LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Soolantra
# (ivermectin)

# SE/H/1428/01/DC

**This module reflects the scientific discussion for the approval of Soolantra. The procedure was finalised on 2015-03-22. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

The application for Soolantra, cream, 10 mg/g, is a Known active substance application made according to Article 8(3) of Directive 2001/83/EC. The active substance is ivermectin, a member of the avermectin class. Avermectin has anti-inflammatory effects by inhibiting lipopolysaccharide-induced production of inflammatory cytokines. Ivermectin also causes death of parasites, primarily through binding selectively and with high affinity to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells. The mechanism of action of Soolantra in treating the inflammatory lesions of rosacea is not known but may be linked to anti-inflammatory effects of ivermectin as well as causing the death of Demodex mites that have been reported to be a factor in inflammation of the skin.
The applicant, Galderma Nordic AB applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LI, LT, LU, LV, MT, NL, NO, PL, PT, RO, SK and UK as concerned member states (CMS).

*PIP –Paediatric Investigation Plan*
The applicant has obtained a product specific PIP waiver from the PDCO/EMA for all subsets of the paediatric population for *ivermectin* in the treatment of rosacea.

For approved indications, see the Summary of Product Characteristics.

# II. QUALITY ASPECTS

## II.1 Introduction

Soolantra is presented in the form of a cream containing 10 mg/g of ivermectin. The excipients are glycerol, isopropyl palmitate, carbomer copolymer, dimeticone, disodium edetate, citric acid monohydrate, cetyl alcohol, stearyl alcohol, macrogol cetostearyl ether, sorbitan stearate, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), phenoxyethanol, propylene glycol, oleyl alcohol, sodium hydroxide and purified water. The cream is filled in laminated tubes with polypropylene child resistant closure.

## II.2 Drug Substance

Ivermectin has a monograph in the Ph Eur.

Ivermectin is a white or yellowish-white, crystalline powder, slightly hygroscopic. It is practically insoluble in water, freely soluble in methylene chloride and soluble in ethanol (96%). The structure of ivermectin has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

## II.3 Medicinal Product

Soolantra cream is formulated using excipients described in the current Ph Eur, except for carbomer copolymer which is controlled according to USP. None of the raw materials used in the product are of human or animal origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as solubility and stability.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

# III. NON-CLINICAL ASPECTS

## III.1 Pharmacology

**Primary pharmacodynamics**
No studies on primary pharmacodynamics were presented and a view on pharmacology published in literature was provided on a general level by the Applicant.

The anti-inflammatory potential of topical application of ivermectin has been evaluated in *in vivo* animal skin pharmacology studies. The studies were: evaluation of anti-inflammatory activity after single topical administration of ivermectin and metronidazole in TPA induced ear edema model, evaluation of ivermectin activity in TPA-induced TNF-α production model, evaluation of anti-inflammatory activity of ivermectin after single topical administration in arachidonic acid-induced ear edema model, and evaluation of topical route of immunomodulatory potential of ivermectin in dermatophagoides-induced AD-like mouse model. The results from these studies showed anti-inflammatory properties of ivermectin and reduction of edema.

**Safety pharmacology**
The core battery safety pharmacology studies have been performed and evaluated regarding effects of ivermectin on the CNS, cardiovascular, respiratory, urinary and gastrointestinal systems. Ivermectin caused decreased motor activity in rats indicating an effect in the CNS at 20 mg/kg. Exposure levels have not been discussed by the Applicant and therefore comparison to the human exposure cannot be made. The dog telemetry study did not show any adverse effects caused by ivermectin in the cardiovascular system at plasma concentrations of approximately 400 ng/mL. Ivermectin caused no adverse effects in the respiratory system after an intravenous dose of up to 0.2 mg/kg after intravenous administration. Ivermectin caused a reduction of gastrointestinal transit in the rat at 20 mg/kg and a reduction of gastric emptying at 7 and 20 mg/kg in the rat.

## III.2 Pharmacokinetics

The absorption of ivermectin was studied using *in vitro* and *in vivo* methods. The *in vitro* absorption of radiolabelled ivermectin 1% cream was studied in the human excised skin model showing a low penetration (2.2%) and the dose was mainly recovered in the stratum corneum. The topical absorption of ivermectin 1% cream *in vivo* was studied in mice, rats, dogs and minipigs showing the bioavailability of 4% in the mouse, 2% in the rat and 0.4% in the dog and minipig. It can be concluded that the absorption of ivermectin in animals was slow after topical administration and was comparable to the absorption in the human skin model. The oral bioavailability of ivermectin was 72% in the mouse, 25%-41% in the rat and 30% - 41% in the dog.

The results from the distribution studies presented showed that ivermectin had high binding to plasma proteins, which was also similar between all species and binds mainly to albumin. [$^3$H]-ivermectin showed low partitioning into red blood cells, with a blood-to-plasma ratio below 0.1 in the mouse, rat, rabbit, dog and in human and < 0.2 in the minipig. Following an iv dose of ivermectin high distribution to tissues were observed. The volume of distribution ($Vd_{ss}$) of ivermectin was of 2.2 L/kg or more in the mouse, rat, dog and minipig.

After repeated dermal application of [$^3$H]-ivermectin 1% cream, radioactivity was distributed in most tissues examined except for brain, bone, pituitary gland, spinal cord and bone marrow. Radioactivity was still measurable in many organs at 48 hours. The radioactivity was below the detection limit for quantification (BLQ) at 168 hours after the last application.

Tissue distribution after a single and repeated dermal application of [$^3$H]-ivermectin 1% cream was studied in rats. After repeated dermal application of [$^3$H]-ivermectin 1% cream, radioactivity was distributed in most tissues examined except for brain, bone, pituitary gland, spinal cord and bone marrow. However, the radioactivity detected in the tissues was about 5% of the applied dose.

When radiolabelled ivermectin was given orally to pregnant rats low amounts of radioactivity were detected in placenta, fetuses and amniotic fluid.

*In vitro* metabolism studies showed that five different metabolites were detected across the different species; mouse, rat, dog, minipig and human. All major metabolites formed *in vitro* in human hepatocytes were also formed *in vitro* in hepatocytes of at least one of the animal species. The main metabolites were: M1: 3’’-O-demethyl ivermectin; M2: 4a-hydroxy ivermectin; M3: O-desmethyl hydroxyl ivermectin; M4: Isomer of M2 (hydroxyl ivermectin); M5: Isomer of M3 (O-desmethyl hydroxyl ivermectin). The main metabolites in the rat and dog were identified as an O-demethylation and a hydroxylated of ivermectin. In the minipig the main metabolites were 3’’-O-desmethyl-monohydroxy and the 3”-O-desmethyl ivermectin. Due to the similarity of the metabolism between human, rat, dog and minipig, these animal species were selected as species to be used in the toxicology studies.

The results showed that ivermectin had a low plasma clearance in rats, dogs and minipigs and a long elimination half-life (≥ 9 hours). Ivermectin and its metabolites are eliminated mainly via feces suggesting biliary excretion as the major route of elimination in all animal species.

The Applicant has not performed any studies to show excretion in milk, but according to the literature ivermectin is excreted in milk in several animal species.

## III.3 Toxicology

**Repeat-dose toxicity**
Two different formulations, A and B have been used in studies with 1% ivermectin cream. Formulations differ by the amount of paraben (0.3% (w/w) in formulation A, and 0.24% (w/w) in formulation B), which was used as anti-microbial agent in the formulation. This slight difference did not affect the outcome of the studies.

Systemic exposure in mice and rats in studies where ivermectin cream was given via dermal application was considerably high compared to human exposure and also compared to systemic exposure of minipigs via dermal application. The Applicant has explained that the difference in systemic exposure levels is probably due to the behaviour of rodents (licking the fur) and thereby getting the test compound also by oral route into systemic circulation. This explanation is plausible and results in high exposures.

**Mouse**
The mouse studies were conducted as dose range finding studies for the carcinogenicity study. In the 4-week study in mice via dermal application no adverse effects were observed in the animals. The mice were carrying special vests to prevent licking and grooming of the application site, which seemed to work well in this study. In the next study, 13-week study, severe toxicity was observed in the group given 5 mL/kg of 1% ivermectin cream corresponding 50 mg/kg of ivermectin. The animals showed severe CNS related clinical signs and were killed preterminally or found dead by study day 5 which seem to be related to the pharmacology of ivermectin. Mice in this study were not carrying special vests to protect from licking and grooming, which supposedly has resulted in high systemic exposure causing CNS effects. Doses up to 10 mg/kg with 1% ivermectin cream were tolerated well and did not result in any adverse effects or local reactions at the application site in the 13-week study.

**Rat**
A 4-week study via dermal application of ivermectin cream 1% was performed with one dose level (20 mg/kg) caused no adverse effects, although systemic exposure in terms of $AUC_{0-24}$ was high compared to the exposure in the mouse study. Rats were not carrying vests to prevent licking and grooming.

**Minipig**
Toxicity studies of 4-week, 13-week and 39-week duration were performed with 1% ivermectin cream in minipigs after dermal application, which is the clinical route of application. No treatment-related adverse effects or local reactions were observed in these studies. Systemic exposure was much lower in these studies than in the rodent studies after oral dosing. The exposure in minipigs via dermal application at the highest dose given in the study was comparable to the systemic exposure in humans at the therapeutic dose.

**Genotoxicology**
Ivermectin was not mutagenic or genotoxic in the tests performed. Ivermectin was negative in *in vitro* photogenotoxicity Ames test and in the assay with CHO cells.

**Carcinogenicity**
In the 104-week dermal carcinogenicity study in mice with ivermectin up to dose levels of 10 mg/kg did not cause any treatment-related in life observations or did not affect the incidence of tumour-related deaths or did not have any effect on the incidence or morphology of tumours.

In the 12-month photo carcinogenicity study in the hairless mouse model repeated topical administration of vehicle cream enhanced UVR-induced skin tumour development, compared with Crl:SKH1-*hr* hairless mice only exposed to UVR. Topical administration of ivermectin cream at concentrations of 0.3% and 1.0% enhanced photo carcinogenesis compared with the vehicle cream. Skin reaction findings indicated that topical administration of vehicle cream to mice also exposed to UVR elicited primary skin irritation when compared with mice only exposed to an equivalent UVR dose. Topical administration of ivermectin cream at concentrations of 0.3% and 1% exacerbated the primary irritation. In addition, concordance occurred between the induction of cutaneous primary irritancy and the enhancement of photo carcinogenesis for both vehicle cream administration and the amplification of this vehicle effect with ivermectin cream 0.3% and 1%. The *in vitro* photo genotoxicity studies were negative giving no evidence of genotoxic mechanism. The results from the *in vivo* phototoxicity study in rats after topical application showed that ivermectin cream was not phototoxic. Ivermectin has shown to have photo allergenic potential via sensitization. The Applicant was requested to discuss the possible mechanism of photo carcinogenicity caused by ivermectin cream in the hairless mouse model and clinical relevance of this finding. The Applicant has drawn the conclusion that the increased incidences of skin irritation caused by the vehicle cream and by ivermectin 0.3% and 1% creams is likely the causal effect for the increased incidence of UVR-induced skin tumours. Furthermore, the Applicant considers that the skin tumours seen in mice after ivermectin cream application are not relevant to humans, since skin irritation was not observed in humans. In addition, the hairless mouse model to study photo carcinogenic potential is not recommended by the regulatory agencies due to difficulties to relate the results to human situation.

In the 104-week oral rat carcinogenicity study benign hepatocellular adenomas were observed in males at 9 mg/kg, which are considered related to the treatment with ivermectin. Increased liver weight was observed in both sexes and increased incidence in basophilic foci was observed in males at 3 mg/kg without incidence of liver tumours. Basophilic focus was considered as preneoplastic finding. Exposure margins to these findings were 282-fold to hepatocellular adenomas and 70-fold to basophilic foci. Islet cell adenoma in pancreas was observed in males at high dose and islet cell carcinoma in females at high dose level. The exposure margin at NOAEL is approximately 100-fold to human exposure. The exposure margins to these findings are high and are therefore not considered to be a safety risk when ivermectin 1% cream is used as topical application in patients.

