since the rosacea did not seem to have major impact on their lives, an effect of treatment is not to be expected.

Investigator’s Global Assessment of Lesions and inflammatory lesion count results

Facial inflammatory lesions associated with rosacea were evaluated based on IGA of Lesions and facial inflammatory lesion counts. Subjects with 3 or more inflammatory lesions at Baseline were not eligible for inclusion in the studies. The IGA of Lesions and facial inflammatory lesion counts were performed on Day 1 at predose (T0), on Day 29 at Hour 1-2, and during the follow-up period (Day 30 and Week 5 in Study 18161 and Week 6 and Week 8 in all 3 studies). These assessments were intended to determine whether treatment of erythema resulted in a worsening of lesions.

A summary of the IGA of Lesions scores in the Phase 2b and Phase 3 pivotal studies during the treatment and follow-up periods is provided in the table below. In each of the studies, the Baseline scores were similar between the brimonidine tartrate 0.5% Gel and Vehicle Gel groups and no significant worsening in the mean IGA of Lesions scores was observed at Hour 12 on Day 29 or during the follow-up period.

Table 33. IGA of Lesions during treatment/follow-up; Studies 18161, 18140, 18141; ITT Population

IGA of Lesions	18161		18140		18141	
	CD07805/47 Gel 0.5% (N=53)	Vehicle Gel (N=55)	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Day 1: Hour 0						
0=Clear	25 (47.2)	35 (63.6)	95 (73.6)	94 (71.8)	102 (68.9)	102 (70.3)
1=Almost Clear	26 (49.1)	18 (32.7)	31 (24.0)	33 (25.2)	36 (24.3)	40 (27.6)
2=Mild	0	0	2 (1.6)	2 (1.5)	2 (1.4)	1 (0.7)
3=Moderate	2 (3.8)	2 (3.6)	1 (0.8)	2 (1.5)	7 (4.7)	2 (1.4)
4=Severe	0	0	0	0	1 (0.7)	0
Mean (SD)	0.6 (0.69)	0.4 (0.69)	0.3 (0.54)	0.3 (0.59)	0.4 (0.80)	0.3 (0.57)
Day 29: Hour 12						
Mean Change (SD)	-0.3 (0.84)	0.1 (0.92)	0.1 (0.74)	0.0 (0.86)	0.1 (0.91)	0.3 (0.93)
Follow-up: Week 6						
Mean Change (SD)	-0.2 (0.76)	0.0 (0.73)	0.0 (0.74)	-0.0 (0.67)	-0.0 (0.99)	0.1 (0.84)
Follow-up: Week 8						
Mean Change (SD)	-0.2 (0.86)	0.1 (0.86)	0.0 (0.77)	-0.0 (0.67)	-0.0 (0.92)	0.2 (0.83)

IGA of Lesions Scores: 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, 4=Severe

Regarding facial inflammatory lesion counts, the baseline assessments were similar between the treatment groups. Only very small increases in facial inflammatory lesion counts from baseline were observed in the Brimonidine Tartrate 0.5% Gel and vehicle gel groups at Day 29. No significant worsening in mean lesion counts was observed during the post-treatment follow-up period (weeks 6 and 8).

Telangiectasia Grading Assessment (TGA)

Telangiectasia's were evaluated based on the TGA performed on Day 1 at predose (T0), on Day 29 at Hour 12, and during the follow-up period (Weeks 6 and 8).

The TGA data during the treatment and follow-up periods are summarized in the table below. In each of the studies, the Baseline TGA severity was similar between the brimonidine tartrate 0.5% Gel and Vehicle Gel groups and no significant worsening in the mean TGA scores was observed at Hour 12 on Day 29 or during the follow-up period.

Table 34. TGA during treatment/follow-up; Studies 18161, 18140, 18141; ITT Population

TGA	18161		18140		18141	
	CD07805/47 Gel 0.5% (N=53)	Vehicle Gel (N=55)	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Day 1: Hour 0						
0=Clear with no signs of telangiectasia	8 (15.1)	6 (10.9)	6 (4.7)	9 (6.9)	22 (14.9)	22 (15.2)
1=Almost clear; scarce, barely visible telangiectasia	9 (17.0)	9 (16.4)	21 (16.3)	19 (14.5)	31 (20.9)	37 (25.5)
2=Mild; few visible telangiectasia	12 (22.6)	16 (29.1)	35 (27.1)	46 (35.1)	45 (30.4)	49 (33.8)
3=Moderate; clearly visible telangiectasia	22 (41.5)	21 (38.2)	60 (46.5)	51 (38.9)	44 (29.7)	34 (23.4)
4=Severe; many clearly visible telangiectasia	2 (3.8)	3 (5.5)	7 (5.4)	6 (4.6)	6 (4.1)	3 (2.1)
Mean	2.0	2.1	2.3	2.2	1.9	1.7
SD	1.17	1.10	0.97	0.98	1.12	1.05
Day 29: Hour 12						
Mean Change	-0.4	-0.5	-0.4	-0.4	-0.2	-0.1
SD	1.02	1.01	0.99	1.03	0.84	0.85
Follow-up: Week 6						
Mean Change	-0.5	-0.3	-0.4	-0.3	-0.2	-0.1
SD	0.88	0.83	0.91	0.89	0.98	0.97
Follow-up: Week 8						
Mean Change	-0.3	-0.4	-0.5	-0.4	-0.1	-0.1
SD	0.99	0.86	1.01	1.04	0.96	0.95

Patient Assessment of Whitening (PAW)

The subjects completed self-assessments of potential over-extended pharmacodynamic effect of the study drug based on the PAW. The assessments were completed by subjects on Day 1, Day 15, and Day 29 at pre-dose (T0), and at 3, 6, 9, and 12 hours after the first application of study drug. Between study visits (Days 2-14 and Days 16-28), the PAW was completed QD just before bedtime.

The PAW scores on Days 1, 15, and 29 in the Phase 2b and Phase 3 pivotal studies are summarized below. Higher percentages of subjects in the Brimonidine Tartrate 0.5% Gel groups in each study reported being bothered by too much whitening compared to the corresponding Vehicle Gel groups. The trend for unwanted over-whitening levelled out over the course of the treatment phase in each study.

Table 35. PAW during treatment; Studies 18161, 18140, 18141; ITT Population

PAW	18161		18140		18141	
	CD07805/47 Gel 0.5% (N=53)	Vehicle Gel (N=55)	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Day 1: Hour 3						
Bothered by Too Much Whitening	7 (13.2)	1 (1.8)	12 (9.3)	4 (3.1)	7 (4.7)	1 (0.7)
Day 1: Hour 6						
Bothered by Too Much Whitening	10 (18.9)	0	8 (6.2)	1 (0.8)	6 (4.1)	2 (1.4)
Day 1: Hour 9						
Bothered by Too Much Whitening	5 (9.4)	0	6 (4.7)	3 (2.3)	8 (5.4)	2 (1.4)
Day 1: Hour 12						
Bothered by Too Much Whitening	3 (5.7)	0	7 (5.4)	2 (1.5)	3 (2.0)	1 (0.7)
Day 15: Hour 3						
Bothered by Too Much Whitening	7 (13.5)	0	5 (3.9)	1 (0.8)	0	2 (1.4)
Day 15: Hour 6						
Bothered by Too Much Whitening	6 (11.5)	0	5 (3.9)	1 (0.8)	2 (1.4)	1 (0.7)
Day 15: Hour 9						
Bothered by Too Much Whitening	4 (7.7)	0	4 (3.1)	1 (0.8)	2 (1.4)	1 (0.7)
Day 15: Hour 12						
Bothered by Too Much Whitening	3 (5.8)	0	3 (2.3)	1 (0.8)	1 (0.7)	2 (1.4)
Day 29: Hour 3						
Bothered by Too Much Whitening	3 (5.9)	0	3 (2.4)	2 (1.6)	0	2 (1.4)
Day 29: Hour 6						
Bothered by Too Much Whitening	4 (7.8)	0	4 (3.1)	2 (1.6)	2 (1.4)	1 (0.7)
Day 29: Hour 9						
Bothered by Too Much Whitening	2 (3.9)	0	3 (2.4)	2 (1.6)	3 (2.1)	1 (0.7)
Day 29: Hour 12						
Bothered by Too Much Whitening	2 (3.9)	0	4 (3.1)	2 (1.6)	3 (2.1)	2 (1.4)

The percentage of days that subjects reported too much whitening and being bothered by too much whitening between visits (Days 2 to 14 and Days 16 to 28) are summarized below. Similar to the observed data for clinic visits, subjects in the brimonidine tartrate 0.5% Gel 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 36. PAW between visits; Studies 18161, 18140, 18141; ITT Population

PAW Between Visits	18161		18140		18141	
	CD07805/47 Gel 0.5% (N=53)	Vehicle Gel (N=55)	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Days 2 to 14						
Percent Days with Too Much Whitening (%)						
Mean	13.02	1.96	7.62	1.17	5.52	2.86
SD	27.142	12.492	19.959	9.076	16.773	15.381
Percent Days Bothered by Too Much Whitening (%)						
Mean	8.73	0.14	4.29	0.88	3.10	1.33
SD	22.645	1.038	14.175	8.778	13.421	9.903
Days 16 to 28						
Percent Days with Too Much Whitening (%)						
Mean	14.94	0.71	7.57	1.08	3.93	2.71
SD	30.172	5.239	21.414	8.511	14.967	15.141
Percent Days Bothered by Too Much Whitening (%)						
Mean	10.06	0	5.53	1.02	1.84	1.30
SD	24.252	0	17.907	8.491	9.715	10.954

Facial inflammatory lesions and telangiectasias are symptoms of rosacea that are not considered specific targets of the brimonidine tartrate 0.5% Gel treatment, however, assessment of these symptoms is of interest to evaluate whether any worsening would occur.

Regarding facial inflammatory lesions, the protocols for the pivotal studies stipulated that subjects with 3 or more inflammatory lesions at Baseline were not eligible for inclusion in the studies. Based on the results at Day 29 and at follow-up visits, no worsening of facial inflammatory lesions seemed to have occurred as a result of treatment.

Regarding telangiectasias, most subjects had mild or moderate telangiectasias at baseline. The mean scores had decreased slightly in both the brimonidine tartrate 0.5% Gel and Vehicle Gel groups at day 29 and there seemed to be no worsening of telangiectasias at the follow-up visits.

A too pronounced pharmacological effect of brimonidine tartrate 0.5% Gel may result in excessive and unwanted whitening, which was addressed by the PAW. Higher percentages of subjects in the brimonidine tartrate 0.5% Gel groups were bothered by too much whitening compared to the corresponding Vehicle Gel groups. However, the number of reports of unwanted over-whitening decreased over the course of the studies. No subject discontinued the studies due to over-whitening.

On Day 29 the percentages of subjects with unwanted over-whitening were rather similar in the brimonidine tartrate 0.5% and Vehicle Gel groups, which may be due to application technique and difference in contrast between treated and untreated areas. The treatment application technique (smooth, even application across all facial surfaces), which generally improves over time in subjects, may reduce noticeable contrasts between treated and untreated areas.

Ancillary analyses

Tachyphylaxis and rebound effects

Rebound effects can occur after withdrawal of alpha2-adrenergic receptor agonist agents in hypertension and for oxymetazoline (an alpha-adrenergic receptor antagonist), both tachyphylaxis and rebound increase in nasal airway congestion have been reported (Geyskes 1979; Vaidyanathan 2010).

The Applicant designed the Phase 2b and the Phase 3 pivotal studies to investigate the potential of brimonidine tartrate Gel to show a reduction in efficacy over time or to cause erythema that was more severe following discontinuation of treatment relative to the level of baseline erythema.

Regarding tachyphylaxis, the Phase 2b and Phase 3 pivotal studies assessed the effects of brimonidine tartrate Gel on erythema over a 12-hour observation period on three separate clinic Days; 1, 15, and 29. There was no notable diminishing in reduction in erythema within the 29-day treatment period, as assessed by the CEA and the PSA in any of these studies. Thus, evidence of tachyphylaxis was not observed.

For the assessment of potential for rebound erythema, a 4-week no treatment follow-up period was included in Studies ROSE-201, 18161, 18140, and 18141, which included assessments of erythema by the Investigators and subjects based on the CEA and PSA.

In the Phase 2b and Phase 3 pivotal studies, the assessment of potential rebound effect was based on mean changes in CEA and PSA scores during the post-treatment follow-up period (Weeks 6 and 8 and also at Day 30 and Week 5 in Study 18161). In each of the studies, the subjects continued to show some reductions in mean CEA and PSA scores relative to Baseline. In Study 18161, the mean reductions in CEA scores ranged from 0.6 to 0.7 points and the mean reductions in PSA scores ranged from 0.8 to 0.9 points relative to Day 1/Hour 0 across the 4 follow-up visits.

For the Phase 3 pivotal studies, the mean changes in CEA scores at Week 6 and Week 8 showed reductions in the brimonidine tartrate 0.5% Gel group of 0.3 points (SRE.18140) and 0.5 points (SRE.18141) for the CEA and 0.7 to 0.8 points (SRE.18140) and 0.7 points (SRE.18141) for the PSA relative to Day 1/Hour 0 up to 4 weeks following cessation of treatment. In the Phase 3 pivotal studies, some subjects showed worsening in CEA and PSA scores relative to Baseline during the follow-up period (see table below).

