LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Aklief
(trifarotene)

SE/H/1863/01/DC

This module reflects the scientific discussion for the approval of Aklief. The procedure was finalised on 2019-12-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Galderma International, France has applied for a marketing authorisation for Aklief, 50 µg/g cream. The active substance is trifarotene. It is a terphenyl acid derivative that is a selective retinoid acid receptor γ (RARγ) agonist, the receptor subtype present in keratinocytes and recognized to be the most relevant in acne. In addition, trifarotene modulates retinoid target genes (differentiation and inflammatory processes) in immortalized keratinocytes and reconstructed epidermis.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

In accordance with article 7 of Regulation 1901/2006, as amended, the applicant has submitted a paediatric investigation plan EMEA-001492-PIP01-13-M01. The European Medicines Agency's decision P/0099/2017 was provided on 11 April 2017. A positive opinion of the paediatric committee on full compliance with the PIP was issued on 29 June 2018 (EMA/PDCO/302110/2018).
For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The non-clinical data package for Aklief included in vitro and in vivo pharmacology, pharmacokinetics (PK), and toxicity studies. The toxicity profile of trifarotene was characterized in mice, rat, dog, rabbit and mini-pig in a toxicology program consistent with ICH M3(R2). The pivotal toxicology studies were conducted in compliance with GLP regulations and standards.

III.2 Pharmacology

Trifarotene (CD5789) is a potent RARγ agonist (retinoid acid receptor γ agonist) and show a high RAR activity and high selectivity for RARγ (EC_{50}=7.7 nM), compared to a 65- and 16-times lower activity for RARα and RARβ, respectively. The selectivity of trifarotene to RARγ is shown to be more pronounced than that of tretinoin and tazarotene. Trifarotene showed no activity on RXRα or RXRβ.

In human immortalized keratinocytes trifarotene showed a modulation of all retinoid-target genes for keratinization, metabolism and adhesion at concentrations which were approximately 10 times lower than those for tazarotene and about 100-times lower than those for tretinoin. Also in reconstructed human epidermis and a human skin explant model trifarotene modulated the expression of retinoid target genes involved in e.g. proliferation, differentiation and inflammation and seemed to be more potent than tretionin and tazaratone, respectively.

When the pharmacological activity of metabolites of trifarotene was analysed, using a transactivation assay and stably transfected reporter cell lines, CD09986 exhibited a similar selective RAR gamma agonist activity as trifarotene, CD06700 and CD06530 exhibited RAR alpha/beta antagonist activity and RAR gamma agonistic activity and CD09717 was found to be a poorly active modulator on all three RAR isoforms. It should be noted that there is a low formation of metabolites after topical administration of trifarotene and therefore less likely that the activity of the metabolites have a significant pharmacological effect after administration of trifarotene.

The comedolytic efficacy of trifarotene in cream B was analysed in vivo in the Rhino mouse model and compared with Retacnyl® 0.05% and Zorac®0.1%. Trifarotene induced a marked comedone reduction and increase in epidermal thickness in the Rhino mouse, which were comparable to effects observed with tretinoin or tazarotene but at about 10-times lower dose. The suggested text for section 5.1 includes an acceptable description of the results obtained in the non-clinical studies.

Secondary pharmacology studies show anti-inflammatory effects of trifarotene in the TPA induced ear edema model in mice, similar to those of tazarotene and depigmentation in vivo in a natural pigmentation model which was stronger and faster than the one induced by tretinoin. Trifarotene also had a depigmenting and anti-pigmenting activity in vivo in an UV induced pigmentation model in mice.

A dose dependent sedative/myorelaxant effect was seen in the Irwin test and lethal effects were observed at 32 mg/kg and at 64 mg/kg with all animals dying after administration of trifarotene. These effects are not considered to be of clinical significance since the exposure at the lowest dose (2 mg/kg) was at least 1000 times higher compared to the expected exposure in the clinic after topical application.

No significant hERG-activity was detected in vitro with an expected IC_{50} > 10µM and administration of trifarotene up to 2.5 mg/kg giving an exposure of 614 ng/mL did not significantly modify arterial blood pressure and did not significantly modify heart rate, PR interval, QT interval or QTc intervals. No arrhythmia or other changes in the morphology of the electrocardiogram which could be attributed to trifarotene were either observed. It may be noted that a clinical thorough QT/QTc study also has been performed in which trifarotene was concluded not to have any effect on cardiac repolarization (see clinical AR).

Trifarotene did not have any significant effects on any of the respiratory parameters evaluated in rats. No safety pharmacology issues were thus identified in the performed studies at dose levels far in excess to those anticipated in the clinical situation.

No significant risk for systemic pharmacodynamics drug interactions is anticipated based on the negligible plasma concentrations of trifarotene and its metabolites detected following topical administration to humans.

III.3 Pharmacokinetics

A complete package of pharmacokinetic studies has been submitted for trifarotene.

Absorption of trifarotene is low after topical application. When penetration was analysed in vitro across non occluded full thickness fresh mouse skin mounted on diffusion cells at a dose of 10 mg/cm² the concentration in the receptor fluid was below LOQ (0.25 ng/mL) after 24 hours. Total penetration of tifarotene represented 21 % of the applied dose and was recovered exclusively from the skin.