There were non-neoplastic changes such as glandular stomach erosion, or ulceration, hepatic periportal to diffuse vacuolisation and peliosis hepatitis and a higher incidence of alveolar histiocytosis, interstitial pneumonia in males, chronic progressive nephropathy in females, and higher adrenal gland weight in both sexes at high dose. Exposure margin to these non-neoplastic changes was approximately 300-fold compared to human exposure to ivermectin 1% cream given topically. These exposure margins are considered large and the findings are not posing a significant risk to humans.

**Reproductive and developmental toxicity**

Ivermectin caused teratogenic effects both in rats and rabbits. Increased proportion of cleft palates in rat fetuses were observed at the high dose, 12 mg/kg. The exposure margin at the NOAEL (4 mg/kg) for this finding was approximately 300-fold compared to human exposure after topical administration. In the rabbit fetal weight decrease was observed at 3.5 mg/kg but no morphological changes that could be related to treatment. At 4.5 mg/kg increase in carpal flexure in several fetuses were observed and are considered to be related to the treatment with ivermectin. The NOAEL for teratogenic effects of ivermectin was 3.5 mg/kg in the rabbit

providing an exposure margin of approximately 70-fold compared to human exposure after topical treatment.

Published data on the effects of ivermectin on pre and postnatal development shows that administration of ivermectin at 4 mg/kg during gestation caused mortality in the pup and affected cliff avoidance, locomotion, geotaxis and swimming development. At lower doses offspring mortality, retarded growth and delayed eye opening, affected cliff avoidance and surface righting reflex, induced negative geotaxis, and delayed locomotion and swimming development. At doses up to 0.4 mg/kg no treatment related mortality or physical signs of toxicity among parents or offspring have been observed. Exposure data is not available in these studies and therefore, no margin calculations can be done.

**Local tolerance**
Ivermectin is considered irritant on the skin and non-irritant on the eye. The results showed that ivermectin 1% cream and vehicle cream were considered as potential skin sensitizers.

**Phototoxicity and photoallergenic potential**
Topical application of ivermectin 1% cream followed by UVR did not cause phototoxic reactions in guinea pigs. The results from the guinea pig sensitization test showed that ivermectin 1% cream may have photo allergenic potential. The results showed that UVR can potentiate cutaneous reactions caused by ivermectin 1% cream. The murine lymph node test did not show sensitizing effect for ivermectin 1% cream.

**Immunomodulatory effects**
Ivermectin did not exert major immunomodulatory effects, had no deleterious effects on hematopoietic progenitors or on progenitor cells of the myeloid lineage, and had only a minor and specific effect on neutrophil progenitors.

### III.4 Ecotoxicity/environmental risk assessment
There is a risk from the use of ivermectin for the aquatic compartment (water and sediment) as well as the terrestrial compartment. This information has been included in the SmPC for Soolantra.

The Applicant has committed to perform a study on bioaccumulation of ivermectin and a study on Early-Life Stage Toxicity Test of ivermectin in fish according to OECD 305 and 210, respectively. The results of these studies will also be included in the SmPC of Soolantra.

## IV. CLINICAL ASPECTS

### IV.1 Pharmacokinetics
Ivermectin is a known active substance but a new chemical entity in the RMS and some of the CMS countries.

Following topical application with Soolantra® 1% (1g cream once daily), the systemic exposure of ivermectin reached steady state within two weeks treatment with a $C_{max}$ level of about 2 ng/ml and an AUC of approximately 35 ng/ml.h. The systemic exposure at steady state is lower than those obtained following a single 6-mg oral dose of ivermectin in healthy volunteers ($AUC_{0-24h}$ 134 ng/ml.h; supratherapeutic concentration for the rosacea indication).

The terminal half-life of ivermectin was calculated to about 6 days. This long half-life is probably due to absorption dependent elimination. The total elimination characteristics of

ivermectin *i.e.* excretion, metabolism, metabolic pathways, enzymes and transporters involved *etc* have not been provided or discussed by the Applicant.

The likelihood of ivermectin to act as metabolic perpertrator *in vivo* is deemed low, based on *in vitro* enzyme inhibition and induction data. However, the risk of ivermectin as a metabolic victim with respect to drug drug interactions has not been discussed. The SmPC 4.5 has been updated with that caution is advised when ivermectin is co-treated potent CYP3A4 inhibitors as the exposure (AUC) may be significantly increased.

In conclusion, a long terminal $t_{1/2}$ of ivermectin, probably due to absorption dependent elimination, was seen following topical treatment with Soolantra® 1%. The elimination characteristics and clinical consequences of potential drug-drug interaction are not discussed in the current application of the known active substance, however, the lack of data is mentioned in the SmPC 4.5.

## IV.2 Pharmacodynamics

Ivermectin has been suggested to have a dual effect of relevance for topical treatment of papulopustular rosacea; both an anti-inflammatory and an anti-parasitic action, which might offer a positive effect on papulopustular lesions in adult patients with rosacea.

The Applicant has not submitted any new primary pharmacology data, which is acceptable considering that ivermectin is a well-known compound with clinical experience both in veterinary and human medicines. The compound causes death of parasites via binding to glutamate-gated chloride channels. In subjects with rosacea, an abnormal number of the hair follicle mite *Demodex folliculorum* has been demonstrated. Furthermore, an anti-inflammatory effect of ivermectin has been demonstrated which could be of clinical relevance at the proposed indication.

No specific studies on secondary pharmacological effects have been performed, which is acceptable considering that ivermectin is a well-known compound.

In conclusion, a plausible mechanism of action for the pharmacological effect of ivermectin in the topical treatment of papulopustular rosacea has been proposed and the data are sufficient.

## IV.3 Clinical efficacy

The efficacy of Soolantra Cream 1% is mainly supported by five clinical studies; two phase 2 studies (40027 and 40106), two pivotal, double-blind, vehicle-controlled phase 3 studies (18170 and 18171) and one investigator-blinded, active-controlled phase 3 study (40173). All these were randomized, parallel-group studies. The two pivotal phase 3 studies were performed in the US and Canada while studies 40106 and 40173 were performed in Europe. Studies relevant to the efficacy assessment for Soolantra are depicted below.

**Table 1. Summary of studies relevant to the efficacy assessment of Ivermectin Cream**

| **Study Number** | **Study Objectives** | **Number of Subjects** | **Primary Efficacy Endpoints** | **Secondary Efficacy Endpoints** |
|---|---|---|---|---|
| **Studies not controlled, different treatment regimen, or treatment free** | | | | |
| **RD.03.SRE.40006** | Exploratory evaluation of efficacy and safety | 147 (ITT)<br>128 (PP | Percent Change in Inflammatory Lesion Counts from | 1) erythema<br>2) telangiectasia<br>3) global severity grade |

| Study Number | Study Objectives | Number of Subjects | Primary Efficacy Endpoints | Secondary Efficacy Endpoints |
|---|---|---|---|---|
| | of twice daily applications of ivermectin 1% cream versus its vehicle and metronidazole 0.75% cream | ) | Baseline at Week 9 | |
| **RD.03.SRE.40037** | Treatment-free follow-up of RD.03.SRE.40027<br><br>Assessment of duration of therapeutic effect | 149 | Time to relapse (and relapse rate) | 1) change from baseline in erythema score.<br>2) change from baseline in telangiectasis score.<br>3) change from baseline in Investigator Global Assessment score 1 and change from Baseline in IGA2,<br>4) change from Baseline in Inflammatory Lesion Count. |
| **RD.03.SRE.40051** | Assessment of efficacy and long-term safety | 484 (ITT)<br>No PP analysis done | 1) IGA score and change from Baseline to the end of treatment.<br>2) Inflammatory lesion counts, change and Percent Change from Baseline to the end of treatment.<br>3) Erythema score and change from Baseline to the end of treatment. | None |
| **Controlled studies evaluating the Ivermectin 1% Cream QD regimen** | | | | |
| **RD.03.SRE.40027** | Assessment of efficacy and safety of three concentrations and two regimens of CD5024 cream versus vehicle and versus Metronidazole cream | 296 (ITT)<br>271 (PP) | Percent change from Baseline in inflammatory lesion from Baseline at Week 12 | 1) Percent Change from Baseline at scheduled time points<br>2) Change at Week 12 in either IGA1 or IGA2<br>3) Success Rate at Week 12, defined as “clear” or “almost clear” for either IGA1 or IGA2<br>4) Change in erythema and telangiectasia scores at Week 12 |
| **RD.03.SRE.40** | Assessment of | 210 (IT | 1)Success Rate | 1) CD5024 PK |

| Study Number | Study Objectives | Number of Subjects | Primary Efficacy Endpoints | Secondary Efficacy Endpoints |
|---|---|---|---|---|
| **106** | potential for induction of neutropenia and assessment of general safety and efficacy | T)<br>186 (PP) | based on IGA, defined as the percentage of subjects who achieved at least a 2 grade improvement<br>2) Change in Inflammatory Lesion Counts from Baseline. | parameters: Ct at each visit from Week 2,<br>2) M1 and M2 PK parameter: Ct at each visit from Week 2 if appropriate. |
| **RD.06.SRE.18170 (Part A)** | Assessment of efficacy and long-term safety | 683 (ITT)<br>606 (PP) | 1) Success rate<br>2) Absolute Change from Baseline in Inflammatory Lesion Counts at Week 12 | Percent Change from Baseline in Inflammatory Lesion Counts at Week 12 |
| **RD.06.SRE.18171 (Part A)** | Assessment of efficacy and long-term safety | 688 (ITT)<br>596 (PP) | 1) Success rate<br>2) Absolute Change from Baseline in Inflammatory Lesion Counts at Week 12 | Percent Change from Baseline in Inflammatory Lesion Counts at Week 12 |
| **RD.03.SRE.40173 (Part A)** | Assessment of efficacy and safety (Part A) | 962 (ITT)<br>865 (PP) | Percent change from Baseline in Inflammatory Lesion Counts at Week 16 | 1) Percent of subjects with IGA ≤1 at each evaluation visit<br>2) IGA and Change from Baseline in IGA at each evaluation visit<br>3) Absolute Change in Inflammatory Lesion Counts from Baseline at each evaluation visit<br>4) Subject's global improvement of rosacea |

**Dose response studies**

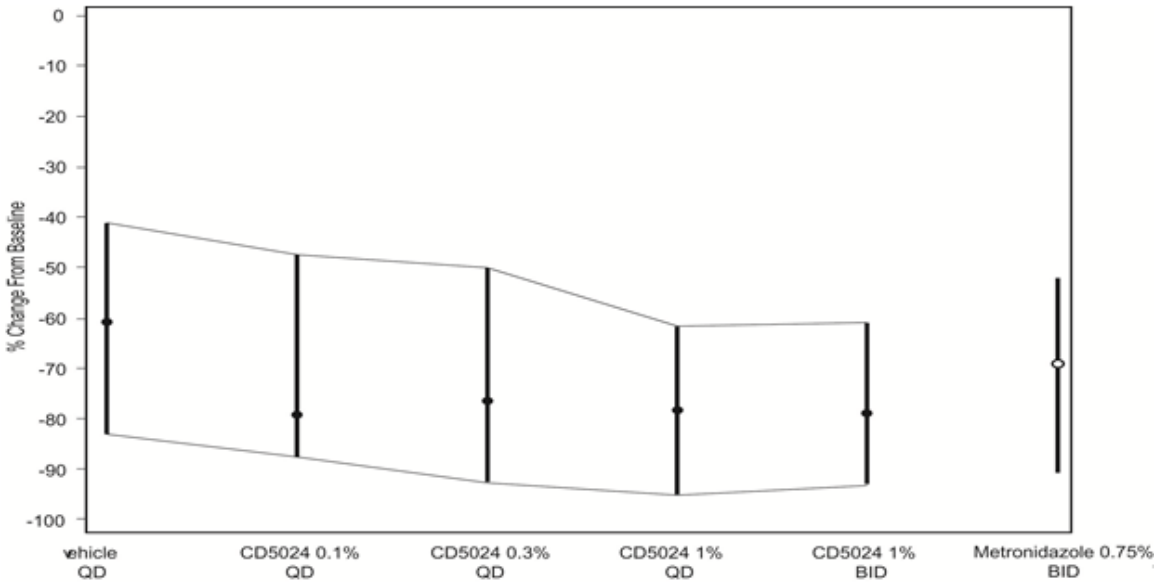
Study **40027** was a 6-arm, dose ranging study with a multicenter, randomized, investigator-blind, vehicle- and active-controlled design. Ivermectin concentrations of 0.1%, 0.3%, and 1% were tested versus its vehicle and versus Metronidazole 0.75% Cream. Ivermectin cream at the three different concentrations and its vehicle were applied QD over 12 weeks, while Ivermectin 1% Cream and Metronidazole 0.75% Cream were applied BID over 12 weeks. The treatment arms of the QD regimens were double blind in that neither the subject nor the Investigator knew the identity of the treatment.