Table 37. Subjects with Worsening CEA or PSA during follow-up relative to Baseline; Studies 18140, 18141; ITT Population

CEA and PSA, n (%)	18140		18141	
	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Follow-up: Week 6				
1-grade CEA Increase	5 (4.0)	3 (2.4)	5 (3.6)	3 (2.1)
1-grade PSA Increase	3 (2.4)	4 (3.1)	6 (4.3)	3 (2.1)
Follow-up: Week 8				
1-grade CEA Increase	6 (4.7)	1 (0.8)	3 (2.1)	1 (0.7)
1-grade PSA Increase	2 (1.6)	1 (0.8)	3 (2.1)	4 (2.8)

The effect of brimonidine tartrate gel on erythema over a 29-day treatment period, as assessed by the CEA and the PSA, did not diminish over time, although the vehicle effect tended to increase somewhat over time. Thus, evidence of tachyphylaxis was not observed during a 4-week treatment period.

After cessation of treatment, no aggravation effect (rebound) of subject's facial erythema, as compared to Baseline/Day 1 levels, was observed during the 4-week follow-up period for either treatment group, based on mean changes in CEA and PSA scores. Some individuals showed worsening in CEA and PSA scores relative to Baseline during the follow-up period. More subjects in the brimonidine tartrate gel groups compared with the vehicle groups tended to experience worsening during the follow-up period, however, the numbers were small (<5% showed 1-grade increases in CEA or PSA).

No worsening of the IGA, increasing facial inflammatory lesion counts, or worsening of the TGA was observed during the 4-week follow-up period in the brimonidine tartrate gel groups.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial 18140

Title: 18140			
Study identifier	18140		
Design	This was a multicenter, randomized, double-blind, parallel-group, vehicle controlled efficacy and safety study of CD07805/47 Gel.		
	Duration of main phase:		29 days
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority over vehicle		
Treatments groups	CD07805/47 Gel 0.5%		N=129
	Vehicle Gel		N=131
Endpoints and definitions	Primary endpoint	2-Grade Composite Success	The primary efficacy endpoint for this study was 2-grade Composite Success at Hours 3, 6, 9, and 12 on Day 29, then on Day 15, and lastly on Day 1, with 2-grade Composite Success defined as a 2-grade improvement on both CEA and PSA at each time point.
	Secondary endpoint	1-Grade composite success	The secondary endpoint was 1 grade composite at 30 minutes on day 1 – Success was defined as 1-grade improvement in both CEA and PSA scales
	Tertiary endpoints	1-grade composite success or 2-grade success or percentage in scores or change from	1-grade Composite Success at Hour 3, 6, 9, 12 on Day 29, Day 15, and Day 1; 1-grade Composite Success was defined as 1-grade improvement on CEA and PSA. 2-grade CEA Success at Hours 3, 6, 9, and 12 on Day 29, Day 15 and Day 1; 2-grade CEA Success was defined as 2-grade improvement on

		pre-dose.	CEA. 2-grade PSA Success at Hours 3, 6, 9, and 12 on Day 29, Day 15 and Day 1; 2-grade PSA Success was defined as 2-grade improvement on PSA. Percentage of Days with PSA scored '0' or '1' between visits. Change in Pre-dose CEA from Baseline (T0 on Day 1) at each post-Baseline visit during treatment and follow-up phases. Change in Pre-dose PSA from Baseline (T0 on Day 1) at each post-Baseline visit during treatment and follow-up phases.
Database lock	23/09/2011		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Day 29, then Day 15, then Day 1		
Descriptive statistics and estimate variability	Treatment group	CD07805/47 Gel 0.5%	Vehicle Gel
	Number of subject	129	131
	Day 29 2-grade Composite Success	From (3h) to (12h) 31,5% - 22,8%	From (3h) to (12h) 10,9%- 8,6%
	Day 15 2-grade Composite Success	From (3h) to (12h) 25,0%- 16,4%	From (3h) to (12h) 3,1%- 2,3%
	Day 1 2-grade Composite Success	From (3h) to (12h) 16,3%- 13,2%	From (3h) to (12h) 3,1%- 3,1%

Effect estimate per comparison	Day 29 2-grade Composite Success	Comparison groups	CD07805/47 Gel 0.5% vs vehicle
		GEE methodology	Multiple imputation
		P-value	0.001
	Day 15 2-grade Composite Success	Comparison groups	CD07805/47 Gel 0.5% vs vehicle
		GEE methodology	Multiple imputation
		P-value	0.001
	Day 1 2-grade Composite Success	Comparison groups	CD07805/47 Gel 0.5% vs vehicle
		GEE methodology	Multiple imputation
		P-value	0.001

Notes	none
Efficacy Analysis	The primary analyses are 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) methodology in the ITT population. The logit link function is used to model the marginal expectation. The dependent variables in the model is Composite Success at Hours 3, 6, 9, and 12 on Day 29 and the independent variables are treatments, analysis center, time points (Hours 3, 6, 9, and 12) and treatment*analysis center. The treatment-by-center interaction for Composite Success on Day 29 was assessed at an alpha level of 0.1 by testing treatment-by-center effect in the GEE model. If interaction effect is statistically significant, the results were further explored to examine the magnitude, direction, and potential impact of the interaction. To handle missing data at any time points (i.e. Hours 3, 6, 9, and 12), the Multiple Imputation (MI) procedure was used as the primary imputation method. Multiple imputed datasets was created by the MI procedure, GEE analysis was performed on each imputed dataset, and the statistical results were generated by combining the parameter estimates and covariance matrix from each imputed dataset. In additional to the MI procedure, 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 is observed on CEA and PSA using the average score of the repeated measurements at Hours 3, 6, 9, and 12.

Summary of efficacy for trial 18141

Title: 18141			
Study identifier	18141		
Design	This was a multicenter, randomized, double-blind, parallel-group, vehicle controlled efficacy and safety study of CD07805/47 Gel.		
	Duration of main phase:		29 days
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority over vehicle		
Treatments groups	CD07805/47 Gel 0.5%		N= 131
	Vehicle Gel		N=129
Endpoints and definitions	Primary endpoint	2-Grade Composite Success	The primary efficacy endpoint for this study was 2-grade Composite Success at Hours 3, 6, 9, and 12 on Day 29, then on Day 15, and lastly on Day 1, with 2-grade Composite Success defined as a 2-grade improvement on both CEA and PSA at each time point.

	Secondary endpoint	1-Grade composite success	The secondary endpoint was 1 grade composite at 30 minutes on day 1 – Success was defined as 1-grade improvement in both CEA and PSA scales
	Tertiary endpoints	1-grade composite success or 2-grade success or percentage in scores or change from pre-dose.	1-grade Composite Success at Hour 3, 6, 9, 12 on Day 29, Day 15, and Day 1; 1-grade Composite Success was defined as 1-grade improvement on CEA and PSA. 2-grade CEA Success at Hours 3, 6, 9, and 12 on Day 29, Day 15 and Day 1; 2-grade CEA Success was defined as 2-grade improvement on CEA. 2-grade PSA Success at Hours 3, 6, 9, and 12 on Day 29, Day 15 and Day 1; 2-grade PSA Success was defined as 2-grade improvement on PSA. Percentage of Days with PSA scored '0' or '1' between visits. Change in Pre-dose CEA from Baseline (T0 on Day 1) at each post-Baseline visit during treatment and follow-up phases. Change in Pre-dose PSA from Baseline (T0 on Day 1) at each post-Baseline visit during treatment and follow-up phases.
Database lock	23/09/2011		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intent to treat Day 29, then Day 15, then Day 1		
Descriptive statistics and estimate variability	Treatment group	CD07805/47 Gel 0.5%	Vehicle Gel
	Number of subject	131	129
	Day 29 2-grade Composite Success	From (3h) to (12h) 21,6% - 19,2%	From (3h) to (12h) 10,2-11,0%
	Day 15 2-grade Composite Success	From (3h) to (12h) 23,8%- 15,1%	From (3h) to (12h) 4,0%- 7,9%
	Day 1 2-grade Composite Success	From (3h) to (12h) 17,6%- 11,5%	From (3h) to (12h) 0%-1,6%
Effect estimate per	Day 29 2-grade	Comparison groups	CD07805/47 Gel 0.5% vs

comparison	Composite Success		vehicle
		GEE methodology	Multiple imputation
		P-value	0.001
	Day 15 2-grade Composite Success	Comparison groups	CD07805/47 Gel 0.5% vs vehicle
		GEE methodology	Multiple imputation
		P-value	0.001
	Day 1 2-grade Composite Success	Comparison groups	CD07805/47 Gel 0.5% vs vehicle
		GEE methodology	Multiple imputation
		P-value	0.001
Notes	none		
Efficacy Analysis	The primary analyses are 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) methodology in the ITT population. The logit link function is used to model the marginal expectation. The dependent variables in the model is Composite Success at Hours 3, 6, 9, and 12 on Day 29 and the independent variables are treatments, analysis center, time points (Hours 3, 6, 9, and 12) and treatment*analysis center. The treatment-by-center interaction for Composite Success on Day 29 was assessed at an alpha level of 0.1 by testing treatment-by-center effect in the GEE model. If interaction effect is statistically significant, the results were further explored to examine the magnitude, direction, and potential impact of the interaction. To handle missing data at any time points (i.e. Hours 3, 6, 9, and 12), the Multiple Imputation (MI) procedure was used as the primary imputation method. Multiple imputed datasets was created by the MI procedure, GEE analysis was performed on each imputed dataset, and the statistical results were generated by combining the parameter estimates and covariance matrix from each imputed dataset. In additional to the MI procedure, 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 is observed on CEA and PSA using the average score of the repeated measurements at Hours 3, 6, 9, and 12.		

Clinical studies in special populations

No studies were performed in special populations.

In the Phase 3 pivotal studies, descriptive summaries were prepared for the primary endpoint of 2-grade Composite Success by gender, race and age group.

With respect to gender, more than 20% of the study population was represented by males and the data indicate no major gender difference in response for the primary end-point.

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.

With respect to age, a majority of subjects (>90%) were 18 to 64 years old, making it difficult to draw conclusions from the subgroup summaries for age groups. In the subgroup of subjects who were 65 years of age or older, no more than 3 subjects showed 2-grade Composite Success in either treatment group at any time point. There were only 24 subjects in the Mirvaso and vehicle groups, respectively, when both studies were pooled. Firm conclusions on efficacy are difficult to make although there is no reason to believe that the effect of Mirvaso would differ to a large extent in this age group.

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. However, the number of subjects ≥65 years of age was relatively small and the age distribution was not presented. The data presented by the applicant raise no concerns although the number of subjects above 65 years is very limited.

With respect to race, the vast majority of subjects were Caucasians (>98%) and only few non-Caucasians were represented (in total 4 subjects in each study). In Study 18140, none of the 2 non-Caucasians who received active treatment reached 2-grade Composite Success at any time point and in Study 18141, 1 out of 3 non-Caucasians reached 2-grade Composite Success on active treatment on Day 29. Section 5.1 of the SmPC includes information that the majority of the subjects studied were Caucasian.

In a subgroup analysis made with respect to baseline severity of erythema, the active treatment showed statistically significant separation from vehicle at each time point in 2-grade Composite Success on Days 1, 15, and 29 in subjects with baseline PSA or CEA severity of 4 (e.g., severe). Across Studies 18140 and 18141, 2-grade Composite Success in subjects with severe erythema at baseline ranged from 8.9% to 26.6% in the active group vs. 0.0% to 11.1% in the vehicle group.

Supportive study
Study RD.06.SRE.18142

A multicentre, open-label study to evaluate the long-term safety and efficacy of CD07805/47 Gel 0.5% applied topically once daily for up to 52 weeks in subjects with moderate to severe facial erythema associated with rosacea

Methods

This was a long-term, open-label, uncontrolled study in subjects with moderate to severe facial erythema of rosacea. The purpose of the study was to evaluate the efficacy and safety of Brimonidine Tartrate 0.5% Gel applied for up to 52 weeks (no less than 365 days). The study was initiated on 10 March 2011 and completed on 13 June 2012.

- **Study participants**

The subjects included were male or female, of any race, 18 years of age or older, with screening and Baseline visit Clinician Erythema Assessment (CEA) scale and Patient Self-Assessment (PSA) scale scores of ≥3. There were two differences in eligibility criteria compared to the Phase 3 pivotal studies regarding inflammatory lesions and concomitant rosacea treatments. Subjects with 3 or more inflammatory lesions were eligible to participate in this study. Additionally, concomitant standard of care treatments (doxycycline, metronidazole, etc.) 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. For subjects who required new therapy for the presence of inflammatory lesions at the time of enrolment or during the course of the study, Investigators were permitted to prescribe the standard of care treatment at the Investigator's discretion.

In contrast to the controlled studies, inclusion of patients with 3 or more inflammatory lesions and with concomitant standard of care treatments (doxycycline, metronidazole, etc.) for inflammatory lesions of rosacea was allowed, which results in a study population probably more reflecting the true rosacea population.