Bioavailability after dermal application was low and approximately 5 % in rats and below LOQ (0.05 ng/mL) in minipigs after a single administration. After 12 days repeated topical application of 100 µg/g cream in minipigs, the highest mean Cmax plasma concentrations detected was 1.05 ng/mL, suggesting limited systemic exposure after topical application. (The 50 µg/g cream was not tested.) Oral bioavailability of trifarotene was 17% and 27% in male and female rats, respectively and 26% to 37% in male and female dogs. Clearance was low to moderate and lower than the cardiac output in all three species investigated and the half-life 3, 4 and 6.5 hours in rat, dog and minipig, respectively. The distribution volume was 24 to 42-fold higher in female and male rats respectively, as compared to the corresponding plasma volume, and 20 fold higher in dogs and 32 fold higher in minipigs suggesting high drug distribution.

A marked gender effect was observed in rats, with a C_{max} and systemic exposure being higher for females than for males. Female rats were exposed 3.6 times, 5.8-times and 3.3-times more than males after IV, oral and dermal administrations, respectively. No relevant gender effect was seen in the dog.

Tissue distribution was studied in Wistar rat (albino) or Lister Hooded rat (pigmented) using doses of 1.5 mg/kg IV or 2 mg/kg PO and Liquid scintillation counting or QWBA for

quantification of radioactivity. Trifarotene was widely distributed through the body of rats, following both oral and IV administration. Highest levels of radioactivity were measured in the liver, kidney, preputial gland, adrenal cortex and salivary gland, with the highest concentrations observed in the liver. The distribution to the brain and melanin-containing tissues was relatively low. The radioactivity was not detectable in the majority of tissues at 48 and 72 h post dose for males and females, respectively. The obtained data thus suggest no risk for accumulation or binding to melanin. Trifarotene crossed the blood placenta barrier and seemed to be rapidly eliminated. Plasma protein binding was high (>99.7%) and not saturable in all species analysed (mouse, rat, rabbit, dog, minipig, human) and binding to HSA found to be similarly high. Binding to human α1-glycoprotein seemed to be somewhat less (97.4%).

Trifarotene was the major circulating radioactive constituent in plasma from both rat and dog after IV and oral administration with only two to three metabolites detected. In rat two metabolites were unambiguously identified, CD06530 (Males 5% Females 3%) and CD06700 (< 2% F only) and in addition a tentative structure was assigned to one metabolite, CD09986 (M 11%, F 5%). In dogs, two peaks in addition to the parent compound were detected but their concentrations in plasma were insufficient to enable identification by LC-MS/MS. Trifarotene was also the major radioactive constituent in faeces from rat (~25% in males and ~60% in females) and dog (~70%). Parent compound was a minor component in bile from rats and the most abundant component observed was instead a glucuronide conjugate of trifarotene.

Repeated daily topical application of trifarotene (50 µg/g) cream in adult and pediatric subjects during 4 weeks resulted in low systemic exposure (lower than or close to the LOQ of 5 pg/mL) and only 37% of adult subjects and 18 % of paediatric subjects had quantifiable trifarotene plasma levels. No quantifiable metabolites were detected. When a higher concentration trifarotene cream (100 µg/g) was used 61% adult subjects and 69 % paediatric subjects had quantifiable trifarotene plasma levels, but metabolites were still only detected in few individuals. 2 adult subjects out of 18 displayed quantifiable levels of CD06530 (C_{max}= 13 and 15 pg/mL) and one quantifiable level of CD09986 (C_{max}=33 pg/mL). Plasma concentrations of CD09717 and CD06700 were below the LOQ (<10 pg/mL). In paediatric subjects treated with Trifarotene 100 µg/g low quantifiable levels of one metabolite (CD06530) was detected (C_{max}=19 pg/mL in the highest exposed individual). (See Clinical AR.)

In spite of the low levels of metabolites detected the applicant has presented data that show that the systemic exposure of each metabolite observed during the non-clinical studies cover the exposures observed in human and thus that the non-clinical toxicology studies are sufficient in this respect.

Faeces were the most important route of excretion of total radioactivity after IV and oral dosing in both rat and dog, representing almost 100% of the administered dose and excretion was almost complete within 48 hours. In rat, biliary elimination accounted for a mean of 31% in males and 38% in females. Milk excretion was observed in lactating rats after single oral administration and mean milk:plasma ratios for total radioactivity increased over the sampling period from 0.53 (1 h post-dose) to 2.42 (8 h post-dose).

The drug-drug interaction (DDI) potential of CD5789 was not studied in animals. Investigations were performed in vitro with human biomaterials, using PBPK modelling and in one clinical DDI study. (See Clinical Pharmacokinetics AR.)

III.4 Toxicology

Trifarotene has been evaluated in a comprehensive set of nonclinical toxicity studies with the active substance administered by the oral route in rats, rabbits and dogs to maximize systemic exposure. Trifarotene dermal cream was administered by the dermal route (which is the clinically relevant route of administration) in mice and minipigs. It is apparent from the pharmacokinetics section that no human-specific metabolite was detected. All phase 1 metabolites detected in human hepatocytes were also detected in hepatocytes of at least one of the toxicological species used for chronic toxicology studies (i.e. rat, dog or minipig).