Male or female subjects with PPR at least 18 years of age and with at least 15 inflammatory lesions and at least mild erythema were included. The primary end-point was Percent Change from Baseline in Inflammatory Lesion Counts at Week 12.

In total, 296 subjects comprised the ITT population and the PP population consisted of 271 subjects. The majority (68%) were female and Caucasian with a mean age of 52 years. The treatment groups were comparable with respect to demographic and disease baseline characteristics.

The results demonstrated a dose response relationship for increasing concentrations of Ivermectin Cream, although rather weak. It was also considered that increasing the dosing frequency to twice daily instead of once daily did not produce a gain in efficacy. Results for the primary end-point are shown in Figure 1.

**Figure 1. Interquartile range and median Percent Change in Inflammatory Lesion Count from Baseline at Week 12 (ITT-LOCF), Study 40027**




For the IGA success rate results, BID dosing showed slightly higher response rates compared with QD dosing. Treatment success rates for IGA1 (scale including erythema), and IGA2 (scale based on inflammatory lesion counts only) are shown in Table 2.

**Table 2. Treatment Success vs. vehicle at Week 12 (ITT-LOCF population), Study 40027**

| | CD5024 0.1% QD | CD5024 0.3% QD | CD5024 1% QD | CD5024 1% BID | metronidazole 0.75% BID | vehicle QD |
|---|---|---|---|---|---|---|
| **Total n (%)** | 51 (100) | 47 (100) | 52 (100) | 48 (100) | 48 (100) | 50 (100) |
| **Investigator Global Assessment score 1** | | | | | | |
| **Success n (%)** | 32 (62.7) | 30 (63.8) | 34 (65.4) | 34 (70.8) | 30 (62.5) | 21 (42) |
| **p-value** | **0.036** | **0.032** | **0.019** | **0.005** | - | - |
| **Investigator Global Assessment score 2** | | | | | | |
| **Success n (%)** | 34 (66.7) | 31 (66) | 37 (71.2) | 36 (75) | 31 (64.6) | 26 (52) |
| **p-value** | 0.1214 | 0.1617 | **0.0498** | **0.0210** | - | - |

From a safety perspective, no differences across the dose range were observed. The 1% Ivermectin Cream was chosen for further development, which seems reasonable. Concentrations higher than 1% have not been studied.

Study **40037** was a treatment-free follow-up study to the dose response study 40027, with the aim to assess time to relapse and relapse rate in subjects who achieved success in study 40027. Different definitions of relapse were used, but based on Definition 1 (IGA2 score ≥2), the *relapse-free* rates were higher with Ivermectin 0.3% Cream QD, Ivermectin 1% Cream QD and BID, compared with the lower Ivermectin concentrations, Metronidazole 0.75% Cream BID and the Vehicle Cream QD. When comparing Ivermectin 1% Cream QD and BID, the group receiving BID dosing had higher relapse-free rates compared with the QD group. The groups were small and no statistically significant differences between treatment groups could be observed.

With respect to the chosen posology (BID vs. QD), the chosen QD regimen is advantageous from a compliance perspective and the potentially, slightly higher efficacy and more sustained effect do not seem sufficient to justify a BID posology for Soolantra. Hence, the QD posology that was chosen for the phase 3 studies is endorsed.

**Main study(ies)**
The two pivotal studies in the application are studies 18170 and 181871, with an identical design. These studies were conducted in parallel (the first subject in each study enrolled in December 2011).

**Studies 18170 and 181871**

*Methods*
The studies were of multicenter, randomized, double-blind, vehicle-controlled, parallel group design with the aim to assess efficacy and safety of Ivermectin (CD5024) 1% Cream applied topically once daily in subjects with papulopustular rosacea.

The phase 3 studies enrolled male and female patients 18 years of age or above, with moderate to severe papulopustular rosacea (IGA 3 or 4), with at least 15 but not more than 70 inflammatory lesions (papules and pustules) on the face. Patients with more than two nodules on the face were excluded and so were patients with particular forms of rosacea (e.g. isolated rhinophyma) or other facial dermatoses (e.g. acne). Other rosacea treatments were not allowed in the controlled studies.

There is no European guideline available for products indicated for treatment of rosacea. Hence, efficacy end-points to be used are not clearly established. The co-primary efficacy end-points in the pivotal studies were success rate based IGA (percentage of subjects with “0 = Clear” or “1 = Almost Clear”) at Week 12 and Absolute Change from Baseline in Inflammatory Lesion Count at Week 12.

The IGA (Investigator´s Global Assessment) (Table 3) is a global assessment scale of rosacea severity and addresses both presence and size of papules/pustules and severity of erythema. IGA scales have been used for assessment of efficacy for other rosacea products and similar IGA scales are also often used in other indications, e.g. psoriasis and acne. Use of IGA as co-primary end-point is supported and so is the use of Absolute Change from Baseline in Inflammatory Lesion Counts.

**Table 3. Investigator’s Global Assessment scale**

| Grade | Score | Clinical Description |
|---|---|---|
| Clear | 0 | No inflammatory lesions present, no erythema |
| Almost Clear | 1 | Very few small papules/pustules, very mild erythema present |

| | | |
|---|---|---|
| Mild | 2 | Few small papules/pustules, mild erythema |
| Moderate | 3 | Several small or large papules/pustules, moderate erythema |
| Severe | 4 | Numerous small and/or large papules/pustules, severe erythema |

Secondary and other end-points addressed *Percent* Change in Inflammatory Lesion Count, Subject's assessment of rosacea improvement at Week 12 (5-point scale ranging from Excellent Improvement to Worse), erythema and nodule counts and quality of life (Dermatology Life Quality Index, DLQI, and RosaQoL™). The end-points used in the pivotal studies are considered relevant.
Subjects were randomized in a 2:1 ratio to receive study drug (Ivermectin 1% Cream QD or Vehicle Cream QD) for an initial period of 12 weeks (Part A). Part A consisted of 7 visits: Screening Weeks -2 and -1, Baseline, Week 2, Week 4, Week 8 and Week 12/Early Termination (ET).

Part B of the pivotal studies was a long-term extension period with Ivermectin 1% Cream QD or Azelaic Acid 15% Gel BID and was an investigator-blind, active-controlled part of the study lasting 40 weeks (up to Week 52). Subjects initially treated with Ivermectin 1% Cream QD were to continue on this treatment while subjects initially treated with Vehicle Cream QD were to switch to Azelaic Acid 15% Gel BID, in the morning and evening. During this 40-week part of the study, the Investigator was to stop the treatment if the subject was considered as "clear" (grade 0) on the IGA scale. The subject was to continue to attend the study visits as planned in the protocol. Treatment was restarted if the IGA score became ≥1 (where 1="almost clear"). Visits occurred every 4 weeks. Part B was followed by a 4-week safety follow-up period (part C) without treatment.

Part A was conducted using a double-blind study design. Study drugs were packaged in the same type of tubes and there was no visible difference between the study drugs administered to subjects. The subjects, Investigators and the Sponsor were blinded to the subject treatment assignment.

During Part B of the pivotal studies, the study materials (study drug and comparator product) were different in appearance, dosage form, and regimen. All products were required to be dispensed by designated trained study personnel, independent from the Investigator/evaluator who assessed the subject. The study personnel instructed the subjects not to discuss the appearance of the study drug or the dose regimen with the Investigator. Part B study drugs were dispensed to subjects only after all Week 12 (Part A) procedures were completed. The procedures used to ensure blinding in the pivotal studies seem acceptable.

The statistical methods used were adequate for the study design and endpoints. The type I error is controlled in the strong sense for the co-primary endpoints and the time of onset analysis.
A number of sensitivity analyses were pre-planned and performed, assessing the impact of missing data at the primary time point of analysis.

*Results*
In study 18170, a total of 875 patients were screened and 683 patients were randomised to Ivermectin Cream (n=451) or Vehicle Cream (n=232) (ITT population). The PP population comprised a total of 606 subjects.

In study 18171, 890 patients were screened and 688 patients were randomised to Ivermectin Cream (n=459) or Vehicle Cream (n=229) (ITT population). The PP population comprised a total of 596 subjects.

In both studies, the majority of included subjects were females (65-70%) with a mean age of approximately 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 PPR (IGA scores of 3 or 4) with the majority (generally >75%) having moderate PPR. The mean number of inflammatory lesions was slightly above 30. 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 (part A) was high (>90%) in the pivotal studies.

Ivermectin 1% Cream met the co-primary end-points and was significantly superior ($p<0.001$) compared to Vehicle Cream. The results were confirmed in the ITT Population using MI, the PP Population and in the sensitivity analyses. At Week 12 (ITT-LOCF), the IGA Success rate was approximately 40% for Ivermectin 1% Cream and 10-20% for Vehicle Cream. For the Absolute Change in Inflammatory Lesion Counts from Baseline, Ivermectin 1% Cream showed a decrease of about 8 more lesions as compared to Vehicle Cream, at Week 12. The results for the primary end-points are depicted in the following tables and figures.

**Table 4. Success Rates based on Investigator's Global Assessment at each post-Baseline visit (ITT Population) Study 18170 (Part A)**

| Variable | CD5024 1% Cream QD (N=451) | Vehicle Cream QD (N=232) | p-value | |
|---|---|---|---|---|
| | | | ITT-LOCF | ITT-MI |
| **Baseline IGA, n (%)** | | | | |
| Moderate (IGA=3) | 369 (81.8) | 191 (82.3) | Not Applicable | Not Applicable |
| Severe (IGA=4) | 82 (18.2) | 41 (17.7) | | |
| **Week 2 (ITT-LOCF), n (%)** | | | | |
| Success | 17 (3.8) | 5 (2.2) | 0.267 | 0.305 |
| Failure | 434 (96.2) | 227 (97.8) | | |
| **Week 4 (ITT-LOCF) n (%)** | | | | |
| Success | 49 (10.9) | 13 (5.6) | 0.021 | 0.020 |
| Failure | 402 (89.1) | 219 (94.4) | | |
| **Week 8 (ITT-LOCF), n (%)** | | | | |
| Success | 104 (23.1) | 23 (9.9) | <0.001 | <0.001 |
| Failure | 347 (76.9) | 209 (90.1) | | |
| **Week 12 (ITT-LOCF), n (%)** | | | | |
| Success | 173 (38.4) | 27 (11.6) | <0.001 | <0.001 |
| Failure | 278 (61.6) | 205 (88.4) | | |
| **Week 12 (Sensitivity 1), n (%)** | | | | |
| Success | 172 (38.1) | 26 (11.2) | <0.001 | Not Applicable |
| Failure | 279 (61.9) | 206 (88.8) | | |
| **Week 12 (Sensitivity 2), n (%)** | | | | |
| Success | 199 (44.1) | 43 (18.5) | <0.001 | Not Applicable |
| Failure | 252 (55.9) | 189 (81.5) | | |

Success was defined as '0 = Clear' or '1 = Almost Clear' on the Investigator Global Assessment (0 to 4 scale).
LOCF = The last observation carried forward in Part A of the study. Baseline value was used if no post-Baseline data were available.
Week 12 (Sensitivity 1): As a sensitivity analysis, 'Failure' was assigned to the missing data at Week 12.