- **Treatments**

CD07805/47 gel 0.5% was applied once daily to the entire face. Qualified, screened subjects were treated for up to 12 months (no less than 365 days) and were to return to the investigational site for evaluations at Baseline, Week 1, and at Months 1, 3, 6, 9, and 12/Early Termination (ET). Laboratory samples were to be obtained at Screening, Month 3, Month 6, and Month 12/ET. Intraocular pressure (IOP) was measured at Baseline, Month 1, Month 6, and Month 12/ET.

Outcomes/endpoints

The primary objective of this study was to evaluate and document the long-term safety of CD07805/47 gel 0.5% applied once daily and long-term efficacy was evaluated as a secondary objective. Efficacy end-points were PSA and CEA, assessed at Hour 0 and Hour 3 at each visit, change in PSA/CEA from Baseline PSA (Hour 0 at Baseline visit) at each post-baseline visit, and change in PSA/CEA between Hour 0 and Hour 3 at each visit. Other end-points were PAA, OTE, IGA, TGA, PAW, inflammatory lesion counts and Productivity and Social Life Questionnaires.

- ***Sample size***

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.

- **Statistical methods**

Summary statistics and frequency distributions for the PSA, CEA, PAA and other assessments were 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). Results from Hour 0 and Hour 3 time points and changes between time points were presented. The PSA, CEA, and PAA assessments were also summarized within the subgroups gender, age group (18 to 64 years versus 65 years and above) and race (Caucasian versus non-Caucasian).No particular statistical method was described.

- **Results**

Of 586 subjects screened, 137 subjects were screen failures, mainly due to not meeting the Inclusion/Exclusion criteria. A total of 449 subjects were enrolled and all subjects were included in the Safety Population. Two hundred seventy-nine (279) subjects (62.1%) completed the study and 335 subjects (74.6%) completed at least 6 months of treatment.

The baseline demographic and disease characteristics in this study were similar to those in the pivotal phase 3 studies. Almost 30% of the subjects took concomitant therapies for inflammatory lesions associated with their rosacea, with Metronidazole being most common (15.6%).

In this study, the open-label study design and subject attrition over time hampers the interpretation of efficacy results. Furthermore, other rosacea treatments were allowed. The PSA and CEA results, however, indicated that the study drug had an effect after the first application and that no obvious tachyphylaxis of the treatment effect occurred over time with chronic use. The results for mean changes in PSA and CEA

at the Month 1 visit were rather similar to the results observed in Phase 2b and Phase 3 controlled clinical studies.

Table 38. PSA, Study 18142, Safety Population

PSA	Baseline (Day 1)	Week 1	Month 1	Month 3	Month 6	Month 9	Month 12	End of Treatment[a]
Hour 0								
0=No redness, n (%)	0	2 (0.5)	3 (0.7)	8 (2.2)	7 (2.2)	4 (1.3)	8 (2.9)	9 (2.0)
1=Very mild redness, n (%)	0	21 (5.1)	31 (7.4)	71 (19.1)	57 (17.5)	69 (23.0)	61 (21.8)	85 (18.9)
2=Mild redness, n (%)	2 (0.4)	98 (23.9)	145 (34.8)	129 (34.7)	110 (33.8)	96 (32.0)	108 (38.6)	155 (34.5)
3=Moderate redness, n(%)	379 (84.4)	235 (57.3)	195 (46.8)	143 (38.4)	118 (36.3)	96 (32.0)	84 (30.0)	160 (35.6)
4=Severe redness, n (%)	68 (15.1)	54 (13.2)	43 (10.3)	21 (5.6)	33 (10.2)	35 (11.7)	19 (6.8)	40 (8.9)
Total, n	449	410	417	372	325	300	280	449
Mean (SD)	3.1 (0.37)	2.8 (0.76)	2.6 (0.80)	2.3 (0.91)	2.3 (0.96)	2.3 (0.99)	2.2 (0.94)	2.3 (0.94)
Change from Baseline (Day 1) Hour 0								
Total, n	-	410	417	372	325	300	280	449
Mean Change (SD)	-	-0.4	-0.6	-0.9	-0.8	-0.9	-1.0	-0.8
Change from Baseline (Day 1) Hour 0[b] to Hour 3								
Total, n	449	410	417	372	325	300	280	449
Mean Change (SD)	-1.0 (0.94)	-1.1 (0.88)	-1.2 (0.93)	-1.6 (0.98)	-1.5 (0.96)	-1.5 (1.00)	-1.7 (0.94)	-1.5 (1.02)
Hour 3 minus Hour 0 at each Clinic Visit								
Total, n	449	410	417	372	325	300	280	449

PSA	Baseline (Day 1)	Week 1	Month 1	Month 3	Month 6	Month 9	Month 12	End of Treatment[a]
Mean (SD)	-1.0 (0.94)	-0.7 (0.94)	-0.7 (0.97)	-0.7 (0.97)	-0.7 (0.98)	-0.7 (1.07)	-0.6 (0.97)	-0.7 (1.05)

Changes are from the Hour 0 assessment at the Baseline (Day 1) visit.

[a] End of Treatment is a summary of the last recorded observation for each subject and occurred at Month 12 for subjects who completed the study, or occurred earlier in the case of subjects who prematurely discontinued the study.

[b] The Change from Baseline (Day 1) Hour 0 values for the Baseline visit are equal to the Hour 3 minus Hour 0 at each Clinic Visit values at the Baseline visit.

Table 39. CEA, Study 18142, Safety Population

CEA	Baseline (Day 1)	Week 1	Month 1	Month 3	Month 6	Month 9	Month 12	End of Treatment[a]
Hour 0								
0=Clear skin with no signs of erythema, n (%)	0	3 (0.7)	1 (0.2)	4 (1.1)	3 (0.9)	2 (0.7)	5 (1.8)	5 (1.1)
1=Almost clear, slight redness, n (%)	0	26 (6.3)	32 (7.7)	61 (16.4)	39 (12.0)	47 (15.7)	45 (16.1)	65 (14.5%)
2=Mild erythema, definite redness, n (%)	0	85 (20.7)	141 (33.8)	106 (28.5)	110 (33.7)	106 (35.3)	113 (40.4)	158 (35.2)
3=Moderate erythema, marked redness, n (%)	394 (87.8)	243 (59.3)	200 (48.0)	174 (46.8)	136 (41.7)	116 (38.7)	97 (34.6)	187 (41.6)
4=Severe erythema, fiery redness, n (%)	55 (12.2)	53 (12.9)	43 (10.3)	27 (7.3)	38 (11.7)	29 (9.7)	20 (7.1)	34 (7.6)
Total, n	449	410	417	372	326	300	280	449
Mean (SD)	3.1 (0.33)	2.8 (0.78)	2.6 (0.78)	2.4 (0.89)	2.5 (0.88)	2.4 (0.89)	2.3 (0.88)	2.4 (0.87)

CEA	Baseline (Day 1)	Week 1	Month 1	Month 3	Month 6	Month 9	Month 12	End of Treatment[a]
Change from Baseline (Day 1) Hour 0								
Total, n	-	410	417	372	326	300	280	449
Mean Change (SD)	-	-0.3 (0.73)	-0.5 (0.75)	-0.7 (0.86)	-0.6 (0.87)	-0.7 (0.86)	-0.8 (0.85)	-0.7 (0.84)
Change from Baseline (Day 1) Hour 0[b] to Hour 3								
Total, n	449	410	417	372	326	300	280	449
Mean Change (SD)	-1.5 (0.88)	-1.4 (0.85)	-1.5 (0.83)	-1.7 (0.84)	-1.8 (0.88)	-1.7 (0.90)	-1.8 (0.83)	-1.7 (0.90)
Hour 3 minus Hour 0 at each Clinic Visit								
Total, n	449	410	417	372	326	300	280	449
Mean (SD)	-1.5 (0.88)	-1.0 (0.96)	-1.0 (0.97)	-1.0 (0.88)	-1.1 (1.05)	-1.0 (0.97)	-1.0 (0.92)	-1.0 (0.98)

Changes are from the Hour 0 assessment at the Baseline (Day 1) visit.

[a] End of Treatment is a summary of the last recorded observation for each subject and occurred at Month 12 for subjects who completed the study, or occurred earlier in the case of subjects who prematurely discontinued the study.

b The Change from Baseline (Day 1) Hour 0 values for the Baseline visit are equal to the Hour 3 minus Hour 0 at each Clinic Visit values at the Baseline visit.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of Mirvaso gel 0.5% is supported by six clinical studies; three phase 2 studies, two pivotal phase 3 studies and one open-label, long-term phase 3 study. Both the phase 2 and the pivotal phase 3 studies were randomized, double-blind, parallel-group and vehicle-controlled. The treatment period was 29 days in all studies except one phase 2a study that was a single dose study. The studies enrolled male and female patients 18 years of age or above, with moderate to severe facial erythema associated with rosacea, with less than 3 inflammatory lesions. Other rosacea treatments were not allowed in the controlled studies.

Mirvaso is a product targeting a single symptom of rosacea, i.e. facial erythema, while other rosacea products mainly affect other symptoms of the condition, e.g. by reducing inflammatory papules and pustules. There is no European guideline available for products indicated for treatment of rosacea and efficacy end-points to be used are not clearly established. The applicant developed the CEA (Clinician Erythema Assessment) scale and the PSA (Patient Self-Assessment) scales that were used as co-primary end-points in the pivotal phase 3 studies as well as phase 2 studies. The development and validation of the CEA and PSA scales have been described in the dossier and specific studies have been performed to address their relevance, e.g. by assessment of inter- and intra-rater agreement and content validity. The

scales are deemed to be sufficiently described and validated for their intended purpose. It should be acknowledged that both the PSA and the CEA are scales that are based on subjective judgements and not objective measures. However, considering the type of condition and the intended use of the product (symptomatic reduction of erythema rather than curative treatment), assessments made by the patient are of relevance.

In addition, other patient rated scales were used, such as Patient Assessment of Appearance (PAA), Overall Treatment Effect (OTE) and Patient Assessment of Whitening (PAW). Furthermore, assessments of inflammatory lesion counts, telangiectasia and quality of life were made by the use of different scales.

In the pivotal phase 3 studies, subjects were randomized to receive study drug for a period of 4 weeks and returned to the investigational centres on Weeks 6 and 8 for follow-up evaluations. . The inclusion and exclusion criteria are overall acceptable. Subject assessments were performed at the investigational center during a 12-hour post-dose evaluation period on Days 1, 15, and 29. On non-clinic days (Days 2-14 and 16-28) subjects were to apply study drug as directed and to complete daily self-assessments (PSA, PAA and PAW). The Overall Treatment Effect (OTE) was assessed by the patient on Day 29. Quality of Life assessed by the SF-12v2™ Acute Health Survey and a Productivity and Social Life Questionnaire were also completed at specified visits. The applicant discussed that the results observed and noted they could have been due to several factors, including small number of subjects, recall bias, and suboptimal timing of the assessment. Nonetheless, the overall results from the OTE favour brimonidine, with significantly more subjects on Mirvaso in each study ($p<0.001$) reporting improvement in the management of their facial erythema as assessed by the OTE compared to vehicle subjects. It seems plausible that in an overall assessment, some subjects experienced the wearing off of the effect at the end of the day as a worsening and that this is more pronounced in the active than the vehicle group. All subjects will not respond to Mirvaso in a satisfactory manner, however, the overall OTE results show that the majority of patients experienced an improvement with Mirvaso; this was agreed by the CHMP.

The investigator/evaluator (a board-certified dermatologist) completed the CEA at each clinic visit. Telangiectasias assessed by TGA and inflammatory lesions assessed by IGA and lesion counts were also performed. Whenever possible, the same investigator/evaluator was to perform the assessments for each individual subject for the entire duration of the study. On Days 1, 15 and 29, CEA and PSA were assessed at the time points 30 minutes and 3, 6, 9, and 12 hours after T0.

The primary efficacy end-point was 2-grade Composite Success at Hours 3, 6, 9, 12 on Day 29, then on Day 15 and lastly on Day 1, with 2-grade Composite Success defined as a 2-grade improvement on both CEA and PSA at each time point. The secondary efficacy end-point was early, 30-minute effect, defined as 1-grade Composite Success (1-grade improvement on both CEA and PSA) at 30 minutes on Day 1. Several tertiary and other end-points were also evaluated.

Efficacy data and additional analyses

Different concentrations of brimonidine tartrate gel were used in the phase 2 studies and based on results of the studies, the 0.5% concentration of brimonidine tartrate Gel administered once daily was selected for the Phase 3 studies. Concentrations higher than 0.5% or BID application of the 0.5% gel have not been studied. The decision to go for the 0.5% QD posology was also based on pharmacokinetic results, since a higher gel concentration or BID application may result in too high systemic exposure to brimonidine. The rationale for not selecting a higher concentration or a BID dose regimen was to maintain an optimized benefit/risk ratio for the product and to avoid excessive, unwanted pharmacodynamic effects (such as “over-whitening”). The applicant has adequately outlined their reasoning behind the choice of the 0.5% concentration and the administration frequency of the product.