Five species (mice, rat, dog, rabbit and mini-pig) have been used in the toxicity characterization, which may be seen as an advantage in that the effects seen can be compared across a number of species. However, the disadvantage of for instance not using the mini-pig for dermal and oral studies is the lack of intra-species comparison possibility. Overall, the lack of systemic exposure in the mini-pig dermal studies, despite (as in the 13-week study) marked dermal toxicities with erythema and scab that required wash-out period, is considered a draw-back. This is not reflective of the clinical situation, where exposures are noted after dermal exposure without severe dermal findings.

Skin

The skin was a sensitive target of toxicity throughout all repeated-dose studies, which was expected considering the pharmacology of retinoids. At the application site in the dermal studies in mice and mini-pig, inflammation with hyperplasia, hyperkeratosis and parakeratosis were observed. In mini-pig, severe skin irritation (erythema) was noted in addition to acanthosis (with spongiosis), inflammatory infiltrates, parakeratosis and minimal or slight crusts. Overall, the local reactions were more marked during the first month of treatment and partly resolved over time. This course of reactions is similar to what is seen in the clinic, where the local reactions usually diminishes over time.

In the oral 13-week study in rats, hyperkeratosis and scabs was noted. In the dog, abdominal skin findings were noted, which consisted of acanthosis, dermal mononuclear cells and lymphocytic exocytosis. Acanthosis was observed in males treated at 0.18 mg/kg/day and in females at 0.02 and 0.18 mg/kg/day. Skin findings were also evident on the head and they consisted of acanthosis, hyperkeratosis, lymphocytic exocytosis and dermal mononuclear cell infiltration. Acanthosis was not observed at 0.02 mg/kg/day. Hyperkeratosis and dermal mononuclear cell infiltration were noted at 0.18 mg/kg/day only. In the ears, acanthosis, hyperkeratosis, lymphocytic exocytosis, spongiosis, dermal mononuclear cell infiltration, and ulceration was seen. All skin findings in the dog were reversible.

The dermal toxicity studies were performed in animals with intact skin. The Applicant agreed that systemic and local absorption will differ on abraded/broken skin (compared to intact skin)and further declared that impact of disease severity was accounted for in the evaluation of the safety of trifarotene. The exposure margins in MUsT study 18237 were based on the systemic exposure of the most exposed patient with moderate to severe acne receiving Trifarotene 50 µg/g cream under maximal use conditions.

Non-glandular stomach

Hyperkeratosis of the mucosa in the non-glandular stomach was evident in the 13-week dermal study in mice, as well as in all the oral studies in rat from 4-week studies an up to 26-weeks. Humans do not have a forestomach, but possess histologically similar organs, including the oral cavity, pharynx, esophagus, and glandular stomach, but the tissue dose in these human organs are not equivalent to that in the forestomach of experimental animals. Thus, overall the human relevance of these findings is unclear.

Spleen

The spleen is a target organ of toxicity in several studies. Thus, an effect in the spleen was noted across studies with increased weight and extramedullary hematopoiesis. The findings were mostly mild, except in the 13-week mouse study where minimal-severe effects were noted. However, overall the findings showed recovery and are attributable to the RAR agonist pharmacological effects of the compound.

Bone

In the rat, main treatment-related finding in the stifle-joints of treated groups consisted of a femoral and/or tibial growth plate disorganization/closure. This was graded minimal to slight and was mainly characterized by tinctorial changes with irregular arrangements/thickness of the dividing cell layers. This finding was shown with increased severity/incidence in females at 0.5g/kg/day (moderate to severe), including a total/partial closure of femoral and/or tibial growth plates. The finding was not reversible in HD females (marked-severe) but signs of recovery were noted in the males. Various changes in bone including growth plate disorganization and increased ossification of epiphyseal cartilage was also noted in the shorter studies in the rat.

Testes

In the testes of treated dogs in the 39-week study, changes consisted of a slight increase in the number of degenerate germ cells (bilateral), which only equivocally involved the low dose group (0.02 mg/kg/day). In the epididymides, there was cell debris as a result of the testicular change. Following the 8-week treatment-free period, these findings were not completely reversible as 1 of 2 recovery-males showed microscopic findings in the testes and epididymides. Therefore, no male NOAEL was set in the dog study. The issue of not setting a NOAEL for both sexes was a matter of discussion. In this case, we have no NOAEL for males as the germ cell degeneration in males was identified also at the lowest dose tested (corresponding to a systemic exposure 1170 times higher than exposures observed in clinical trials). However, it was concluded that the most appropriate approach is to accept that only a LOAEL can be given for the effect and highlight this fact in the SmPC labelling.

Genotoxicity

A test-battery of genotoxicity studies has been performed. As some chemicals may become potent mutagens and clastogens when photosensitized, the mutagenic and clastigenic potential of trifarotene was also evaluated in the absence and presence of UV light.

In the reverse mutation assays, reductions in revertants were noted. This is often regarded as a sign of toxicity, and in study RDS.03.SRE.12526 this effect was only noted above the precipitation limit and without S9 supporting this explanation. In study RDS.03.SRE.12525, a

reduction in revertants was only noted in the presence of UV-exposure. This reduction may (also) be due to a shadowing effect of precipitates, reducing the UV-induced increase in revertants expected. Collectively it is agreed the studies do not support a mutagenic effect of trifarotene in the absence or presence of UV-light.