Week 12 (Sensitivity 2): As a sensitivity analysis, 'Success' was assigned to the missing data at Week 12.
P-value was based on the CMH general association statistic, controlling for analysis center.
Pair-wise Breslow-Day tests for homogeneity of the odds ratios were used to assess the treatment by center interaction.
MI = Multiple imputations. Multiple Imputations (5 times) were applied to IGA scores at Week 2, 4, 8, 12 using Markov Chain Monte Carlo (MCMC) method with single chain.
Combined p-values from MI are presented using method described in Schafer 1997.

**Table 5. Success Rates based on Investigator's Global Assessment at each post-Baseline visit (ITT Population) Study 18171 (Part A)**

| Variable | CD5024 1% Cream QD (N=459) | Vehicle Cream QD (N=229) | p-value | |
|---|---|---|---|---|
| | | | ITT-LOCF | ITT-MI |
| **Baseline IGA, n (%)** | | | | |
| Moderate (IGA=3) | 346 (75.4) | 176 (76.9) | Not Applicable | Not Applicable |
| Severe (IGA=4) | 113 (24.6) | 53 (23.1) | | |
| **Week 2 (ITT-LOCF), n (%)** | | | | |
| Success | 16 (3.5) | 6 (2.6) | 0.551 | 0.526 |
| Failure | 443 (96.5) | 223 (97.4) | | |
| **Week 4 (ITT-LOCF), n (%)** | | | | |
| Success | 54 (11.8) | 13 (5.7) | 0.014 | 0.024 |
| Failure | 405 (88.2) | 216 (94.3) | | |
| **Week 8 (ITT-LOCF), n (%)** | | | | |
| Success | 126 (27.5) | 28 (12.2) | <0.001 | <0.001 |
| Failure | 333 (72.5) | 201 (87.8) | | |
| **Week 12 (ITT-LOCF), n (%)** | | | | |
| Success | 184 (40.1) | 43 (18.8) | <0.001 | <0.001 |
| Failure | 275 (59.9) | 186 (81.2) | | |
| **Week 12 (Sensitivity 1), n (%)** | | | | |
| Success | 183 (39.9) | 43 (18.8) | <0.001 | Not Applicable |
| Failure | 276 (60.1) | 186 (81.2) | | |
| **Week 12 (Sensitivity 2), n (%)** | | | | |
| Success | 203 (44.2) | 63 (27.5) | <0.001 | Not Applicable |
| Failure | 256 (55.8) | 166 (72.5) | | |

Success was defined as '0 = Clear' or '1 = Almost Clear' on the Investigator Global Assessment (0 to 4 scale).
LOCF = The last observation carried forward in Part A of the study. Baseline value was used if no post-Baseline data were available.
Week 12 (Sensitivity 1): As a sensitivity analysis, 'Failure' was assigned to the missing data at Week 12.
Week 12 (Sensitivity 2): As a sensitivity analysis, 'Success' was assigned to the missing data at Week 12.
P-value was based on the CMH general association statistic, controlling for analysis center.
Pair-wise Breslow-Day tests for homogeneity of the odds ratios were used to assess the treatment by center interaction.
MI = Multiple imputations. Multiple Imputations (5 times) were applied to IGA scores at Week 2, 4, 8, 12 using Markov Chain Monte Carlo (MCMC) method with single chain.
Combined p-values from MI are presented using method described in Schafer 1997.

**Figure 2. IGA Success Rates over time (ITT-LOCF), Study 18170 Part A (left), Study 18171 Part A (right)**

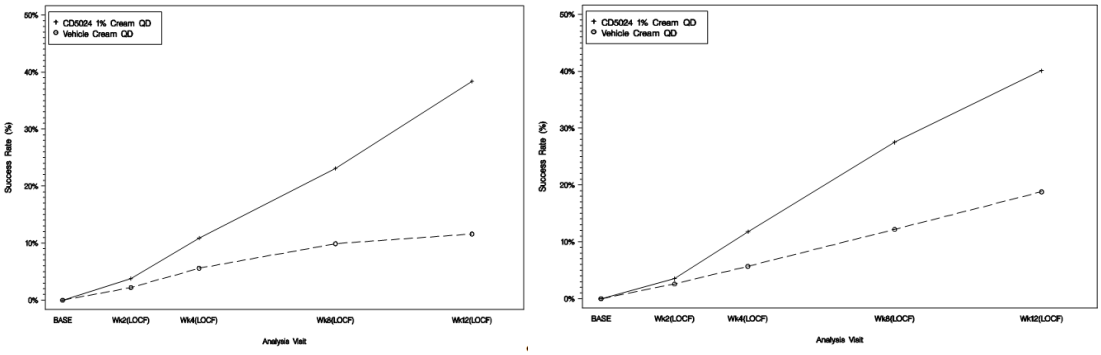



**Table 6. Absolute Change in Inflammatory Lesion Counts from Baseline (ITT Population) Study 18170 (Part A)**

| Variable | CD5024 1% Cream QD (N=451) | | Vehicle Cream QD (N=232) | | p-value | |
|---|---|---|---|---|---|---|
| | Raw Data | Change from Baseline | Raw Data | Change from Baseline | ITT-LOCF | ITT-MI |
| **Baseline Count** | | | | | | |
| Mean | 31.0 | - | 30.5 | - | Not Applicable | Not Applicable |
| SD | 14.28 | - | 14.44 | - | | |
| Median | 27.0 | - | 26.5 | - | | |
| P25,P75 | 20, 37 | - | 20, 36 | - | | |
| Min, Max | 15, 70 | - | 15, 71 | - | | |
| **Week 2 (LOCF)** | | | | | | |
| Mean | 22.2 | -8.8 | 25.4 | -5.1 | <0.001 | <0.001 |
| SD | 14.79 | 13.40 | 17.02 | 11.11 | | |
| Median | 19.0 | -8.0 | 21.0 | -5.0 | | |
| P25,P75 | 12, 29 | -14, -2 | 14, 32 | -11, 0 | | |
| Min, Max | 1, 126 | -58, 79 | 0, 109 | -56, 50 | | |
| **Week 4 (LOCF)** | | | | | | |
| Mean | 17.4 | -13.6 | 22.8 | -7.7 | <0.001 | <0.001 |
| SD | 14.33 | 14.93 | 16.62 | 12.31 | | |
| Median | 15.0 | -12.0 | 18.0 | -8.0 | | |
| P25,P75 | 8, 23 | -19, -7 | 12, 29 | -14, -1 | | |
| Min, Max | 0, 141 | -69, 79 | 0, 97 | -55, 42 | | |
| **Week 8(LOCF)** | | | | | | |
| Mean | 13.2 | -17.9 | 20.5 | -10.1 | <0.001 | <0.001 |
| SD | 13.39 | 14.75 | 17.51 | 13.96 | | |
| Median | 10.0 | -16.0 | 14.0 | -10.0 | | |
| P25,P75 | 5, 17 | -24, -9 | 9, 28 | -18, -3 | | |
| Min, Max | 0, 126 | -67, 79 | 0, 97 | -51, 42 | | |
| **Week 12 (LOCF)** | | | | | | |
| Mean | 10.6 | -20.5 | 18.5 | -12.0 | <0.001 | <0.001 |
| SD | 13.05 | 15.95 | 16.75 | 13.55 | | |
| Median | 7.0 | -18.0 | 13.0 | -12.0 | | |
| P25,P75 | 3, 14 | -28, -13 | 8, 22 | -20, -7 | | |
| Min, Max | 0, 107 | -69, 79 | 0, 97 | -51, 42 | | |
| **Week 12 (Sensitivity 3)** | | | | | | |
| Mean | 9.7 | -21.3 | 18.0 | -12.6 | <0.001 | Not Applicable |
| SD | 11.95 | 14.63 | 15.97 | 11.94 | | |
| Median | 6.0 | -18.0 | 12.0 | -11.5 | | |
| P25,P75 | 3, 13 | -28, -13 | 7, 22 | -19, -8 | | |
| Min, Max | -2, 102 | -69, 64 | 0, 83 | -51, 26 | | |
| **Week 12 (Sensitivity 4)** | | | | | | |
| Mean | 9.4 | -21.6 | 17.5 | -13.1 | <0.001 | Not Applicable |
| SD | 12.03 | 14.59 | 15.97 | 12.02 | | |
| Median | 6.0 | -20.0 | 12.0 | -13.0 | | |
| P25,P75 | 2, 13 | -28, -13 | 7, 22 | -19, -8 | | |
| Min, Max | -7, 102 | -69, 64 | -3, 83 | -51, 26 | | |

LOCF = The last observation carried forward in Part A of the study. Baseline value was used if no post-Baseline data were available.
Week 12 (Sensitivity 3): As sensitivity analysis, median Change in Lesion Count from 'Failure' was assigned to the missing data in each arm at Week 12.
Week 12 (Sensitivity 4): As sensitivity analysis, median Change in Lesion Count from 'Success' was assigned to the missing data in each arm at Week 12.

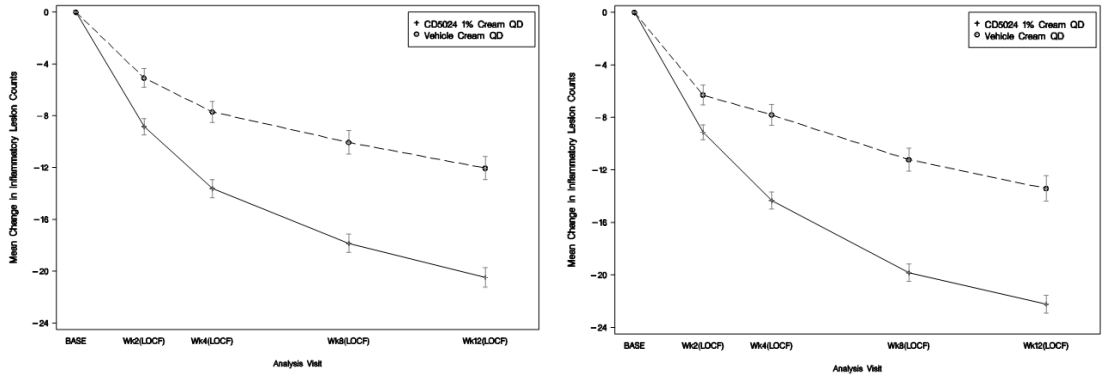
**Table 7. Absolute Change in Inflammatory Lesion Counts from Baseline (ITT Population) Study 18171 (Part A)**