In the pivotal phase 3 studies, the majority of included subjects were females (>70%) with a mean age of 45-50 years. Almost only Caucasian or white subjects were included. Most subjects had a Fitzpatrick skin phototype of II or III. The population included reflects the population most commonly affected by rosacea, i.e. mainly females, aged 30-50 years and with fair skin. The subjects included had moderate to severe facial erythema (PSA and CEA scores of 3 or 4) with the majority (generally >80%) having moderate erythema. There were no major differences between the active treatment and the vehicle groups in baseline characteristics in the two pivotal studies. The number of subjects completing the studies was high (>96%) in both studies.

In both pivotal studies, brimonidine tartrate 0.5% Gel 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). Statistical superiority of brimonidine tartrate 0.5% Gel versus Vehicle Gel was also demonstrated on Days 1 and 15 ($p<0.001$). The results were confirmed in the ITT Population using the LOCF method, in the MITT population (in Study 18141) and the PP Population, and in sensitivity analyses.

There was a tendency to an increased response across days 1, 15 and 29 both in the active and vehicle gel treated groups. On Day 29, the vehicle response was approximately 10% and for Brimonidine Tartrate 0.5% Gel, the response at different time points ranged between 17.6% and 31.5%. This fact also observed at 2 additional centres in study 18141 and also in 3 centres in study 18140. Although this could be due to normal variation, it could also indicate problems related to blinding. The applicant was asked to discuss this finding and analyse the efficacy data from both studies without these centres.

The requested analyses were provided with exclusion of sites for which none of the vehicle subjects achieved 2-grade Composite Success on Day 29. This concerned a fairly large number of sites (a total of 12 out of 30). Still, statistical significance vs. vehicle was maintained for all comparisons, except for the Day 29 results in study 18141. It is agreed that with an anticipated 10% incidence of 2-grade Composite Success in the vehicle group it is not unlikely that there would be several sites without any vehicle subjects achieving 2-grade Composite Success.

The highest response was observed at the 3 and 6 hour time points and the effect tended to wear off at the later time points.

For the secondary endpoint (30-Minute effect), brimonidine tartrate 0.5% Gel produced a statistically significant ($p<0.001$) earlier effect compared to the Vehicle Gel groups in both pivotal studies based on the definition used. 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 5-7% of Vehicle Gel subjects.

Tertiary efficacy end-points also supported the superiority of brimonidine tartrate 0.5% Gel over vehicle gel. However, the patient self-assessments PAA and OTE also showed that quite substantial numbers of patients were not satisfied with their appearance or experienced worsening of the condition at the end of treatment. For the OTE, twice as many subjects in the active treatment group vs. the vehicle group considered that their condition had worsened as a result of the treatment; but overall, more subjects considered that their condition had improved in the Mirvaso vs. the vehicle group. No effect on Quality of life assessments could be shown.

The studies were performed under rather standardised, experimental conditions, i.e. the patients arrived at the investigational center 1 hour prior to study drug application to allow acclimation to the environment and were required to rest comfortably for 15 minutes before assessments were completed. Thus, the conditions may not reflect “real-life” conditions, e.g. situations that may cause the erythema of rosacea to flare up, e.g. sun, cold or wind, exercise and stress. The applicant adequately justified that the effect seen in the pivotal studies can be extrapolated to normal, “real-life” conditions. During the 12-hour post-dosing period on clinic days, subjects were permitted to leave the investigative sites between

assessments and were not confined to the site for the entire 12 hours, and activities/behaviours/food intake were not monitored or restricted between the assessment time points. Subjects were educated on typical factors that may exacerbate rosacea and were encouraged to maintain a consistent lifestyle regarding these factors but were not required to agree to abstain from consumption of alcohol or spicy food or from exercise during the study in order to be eligible. The non-clinic days are also representative of real-life conditions since the subject applied the study drug themselves at home and participated in typical daily activities and made self-assessments of the treatment effect by PSA. It is concluded that the conditions in the pivotal studies are sufficiently representative of real-life conditions. Study 18142, although open-label also provides support for use of Mirvaso during real-life conditions, including the possibility to use together Mirvaso with other rosacea medications.

The efficacy and safety of brimonidine tartrate 0.5% Gel in patients treated with other topical products for the treatment of rosacea, e.g. metronidazole or azelaic acid gel, has not been systematically investigated. In clinical practice, a combination of Mirvaso and metronidazole gel is likely, since a rapid onset of effect on erythema may be desirable or if metronidazole does not sufficiently reduce erythema. In the open-label long-term study, other rosacea treatments were allowed and a fairly large percentage of the subjects (almost 30%) used other topical rosacea products although the number of subjects (n=131) does not constitute a large database. Of these, metronidazole use was most common (70 subjects, 15.6 %) and azelaic acid less common (27 subjects, 6.0%). Efficacy results show roughly similar results for 2-grade composite success for subjects with or without concomitant rosacea medication. Also from a safety perspective, concomitant use of Mirvaso with other topical rosacea products did not seem to result in safety problems, e.g. related to local tolerability.

In section 4.2 of the SmPC, it is stated that other cutaneous products for the treatment of inflammatory lesions of rosacea may be used and should be applied after the applied Mirvaso has dried. Information is also included in section 5.1 and it is stated that the use of Mirvaso with other medications for the treatment of inflammatory lesions of rosacea has not been systematically investigated.

Long-term efficacy data is limited to the open-label safety study 18142, with efficacy assessed as secondary endpoint and only up to three hours after application. Aspects related to the risk of tachyphylaxis have been adequately addressed. A comparison of efficacy results at 3 hours among studies 18140, 18141 and 18142 has shown a similar level of activity after 28 days and after 1 year of use. These results support the notion that efficacy, once the peak is reached, is maintained over time.

PK data show no accumulation of the drug in the plasma, in line with the known half-life of brimonidine. The decrease of activity over time registered during the single day of application is presumably linked to the half-life of the active substance more than to a significant down regulation of receptors. Also, an assessment of the correlation between the amount of drug used and PSA scores has shown no deliberate over-usage (which would have indicated a potential decrease in efficacy) after several days of use.

All studies have been performed in the US or Canada, while no data in the EU is available. For this type of condition, a difference between populations and the disease is not expected and it is considered acceptable to extrapolate the data from the US/Canadian population to the EU population.

No study including an active comparator has been performed. Currently, there are no approved medicinal products in the EU that directly target the persistent facial erythema of rosacea and available products primarily target the papulopustular rosacea subtype of the disease, reducing rosacea inflammatory lesions through anti-inflammatory mechanisms. Comparisons with topical metronidazole or azelaic acid gel may therefore not be relevant, although since at least topical metronidazole is claiming some effect towards reducing the erythema component of rosacea, a comparison would have added further information. However, as brimonidine tartrate gel and these other products have different time courses for effect, with brimonidine tartrate gel showing a rapid effect on facial erythema while metronidazole or

azelaic acid have slower onset of effect, a comparison would likely have been difficult. Thus, it is agreed that active comparator studies are not necessary.

2.5.4. Conclusions on the clinical efficacy

A significantly superior effect for brimonidine tartrate 0.5% Gel compared to Vehicle Gel was demonstrated for the primary endpoint on Days 29 (2-grade Composite Success for CEA and PSA at Hours 3, 6, 9, and 12 on Day 29) and then on Day 15 and lastly on Day 1, with 2-grade Composite Success defined as a 2-grade improvement on both CEA and PSA at each time point. For the Overall Treatment Effect (OTE), twice as many subjects in the active treatment group compared with the vehicle group considered that their condition had worsened as a result of treatment, though. This could have been due to several factors, including small number of subjects, recall bias, and suboptimal timing of the administration of the assessment. It seems plausible that in an overall assessment, some subjects experienced the wearing off of the effect at the end of the day as a worsening and that this is more pronounced in the active than the vehicle group. The overall OTE results showed that the majority of patients experienced an improvement with Mirvaso.

For the TGA, chronic long-term use of the study drug did not seem to exacerbate telangiectasia severity. For the PAW, the proportions of subjects who reported too much whitening and being bothered by too much whitening were rather high initially but tended to decrease throughout the course of the study. No subjects discontinued the study due to too much whitening or blanching of the skin.

A positive psychosocial impact on rosacea patients' lives upon long-term use of brimonidine tartrate 0.5% Gel, based on results from the social life questions in the Productivity and Social Life Questionnaire, is claimed by the applicant. However, these results are interpreted very cautiously by the CHMP considering the open-label study design.

There is no data available to assess efficacy of brimonidine tartrate 0.5% Gel in patients treated with other topical products for the treatment of rosacea, e.g. metronidazole or azelaic acid gel. In clinical practice, a combination of Mirvaso and metronidazole gel is likely, since a rapid onset of effect on erythema may be desirable or if metronidazole does not sufficiently reduce erythema. In the open-label long-term study, other rosacea treatments were allowed and a fairly large percentage of the subjects (131, almost 30%) used other topical rosacea products. Efficacy results show roughly similar results for 2-grade composite success for subjects with or without concomitant rosacea medication. In conclusion, the applicant has adequately outlined their reasoning behind the choice of the 0.5% concentration and the administration frequency of the product.

Overall, Brimonidine tartrate gel 0.5% has demonstrated a positive symptomatic effect on the erythema of facial rosacea, which is deemed clinically relevant.

2.6. Clinical safety

The safety monitoring of brimonidine tartrate gel for each study was performed adequately by collecting treatment-emergent adverse events (TEAEs) and routine laboratory data, physical examination, and vital signs and, in some studies, intraocular pressure (IOP) measurements. Because ophthalmic brimonidine tartrate is approved for treating high IOP when applied as an aqueous solution, the Applicant evaluated any potential of topical brimonidine tartrate gel to reduce IOP systemically or after unintended contact with the eye.

The submission consists of 18 studies supporting safety and efficacy of brimonidine tartrate in cutaneous treatment of facial erythema of rosacea in adult patients. Ten (10) of the 18 studies were conducted in subjects with rosacea and 8 studies were conducted in healthy subjects.

Five safety populations were presented to support the analysis of clinical safety data. The parameters used to determine the groupings were based on subject population, study design, study drug concentration, length of treatment, and type of control. The populations are:

1. Dose Range-finding Studies: COL-118-ROSE-101, COL-118-ROSE-102, COL-118-ROSE-201, RD.06.SRE.18144, and RD.06.SRE.18161
2. Dermal Safety Studies: COL-118-Phototoxicity-104, RD.06.SRE.18123, RD.06.SRE.18124, RD.06.SRE.18125, RD.06.SRE.18137, and RD.06.SRE.18189
3. Pharmacokinetic Studies: COL-118-BAPK-101, RD.06.SRE.18126, RD.06.SRE.18143, and RD.06.SRE.18139
4. Core Studies: RD.06.SRE.18161, RD.06.SRE.18140, RD.06.SRE.18141, and RD.06.SRE.18142 (first 29 days of therapy)
5. Open-label Long-Term (12 months) Safety and Efficacy Study: RD.06.SRE.18142

The CHMP has drawn their particular attention on the pivotal studies.

- **Pivotal Studies** (including 2 identically designed clinical trials in subjects with rosacea)

RD.06.SRE.18140: A multicenter, randomized double-blind, vehicle-controlled, parallel-group study to demonstrate the efficacy and assess the safety of Brimonidine Tartrate 0.5% Gel applied topically once daily in subjects with moderate to severe facial erythema associated with rosacea

RD.06.SRE.18141: A multicenter, randomized double-blind, vehicle-controlled, parallel-group study to demonstrate the efficacy and assess the safety of Brimonidine Tartrate 0.5% Gel applied topically once daily in subjects with moderate to severe facial erythema associated with rosacea

RD.06.SRE.18161: A 4-week, randomized, double-blind, parallel group, vehicle-controlled, multicenter study investigating the efficacy and safety of Brimonidine Tartrate Gel 0.50% applied topically once daily (QD), and Brimonidine Tartrate Gel 0.18% applied topically QD or twice daily (BID) in subjects with moderate to severe facial erythema associated with rosacea only 0.50% QD and vehicle QD data

RD.06.SRE.18142: A multicenter, open-label study to evaluate the long-term safety and efficacy of Brimonidine Tartrate 0.5% Gel applied topically once daily for up to 52 weeks in subjects with moderate to severe facial erythema of rosacea only first 29 days of therapy

- **Open-Label Long-Term Safety and Efficacy Study** (1 study)

RD.06.SRE.18142: A multicenter, open-label study to evaluate the long-term safety and efficacy of Brimonidine Tartrate 0.5% Gel applied topically once daily for up to 52 weeks in subjects with moderate to severe facial erythema of rosacea (full 12 months)

Table 40. 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

Data Source: Statistical Analysis Plan for ISS (Section 5.3.5.3)

Patient exposure

In total, 1619 subjects were exposed to brimonidine tartrate 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 RD.06.SRE.18126 and RD.06.SRE.18143 were treated with the 0.2% ophthalmic solution.

A total of 1210 subjects have been exposed to brimonidine tartrate 0.5% QD, of which 330 rosacea subjects were included in the pivotal phase 3 studies (RD.06.SRE.18140 and RD.06.SRE.18141) and the phase 2b study (18161). In the long term safety study, 276 patients were exposed for more than 1 year. Thus, the number of patients exposed to brimonidine tartrate at the recommended dosage is considered sufficient.