One in vitro (lymphocytes) and one in vivo (bone marrow) micronucleus assay has been performed. The data provided supports a weak but positive signal of clastogenicity in vitro. The in vivo study, which may be considered more important, evidenced an increased frequency of polychromatic erythrocytes in males exposed to 7.5 mg/kg, compared to the control group. However, while significant, the signal is considered weak (in absolute terms) and not considered sufficient to label trifarotene a clastogen.

A test of chromosome aberrations in cultured Chinese hamster ovary (CHO) cells in the absence and presence of ultra violet light structural chromosome aberrations that were similar to those observed in concurrent vehicle controls. A small increase in endoreduplication was observed following exposure in the presence of UV-light. The significance of this finding is unknown.

Carcinogenicity

To evaluate the carcinogenicity potential of trifarotene, two carcinogenicity studies over 104-weeks have been performed in Wistar rats (oral) and CD-1 mice (dermal). In the dermal study in mice, 0.05mg/kg/day and 0.1 mg/kg/day were not tolerated by the animals and these groups were removed from the study and replaced by a 0.01mg/kg/day group from week 14. There was no increased incidence of neoplastic findings in the treated animals. However, scab, ulceration and hyperplasia/hyperkeratosis were noted dose-dependently, which were also correlated with enlargement of lymph nodes and lymphoid hyperplasia in axillary and mandibular lymph nodes as well as the spleen. In the oral study, treatment resulted in mild but dose-dependent reductions in body-weight and food consumption. No neoplastic changes were noted that are considered treatment related. However, gross and histopathologic changes were evident in the stomach, skin and liver. In addition, the growth plate of the femur displayed an irregular thickness in more than half of male and female rats given HD. Thus, overall there is no data to suggest that trifarotene is associated with a carcinogenic potential. The non-neoplastic findings noted after 2 –year exposures are similar to the findings evidenced in the repeated-dose toxicity studies and in accordance with what is expected from a RAR-agonist.

According to the Applicant, through its effect on skin, treatment may have stimulated the lymphoid compartment generally, as the mandibular and inguinal lymph nodes as well as the spleen also showed treatment-related lymphoid hyperplasia. Therefore, the effects noted are considered procedure related rather than a sign of toxicity. It is also the Applicant’s view that increased cellularity of the sternal bone marrow was also an indirect procedure-associated finding.

While it may be agreed that the effect on skin resulted in the stimulation of the lymphoid compartment, it is not agreed that the effects are procedure related. If the effects were procedure related, then the same findings with a similar severity would have been seen in the control group. Rather, the effects are an indirect effect of the toxicities seen dermally, and they are induced by trifarotene. In any case the clinical relevance of these findings is limited, as the underlying dermal irritation would be monitorable and thus treatment suspended before progression to clinically relevant lymphoid effects.

Reproductive and developmental toxicity

A full package of required reproductive toxicology studies has been performed, including a preliminary juvenile toxicity study. Rat and rabbit were the species used for the studies. In the fertility study, there was a slight reduction in body-weight at the highest dose in males, but there were no effects on mean sperm count, the mean percentage of motile sperm or the sperm motility parameters. Post-implantation loss was significantly higher in the low-dose group. However, a single female had no viable embryos which influenced the mean value, and since no effects were noted at higher exposures, the finding is not considered related to treatment. Thus collectively, trifarotene did not induce effects on mating performance or fertility in exposed males or females.

In the EFD-study, trifarotene exposure in the pregnant SD rat was associated with dose-dependent maternal toxicity from 0.3mg/kg/day manifested as reductions in bodyweight and food consumption. Post-implantation loss (both early and late resorptions) was clear in dams of the 1mg/kg/day dose-group. However, on closer inspection a difference in percentage post-implantation loss was evident for all dose groups compared to control. According to the Applicant, this is incidentally so and is based on low numbers of resorptions in the concurrent control group compared with historical control data.

Trifarotene is clearly teratogenic. At the highest dose, all fetuses displayed a syndrome of multiple malformations expected from a RAR-agonist and the majority of fetuses exposed at 0.3mg/kg/day were also grossly malformed. At the 0.03 dose-level, one fetus had umbilical hernia and one fetus had cleft palates, findings which were both also noted at the 0.3 and 1mg/kg/day dose groups. No cleft palates were seen in the 0.1mg/kg/day dose group, why the Applicant considers the finding in the 0.03mg/kg/day dose group an incidental and isolated finding. However, while no cleft palates were seen at 0.1mg/kg/day, incomplete ossification of the palate was noted, suggesting effects on bone formation. Cleft palate is one of the most common birth defects in humans, and RA plays important roles during palate development. It is also established that excess RA increases the incidence of cleft palate in rodents as well as humans, why it is curious with findings in low-dose trifarotene exposed fetuses but no findings in controls. However, given the single occurrence in the 0.03mg/kg/day group and the lack of findings at the 0.1mg/kg/day-level, it is not an obvious treatment-related effect.