| Variable | CD5024 1% Cream QD (N=459) | | Vehicle Cream QD (N=229) | | p-value | |
|---|---|---|---|---|---|---|
| | Raw Data | Change from Baseline | Raw Data | Change from Baseline | ITT-LOCF | ITT-MI |
| **Baseline** | | | | | | |
| Mean | 33.3 | - | 32.2 | - | Not Applicable | Not Applicable |
| SD | 13.62 | - | 13.86 | - | | |
| Median | 30.0 | - | 29.0 | - | | |
| P25,P75 | 23, 41 | - | 22, 39 | - | | |
| Min, Max | 15, 70 | - | 14, 69 | - | | |
| **Week 2 (LOCF)** | | | | | | |
| Mean | 24.1 | -9.1 | 25.9 | -6.3 | 0.006 | 0.003 |
| SD | 14.83 | 12.27 | 15.58 | 11.67 | | |
| Median | 22.0 | -8.0 | 23.0 | -6.0 | | |
| P25,P75 | 14, 31 | -15, -2 | 15, 34 | -12, -1 | | |
| Min, Max | 1, 90 | -65, 42 | 2, 110 | -63, 43 | | |
| **Week 4 (LOCF)** | | | | | | |
| Mean | 18.9 | -14.3 | 24.4 | -7.8 | <0.001 | <0.001 |
| SD | 14.21 | 13.83 | 17.34 | 11.86 | | |
| Median | 15.0 | -14.0 | 20.0 | -8.0 | | |
| P25,P75 | 8, 25 | -21, -6 | 13, 31 | -14, -1 | | |
| Min, Max | 0, 83 | -64, 35 | 0, 123 | -40, 56 | | |
| **Week 8 (LOCF)** | | | | | | |
| Mean | 13.4 | -19.8 | 21.0 | -11.2 | <0.001 | <0.001 |
| SD | 12.32 | 14.35 | 16.89 | 13.26 | | |
| Median | 10.0 | -18.0 | 17.0 | -12.0 | | |
| P25,P75 | 5, 18 | -27, -11 | 9, 27 | -18, -4 | | |
| Min, Max | 0, 83 | -66, 26 | 0, 105 | -60, 45 | | |
| **Week 12 (LOCF)** | | | | | | |
| Mean | 11.0 | -22.2 | 18.8 | -13.4 | <0.001 | <0.001 |
| SD | 11.65 | 14.87 | 17.49 | 14.48 | | |
| Median | 7.0 | -20.0 | 13.0 | -14.0 | | |
| P25,P75 | 3, 15 | -31, -14 | 8, 24 | -20, -7 | | |
| Min, Max | 0, 83 | -65, 28 | 0, 149 | -63, 82 | | |
| **Week 12 (Sensitivity 3)** | | | | | | |
| Mean | 10.8 | -22.5 | 17.9 | -14.3 | <0.001 | Not Applicable |
| SD | 11.07 | 14.39 | 16.73 | 13.70 | | |
| Median | 7.0 | -20.0 | 13.0 | -14.0 | | |
| P25,P75 | 3, 15 | -30, -15 | 8, 22 | -20, -8 | | |
| Min, Max | -2, 65 | -65, 28 | 0, 149 | -63, 82 | | |
| **Week 12 (Sensitivity 4)** | | | | | | |
| Mean | 10.5 | -22.8 | 17.4 | -14.8 | <0.001 | Not Applicable |
| SD | 10.81 | 14.34 | 16.79 | 13.76 | | |
| Median | 7.0 | -21.0 | 12.0 | -16.0 | | |
| P25,P75 | 3, 14 | -30, -15 | 8, 21 | -20, -8 | | |
| Min, Max | -9, 65 | -65, 28 | -4, 149 | -63, 82 | | |

LOCF = The last observation carried forward. Baseline value was used if no post-Baseline data were available.
Week 12 (Sensitivity 3): As a sensitivity analysis, median Change in Lesion Count from 'Failure' was assigned to the missing data in each arm at week 12.

Week 12 (Sensitivity 4): As a sensitivity analysis, median Change in Lesion Count from 'Success' was assigned to the missing data in each arm at week 12.

**Figure 3. Mean Absolute Change (plus or minus SEM) in Inflammatory Lesion Counts from Baseline over time (ITT-LOCF), Study 18170 Part A (left), Study 18171 Part A (right)**




Time to onset of efficacy was 4 weeks in both studies, based on achieving statistical significance for both co-primary end-points. For the Absolute Change in Inflammatory Lesion Counts from Baseline, statistical significance for Ivermectin Cream vs. the vehicle was observed already after 2 weeks.

Both studies also met their secondary end-points. For the Percent Change from Baseline in Inflammatory Lesion Counts, a treatment effect of 20-25% for Ivermectin 1% Cream QD over its vehicle was observed.

For the Subject's Assessment of Rosacea Improvement, larger proportions of patients reported excellent or good improvement at Week 12 with Ivermectin Cream compared with vehicle. Some patients reported worsening of the condition, however, the percentages reporting worsening with vehicle were twice as high as for Ivermectin Cream.

Regarding erythema, more subjects in the Ivermectin 1% Cream groups than in the Vehicle Cream groups showed improvement in both studies. No change in nodule counts across the study periods was observed either for subjects who received Ivermectin 1% Cream or Vehicle. The majority of patients (generally 90% or more) had no nodules.

Telangiectasias is a symptom of rosacea that is not mentioned as a specific target of the Soolantra treatment, however, assessment of these can be of interest to evaluate whether any worsening would occur as a results of treatment. No specific assessments of telangiectasias were performed in the phase 3 studies. However, assessments were made in phase 2 studies, where Ivermectin creams of different concentrations and with QD or BID posologies were used, as well as vehicle and active control. In both studies, the majority of subjects in all treatment groups showed no change from Baseline in their telangiectasia score and only a few subjects reported worsening of telangiectasia. These data do not give cause for concern with respect to potential worsening of telangiectasia.

For Quality of life assessments, some improvements in the QoL measures used in the pivotal studies (RosaQoL™ and DLQI) could be observed and also showed statistically significant differences in favour of Ivermectin vs. vehicle. However, the baseline QoL scores were not that poor and, hence, huge improvements could not be expected.

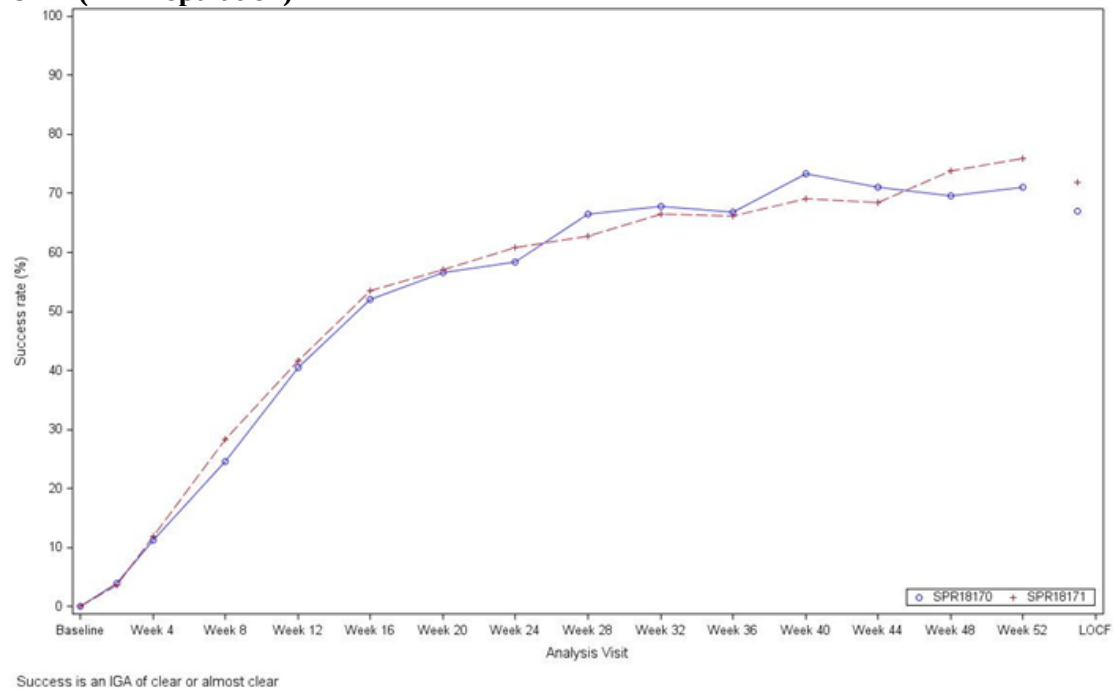
In conclusion, both pivotal studies have demonstrated a significantly superior ($p<0.001$) effect for Ivermectin 1% Cream compared to Vehicle for the co-primary endpoints. The secondary efficacy end-points and other end-points also supported the superiority of Ivermectin 1% Cream over vehicle. The treatment duration of part A in the pivotal studies was 12 weeks, which is deemed adequate. Ivermectin 1% Cream provides effect rather rapidly and onset of effect (defined as statistical significance achieved for both co-primary end-points) was observed at 4 weeks.

From a statistical point of view, the efficacy results from the phase 3 studies are robust, the SAP, finalized before analysis, has been followed. The sensitivity analyses are all supportive of the primary analysis. No post-hoc analyses were performed.

Part B of the pivotal studies was a long-term extension period with Ivermectin 1% Cream QD or Azelaic Acid 15% Gel BID and was an investigator-blind, active-controlled part of the study lasting 40 weeks (up to Week 52). The number of subjects completing part B of both studies was rather high (85%). The mean daily study drug use did not differ to a large extent between parts A and B of the studies, indicating that there seemed to be no need to increase the daily dose to maintain the effect over time. The data indicated that the therapeutic effect of Ivermectin 1% Cream QD was maintained and the number of responders continued to increase over 52 weeks. The percentages of subjects with an IGA score of 0 (clear) at Week 12 were low (3-4%) and increased up to about 25% at Week 52.

It was concluded that more than a third of the subjects were able to reach an IGA score of 0 (clear) at some point during the extension period. This may be compared with the low number of patients reaching an IGA of 0 at Week 12; 4% and 3% in Study 18170 and 18171 respectively. A fairly large proportion of the subjects (around 70%) needed retreatment during part B, generally within 1-2 months. The criterion for retreatment was set quite low (IGA≥1), while during part A, success was defined as reaching an IGA of 0 or 1.

**Figure 4. Success Rate over time in Ivermectin randomized groups in Studies 18170 and 18171 (ITT Population)**




Success is an IGA of clear or almost clear

**Study 40173**

*Methods*
This was a multicenter, randomized, active controlled, parallel-group, Investigator-blind study comparing the efficacy and safety of Ivermectin 1% Cream QD versus Metronidazole 0.75% Cream BID in subjects with PPR over 16 weeks' treatment (Part A), followed by a 36-week extension period (Part B). Period B was still ongoing at the time of submission and thus, these results were not included the MAA. This study was performed in 64 sites in Europe.

The primary efficacy objective was to show the superior efficacy of Ivermectin 1% Cream versus metronidazole 0.75% cream, as determined by the percent reduction in inflammatory lesion counts after a 16-week treatment period. The objective of the second study period (Period B) was to generate efficacy data of CD5024 1% cream versus Metronidazole 0.75% Cream, for subjects successfully treated over the initial 16 weeks of treatment.

The inclusion and exclusion criteria were almost identical to those used in the pivotal, vehicle-controlled phase 3 studies and are acceptable. Metronidazole cream was used as active comparator in this study. Subjects with known allergies or sensitivities to any components of the formulation of the study drugs being tested (either Ivermectin 1% cream or metronidazole 0.75% cream) at the Screening visit were excluded. For previous use of other topical facial treatments, a washout period for antibiotics, e.g. metronidazole, of at least 4 weeks was applied. It is likely that several patients would have been exposed to previous treatment with topical metronidazole for their rosacea since this is a commonly used product for topical treatment of rosacea (see below).

Ivermectin 1% Cream was applied QD as in previous studies and the active comparator metronidazole 0.75% cream was applied BID in accordance with its labelling. A vehicle arm was not included in the present study. This is acceptable since superiority vs. vehicle has been demonstrated for Ivermectin 1% Cream in several other studies. Furthermore, this study aimed to show superiority and not non-inferiority vs. the comparator, thus, assay sensitivity is less of an issue.