In the long-term study RD.06.SRE.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 in this study.

The mean age of subjects is approximately 50 years. No subjects below the age of 18 were exposed to the study drug which is as anticipated since rosacea is a very rare disease in children/adolescents. 25 patients above 65 years of age were exposed to brimonidine gel in the core studies and 54 were exposed in the LTS study. Women are more common than men (approximately 75%) among study subjects, which reflect

the gender distribution of the disease. Further, subjects with fair skin (photo skin type II and III) are more frequently affected than those with darker skin types, also reflected in the demographics of rosacea subjects.

Table 41. Subjects exposed to Brimonidine Tartrate, pivotal efficacy and safety 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%	
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.
Note: Subjects may participate in more than 1 treatment group; therefore, total may not equal the sum of all treatment columns.
Data Source: Table 1.1 in ISS tables in Section 5.3.5.3

Adverse events

The TEAEs that occurred in the controlled pivotal studies and were assessed as drug-related in at least 1% of subjects treated with brimonidine tartrate 0.5% Gel are summarized in the table below, which includes the corresponding rates in vehicle gel subjects. The most commonly reported related TEAEs in subjects treated with brimonidine tartrate 0.5% Gel in the controlled pivotal studies were erythema, pruritus, skin burning sensation, and flushing (see table below).

Table 42. Treatment-related TEAEs in ≥1% of subjects treated with Brimonidine Tartrate 0.5% Gel, Controlled Core Studies, Safety Population

SYSTEM ORGAN CLASS Preferred Term	CD07805/47 Gel 0.5% (N=330) n (%)	Vehicle Gel (N=331) n (%)
SUBJECTS REPORTING ANY RELATED ADVERSE EVENT, N(%)	39 (11.8)	29 (8.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	32 (9.7)	22 (6.6)
Erythema	11 (3.3)	3 (0.9)
Pruritus	8 (2.4)	6 (1.8)
Skin burning sensation	4 (1.2)	2 (0.6)
VASCULAR DISORDERS	4 (1.2)	1 (0.3)
Flushing	4 (1.2)	0

[a] 3 subjects reported transient facial flushing with consumption of alcohol that were miscoded to PT of alcohol intolerance and should have been coded to SOC Vascular Disorders, PT Flushing

All treatment-related adverse events in the pivotal studies

All TEAEs (an AE with an onset date on or after the day of first dose) occurring in the pivotal studies, independent of causality, selected by ≥1% frequency of occurrence, are shown in the table below. In the first month of the LTS Study RD.06.SRE.18142, the four most frequently reported TEAEs were, in order of decreasing frequency, flushing (5.8%), erythema (4.5%), headache (3.3%) and rosacea (2.2%). The

incidences of erythema and headache occurring with 0.50% gel treatment in the Controlled Core Studies are similar with that in the LTS study. Flushing, however, occurred more frequently in the first month of the LTS study than in the controlled active group or the vehicle group.

Table 43. Treatment-related TEAEs in at least 1 subject treated with Brimonidine Tartrate 0.5% Gel, Controlled Core Studies, Safety Population

SYSTEM ORGAN CLASS Preferred Term	CD07805/47 Gel 0.5% (N=330) n (%)	Vehicle Gel (N=331) n (%)
SUBJECTS REPORTING ANY RELATED ADVERSE EVENT, N(%)	39 (11.8)	29 (8.8)
EYE DISORDERS	1 (0.3)	1 (0.3)
Eyelid oedema	1 (0.3)	0
GASTROINTESTINAL DISORDERS	1 (0.3)	0
Dry mouth	1 (0.3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.6)	0
Peripheral coldness (Lower-level Term: Coldness of skin)	1 (0.3)	0
Feeling hot	1 (0.3)	0
METABOLISM AND NUTRITION DISORDERS	3 (0.9)	0
Alcohol intolerance (Lower-level Term: Alcohol-induced flushing)	3 (0.9)[b]	0
NERVOUS SYSTEM DISORDERS	4 (1.2)[a]	3 (0.9)
Headache	1 (0.3)	2 (0.6)
Paraesthesia	2 (0.6)	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (0.9)[a]	0
Rhinalgia (Lower-level Term: Nasal stinging)	1 (0.3)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	32 (9.7)	22 (6.6)
Erythema	11 (3.3)	3 (0.9)
Pruritus	8 (2.4)	6 (1.8)
Rosacea	3 (0.9)	3 (0.9)
Skin burning sensation	4 (1.2)	2 (0.6)
Skin irritation	2 (0.6)	4 (1.2)
Skin warm	2 (0.6)	0
Dry skin	1 (0.3)	0
Skin discomfort	1 (0.3)	0
Rash papular	1 (0.3)	2 (0.6)
Dermatitis	2 (0.6)	1 (0.3)
Acne	1 (0.3)	1 (0.3)
Dermatitis contact	1 (0.3)	0
Pain of skin	1 (0.3)	0
VASCULAR DISORDERS	4 (1.2)	1 (0.3)
Flushing	4 (1.2)	0

[a] 3 subjects reported transient facial flushing with consumption of alcohol that were miscoded to Preferred Term of alcohol intolerance and should have been coded to flushing within the Vascular Disorders System Organ Class.

Systemic TEAEs related to study drug

No related TEAEs were observed regarding Respiratory, Infections/Infestations, Cardiac, or Metabolic Disorders. Alcohol intolerance reported for 3 subjects in RD.06.SRE.18140 should have been coded to PT Flushing in Vascular Disorders, given that the transient episodes of facial flushing were triggered by alcohol ingestion. The incidences of Nervous System Disorders related to the study drug were similar in

the controlled active and vehicle populations and were slightly higher for headache in the LTS group. Systemic adverse events do not seem to be a problem.

Local tolerance

A dermal tolerance program has been conducted, which included sensitization, cumulative irritation, photosensitization, and phototoxicity in healthy subjects. Local tolerability effects (as observed in the 5 dermal safety studies) were assessed with respect to the application site in accordance with accepted standards for dermatology studies. In addition to the dermal tolerance studies, the Applicant monitored subjects closely for suspected local skin reactions.

Local tolerability studies

The Applicant conducted six dermal safety studies in healthy subjects: 2 phototoxicity studies (COL-118-Phototoxicity-104 and RD.06.SRE.18189), 2 sensitization studies (RD.06.SRE.18123 and RD.06.SRE.18124), 1 cumulative irritation study (RD.06.SRE.18125), and 1 SPF study of the Vehicle Gel (RD.06.SRE.18137). In this group of studies, the study drugs were not applied to the face but to a small area on the back.

All applications were performed under patch occlusion except for those applications in the SPF study RD.06.SRE.18137. In RD.06.SRE.18137, the Vehicle Gel was compared to an active control, homosalate 8% lotion.

In the Brimonidine Tartrate gel formulation, titanium dioxide (TiO_2) accounts for only 0.625% of the total composition. Titanium dioxide is a compound known to have a high refractive index and strong ultraviolet (UV) light absorbing capacity. The SPF of the vehicle was measured to support the contention that TiO_2 serves only a structural function, and does not convey significant UV blocking/absorbing capacity to the product.

In all studies, safety was followed by collecting AEs, local tolerability measurements and concomitant medications; no laboratory measurements, vital sign determinations, or physical examinations were performed.

Phototoxicity studies COL-118-Phototoxicity-104 and RD.06.SRE.18189

Two phototoxicity studies were conducted in healthy subjects to determine the effect of exposure to UV light on skin pre-treated with duplicate single applications of Brimonidine Tartrate Gel 0.20% (COL-118-Phototoxicity-104, 30 subjects) or Brimonidine Tartrate Gel 0.07%, 0.18%, and 0.50% (RD.06.SRE.18189, 35 subjects) to opposite sides of the back. In both studies, the Vehicle Gel was also tested. In COL-118-Phototoxicity-104, an unirradiated set of treated areas served as controls.

No phototoxic effects were reported in either study.

Photosensitization potential of Brimonidine Tartrate Gel (RD.06.SRE.18124)

In Study SRE.18124, the photosensitization potential of Brimonidine Tartrate Gel was investigated after repeated applications followed by ultraviolet (UV) exposure in 57 healthy subjects. The study drugs included Gel Vehicle, white petrolatum (negative control), and Brimonidine Tartrate Gel (0.07%, 0.18%, and 0.50%).

The study consisted of the following phases: a 3-week induction phase during which the study drugs were applied under occlusion 3 times a week for 3 weeks, a 2-week rest period, a challenge phase lasting up to 1 week, and a re-challenge phase if applicable. The individual minimum erythemal dose (MED) for each subject was determined prior to initial study drug application and the skin was irradiated at pre-specified

times during the induction and challenge phases. In this study, 1 site was left untreated and irradiated as a control for radiation sensitivity.

No skin reaction worse than mild erythema occurred at any test site.

Cumulative irritation study RD.06.SRE.18125

The cumulative irritancy of increasing concentrations of active gel (0.0%, 0.07%, 0.18%, and 0.50%) was assessed versus white petrolatum (negative control) and 0.25% SLS (positive control) applied to the upper backs of 38 healthy subjects exposed for up to 22 days to the test treatments.

Overall, 7 out of 38 subjects reported TEAEs during this study. These included 1 serious (and severe) TEAE, gastroenteritis, which resulted in study discontinuation. The SAE plus all of the other 6 TEAEs (gastroenteritis (2 subjects), nasopharyngitis, venomous bite, arthralgia, headache, and dysmenorrhoea) were not considered to be related to the study treatment.

SPF Study of the Vehicle Gel RD.06.SRE.18137

Following a 30-minute application of the test formulation in 25 subjects, the static SPF value of the Gel Vehicle was measured and compared to that of active control, homosalate 8% lotion (sunscreen) and an untreated site in an intra-individual comparison in 25 healthy subjects.

No adverse events were reported in this study.

Sensitization potential of Brimonidine Tartrate Gel (RD.06.SRE.18123)

In Study RD.06.SRE.18123, the sensitization potential of Brimonidine Tartrate Gel was investigated in 247 healthy subjects after repeated applications. The study drugs included Gel Vehicle, white petrolatum (negative control), and Brimonidine Tartrate Gel (0.07%, 0.18%, and 0.50%). The gel formulation used in Study RD.06.SRE.18123 contained 0.3% methylparaben while that used in Study RD.06.SRE.18124 contained 0.1% methylparaben. The reduction of the quantity of methylparaben did not reduce preservative efficacy nor impact the validity of the study results.

The study consisted of the following phases: a 3-week induction phase during which the study drugs were applied under occlusion 3 times a week for 3 weeks, a 2-week rest period, a challenge phase lasting up to 1 week, and a re-challenge phase if applicable.

There were few observations of mild erythema and a few cases of moderate erythema.

Conclusions on dermal tolerance studies

The dermal tolerance studies showed no detectable phototoxicity or photosensitization potential, low contact sensitization potential, and low cumulative irritancy potential for the active formulations and for the vehicle, which was consistent with non-clinical local tolerance studies.

Sensitization reactions observed in clinical trials

Possible sensitization reactions were reported in 2 out of the 18 clinical trials conducted for Brimonidine Tartrate Gel: Studies 18123 and 18142.

In Study 18123, the evaluation of 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 Brimonidine Tartrate 0.07% Gel and Vehicle and exhibited equivocal results during a re-challenge with the original test products. This subject was unavailable for a second confirmatory re-challenge. Given that the subject showed reactions at both challenge and rechallenge to sites patched with active and vehicle, this suggests that the skin reaction was likely due to a vehicle excipient rather than the active drug substance.

In Study 18142, 24 of the 449 enrolled subjects (5.3%) developed adverse reactions for which the Investigators requested patch testing in order to rule out an allergic sensitization to the study product (contact dermatitis). Of these 24 subjects, 17 agreed to undergo diagnostic patch testing. Fourteen (14) 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 3 positive cases, 2 agreed to further testing with individual study product

ingredients. One of the 2 subjects was found to be allergic to brimonidine tartrate and the other subject was found to be allergic to phenoxyethanol, a preservative excipient.

Based on the incidences of AEs from the 7 subjects who refused rechallenge/patch testing (1.6%) and the 3 subjects who had a positive patch test (0.7%), it could be conservatively estimated that the sensitization rate for this study was approximately 2.2%. Of the 17 subjects who had a rechallenge/patch test, 3 had a positive result (17.6%), and it is likely that not all of the 7 subjects who refused the rechallenge/patch test would be allergic to the study drug. If a similar incidence (17.6%) is applied, it is likely that 1 or 2 subjects who refused rechallenge/patch testing may have had a positive result, which would lead to an overall sensitization rate of approximately 1% for this study. For these 10 subjects, all of the suspected allergic reactions occurred after 4 weeks of exposure, with the onset between 3 and 6 months in the majority of these subjects.

The rate of sensitization for the 1619 subjects exposed to Brimonidine Tartrate Gel was estimated at <1% across the entire clinical development program. This estimate was based on 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.