Severe gross disruptions of the skeleton were noted in the two higher groups. This was expected based on the apparent external malformations. At the 0.1mg/kg/day-level misshapen tibias and fibulas were noted in addition to retarded ossification (and on some places increased ossification) of various bones. Findings at the 0.03 levels were mostly related to effects on ossification. However, there was an increased incidence of unilateral or bilateral rudimentary 14th ribs and incomplete ossification of the 6th sternebra. These findings are considered variations of unclear toxicological significance.

Trifarotene was not tolerated at 50mg/kg/day (the highest dose) in the New Zealand white rabbit. Almost all animals died or were prematurely sacrificed. Treatment was terminated on SD 14-15 in this group, but most animals did not recover.Only one dam in this group had viable fetuses (2♀) which all were severely malformed.

As for HD, treatment with 5mg/kg/day was associated with malformations, mainly acaudia and bent tail. One fetus was also severely malformed with amelia and hemimelia of hindlimbs and

gastroschisis. In the low-dose group, one severely malformed (similar findings as the fetus at 5mg/kg/day). In addition, the incidence of bent tail was above both treatment control values and historical control data, suggesting clear treatment causality. Fetal visceral malformations of the urinary system were evident in fetuses to dams exposed to 5 or 50 mg/kg/day and one fetus at 0.5 had a malformed kidney. The skeletal malformations were mainly located to the caudal region of the vertebrae. This correlates well with the tail-related findings in all treated groups.

Thus collectively, the EFD-studies show that trifarotene, as other retinoid receptor agonists, is a teratogen at sufficiently high doses. It is interesting to note the very wide spectrum of malformative effects induced, and the wide dose-spectrum in which they can be produced. It can also be concluded that the selectivity for the RAR-γ over RAR-α and RAR-β, has no apparent influence on the malformative effects of the substance. The labelling in section 4.6 for pregnancy should be the same as for other dermal retinoids.

In the pre-and postnatal development study, there were no treatment related deaths. Pre-birth loss (F1) was increased in the 0.03 and 0.1mg/kg/day dose-groups (11% and 13.4% compared to 6.2% for controls). According to the Applicant, this data was within historical control data. However, the collective trend across the EFD and PPND studies is that post-implantation loss is seen at trifarotene treatment with doses not associated with maternal toxicity. Even so, due the lack of clear data supporting this trend, this issue was considered resolved.

A 4-wek DRF study in juvenile animals was submitted by the Applicant, but no definite study. However, as no definite juvenile toxicity study has been submitted, this study has not been further considered. In addition, according to the PIP provided, the PDCO has agreed to a waiver that applies to the paediatric population from birth to less than 9 years. Further, the agreed PIP does not include any non-clinical studies.

Local tolerance studies
Dermal and ocular irritation studies were performed. The dermal local tolerance studies were not assessed. They were not performed with the clinical formulation, and the dermal irritation potential of the substance has become apparent in the repeated-dose studies in mice and mini-pigs.

Ocular tolerance studies are considered important, since the application of the product will include the periorbital area of the face.Trifarotene 100 µg/g gel was irritating when administered by the ocular route to rabbits. Trifarotene cream HE1 at up to 400 µg/g was minimally irritating when administered by the ocular route to rabbits. While the relation of the used gel/cream to the clinical formulation is unclear, it can be concluded that trifarotene is an eye-irritant, why appropriate warnings should be included in section4.3 of the SmPC.

Sensitization
Skin sensitization has been evaluated in two studies with trifarotene. Trifarotene cream was studied using the Buehler test and the gel was used in the local lymph-node assay. No sensitization potential was noted in the Buehler assay.

In a Photoirritation and photosensitization study of trifarotene in guinea pig, study data show that a photosensitizing potential of trifarotene was evident, with reactions in 80% of treated animals versus 40% for placebo controls. According to the Applicant, the irritation seen in the induction period may be responsible for the effect noted. While the acute photoirritation observed in these studies is considered relevant to humans, the predictivity of these studies for

human photoallergy is unknown. Thus, for regulatory purposes, such nonclinical photoallergy testing is generally not recommended. It is, however, expected that the issue of photosafety assessment is further addressed clinically.

III.5 Ecotoxicity/environmental risk assessment

An Environmental risk assessment was performed in accordance with the relevant guideline. As the PECsurface water value obtained (0.0005 µg/L) is lower than the trigger value of 0.01 µg/L, a Phase II environmental fate and effects analysis was not considered required. However, the Applicant was asked to provide with the Kow study, which is referring to Report No. 83762186, Fieseler A. (2015) and to conduct a step-wise PBT assessment. In the response, the report was submitted. The applicant points out that at pH 7, which should be used as the reference according to ERA Q&A document and ECHA, Chapter R7a, the log Dow of trifarotene is only 3.13 at pH 7 and assuming linearity within the pH range of 5-7, the applicant states that the log Dow can be calculated as 4.05 at pH 6. The applicant thus concludes that the log Dow of trifarotene is below the trigger point at pH 7 and pH 6 and that Trifarotene may be considered unlikely to represent a risk for the environment following its prescribed use in patients. It is agreed that the higher log D value at pH 5 can be considered less relevant, especially considering the large difference between the log D values at pH 7 and pH 5, (3.13 vs 4.93) and thus, that the log D value at pH 7 is not close to the trigger value. The use of the measured and calculated log Dow obtained at pH 7 and pH 6, respectively, as basis for concluding that no further PBT-assessment is needed is considered acceptable.