Study 40173 was not double-blind, only Investigator-blind, due to the different posologies of the two products (QD vs. BID). A double-dummy design could have been considered to overcome this issue. However, the procedures used to ensure blinding for the Investigator/Evaluator seem acceptable. The two pivotal studies were double-blind and the present study is not considered as pivotal by the Applicant. Hence, the single-blind design of this study is not considered an issue.

*Results*
A total of 1034 subjects were screened, among which 962 were randomized to receive Ivermectin 1% Cream (n=478) or Metronidazole 0.75% Cream (n=484). The PP population comprised a total of 865 subjects.

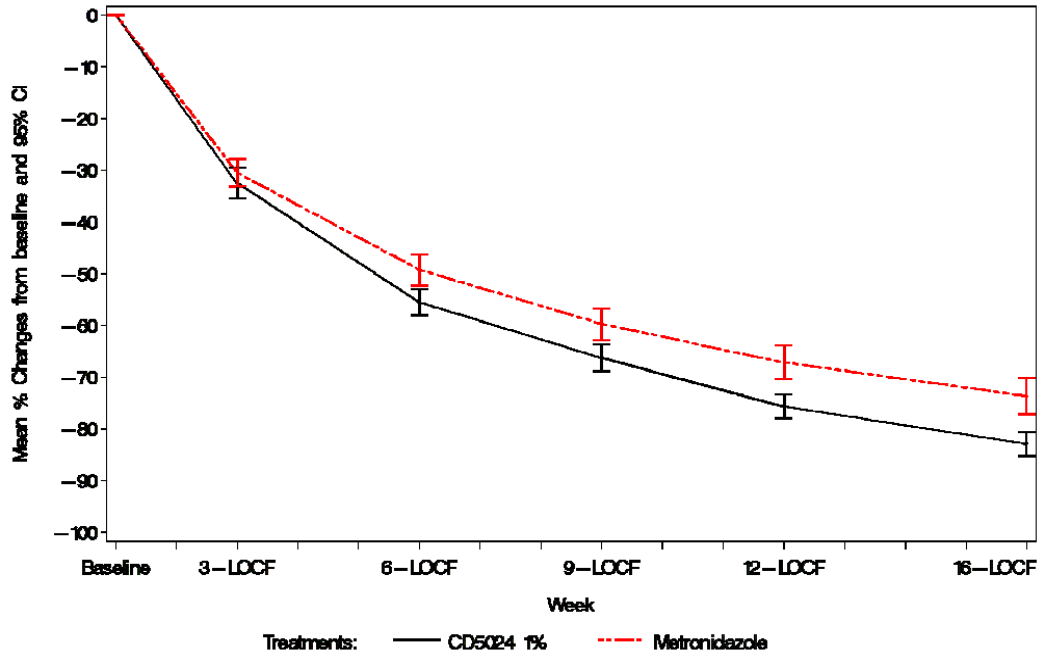
The number of subjects completing part A of study 40173 was >93%. The study population was very similar in study 40173 as in the pivotal studies and there were no major differences between the two treatment groups in baseline characteristics. Two thirds of the patients were females, the mean age was around 50 years and almost only Caucasian subjects were included. The majority (>80%) had moderate PPR based on IGA. Less than 10% of the subjects reported previous treatment with Metronidazole Gel or Cream, with a slight imbalance between the

groups (9.6% in the CD5024 group and 6.4% in the metronidazole group reporting prior therapy with “other chemotherapeutics”, i.e. Metronidazole Gel or Cream).

The efficacy results of this active-controlled study showed that the *median* Percent Change from Baseline in Inflammatory Lesion Counts from Baseline was -92% with Ivermectin 1% Cream QD and -88% with Metronidazole 0.75% Cream BID at Week 16 and the difference between treatments was statistically significant (p<0.001, ITT-LOCF). Corresponding *mean* (±SD) Percent Changes were -83±26% and -74±40% for Ivermectin Cream QD and Metronidazole Cream BID, respectively (ITT-LOCF, p<0.001).

Regarding time to first difference between treatments, a statistically significant difference between the treatment groups in the percent reduction in inflammatory lesion counts occurred at Week 3 (ITT-LOCF, p=0.040) and was sustained until Week 16.

**Figure 5. Mean Percent Change in Inflammatory Lesion Counts from Baseline (and 95% CI) (ITT-LOCF), Study 40173 (Part A)**




Thus, study 40173 met its primary efficacy end-point, to show superior effect on Percent change in inflammatory lesions from Baseline to Week 16 (ITT-LOCF) vs. Metronidazole. The difference between the two treatments was almost 4% based on median change and almost 10% based on mean changes. In the sample size estimation, a 10% difference between CD5024 1% Cream and Metronidazole 0.75% Cream on the percent change from Baseline in lesion counts was anticipated and the difference observed in the study almost reached the expected difference.

For the secondary end-point IGA Success Rate, the number of subjects who achieved Clear or Almost Clear outcomes (IGA≤1) were 85% for the Ivermectin 1% Cream QD group and 75% for the Metronidazole 0.75% Cream BID group at Week 16 (ITT-LOCF) (p<0.001). The difference occurred at Week 6 (p<0.02) and was sustained until Week 16 (ITT-LOCF). Thus, the response rate at Week 16 was 10% higher for Ivermectin vs. Metronidazole. More subjects with severe rosacea at Baseline (IGA=4) reached IGA success with Ivermectin. There were

also more subjects overall who reached the outcome “clear” (IGA=0) in the Ivermectin group compared to the Metronidazole group.

For the Absolute Change from Baseline in inflammatory lesion counts, the mean (±SD) Absolute Change from Baseline was -28±15 lesions with Ivermectin 1% Cream QD and -24±16 lesions with Metronidazole 0.75% Cream BID at Week 16 (ITT-LOCF, $p<0.001$).

The Subject’s Assessment of Rosacea Improvement was performed at Week 16 in Study 40173 and larger proportions of patients reported excellent or good improvement with Ivermectin Cream compared with Metronidazole Cream. However, the non-blinded assessment by the subjects in this study makes the better ratings for Ivermectin Cream vs. Metronidazole Cream less convincing. The percentage reporting excellent or good improvement with Ivermectin Cream was somewhat higher in this study compared with the pivotal studies (85% vs. 65-70%), which may be due to the non-blinded assessment in study 40173 or partly due to different time points for assessment (16 vs. 12 weeks).

Results for Part B

In Period A, 962 subjects were randomized to receive CD5024 1% Cream (N=478) or Metronidazole 0.75% Cream (N=484) in 64 centres in 10 countries. In total, 762 subjects were eligible for entering in Period B and 757 out of these subjects decided to continue in Period B: 399 subjects in the CD5024 1% Cream group and 358 subjects in the Metronidazole 0.75% Cream group. When entering Period B, overall 487 subjects had an IGA of 1 (i.e., “Almost Clear” rosacea) and 270 subjects had an IGA of 0 (i.e., “Clear” rosacea). A total of 692 subjects (91%) completed Period B of the study, 366 subjects (92%) in the CD5024 group and 326 subjects (91%) in the metronidazole group. Sixty-five (65) subjects discontinued during Period B.

The treatment groups were comparable with respect to demographic characteristics. Disease characteristics at Baseline (i.e., at Week 0 of Period A) for the set of subjects who entered in Period B were comparable between the 2 treatment groups, with 85% having IGA 3 and a median inflammatory lesion count of 28. At the end of Period A, disease characteristics for subjects who entered in Period B were comparable in the 2 treatment groups in terms of inflammatory lesion, nodule, papule, and pustule counts. However, the percentage of subjects with an IGA of 0 (Clear) was higher in the CD5024 group (42%) than in the metronidazole group (29%).

From Week 16, the median times to first relapse were 115 days in the ivermectin group and 85 days in the metronidazole group ($p=0.0365$), based upon IGA only. When taking into account major protocol deviations, median times to first relapse were longer in the ivermectin group than in the metronidazole group (114 days in the CD5024 group and 85 days in the metronidazole group ($p=0.0410$). It can be noted that in this study, relapse was defined as an IGA$\geq$ 2 (in contrast to studies 18170 and 18171 in which the criterion for retreatment was IGA$\geq$1).

From the start of Period B, relapse rates were 63% in the ivermectin group and 68% in the metronidazole group, based on IGA only, thus, after the initial 16-week treatment period, 37% of subjects in the ivermectin group and 32% in the metronidazole group did *not* relapse during the 36-week extension period.

The mean numbers of days free of treatment were approximately 180 days in the ivermectin group and 170 days in the metronidazole group, from the start of Period B.

Results for other efficacy variables (e.g. Subject's global improvement of rosacea, nodule counts, QoL and other questionnaires) provided further support for the efficacy of ivermectin cream and generally showed better results in comparison with metronidazole.

*Conclusions, Study 40173*
It is appreciated that a study including an active comparator has been performed and the comparison with topical metronidazole in study 40173 is highly relevant. From a statistical point of view, no issues are raised. A better response for Ivermectin 1% Cream QD vs. Metronidazole 0.75% Cream BID was observed for most end-points that were assessed, also showing statistical significance. However, in absolute numbers, the response rate was up to 10% higher. It should be noted that study 40173 was only single-blinded (Investigator-blind) and that patients with rosacea are likely to have been exposed to previous treatment with topical metronidazole. Less than 10% of the subjects reported previous treatment with Metronidazole Gel or Cream, which is not that high. There was a slight imbalance between the groups (9.6% in the Ivermectin group and 6.4% in the metronidazole group reporting prior therapy with Metronidazole Gel or Cream).

Results from part B of the study showed that relapse occurred later in the ivermectin group (median time almost 4 months) compared with the metronidazole group (median time slightly less than 3 months) and more subjects in the ivermectin group compared with the metronidazole group did not relapse during the 36-week extension period.

**Study 40106**
Efficacy data from Study 40106, a phase 2 study with the primary objective to investigate a potential effect of Ivermectin 1% Cream on the induction of neutropenia in subjects with PPR in comparison to its vehicle, were similar to those obtained in the phase 3 studies and are, thus, considered supportive.

Long-term efficacy
With respect to long-term efficacy, information was obtained from Part B of studies *18170* and *18171*, as described above. The therapeutic effect of Ivermectin 1% Cream QD seemed to be maintained and the number of IGA responders continued to increase over 52 weeks. The percentages of subjects with an IGA score of 0 (clear) at Week 12 were low (3-4%) and increased up to about 25% at Week 52. It was concluded that more than a third of the subjects were able to reach an IGA score of 0 (clear) at some point during the extension period. A fairly large proportion of the subjects (around 70%) needed retreatment during part B, generally within 1-2 months. The criterion for retreatment was set quite low (IGA≥1), while during part A, success was defined as reaching an IGA of 0 or 1.

For study *40173*, results from part B showed that relapse occurred later in the ivermectin group (median time almost 4 months) compared with the metronidazole group (median time slightly less than 3 months) and more subjects in the ivermectin group compared with the metronidazole group did not relapse during the 36-week extension period.

Study *40037* also assessed time to relapse and relapse rate in subjects who achieved success in study 40027. It was a treatment-free follow-up study to the phase 2 dose response study 40027. Based on a definition of relapse of an IGA2 score ≥2, the *relapse-free* rates were higher with Ivermectin 0.3% Cream QD, Ivermectin 1% Cream QD and BID, compared with the lower Ivermectin concentrations, Metronidazole 0.75% Cream BID and the Vehicle Cream QD. When comparing Ivermectin 1% Cream QD and BID, the group receiving BID dosing had higher relapse-free rates compared with the QD group (e.g. 80.3% vs. 88.5% up to Week 12,

61% vs. 80% up to week 24). The groups were small and no statistically significant differences between treatment groups could be observed, though.