Serious adverse event / deaths / other significant events

Deaths

There was one death reported in one of the 18 clinical studies performed. In the long term safety study, RD.06.SRE.18142, one subject had an SAE of lung cancer that led to death. The SAE was considered by the Investigator to be unrelated to brimonidine tartrate treatment, and this is agreed.

Serious adverse events

Of the 18 studies in the brimonidine tartrate gel development program, seven studies reported one or more SAEs. Serious adverse events were pooled for the controlled pivotal studies RD.06.SRE.18140, RD.06.SRE.18141, and RD.06.SRE.18161 (0.50% gel treatment group). None of the SAEs was attributed to study treatment.

Accidental drug intake by children

Two children of a subject assigned to 0.50% gel in Study RD.06.SRE.18140 mistook the study drug for toothpaste and hence ingested the study product. They experienced the following TEAEs; lethargy, respiratory distress, irregular heart rate, and psychomotor hyperactivity. It is agreed that the TEAEs resulting from accidental ingestion by young children do not affect the overall safety profile in the target population, as this TEAE is not observed after normal usage in a study subject.

Laboratory findings

Brimonidine tartrate gel did not induce any laboratory findings as could be expected considering the relatively low systemic uptake of the active compound. The decrease in white blood cell count in one subject does not raise cause for concern.

Safety in special populations

Subgroup analyses were conducted to explore the potential differences of common TEAEs within a subgroup compared with the entire population. The incidence rates for common TEAEs were summarized by main intrinsic factors (gender, age, race, ethnicity).

Gender

Table 44. Summary of overall treatment-emergent adverse events by gender, Safety Population, Core Studies

	Controlled Core Studies				**LTS Study (first 29 days)**	
	Brimonidine Tartrate 0.5% Gel		**Vehicle Gel**		**Brimonidine Tartrate 0.5% Gel**	
	Male (N=79)	**Female (N=251)**	**Male (N=76)**	**Female (N=255)**	**Male (N=113)**	**Female (N=336)**
Subjects With At Least One TEAE	**19 (24)**	**90 (36)[a]**	**13 (17)**	**78 (31)**	**25 (22)**	**108 (32)**
Related	5 (6)	34 (14)[a]	3 (4)	26 (10)	13 (12)	62 (18)
Unrelated	15 (19)	67 (27)	10 (13)	56 (22)	15 (13)	63 (19)
Subjects with at Least One Serious AE	**0**	**2 (1)[a]**	**0**	**1 (<1)**	**0**	**1 (<1)**
Related	0	1 (<1)[a]	0	0	0	0
Unrelated	0	1 (<1)	0	1 (<1)	0	1 (<1)
Subjects with at Least One TEAE Leading to Discontinuation	**0**	**3 (1)**	**1 (1)**	**1 (<1)**	**3 (3)**	**19 (6)**
Related	0	2 (1)	0	1 (<1)	2 (2)	18 (5)
Unrelated	0	1 (<1)	1 (1)	0	1 (1)	1 (<1)
Subjects with at Least One Severe TEAE	**0**	**4 (2)**	**0**	**1 (<1)**	**1 (1)**	**11 (3)**
Related	0	1 (<1)	0	0	0	8 (2)
Unrelated	0	3 (1)	0	1 (<1)	1 (1)	3 (1)

[a] Subject 18140-8076-028 was assigned to the 0.50% gel group; her 2 children accidentally ingested the study drug and their mother is counted here.

Both the controlled active groups (36% vs. 24%) and the controlled vehicle groups (31% vs. 17%) show a higher percentage of females to males reporting TEAEs.

TEAEs occurring at ≥1% frequency that were considered related to the study drug are presented by gender below.

Table 45. Treatment-emergent adverse reactions related to study drug by System Organ Class and Preferred Term occurring at ≥1% frequency, by gender, Safety Population, Core Studies

	Controlled Core Studies				**LTS Study (first 29 days)**	
System Organ Class	**Brimonidine Tartrate 0.5% Gel**		**Vehicle Gel**		**Brimonidine Tartrate 0.5% Gel**	
Preferred Term	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
	N=251	**N=79**	**N=255**	**N=76**	**N=336**	**N=113**
Subjects Reporting any AE, N(%)	**34 (13.5)[a]**	**5 (6.3)[a]**	**26 (10.2)**	**3 (3.9)**	**62 (18.5)**	**13 (11.5)**
Investigations	**1 (0.4)** [a]	**0**	**1 (0.4)**	**1 (0.3)**	**1 (0.3)**	**1 (0.9)**
Intraocular pressure decreased	0	0	0	1 (1.3)	1 (0.3)	1 (0.9)
Metabolism	**3 (1.2)[b]**	**0**	**0**	**0**	**0**	**0**
Alcohol intolerance	3 (1.2) [b]	0	0	0	0	0
Nervous System Disorders	**4 (1.6)** [a]	**0**	**3 (1.2)**	**0**	**9 (2.7)**	**2 (1.8)**
Headache	1 (0.4)	0	2 (0.8)	0	7 (2.1)	1 (0.9)
Paraesthesia	2 (.08)	0	1 (0.4)	0	0	0
Skin and Subcutaneous Tissue Disorders	**27 (10.8)**	**5 (6.3)**	**20 (7.8)**	**2 (2.6)**	**40 (11.9)**	**10 (8.8)**
Acne	0	1 (1.3)	1 (0.4)	0	0	0
Dermatitis	1 (0.4)	1 (1.3)	1 (0.4)	0	0	0
Erythema	10 (4.0)	1 (1.3)	3 (1.2)	0	13 (3.9)	5 (4.4)
Pruritus	6 (2.4)	2 (2.5)	5 (2.0)	1 (1.3)	4 (1.2)	1 (0.9)
Rosacea	3 (1.2)	0	2 (0.8)	1 (1.3)	7 (2.1)	1 (0.9)
Skin burning sensation	4 (1.6)	0	2 (0.8)	0	6 (1.8)	0
Skin discomfort	1 (0.4)	0	0	0	2 (0.6)	2 (1.8)
Skin irritation	2 (0.8)	0	4 (1.6)	0	3 (0.9)	0
Skin warm	2 (0.8)	0	0	0	4 (1.2)	2 (1.8)
Vascular disorders	**4 (1.6)**	**0**	**1 (0.4)**	**0**	**23 (6.8)**	**1 (0.9)**

	Controlled Core Studies				LTS Study (first 29 days)	
System Organ Class	Brimonidine Tartrate 0.5% Gel		Vehicle Gel		Brimonidine Tartrate 0.5% Gel	
Preferred Term	Female N=251	Male N=79	Female N=255	Male N=76	Female N=336	Male N=113
Subjects Reporting any AE, N(%)	**34 (13.5)[a]**	**5 (6.3)[a]**	**26 (10.2)**	**3 (3.9)**	**62 (18.5)**	**13 (11.5)**
Flushing	4 (1.6)	0	0	0	23 (6.8)	0

[a] Subject 18140-8076-028 was assigned to the 0.50% gel group; her 2 children accidentally ingested the study drug and their mother is counted here.

[b] 3 subjects reported transient facial flushing with consumption of alcohol that were miscoded to PT of alcohol intolerance and should have been coded to SOC Vascular Disorders, PT Flushing

Subjects reporting a particular adverse event more than once are counted only once for that adverse event.

Age

Treatment-emergent adverse events (TEAEs) were categorized by age for the Core Studies: subjects 18 to 64 years of age (adult; 1005 subjects) and subjects ≥65 years of age (geriatric; 105 subjects). 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. However, the number of subjects ≥65 years of age was relatively small and the age distribution was not presented.

Table 46 Summary of AEs in Geriatric Subjects; Studies 18161, 18140, 18141; Safety Population

AE Category	CD07805/47 0.5% QD				CD07805/47 Vehicle QD			
	<65 Years (N=305)	65-74 Years (N=23)	75-84 Years (N=2)	85+ Years (N=0)	<65 Years (N=305)	65-74 Years (N=24)	75-84 Years (N=1)	85+ Years (N=1)
Total	101 (33.1%)	8 (34.8%)	0	0	85 (27.9%)	4 (16.7%)	1 (100.0%)	1 (100.0%)
Fatal	0	0	0	0	0	0	0	0
Serious	2 (0.7%)	0	0	0	1 (0.3%)	0	0	0
Withdrawal	3 (1.0%)	0	0	0	1 (0.3%)	1 (4.2%)	0	0
CNS (Confusion/ Extrapyramidal)								
Hallucination, Visual	1 (0.3%)	0	0	0	0	0	0	0
AE Related to Falling	0	0	0	0	0	0	0	0
CV Events								
Chest Pain	0	0	0	0	1 (0.3%)	0	0	0
Oedema Peripheral	0	0	0	0	0	0	0	1 (100%)
Heart Rate Increased	0	0	0	0	1 (0.3%)	0	0	0
Deep Vein Thrombosis	0	0	0	0	1 (1.3%)	0	0	0
Flushing	6 (2.0%)	0	0	0	0	0	0	0
Hypertension	1 (0.3%)	0	0	0	2 (0.7%)	0	0	0
Orthostatic Hypotension	0	0	0	0	1 (0.3%)	0	0	0

AE Category	CD07805/47 0.5% QD				CD07805/47 Vehicle QD			
	<65 Years (N=305)	65-74 Years (N=23)	75-84 Years (N=2)	85+ Years (N=0)	<65 Years (N=305)	65-74 Years (N=24)	75-84 Years (N=1)	85+ Years (N=1)
Thrombosis	1 (0.3%)	0	0	0	0	0	0	0
Cerebrovascular Events	0	0	0	0	0	0	0	0
Infections								
Appendicitis	1 (0.3%)	0	0	0	0	0	0	0
Cellulitis	1 (0.3%)	0	0	0	0	0	0	0
Diverticulitis	0	1 (4.3%)	0	0	0	0	0	0
Fungal Infection	1 (0.3%)	0	0	0	0	0	0	0
Furuncle	0	0	0	0	1 (0.3%)	0	0	0
Gastroenteritis	1 (0.3%)	0	0	0	1 (0.3%)	0	0	0
Gastroenteritis Viral	2 (0.7%)	0	0	0	0	0	0	0
Herpes Zoster	0	1 (4.3%)	0	0	0	0	0	0
Hordeolum	0	0	0	0	2 (0.7%)	0	0	0
Impetigo	0	0	0	0	1 (0.3%)	0	0	0
Influenza	1 (0.3%)	0	0	0	0	0	0	0
Influenza Like Illness	1 (0.3%)	0	0	0	0	0	0	0
Nasopharyngitis	8 (2.6%)	0	0	0	7 (2.3%)	0	0	0
Pharyngitis	2 (0.7%)	0	0	0	0	0	0	0
Pharyngitis Streptococcal	1 (0.3%)	0	0	0	0	0	0	0
Rash Pustular	0	0	0	0	1 (0.3%)	0	0	0
Sinusitis	1 (0.3%)	0	0	0	4 (1.3%)	0	0	0
Tooth Abscess	1 (0.3%)	0	0	0	0	0	0	0
Tooth Infection	0	0	0	0	0	1 (4.2%)	0	0
Upper Respiratory Tract Infection	4 (1.3%)	0	0	0	1 (0.3%)	0	0	0
Urinary Tract Infection	1 (0.3%)	1 (4.3%)	0	0	1 (0.3%)	0	0	0
Viral Infection	0	0	0	0	1 (0.3%)	0	0	0
Viral Pharyngitis	1 (0.3%)	0	0	0	0	0	0	0
Viral Upper Respiratory Tract Infection	0	0	0	0	1 (0.3%)	0	0	0
Vulvovaginal Mycotic Infection	1 (0.3%)	0	0	0	0	0	0	0

Data Source: Applicant internal data

Table 47. Summary of overall treatment-emergent adverse events by age, Safety Population, Core Studies

	Controlled Core Studies				**LTS Study (first 29 days)**	
	Brimonidine Tartrate 0.5% Gel		**Vehicle Gel**		**Brimonidine Tartrate 0.5% Gel**	
	18 to 64 years (N=305)	**≥65 years (N=25)**	**18 to 64 years (N=305)**	**≥65 years (N=26)**	**18 to 64 years (N=395)**	**≥65 years (N=54)**
Subjects with at least one	**101 (33)[a]**	**8 (32)**	**85 (28)**	**6 (23)**	**119 (30)**	**14 (26)**

	Controlled Core Studies				LTS Study (first 29 days)	
	Brimonidine Tartrate 0.5% Gel		Vehicle Gel		Brimonidine Tartrate 0.5% Gel	
	18 to 64 years (N=305)	≥65 years (N=25)	18 to 64 years (N=305)	≥65 years (N=26)	18 to 64 years (N=395)	≥65 years (N=54)
TEAE						
Related	39 (13)[a]	0	27 (9)	2 (8)	66 (17)	9 (17)
Unrelated	74 (24)	8 (32)	62 (20)	4 (15)	71 (18)	7 (13)
Subjects with at least one SAE	**2 (1)[a]**	**0**	**1 (<1)**	**0**	**1 (<1)**	**0**
Related	1 (<1)[a]	0	0	0	0	0
Unrelated	1 (<1)	0	1 (<1)	0	1 (<1)	0
Subjects with at least one TEAE leading to discontinuation	**3 (1)**	**0**	**1 (<1)**	**1 (4)**	**20 (5)**	**2 (4)**
Related	2 (1)	0	1 (<1)	0	18 (5)	2 (4)
Unrelated	1 (<1)	0	0	1 (4)	2 (1)	0
Subjects with at least one severe TEAE	**4 (1)**	**0**	**1 (<1)**	**0**	**12 (3)**	**0**
Related	1 (<1)	0	0	0	8 (2)	0
Unrelated	3 (1)	0	1 (<1)	0	4 (1)	0

[a] Subject 18140-8076-028 was assigned to the 0.50% gel group; her 2 children accidentally ingested the study drug and their mother is counted here.