It can thus be concluded that Aklief in the proposed use, is not likely to pose a risk to the environment.

Summary of main study results

Substance (INN/Invented Name):Trifarotene			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Dow = 4.93 at pH 5 log Dow = 3.13 at pH 7 log Dow = 3.50 at pH 9.5	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default or refined (e.g. prevalence, literature)	**0.0005**	µg/L	< 0.01 threshold (Y)

III.6 Conclusion on the non-clinical aspects

The non-clinical data package for Aklief included in vitro and in vivo pharmacology, pharmacokinetics (PK), and toxicity studies. Trifarotene induced a marked comedone reduction and increase in epidermal thickness in the Rhino mouse, which were comparable to effects observed with tretinoin or tazarotene but at about 10-times lower dose. Secondary pharmacology studies show anti-inflammatory effects of trifarotene in the TPA induced ear edema model in mice, similar to those of tazarotene and depigmentation in vivo in a natural pigmentation model which was stronger and faster than the one induced by tretinoin. No safety pharmacology issues

were thus identified in the performed studies at dose levels far in excess to those anticipated in the clinical situation. Further, no significant risk for systemic pharmacodynamics drug interactions is anticipated based on the negligible plasma concentrations of trifarotene and its metabolites detected following topical administration to humans. Overall, the non-clinical pharmacology studies support the proposed clinical use of the product.
Absorption and bioavailability after dermal trifarotene application was low. After 12 days repeated topical application of 100 µg/g cream in minipigs, the highest mean C_{max} plasma concentrations detected was 1.05 ng/mL, suggesting limited systemic exposure after topical application. Trifarotene was widely distributed through the body of rats, following both oral and IV administration. Faeces were the most important route of excretion of total radioactivity after IV and oral dosing in both rat and dog, representing almost 100% of the administered dose and excretion was almost complete within 48 hours.
The toxicity profile of Trifarotene was characterized in mice, rat, dog, rabbit and mini pig in a toxicology program consistent with ICH M3(R2). The pivotal toxicology studies were conducted in compliance with GLP regulations and standards. The program of toxicity studies performed and provided is considered sufficient to characterize the toxicity profile of Aklief. The overall toxicities presented are similar to other known RAR-agonists and includes dermal irritation and inflammation, effects on bone mineralization and effects on gastric mucosa. Given that the dermal route (with limited systemic exposure) is intended for clinical use of the product, the exposure margins to toxic effects are generally wide. As for all retinoids currently known, teratogenicity has been shown in the reproductive and developmental toxicity studies with trifarotene. This is a (well-known) limitation of the retinoids, especially since they are often used to treat women of reproductive age, why strict recommendations regarding the use of the product during pregnancy and lactation is evident in section 4.6.

IV. CLINICAL ASPECTS

IV.1 Introduction

The data package for Aklief included pharmacodynamics, clinical pharmacokinetics (PK) including one drug-drug interaction study with contraceptive pill, and two clinical phase 3 efficacy and safety studies including a long-term follow-up study investigating mainly safety, but also the maintenance of efficacy up to 52 weeks of treatment.

IV.2 Pharmacokinetics

For Aklief cream, being a locally acting product, the systemic exposure of the active substance is not relevant for efficacy, and the pharmacokinetic evaluation is made primarily from a safety perspective.

Absorption
A very low or, in most cases, non-quantifiable systemic exposure of trifarotene was confirmed in adult and adolescent (≥12 years) patients with acne after topical administration of Aklief 50 µg/g cream. After maximal-use administration (2 g of the 50 µg/g cream applied once daily on all the acne-affected area) for 4 weeks in adolescent and adult patients with acne vulgaris, steady state plasma concentrations of trifarotene were quantifiable in in only 3/17 adolescent patients and 7/19 adult patients and were then just above the LOQ of the analytical method (5-10 pg/mL). The quantifiable $AUC_{0\text{-}24\,h}$ values (75-106 pg*h/mL) were about 100- to 2000-fold lower than the no-effect or low-effect levels in non-clinical studies (NOAEL/LOAEL). There were no notable differences between adolescents and adults in terms of systemic exposure.

Distribution
The binding of trifarotene to plasma proteins was high (≥ 99.7 %) *in vitro*, not saturable and not species-specific.

Elimination
In vitro, trifarotene was extensively metabolised via CYP2C9, CYP2C8 and CYP3A4, with CYP2C9 being the major contributing enzyme *in vitro*. No mass-balance study has been performed in human to elucidate the major elimination pathways for trifarotene *in vivo*. This is acceptable, given the low systemic exposure after topical administration. Five main metabolites were identified *in vitro*, including one secondary glucuronide. Metabolites CD09986, CD06700 and CD06530 were pharmacologically active in non-clinical *in vitro* studies, but none of the major metabolites were quantifiable in plasma in humans after topical administration of the 50 µg/g cream. Terminal half-life of trifarotene in humans could not be adequately determined as plasma levels were low and rapidly fell below the limit of quantification (<5 pg/mL).

Special populations
Given the low systemic exposure to trifarotene after topical administration and the large margin to non-clinical NOAEL/LOAEL, a potentially increased systemic exposure to trifarotene due to different intrinsic factors is unlikely to constitute a safety problem. The lack of studies in patients with renal or hepatic impairment is therefore acceptable.