Sub-group analyses
Sub-group analyses were conducted using combined data from the pivotal Studies 18170 and 18171 to evaluate the relative efficacy in subgroups based on age, gender, race and disease severity at Baseline.

With respect to gender, approximately one third of the study population was represented by males and the data indicate no relevant gender difference in response for the primary end-points, although females had a higher IGA response rate.

With respect to race, only a few non-Caucasian subjects were represented while >95% of the subjects were Caucasians. For the group of Non-Caucasians, the upper bounds of the 95% CI extended above zero, likely due to the small sample size of this subgroup. Information about the predominantly Caucasian study population is included in section 5.1 of the SmPC, which is endorsed.

Regarding age, less than 15% of the studied subjects were above 65 years, but available data suggest no relevant difference compared with younger subjects.

Baseline rosacea severity according to the IGA scale was also included in the analyses. The treatment effect in terms of IGA success rate was very similar irrespective of baseline IGA. For the Absolute Change in Inflammatory Lesion Counts from Baseline, those with a baseline IGA of 4 had more lesions at baseline and were able to achieve a larger reduction in number of lesions compared with the group with baseline IGA of 3.

Concerning region, the pivotal phase 3 studies were performed in US/Canadian sites while no European sites were included. Study 40173 (active-controlled vs. Metronidazole) and the phase 2 study 40106 were performed in Europe. The results of all these studies were concordant; hence, no concerns related to regional differences are identified and for a condition like rosacea differences between a US/Canadian and a European population are not expected.

There is no data available to assess efficacy of Ivermectin 1% Cream in patients concomitantly treated with other topical products for the treatment of rosacea, e.g. metronidazole or azelaic acid gel. In clinical practice, a combination of Soolantra and another anti-inflammatory topical rosacea product does not appear to be a relevant combination. The lack of data on combined treatment is adequately reflected in the SmPC.

## IV.4 Clinical safety

**Short term risks**
Overall, 2047 subjects were exposed to Ivermectin 1% Cream QD out of 3999 participants in the 18 studies in the clinical development program. Of these 2047 subjects, 1555 subjects were exposed to the formulation proposed for marketing for at least 3 months, and 519 subjects were exposed for 1 year of more. Thus, a fairly large number of patients have been exposed to ivermectin at the recommended dosage and the safety database is considered sufficient.

The most common adverse events associated with topical use of ivermectin are skin burning sensation (1.3%), skin irritation (1.0%), pruritus (0.8%) and dry skin (0.7%) (see table below)

reported by subjects over the whole duration of the Phase 3 pivotal studies (Parts A, B and C). 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.

The observed local effects are common adverse events for topically applied medicinal products, often associated with the vehicle used, and do not raise cause for concern.

If a patient wished to receive an increased clinical efficacy compared with what is obtained according to the recommended posology, the product may be applied repeatedly during the day. No or only slight increased local adverse events are to be expected with twice versus daily dosing.

The dermal local tolerance studies showed a low cumulative irritancy potential for the product proposed for marketing and the vehicle cream. The repair insult patch test (RIPT) was performed with an early form of formulation which differed in the paraben concentration compared to the formulation proposed for marketing. Parabens are widely used as antimicrobial preservatives in pharmaceutical formulations as well as in cosmetics with maximal concentrations of up to 0.3% for methylparaben and 0.6% for propylparaben. The concentrations of parabens in the formulation proposed for marketing is slightly higher than the concentrations used in the performed RIPT study, however below that maximal concentrations allowed for. The results of the RIPT study demonstrated a low irritancy potential and a negative sensitization score.

Patients with rosacea are in general more susceptible to sensitization than the average population. Since parabens are considered weak sensitizers, the sensitization potential of the product proposed for marketing was evaluated in 2163 subjects with PPR. A sensitization rate of 0.1% was by the Applicant calculated for Ivermectin 1% Cream which seems to be in a range observed for currently approved topical products. As a precautionary measure, skin sensitization has by the Applicant been suggested to be included in the RMP as an important potential risk.

**Table 8: Incidence of related treatment emergent adverse events by System Organ Class and by Preferred Term for Phase 3 pivotal studies Safety Population**

| System Organ Class | Preferred Term | | |
|---|---|---|---|
| | | CD5024 1 % CD5024 1 % (N=912) | Vehicle/ Azelaic Acid (N=463) |
| TOTAL NUMBER OF AEs | - | 62 | 80 |
| TOTAL NUMBER OF SUBJECTS WITH AEs, n (%) | - | 48 (5.3) | 54 (11.7) |
| Blood and lymphatic system disorders, n (%) | ALL | 1 (0.1) | 0 |
| | Neutropenia | 1 (0.1) | 0 |
| Cardiac disorders, n (%) | ALL | 0 | 1 (0.2) |
| | Tachycardia | 0 | 1 (0.2) |
| Eye disorders, n (%) | ALL | 6 (0.7) | 4 (0.9) |
| | Dry eye | 2 (0.2) | 0 |
| | Eye irritation | 2 (0.2) | 2 (0.4) |
| | Eye pain | 1 (0.1) | 1 (0.2) |
| | Lacrimation increased | 1 (0.1) | 0 |
| | Photophobia | 1 (0.1) | 0 |

| System Organ Class | Preferred Term | | |
|---|---|---|---|
| | | CD5024 1 % CD5024 1 % (N=912) | Vehicle/ Azelaic Acid (N=463) |
| | Blepharitis | 0 | 1 (0.2) |
| Gastrointestinal disorders, n (%) | ALL | 0 | 1 (0.2) |
| | Nausea | 0 | 1 (0.2) |
| General disorders and administration site conditions, n (%) | ALL | 0 | 1 (0.2) |
| | Xerosis | 0 | 1 (0.2) |
| Infections and infestations, (n %) | ALL | 1 (0.1) | 1 (0.2) |
| | Erysipelas | 1 (0.1) | 0 |
| | Urinary tract infection | 0 | 1 (0.2) |
| Injury, poisoning and procedural complications, n (%) | ALL | 4 (0.4) | 1 (0.2) |
| | Overdose | 2 (0.2) | 0 |
| | Accidental exposure | 1 (0.1) | 1 (0.2) |
| | Sunburn | 1 (0.1) | 0 |

| System Organ Class | Preferred Term | | |
|---|---|---|---|
| | | CD5024 1 % CD5024 1 % (N=912) | Vehicle/ Azelaic Acid (N=463) |
| Investigations, n (%) | ALL | 1 (0.1) | 1 (0.2) |
| | Hepatic enzyme increased | 1 (0.1) | 0 |
| | C-reactive protein increased | 0 | 1 (0.2) |
| Metabolism and nutrition disorders, n (%) | ALL | 1 (0.1) | 0 |
| | Alcohol intolerance | 1 (0.1) | 0 |
| Nervous system disorders, n (%) | ALL | 1 (0.1) | 0 |
| | Paraesthesia | 1 (0.1) | 0 |
| Psychiatric disorders, n (%) | ALL | 0 | 1 (0.2) |
| | Irritability | 0 | 1 (0.2) |
| | Sleep disorder | 0 | 1 (0.2) |
| Skin and subcutaneous tissue disorders, n (%) | ALL | 34 (3.7) | 48 (10.4) |
| | Skin burning sensation | 12 (1.3) | 14 (3.0) |
| | Skin irritation | 9 (1.0) | 16 (3.5) |
| | Pruritus | 7 (0.8) | 9 (1.9) |
| | Dry skin | 6 (0.7) | 9 (1.9) |
| | Hair growth abnormal | 2 (0.2) | 0 |
| | Pain of skin | 2 (0.2) | 9 (1.9) |
| | Dermatitis | 1 (0.1) | 1 (0.2) |
| | Dermatitis allergic | 1 (0.1) | 0 |
| | Erythema | 1 (0.1) | 0 |
| | Eyelids pruritus | 1 (0.1) | 0 |
| | Rosacea | 1 (0.1) | 1 (0.2) |
| | Skin exfoliation | 1 (0.1) | 1 (0.2) |
| | Skin discomfort | 0 | 5 (1.1) |
| Vascular disorders, n (%) | ALL | 1 (0.1) | 0 |
| | Flushing | 1 (0.1) | 0 |

**Data source: Section 5.3.5.3, SCS Table 6.3.9.**

The Applicant has not conducted any clinical photosafety testing. Neither the active compound nor the main ingredients of the product proposed for marketing absorb UV light.

In conclusion on short term risks, no other than local adverse events are to be anticipated at the recommended use of Ivermectin 1% cream.

**Potential long term risks**

Ivermectin has a well known safety profile from veterinary use as anti-parasitic agent against a wide range of endo- and ectoparasites. The clinical experience in humans is not equally extensive, however oral ivermectin has been approved for human use in the treatment and chemoprophylaxis of strongyloidiasis and onchocerciasis since 1988 in France and since 1996 in the United States. The systemic exposure to ivermectin following treatment with ivermectin cream 1% QD at the recommended dosage is approximately 15% of that obtained following oral dosage.

No systemic adverse events were reported in any of the performed clinical studies and are not anticipated at the proposed use of the product.

There is no preclinical or mechanistic rationale to suspect that ivermectin would increase the risk of cardiovascular events. The thorough QT study was performed with oral administration of ivermectin and the applicant claims that the study was performed with a supra-therapeutic dose. However, the pharmacokinetic data obtained demonstrate a higher systemic exposure compared with the exposure obtained with at therapeutic use. No adverse effects on cardiovascular parameters were observed which are not to be expected considering the low systemic exposure of ivermectin. Overall, no treatment related potential risks were observed regarding respiratory, infections/infestations, cardiac, or metabolic disorders.

The most common local adverse events associated with topical use of ivermectin are skin burning sensation, skin irritation, pruritus and dry skin (see above). The incidence of TEAEs was essentially similar when investigated over time each quarter in the long-term extension of the Phase 3 pivotal studies, compared to the initial 3-months period.

Three cases of neutropenia were found in the open-label safety study 40051 and the study was placed on hold in January 2009. The findings were detected at the first laboratory sampling visit at Week 10 of treatment and were not associated with any clinical signs or symptoms. A Phase 2 Study was specially designed to investigate the potential effect of ivermectin on neutrophils. Moreover, neutrophil counts were closely monitored for in the subsequent Phase 3 clinical trials. These data indicate a similar or lower incidence of neutropenia in subjects treated with Ivermectin 1% Cream compared to subjects treated with either Vehicle Cream, Azelaic Acid 15% Gel, or Metronidazole 0.75% Cream. It is assessed that neutropenia is of no concern at the proposed clinical use of Ivermectin 1% cream.

**Subpopulations**

Subgroup analyses were conducted to explore the potential differences of common TEAEs within a subgroup (gender, age and race) 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.

There was no difference in the TEAE profiles based on race, however, based on the very low number of Non-Caucasian participants, conclusions on AEs based on race are difficult to make.

There was no difference in incidence of TEAS's based on skin-phototype or disease severity at baseline.

Thirteen pregnancies were reported during the clinical development program. Non-clinical data have demonstrated adverse effects in oral teratology studies in the rat and rabbit, with exposure margins 68 and 334 times those obtained at the maximum recommended human dose, respectively. When considering the topical route of administration with fairly low systemic exposure of ivermectin, and the large exposure margin obtained in the non-clinical studies, the safety concern for a human fetus is assessed as low.

In conclusion on potential long term risks, no risks due to systemic uptake of ivermectin are to be anticipated at the proposed clinical use if the product.