The incidence of TEAEs overall for adult subjects on active therapy was slightly higher than that for geriatric subjects on active therapy across the pivotal 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.

Skin and Subcutaneous Tissue Disorders was the predominant SOC and more adult subjects reported these TEAEs (13-14%) when compared to their older counterparts (7-8%). No treatment-related TEAEs were seen in any geriatric subject treated with 0.50% gel in the Controlled Core Studies. Nine (9) geriatric

subjects (16.7%) reported treatment-related TEAEs in the first 29 days of the LTS study, the most frequently being flushing (4 subjects, 7.4%) and erythema (2 subjects, 3.7%).

Race

There were a very small number of Non-Caucasian participants (in total 12 subjects in the Controlled Core Studies and 11 subjects in the LTS study); hence, analyses of TEAEs by race are difficult.

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. There were 2 Non-Caucasian subjects in the 0.50% group and 1 Non-Caucasian subject in the vehicle group in the Controlled Core Studies who reported TEAEs overall, and of these subjects, only 1 subject in the vehicle group had a related TEAE (skin tightness). No Non-Caucasian subjects reported any SAEs, TEAEs resulting in discontinuation, or severe TEAEs in any Core study.

Pregnant women

Pregnant or lactating women with erythema of rosacea were 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.

There were 4 pregnancies reported during the clinical development program, 1 in Study RD.06.SRE.18123, 1 in Study COL-118-ROSE-201, and 2 in Study RD.06.SRE.18142. No reports of hospitalization during pregnancy, foetal distress, miscarriage, or birth defects were received.

Immunological events

The observed rate of sensitization in the clinical studies does not seem to be cause for concern and seems to be in a range observed for currently approved topical products. No concerns are raised.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed with other topical or systemic products for the treatment of rosacea or with cosmetics. In the pivotal, controlled phase 3 studies, use of other topical or systemic products for the treatment of rosacea was not permitted, whereas in the open-label, long-term phase 3 study, other rosacea treatments were allowed.

Of the subjects randomized to 0.50% gel in the Controlled Core Studies, 77% received 1 or more concomitant medications and 71% of subjects treated with vehicle received concomitant medications. At least 10% of subjects in the Controlled Core Studies were concomitantly treated with 1 of the following categories of medications: multivitamins, specific vitamins, HMG CoA reductase inhibitors, ACE inhibitors (including angiotensin II antagonists), emollients and protectives, and proton pump inhibitors. Other classes of medications that were frequently taken during the studies (approximately 8% to 9% of subjects) included anilides, progestogens, propionic acid derivatives, beta blockers and thyroid hormones.

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.

Discontinuation due to adverse events

Discontinuation due to adverse events in the Core studies and the long term safety study can be seen in the tables below.

Table 48. Summary of treatment-emergent adverse events leading to discontinuation by System Organ Class and Preferred Term, Safety Population, Core Studies

	Controlled Core Studies		**Open Label Study (first 29 days)**
System Organ Class Preferred Term	**Brimonidine Tartrate 0.5% Gel (N=330)**	**Vehicle Gel (N=331)**	**Brimonidine Tartrate 0.5% Gel (N=449)**
Subjects Reporting Any Adverse Event Leading to Discontinuation, N(%)	**3 (0.9)**	**2 (0.6)**	**22 (4.9)**
Infections and Infestations	**0**	**0**	**1 (0.2)**
Pneumonia primary atypical	0	0	1 (0.2)
Sepsis	0	0	1 (0.2)
Nervous System Disorders	**0**	**0**	**2 (0.4)**
Headache	0	0	2 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**1 (0.2)**
Hypoxia	0	0	1 (0.2)
Skin and Subcutaneous Tissue Disorders	**3 (0.9)**	**2 (0.6)**	**13 (2.9)**
Dermatitis contact	2 (0.6)	0	0

Erythema	1 (0.3)	0	5 (1.1)
Flushing	0	0	1 (0.2)
Rosacea	0	0	4 (0.9)
Skin burning sensation	0	0	2 (0.4)
Skin hyperpigmentation	0	0	1 (0.2)
Vascular Disorder	**0**	**0**	**9 (2.0))**
Flushing	0	0	8 (1.8)
Hypertension	0	0	1 (0.2)

Subjects reporting a particular adverse event more than once are counted only once for that adverse event.

Table 49. Treatment-emergent adverse events leading to discontinuation by System Organ Class and Preferred Term, Safety Population, RD.06.SRE.18142

	Entire Study (N=449)	By Day 29 (N=449)	First Quarter (N=449)	Second Quarter (N=382)	Third Quarter (N=337)	Fourth Quarter (N=308)
System Organ Class Preferred Term						
Subjects Reporting Any Adverse Event Leading to Discontinuation, N(%)	**75 (16.7)**	**22 (4.9)**	**36 (8.0)**	**17 (4.5)**	**14 (4.2)**	**9 (2.9)**
Immune System Disorders	**1 (0.2)**	**0**	**0**	**0**	**1 (0.3)**	**0**
Hypersensitivity	1 (0.2)	0	0	0	1 (0.3)	0
Infections and Infestations	**2 (0.4)**	**1 (0.2)**	**1 (0.2)**	**0**	**1 (0.3)**	**0**
Cellulitis	1 (0.2)	0	0	0	1 (0.3)	0
Pneumonia primary atypical	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Sepsis	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)	**1 (0.2)**	**0**	**0**	**1 (0.3)**	**0**	**0**
Breast Cancer	1 (0.2)	0	0	1 (0.3)	0	0
Nervous System Disorders	**2 (0.4)**	**2 (0.4)**	**2 (0.4)**	**0**	**0**	**0**
Headache	2 (0.4)	2 (0.4)	2 (0.4)	0	0	0
Psychiatric Disorders	**1 (0.2)**	**0**	**0**	**0**	**0**	**1 (0.3)**
Depression	1 (0.2)	0	0	0	0	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.2)**	**1 (0.2)**	**1 (0.2)**	**0**	**0**	**0**
Hypoxia	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0

	Entire Study (N=449)	By Day 29 (N=449)	First Quarter (N=449)	Second Quarter (N=382)	Third Quarter (N=337)	Fourth Quarter (N=308)
System Organ Class Preferred Term						
Subjects Reporting Any Adverse Event Leading to Discontinuation, N(%)	**75 (16.7)**	**22 (4.9)**	**36 (8.0)**	**17 (4.5)**	**14 (4.2)**	**9 (2.9)**
Skin and Subcutaneous Tissue Disorders	**57 (12.7)**	**13 (2.9)**	**24 (5.3)**	**14 (3.7)**	**11 (3.3)**	**8 (2.6)**
Acne	1 (0.2)	0	0	0	1 (0.3)	0
Dermatitis	2 (0.4)	0	0	1 (0.3)	0	1 (0.3)
Dermatitis allergic	7 (1.6)	0	1 (0.2)	3 (0.8)	2 (0.6)	1 (0.3)
Dermatitis contact	7 (1.6)	0	1 (0.2)	2 (0.5)	1 (0.3)	3 (1.0)
Dry skin	1 (0.2)	0	0	0	0	1 (0.3)
Eczema weeping	1 (0.2)	0	0	1 (0.3)	0	0
Erythema	8 (1.8)	5 (1.1)	8 (1.8)	0	0	0
Face oedema	1 (0.2)	0	0	1 (0.3)	0	0
Flushing	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Pain of skin	1 (0.2)	0	0	0	1 (0.3)	0
Pruritus	3 (0.7)	0	0	2 (0.5)	1 (0.3)	0
Rash papular	1 (0.2)	0	0	0	1 (0.3)	0
Rash pruritic	1 (0.2)	0	0	0	1 (0.3)	0
Rosacea	11 (2.4)	4 (0.9)	7 (1.6)	2 (0.5)	1 (0.3)	1 (0.3)
Skin burning sensation	8 (1.8)	2 (0.4)	5 (1.1)	3 (0.8)	0	0
Skin hyperpigmentation	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Skin irritation	8 (1.8)	1 (0.2)	1 (0.2)	3 (0.8)	3 (0.9)	1 (0.3)
Vascular Disorders	**19 (4.2)**	**9 (2.0)**	**14 (3.1)**	**3 (0.8)**	**2 (0.6)**	**0**
Flushing	17 (3.8)	8 (1.8)	12 (2.7)	3 (0.8)	2 (0.6)	0
Hypertension	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Orthostatic hypotension	1 (0.2)	0	1 (0.2)	0	0	0

Subjects reporting a particular adverse event more than once are counted only once for that adverse event

Data Source: Table 2.5.C in ISS Tables in Section 5.3.5.3

The level of discontinuation due to TEAEs was low. The most common TEAEs resulting in discontinuation from any study were related to rosacea (e.g. erythema, flushing), which were mild or moderate in

intensity and eventually resolved. Other TEAEs that resulted in discontinuation were skin burning sensation, skin irritation, contact dermatitis and allergic dermatitis.

Post marketing experience

No post marketing experience was available.

2.6.1. Discussion on clinical safety

Short term risks

Overall, 1619 subjects 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, of which 330 subjects were included in the pivotal phase 3 studies and the phase 2b study. In the long term safety study, 276 patients were exposed for more than 1 year. Thus, an adequate number of patients have been exposed to brimonidine tartrate at the recommended dosage and the safety database is in general considered sufficient.

The most common adverse events associated with topical use of brimonidine tartrate are erythema, pruritus, flushing and skin burning sensation occurring in 1.2 to 3.3% of patients. It is agreed with the Applicant that concerning intensity of these local adverse reaction they are usually transient, mild to moderate in severity, and usually do not require discontinuation of treatment. This is also included in the labelling of the product which is supported.

Erythema and flushing are included in the clinical symptomatology of rosacea, and it is therefore difficult to assess if these symptoms are due to lack of efficacy or true adverse events. Pruritus and skin burning sensation are common adverse events for topically applied medicinal product, for instance metronidazole, and do not raise cause for concern.

The dermal local tolerance studies showed no detectable phototoxicity or photosensitization potential, low contact sensitization potential, and low cumulative irritancy potential for the active formulations and for the vehicle, consistent with non-clinical local tolerance studies. In the long term safety study, a few cases of contact dermatitis were observed which are included in the labelling of the product.

It is likely that Brimonidine Tartrate 0.5% Gel will be combined with other topical treatments i.e. if the therapeutic effect is insufficient on the erythema by the use of for example topical metronidazol or azelaic acid. The revised SmPC section 4.2 now gives advice regarding concomitant use with other topical products intended for the treatment of rosacea.

Accidental overdose has been reported in two young children of one clinical study subject who mistook the study drug for toothpaste. The children experienced symptoms consistent with previously reported oral overdoses of alpha$_2$-agonists and were reported to have made a full recovery within 24 hours. This information is included in section 4.9 Overdose of the SmPC. Furthermore, the Applicant has in order to avoid repetition of this accident added child resistant closure to the tubes containing brimonidine tartrate, which is considered an appropriate measure.

In conclusion on short term risks, no other than local adverse events are to be anticipated at the recommended use of brimonidine tartrate 0.5% Gel.

Potential long term risks

Brimonidine tartrate has a well kown safety profile and clinical experience in ophtalmic solutions. The systemic exposure to brimonidine tartrate following treatment with brimonidine tartrate gel 0.5% QD at

the recommended dosage is similar to that obtained with ophtalmic solutions containing brimonidine tartrate. No systemic adverse events were reported in any of the performed studies except those caused by accidental oral ingestion and are not to be anticipated at the proposed clinical use.

There is no preclinical or mechanistic rationale to suspect that brimonidine tartrate would increase the risk of cardiovascular events. The thorough QT study (RD.06.SRE.18139) was performed with ocular administration of brimonidine tartrate and the applicant claims that the study was performed with a supra-therapeutic dose. However, the pharmacokinetic data obtained from this study do not demonstrate a higher systemic exposure compared with the exposure obtained with topical administration of brimonidine tartrate gel 0.5% QD. No adverse effects on cardiovascular parameters were observed which are not to be expected considering the low systemic exposure of brimonidine tartrate. Overall, no treatment related potential risks were observed regarding respiratory, infections/infestations, cardiac, or metabolic disorders.

Brimonidine tartrate gel administered daily seems to have little or no effect on intra-ocular pressure (TEAE IOP increased or decreased) in the target population under short-term or long-term use conditions. A change in IOP was not a reason for discontinuation from any study. IOP decreases may have been due to inadvertent contamination of the eye with the topical gel.