It has been suggested that severity of acne would be the main factor contributing to variability in skin penetration and thereby in systemic exposure. Patients with severe acne were included in the pivotal studies and in the maximal-use pharmacokinetic studies of trifarotene and, thus, the clinical safety evaluation included this potential source of increased systemic absorption. There was no difference in systemic exposure of trifarotene between male and female subjects or between Japanese and non-Japanese patients with acne after topical administration. Other ethnicities have not been studied from a pharmacokinetic/systemic exposure perspective.

Rich pharmacokinetic data are available from two paediatric patients <12 years of age (10 and 11 years, respectively). Sparse PK data are available from nine paediatric patients <12 years of age (10 and 11 years). These subjects had no quantifiable plasma levels of trifarotene during 4 weeks of maximal-use administration of Aklief 50 µg/g cream. There were no patients above 65 years of age in the pharmacokinetic studies.

Pharmacokinetic interaction potential
The risk for clinically relevant pharmacokinetic interactions with topically administered trifarotene is expected to be low, given the low systemic exposure and large margins to non-clinical NOAEL/LOAEL. *In vitro* data indicate that trifarotene is a substrate for CYP2C9 and data indicate that at these low concentrations, trifarotene has no potential to inhibit or induce CYP enzymes or to inhibit major transporters and is, thus, not expected to affect the plasma concentrations of concomitantly administered drugs.

Nevertheless, due to the teratogenic potential of retinoids, a clinical drug-drug interaction study with a contraceptive pill was performed. This study demonstrated no effect of topically administered trifarotene 100 µg/g cream (2 g/day for 14 days) on the plasma concentrations of ethinyl oestradiol or levonorgestrel.

Exposure-response relationship
Trifarotene is a locally acting product and establishing an exposure/effect relationship is not relevant. Moreover, due to the very low or, in most cases, non-quantifiable plasma levels it is not possible to establish an exposure/safety relationship.

IV.3 Pharmacodynamics

Trifarotene (CD5789) is a retinoid acid receptor γ (RARγ) agonist. It has high specificity to this receptor over RARα & RARβ (65- and 16-fold, respectively, with no Retinoid X Receptor (RXR) activity.

When trifarotene binds to RARγ receptors present on keratinocytes, a pharmacological cascade is initiated, leading to the modulation of the differentiation of the keratinocytes in acne vulgaris. The functional profile of trifarotene was studied in different cellular pharmacology studies, which demonstrated overall similar potency in the performed assays as tazoratene and tretinoin when present.

In the Rhino mouse model, which is a relevant *in vivo* model to evaluate the comedolytic activity of topical retinoids, a marked comedonic effect was noted. This result confirms that trifarotene has RARγ agonistic properties.

Secondary pharmacodynamics effects of trifarotene are anti-inflammatory effects in the TPA-induced ear edema model in mice and depigmentation in two experimental models.

IV.4 Clinical efficacy

Design and conduct of clinical studies

The study design and endpoints in the Phase 3 studies RD.03.SRE.18251 and RD.03.SRE.18252 were identical. In both studies the efficacy and safety of trifarotene (CD5789) 50 µg/g cream, the concentration proposed for marketing, and its cream vehicle was investigated in subjects with acne vulgaris on the face and trunk. No active comparator was included which would have been of interest. However, comparison with vehicle cream in the pivotal studies is according to guidelines and accepted.

Different concentrations of CD5789 cream was investigated on the efficacy and safety in subjects with acne vulgaris on the face in the dose-response study RD.06.SRE.18223. The subjects included in the study were dosed once daily for twelve weeks. An active comparator was included, tazarotene 0.1%. Two exploratory studies have been performed; one study RD.06.SRE.18214 which investigated the efficacy and safety of different formulation and concentrations of CD5789 in subjects with acne vulgaris on the face and the other, study RD.03.SRE.40129, assessed the facial tolerability after daily application of several concentrations and formulations containing CD5789 in acne vulgaris subjects. The results of these studies are briefly described and assessed below.

The Phase 3 studies RD.03.SRE.18251 and RD.03.SRE.18252 are fairly large studies with in total 1214 subjects enrolled to the active CD5789 50 µg/g cream groups, and 1206 subjects enrolled the cream vehicle groups. The studies enrolled male and female patients 9 years of age or above having acne vulgaris lesions on the face and trunk which were eligible for treatment.

The co-primary efficacy endpoints in both studies were the percentage of subjects who achieved an Investigator's Global Assessment (IGA) score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12 on facial acne vulgaris lesions, absolute change in facial inflammatory lesion count from Baseline to Week 12, and absolute change in facial non-inflammatory lesion count from Baseline to Week 12.

The co-secondary efficacy endpoints in both studies were the percentage of subjects who achieved a Physician Global Assessment (PGA) score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12 on truncal acne vulgaris lesions, absolute change in truncal inflammatory lesion count from Baseline to Week 12, and absolute change in truncal non-inflammatory lesion count from Baseline to Week 12.