## IV.5 Discussion on the clinical aspects

**Efficacy**
A significantly superior effect for Ivermectin 1% Cream compared to Vehicle Cream was demonstrated for the co-primary endpoints at Week 12 in the pivotal studies. The secondary efficacy end-points and other endpoints also supported the efficacy of Ivermectin Cream. The number of IGA responders was approximately 40% for Ivermectin 1% Cream as compared to 10-20% for the Vehicle Cream and for the Absolute Change in Inflammatory Lesion Counts from Baseline, Ivermectin 1% Cream showed a decrease of about 8 more lesions as compared to Vehicle Cream, at Week 12. Time to onset of efficacy was 4 weeks in both studies. These results are deemed clinically relevant.

Sub-group analyses of the pivotal studies indicated no relevant impact of age, gender, race or disease severity at Baseline on the efficacy of Ivermectin Cream.

In study 40173, superiority of Ivermectin 1% Cream vs. the active comparator Metronidazole Cream was demonstrated for the primary end-point (Percent Change from Baseline in Inflammatory Lesion Counts from Baseline) as well as for secondary end-points (IGA Success rate and Absolute Change from Baseline in Inflammatory Lesion Counts from Baseline).

With respect to long-term efficacy, data from the pivotal studies indicate that the therapeutic effect of Ivermectin 1% Cream QD was maintained and the number of IGA responders continued to increase over 52 weeks. Results from part B of study 40173 showed that relapse occurred later in the ivermectin group (median time almost 4 months) compared with the metronidazole group (median time slightly less than 3 months) and more subjects in the ivermectin group compared with the metronidazole group did not relapse during the 36-week extension period.

Recommendations on duration of treatment with Soolantra are included in the SmPC and these are acceptable. The treatment course may be repeated, if necessary. Advice has also been provided on when to stop treatment in case of no improvement, which is endorsed.

**Safety**
The safety profile for topical use of ivermectin is in general considered benign with only local adverse events (e.g. skin burning sensation, skin irritation, pruritus and dry skin) 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 and are not to be expected at the proposed clinical use.

With regard to the long-term safety, no serious concerns for human safety have been detected.

## IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Soolantra.

Safety concerns from non-clinical studies

The Applicant has submitted a presentation of and discussion around key findings from non-clinical studies. The majority of findings in the toxicology studies were seen following oral dosage and are considered less relevant due to the proposed topical administration of Soolantra.

The Applicants conclusion of non-clinical data can be seen in the table below.

| **Safety concerns** |
|---|
| Important identified risks (confirmed by clinical data)<br>• None |
| Important potential risks (not refuted by clinical data or which are of unknown significance)<br>• Hypersensitivity |
| Missing information<br>• Exposure during pregnancy<br>• Exposure during lactation |

Hypersensitivity was concluded to be an important potential risk due to positive findings in a guinea pig Buehler sensitization test. However, based on results from human dermal local tolerance studies and results from performed clinical trials, the risk for hypersensitivity is assessed in the similar range as for other topical products, i.e. acne products or topical glucocorticoids.

Summary of safety concerns

The summary of safety concerns as presented by the Applicant can be seen in the table below.

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | Skin sensitization (hypersensitivity)<br>Accidental oral ingestion |
| Missing information | Exposure during pregnancy<br>Exposure during lactation<br>Use longer than one year<br>Off-label use<br>Use with other concomitant topical rosacea treatments<br>Use with laser or UV radiation |

Skin sensitization has been suggested as an important potential risk. A conservative estimate of skin sensitization in the clinical development studies is 0.1%. However, patients with rosacea may be more susceptible than the general population for risk of developing hypersensitivity reactions. As a precautionary measure, it is agreed that skin sensitization is an important potential risk.

Accidental oral ingestion has also been included as an important potential risk. There has not been any case of accidental oral ingestion with Soolantra. However, ivermectin is a potent compound with ability to induce CNS toxicity. In order to avoid accidental oral ingestion, all sizes of tubes 15, 30, 45 and 60 mg of Soolantra, will be supplied with child resistant cap look. The product is also presented as a 2g tube which does not have a child resistant cap. The 2g tube of Soolantra will be clearly labelled and supplied with a PIL that communicates the risk of accidental ingestion to the patient.

Missing information are exposure during pregnancy and lactation, use longer than one year, off-label use, use with other concomitant rosacea treatments and use with laser or UV radiation.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the Risk Minimisation Plan
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.

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

# V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

***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 show persistent erythema of the central portion of the face and other primary symptoms include papules, pustules, flushing and telangiectasias. Available treatments are topical metronidazole (cream or gel) and topical azelaic acid gel, both intended for twice daily application and with primarily anti-inflammatory actions. In addition, the product Mirvaso (brimonidine tartrate 0.5% gel) targets facial erythema of rosacea via local vasoconstriction. Rosacea can also be treated with systemic antibiotics, e.g. tetracyclines, for instance Oracea containing doxycycline in a sub-antimicrobial dose, indicated for reduction of papulopustular lesions in facial rosacea.

Soolantra 10 mg/g cream contains Ivermectin, which has been suggested to have a dual effect of relevance for topical treatment of papulopustular rosacea; both an anti-inflammatory and an anti-parasitic action, which might offer a positive effect on papulopustular lesions in adult patients with rosacea.

The efficacy of Soolantra Cream 1% is mainly supported by two pivotal, double-blind, vehicle-controlled phase 3 studies (18170 and 18171) and one investigator-blinded, active-controlled phase 3 study (40173).

In both pivotal studies, a significantly superior effect for Ivermectin 1% Cream compared to Vehicle Cream was demonstrated for the co-primary endpoints on Week 12. The IGA Success rate was approximately 40% for Ivermectin 1% Cream and 10-20% for Vehicle Cream (ITT-LOCF). For the Absolute Change in Inflammatory Lesion Counts from Baseline, Ivermectin

1% Cream showed a decrease of about 8 more lesions as compared to Vehicle Cream, at Week 12. Time to onset of efficacy was 4 weeks in both studies.

The secondary efficacy end-points and other endpoints also supported the efficacy of Ivermectin Cream. For the Subject's Assessment of Rosacea Improvement, larger proportions of patients reported excellent or good improvement at Week 12 with Ivermectin Cream compared with vehicle (65-70% vs. 35-40%).

For Quality of life assessments, some improvements in the QoL measures used in the pivotal studies (RosaQoL™ and DLQI) could be observed and also showed statistically significant differences in favour of Ivermectin vs. vehicle. However, the baseline QoL scores were not that poor and, hence, huge improvements could not be expected.

Regarding erythema, more subjects in the Ivermectin 1% Cream groups than in the Vehicle Cream groups showed improvement in both studies. No change in nodule counts across the study periods was observed either for subjects who received Ivermectin 1% Cream or Vehicle.

Sub-group analyses of the pivotal studies indicated no relevant impact of age, gender, race or disease severity at Baseline on the efficacy of Ivermectin Cream.

In the active-controlled study, superiority of Ivermectin 1% Cream vs. the active comparator Metronidazole Cream was demonstrated for the primary end-point (Percent Change from Baseline in Inflammatory Lesion Counts from Baseline) as well as for secondary end-points (IGA Success rate and Absolute Change from Baseline in Inflammatory Lesion Counts from Baseline). At Week 16, the median Percent Change from Baseline in Inflammatory Lesion Counts from Baseline was -92% with Ivermectin 1% Cream QD and -88% with Metronidazole 0.75% Cream BID ($p<0.001$, ITT-LOCF).

With respect to long-term efficacy, data from the pivotal studies indicate that the therapeutic effect of Ivermectin 1% Cream QD was maintained and the number of IGA responders continued to increase over 52 weeks. For study 40173, results from part B assessing persistence of efficacy showed that relapse occurred later in the ivermectin group (median time almost 4 months) compared with the metronidazole group (median time slightly less than 3 months) and more subjects in the ivermectin group compared with the metronidazole group did not relapse during the 36-week extension period.

The pivotal phase 3 studies were performed in US/Canadian sites while no European sites were included. Study 40173 (active-controlled vs. Metronidazole) and the phase 2 study 40106 were performed in Europe. The results of all these studies were concordant; hence, no concerns related to regional differences are identified and for a condition like rosacea differences between a US/Canadian and a European population are not expected.

Ivermectin 1% Cream is a topically applied product and the systemic exposure at steady state is much lower than those obtained following oral administration. No systemic adverse events were reported in any of the performed studies. There are no concerns for adverse events caused by systemic absorption of Ivermectin at the recommended posology of the product.

***Uncertainty in the knowledge about the beneficial effects***

There is no data available to assess efficacy of Ivermectin 1% Cream in patients concomitantly treated with other topical products for the treatment of rosacea, e.g. metronidazole or azelaic

acid gel. In clinical practice, a combination of Soolantra and another anti-inflammatory topical rosacea product does not appear to be a relevant combination. Hence, the lack of data is acceptable and this is adequately reflected in section 4.5 of the SmPC.

***Risks***

***Unfavourable effects***
The most common adverse events associated with topical use of ivermectin are skin burning sensation (1.3%), skin irritation (1.0%), pruritus (0.8%) and dry skin (0.7%). 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.

The observed local effects are common adverse events for topically applied medicinal products, often associated with the vehicle used, and do not raise cause for concern.

No systemic adverse events were reported in any of the performed clinical studies and are not anticipated at the proposed use of the product.

***Uncertainty in the knowledge about the unfavourable effects***
There are at present no uncertainties in the knowledge of the unfavorable effects.

***Balance***

***Importance of favourable and unfavourable effects***
A significantly superior effect for Ivermectin 1% Cream compared to Vehicle Cream was demonstrated for the co-primary endpoints on Week 12 in the pivotal studies. The IGA response rate of 40% for Ivermectin 1% Cream was clearly above that of the Vehicle Cream (10-20%). The secondary efficacy end-points and other endpoints also supported the efficacy of Ivermectin Cream. Time to onset of efficacy was quite rapid (4 weeks). These results are deemed clinically relevant.

Superiority of Ivermectin 1% Cream vs. the active comparator Metronidazole Cream was demonstrated for the primary end-point (Percent Change from Baseline in Inflammatory Lesion Counts from Baseline) as well as for secondary end-points (IGA Success rate and Absolute Change from Baseline in Inflammatory Lesion Counts from Baseline).

With respect to long-term efficacy, data from the pivotal studies indicate that the therapeutic effect of Ivermectin 1% Cream QD was maintained and the number of IGA responders continued to increase over 52 weeks. Results from study 40173 showed that relapse occurred later in the ivermectin group (median time almost 4 months) compared with the metronidazole group (median time slightly less than 3 months) and more subjects in the ivermectin group compared with the metronidazole group did not relapse during the 36-week extension period.

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

***Benefit-risk balance***

***Discussion on the benefit-risk assessment***
Soolantra 10 mg/g cream has demonstrated a positive effect on papulopustular rosacea, which is deemed clinically relevant. Efficacy is maintained over time. Relapse after cessation of treatment generally occurs after a median time of almost 4 months. The safety profile is benign with mainly local adverse events that are commonly observed for other topically applied rosacea products.

***Conclusions***
The risk/benefit ratio is considered positive and Soolantra, cream, 10 mg/g, is recommended for approval.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results 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.

# VI. APPROVAL

The Decentralised procedure for Soolantra, cream, 10 mg/g, was successfully finalised on 2015-03-22.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected (Yes/No) | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| SE/H/1428/01/II/18 | Type II, C.I.6 Change to therapeutic indication - Modification of an approved one: Addition of the possibility to use as part of combination treatment following a phase 3b study to evaluate the efficacy of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified Release capsules (hereafter called IVM with DMR) versus Ivermectin 1% topical cream associated with Placebo (hereafter called IVM with PBO) in the treatment of severe rosacea for 12 weeks, as well as its safety profile and patient reported outcomes. | Yes | 2020-06-12 | Approval | In the variation procedure, no change to the therapeutic indication was made. In the posology section, information has been added stating that Soolantra can be applied as monotherapy or as part of combination treatment with reference to section 5.1. Section 5.1 describes a clinical study evaluating efficacy of Soolantra in combination with doxycycline treatment. |

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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