The most common local adverse events associated with topical use of brimonidine tartrate are erythema, pruritus, flushing and skin burning sensation (see above).

Subpopulations

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. However, the number of subjects ≥65 years of age was relatively small and the age distribution was not presented. A summary of AEs in geriatric subjects in Studies 18161, 18140 and 18141 according to the age categories and AE groupings was provided in the question. A statement concerning this observation has been reflected in the SmPC and the PIL in Section 4.8. No meaningful differences in the safety profile were observed between the elderly subject population and subjects 18 to 64 years of age.

The data presented by the applicant raise no concerns although the number of subjects above 65 years is very limited.

Based on the very low number of Non-Caucasian participants, conclusions on AEs based on race are difficult to make, the condition affects mainly fair skinned population and therefore the use in Non-Caucasian participants would be expected to be low.

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.

In conclusion on potential long term risks, no risks due to systemic uptake of brimonidine tartrate are to be anticipated.

2.6.2. Conclusions on the clinical safety

The safety profile for topical use of brimonidine tartrate is in general considered benign with only local adverse events (e.g. erythema, pruritus, flushing and skin burning sensation) that mostly are transient, mild to moderate in severity, and usually do not require discontinuation of treatment.

No systemic adverse events were reported in any of the performed studies except those caused by accidental oral ingestion and are not to be expected at the proposed clinical use.

No long-term safety concerns are foreseen.

From the safety database all the adverse reactions reported in clinical trials have been included in the product information.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

The Risk Management Plan is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The Applicant states that the most significant identified risk for brimonidine gel 5 mg/g is accidental oral ingestion, particularly by children, which may be associated with systemic toxicity. Other identified risks include adverse reactions related to skin and subcutaneous tissue disorders and to vascular flushing. These risks are predominantly mild to moderate in nature and are associated with low discontinuation rates. Skin sensitisation is an identified risk. This was less than 1% of exposed subjects and has not been associated with systemic hypersensitivity.

Missing information includes experience in patients with specific severe/complex forms of rosacea and in patients with significant concurrent disease including depression. The Applicant adds that there is no experience in European patients and patients with other ethnicity. Paediatric, pregnancy, lactation, renal and hepatic dysfunction information is missing. The Applicant provided the following table of Summary of Safety Concerns.

Table 50 Summary of the Safety Concerns

Important identified risks	Accidental oral ingestion Skin sensitisation to brimonidine or excipients
Important potential risks	Drug interactions Systemic allergic reactions to brimonidine or excipients
Missing information	Exposure during pregnancy Exposure during lactation Use longer than one year Off-label use Use with laser or UV radiation Use in patients with specific intercurrent diseases

The PRAC agreed.

- **Pharmacovigilance plans**

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Table 51: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Accidental oral ingestion	SmPC text in Section 4.9 describes possible consequences of oral ingestion and treatment of overdose. Also describes occurrences of oral ingestion so far reported. Product packaging with CPL is described PIL warnings with respect to 2 g tube are described	
Skin sensitisation to brimonidine or excipients	Known hypersensitivity to active substance or excipients included in Section 4.3 of SmPC. Section 4.4 warns that excipients may cause allergic reactions (possibly delayed) and skin irritation. Allergic contact dermatitis included in SmPC Section 4.8.	
Important potential risks		
Drug interactions	SmPC Section 4.3 includes contraindication with MAOI and tricyclic/tetracyclic anti-depressants. SmPC Section 4.2 describes	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	method of application with other rosacea products. Section 4.3 contraindicates use in patients receiving MAO inhibitors and tricyclic or tetracyclic antidepressants Section 4.4 includes warnings regarding potential interactions based on pharmacology. Also included in Section 4.5 of SmPC. Section 5.1 describes experience of concomitant rosacea treatment experience from clinical studies.	
Systemic allergic reactions to brimonidine or excipients	Known hypersensitivity to active substance or excipients included in Section 4.3 of SmPC. Section 4.4 warns that excipients may cause allergic reactions (possibly delayed) and skin irritation.	
Missing information		
Exposure during pregnancy	Lack of data concerning exposure during pregnancy is included in SmPC Section 4.6 with recommendation to avoid use during pregnancy.	
Exposure during lactation	Lack of data concerning lactation is included in SmPC Section 4.6 with recommendation not to use during breast feeding	
Use longer than one year	No routine minimisation measures are proposed	
Off-label use	SmPC Section 4.2 describes indication, target patients, dose and appropriate administration method and application only to face. SmPC Section 4.3 Contraindicates use in children < 2 years of age SmPC Section 4.4 includes warning not to apply on irritated skin, open wounds or near eyes. Additionally warns to avoid increases in daily amount or frequency of application.	
Use with laser or UV radiation	No routine minimisation measures are proposed	
Use in patients with specific intercurrent diseases	SmPC Section 4.2 states product has not been studied in patients with hepatic and/or renal impairment and recommends caution in such patients. SmPC Section 4.4 includes warnings concerning use in patients with specified intercurrent diseases and	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	recommends caution in such patients	

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Rosacea is a chronic dermatological disease commonly classified into four subtypes based upon clinical signs and symptoms. Of these, erythematotelangiectatic and papulopustular rosacea (subtypes 1 and 2) both have a presence of persistent erythema of the central portion of the face. Other primary symptoms include flushing, papules, pustules and telangiectasias.

Mirvaso (brimonidine tartrate 0.5% gel) targets a single symptom of rosacea, i.e. facial erythema, while other rosacea products on the market mainly affect other symptoms of the condition, e.g. by reducing inflammatory papules and pustules. There is no European guideline available for products indicated for treatment of rosacea and efficacy end-points to be used are not clearly established. The applicant developed the CEA (Clinician Erythema Assessment) scale and the PSA (Patient Self-Assessment) scales that were used as co-primary end-points in the pivotal phase 3 studies and phase 2 studies. The development and validation of the CEA and PSA scales have been described and specific studies have been performed to address their relevance, e.g. by assessment of inter- and intra-rater agreement and content validity. The scales are deemed to be sufficiently described and validated for their intended purpose. It should be acknowledged that both the PSA and the CEA are scales that are based on subjective judgements and not objective measures. However, considering the type of condition and the intended use of the product (symptomatic reduction of erythema rather than curative treatment), assessments made by the patients are of relevance.

In both pivotal studies, brimonidine tartrate 0.5% gel 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 Days 1, 15 and 29. The response rate at different time points on Day 29 ranged between 17.6% and 31.5% for brimonidine tartrate 0.5% Gel and the vehicle response was approximately 10%.

Brimonidine Tartrate 0.5% Gel produces effect rapidly and 28% of the 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 5-7% of Vehicle Gel subjects.

For the tertiary end-point 1-grade Composite Success, brimonidine tartrate 0.5% Gel was also superior to Vehicle Gel, with a response rate ranging from 53.5% to 71% and a vehicle effect of 30-40%.

Other subject self-assessments generally supported the above results, e.g. the number of subjects reporting satisfactory results for Patient Assessment of Appearance (PAA) and Overall Treatment Effect (OTE) were higher in the brimonidine tartrate 0.5% Gel groups compared with Vehicle Gel groups.

No signs of tachyphylaxis or rebound effects were observed and no worsening of facial inflammatory lesions or telangiectasias occurred as a result of treatment.

Higher percentages of subjects in the brimonidine tartrate 0.5% Gel groups were bothered by too much whitening (excessive pharmacological effect) compared to the corresponding Vehicle Gel groups (about 5% vs. 1-3% at each time point on Day 1). However, the number of reports of unwanted over-whitening decreased over the course of the studies and no subject discontinued the studies due to over-whitening.

Brimonidine tartrate is a topically applied product and has a well known safety profile and clinical experience from ophthalmic use. The systemic exposure to brimonidine tartrate following treatment with brimonidine tartrate gel 0.5% QD at the recommended dosage is similar or lower to that obtained with

ophthalmic solutions containing brimonidine tartrate. No systemic adverse events were reported in any of the performed studies. There are no concerns for adverse events caused by systemic absorption of brimonidine tartrate at the recommended posology of the product.

Uncertainty in the knowledge about the beneficial effects.

The efficacy and safety of brimonidine tartrate 0.5% Gel in patients treated with other topical products for the treatment of rosacea, e.g. metronidazole or azelaic acid gel, has not been systematically investigated. In clinical practice, a combination of brimonidine tartrate and metronidazole gel is likely, since a rapid onset of effect on erythema may be desirable or if metronidazole does not sufficiently reduce erythema. In the open-label long-term study, other rosacea treatments were allowed and a fairly large percentage of the subjects (n=131, almost 30%) used other topical rosacea products, mainly metronidazole (16 %). Efficacy results show roughly similar results for 2-grade composite success for subjects with or without concomitant rosacea medication. Also from a safety perspective, concomitant use of brimonidine tartrate with other topical rosacea products did not result in safety problems, e.g. related to local tolerability. Sections 4.2 and 5.1 of the SmPC contain adequate information related to the use of brimonidine tartrate with other rosacea medications.

The clinical studies were performed under standardised, experimental conditions that may not reflect the environmental factors (sun, cold or wind, exercise, stress, etc) that can cause the erythema of rosacea to flare up. Subjects were educated on typical factors that may exacerbate rosacea and were encouraged to maintain a consistent lifestyle regarding these factors but were not required to agree to abstain from consumption of alcohol or spicy food or from exercise during the study in order to be eligible. The non-clinic days and the open-label study (which also included the possibility to use together brimonidine tartrate with other rosacea medications) are considered to represent real-life conditions.

For the Overall Treatment Effect (OTE), twice as many subjects in the active treatment group compared with the vehicle group considered that their condition had worsened as a result of treatment, though. This could have been due to several factors, including small number of subjects, recall bias, and suboptimal timing of the administration of the assessment. It seems plausible that in an overall assessment, some subjects experienced the wearing off of the effect at the end of the day as a worsening and that this is more pronounced in the active than the vehicle group. The overall OTE results showed that the majority of patients experienced an improvement with Mirvaso.

No effect on Quality of life assessments could be shown, but the scales do not appear suitable for this indication, since the baseline Quality of life assessments were not poor.

Risks

Unfavourable effects

The most common adverse events associated with topical use of brimonidine tartrate are erythema, pruritus, flushing and skin burning sensation occurring in 1.2 to 3.3% of patients. Concerning intensity of these local adverse reaction they are usually transient, mild to moderate in severity, and usually do not require discontinuation of treatment, which is also included in the labelling of the product.

Pruritus and skin burning sensation are common adverse events for topically applied medicinal products, for instance metronidazole gel, and do not raise cause for concern.

No systemic adverse events were reported in any of the performed studies except those caused by accidental oral ingestion and are not to be expected at the proposed clinical use. Pack design has been modified to reduce the risk of accidental overdose by children, the 2 gram sample tube will not have child resistant closure however it is expected to be used very quickly (over 1 to 2 days) limiting the amount of time during which accidental exposure could occur. Key prevention messages “Do not swallow” and “Keep

out of the sight and reach of children" will be highlighted in red on 2g tubes and carton labels. Management of overdose is proposed in Section 4.9 of the SmPC.

Off label use has been added to Missing Information in the Safety Concerns with routine pharmacovigilance activities and risk minimisation through the product labelling in the SmPC and PIL.

Uncertainty in the knowledge about the unfavourable effects

The most common local adverse events associated with topical use of brimonidine tartrate are erythema, pruritus, flushing and skin burning sensation, which could be difficult to distinguish from lack of effect.

Benefit-risk balance

Importance of favourable and unfavourable effects

Brimonidine tartrate gel 0.5% provides a significant effect on the erythema of facial rosacea as assessed both by the patient and the clinician. The onset of effect is rapid and the effect is maintained over a 12-hour period, although the effect wears off at the later time points. The response rate of 20-30% for brimonidine tartrate 0.5% Gel for the primary efficacy end-point (2-grade composite success for PSA and CEA) may not be impressive, but is clearly above the vehicle response rate of 10% and is deemed clinically relevant. The number of subjects reaching 1-grade composite success was clearly higher. Other subject self-assessments generally supported the above results.

No signs of tachyphylaxis or rebound effects were observed and no worsening of facial inflammatory lesions or telangiectasias occurred as a result of treatment. Limited long-term efficacy data is available since the duration of the two pivotal studies was 4 weeks, but a comparison of efficacy results across studies has shown a similar level of activity after 28 days and after 1 year of use. These results support that efficacy is maintained over time.

The safety profile is benign with mainly local adverse events like erythema, pruritus, flushing and skin burning sensation. These are common adverse events for other topically applied medicinal products, for instance metronidazole gel, and do not raise cause for concern.

Benefit-risk balance

Discussion on the benefit-risk balance

Brimonidine tartrate gel 0.5% has demonstrated a positive symptomatic effect on the erythema of facial rosacea, which is deemed clinically relevant. The data on long-term efficacy are limited but available information supports that efficacy is maintained over time. The safety profile is benign with mainly local adverse events that are commonly observed for other topically applied rosacea products. Thus, from a quality, clinical and non-clinical point of view, the benefits outweigh the risks.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Mirvaso in the "symptomatic treatment of facial erythema of rosacea in adult patients" is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.