The IGA scale is a validated and well-known scale used for evaluating efficacy of medicinal products in the treatment of facial acne vulgaris. The PGA scale is a scale like the IGA scale used for efficacy evaluation of acne vulgaris of the trunk. The IGA and PGA are static scales and were dichotomized for analysis, with a score of 1 (Almost Clear) or 0 (Clear) (and a reduction of at least 2 grades from Baseline) indicating treatment success. Furthermore, counting the number of inflammatory and non-inflammatory lesions is an established efficacy assessment method for dermatological products used for treatment of acne vulgaris.

Supportive efficacy endpoints were Percent change from Baseline in lesion count at Week 12, Change in Dermatology/Children's Dermatology Life Quality Index, Subject's assessment of facial improvement and Overall Success Rate.

A primary efficacy subgroup analyses was also performed by gender, age, ethnicity, race and number of lesions at baseline for the ITT population in the combined studies RD.03.SRE.18251 and RD.03.SRE.18252.

The statistical analysis performed is overall considered acceptable. The study was appropriately powered at 90% using difference in IGA response of 8%. There was an issue with the stratification by centre in studies 18251 and 18252. However, the Applicant has provided information on how many patients were randomised without respective with the stratification. Both randomisations are considered valid.

The Phase 3 long-term follow-up study RD.03.SRE.18250 investigated mainly safety, but also the maintenance of efficacy up to 52 weeks of treatment.

Efficacy data and additional analyses

In the pivotal Phase 3 studies, the genders were equally distributed in study RD.03.SRE.18251, while females were in majority in study RD.03.SRE.18252. The mean age was 19-20 years of age. Most subjects were Caucasians with Fitzpatrick skin type I-III. All subjects had moderate facial acne (IGA grade = 3) and also moderate truncal acne (PGA grade = 3).

The subjects had more non-inflammatory than inflammatory acne vulgaris lesions, on both the face and trunk. The mean number at baseline of inflammatory and non-inflammatory acne vulgaris lesions were in study RD.03.SRE.18251 34.8 (SD = 13.31) and 53.4 (SD = 27.35) on the face, respectively, and on the trunk, 36.3 (SD = 17.32) and 46.9 (SD = 21.75), respectively. In study RD.03.SRE.18252 at baseline, mean counts of inflammatory and non-inflammatory lesions on the face were 36.6 (SD = 13.84) and 50.9 (SD = 25.83), respectively, and on the trunk, 39.1 (SD = 16.80) and 45.9 (SD = 19.87), respectively.

The studies were performed in the US and several other countries around the world, of which a minority were countries within the EU. Acne vulgaris lesions are not considered to significantly differ between countries nor regions. The subjects enrolled in the study are therefore considered to be representative of the acne vulgaris population.

Study completion was high in all treatment groups. Withdrawal by subject was in the majority of cases reason for treatment discontinuation, which was noted in a similar frequency in the active compared with vehicle treated groups.

Brief summary of results obtained in the Phase 2 study

The performed dose response study RD.06.SRE.18223 evaluated three concentrations of the CD5789 cream; 25 µg/g cream, 50 µg/g cream and 100 µg/g cream which were compared with the cream vehicle, and the active comparator tazarotene 0.1% gel. Study drugs were applied on the face by the subjects once daily in the evening for 12 weeks.

The objective of this study was to identify a safe and effective concentration of CD5789 cream to be evaluated in the Phase 3 studies. Overall, it is assessed that CD5789 had efficacy on acne vulgaris lesions in all treatment groups. The magnitude of the observed efficacy is however not large and similar across the concentrations of CD5789 investigated. The active comparator tazarotene has an efficacy level, similar, or slightly higher, than CD5789. CD5789 100 µg/g cream caused more local irritation than CD5789 50 µg/g cream. The safety and local tolerability profile of CD5789 50 µg/g cream supported the use of this dose in the pivotal Phase 3 studies.

Study RD.06.SRE.18214 is an exploratory study in a small number of patients that compared the cream formulations of CD5789 25 µg/g, CD5789 50 µg/g and CD5789 50 µg/g gel with their respective vehicle formulations in subjects with facial acne vulgaris applied for four weeks in a split-face design.

The primary efficacy endpoints were the total acne lesion count and the percent reduction at the end of the treatment (day 29/ET). The total lesion count was significantly reduced with CD5789 50 µg/g cream (median value decreased from 37.0 to 18.0). Also, the percent reduction in lesion count at day 29 was statistically significant for CD5789 50 µg/g cream, with a median reduction of 54% compared with 38.0% for vehicle cream. The efficacy of CD5789 25 µg/g cream and CD5789 50 µg/g gel did not reach statistical significance.

The secondary efficacy endpoints supported the results of the primary efficacy endpoints. Statistically significant reductions in inflammatory and non-inflammatory lesions counts were observed for active treatments. The most marked efficacy was seen on non-inflammatory lesions counts. The subject’s preference of CD5789 50 µg/g cream, was high, almost 80%.

Study RD.03.SRE.40129 is a Phase 2a exploratory study that assessed the facial tolerability of the formulation proposed for marketing CD5789 50 µg/g cream, CD5789 50 µg/g gel and an earlier formulation called trifarotene cream A. No vehicle formulations were included in the study but an active comparator arm, tazarotene 0.1% gel.

The mean reduction in total acne vulgaris lesion count was 66% at day 29. The mean reduction in inflammatory lesion counts was 57.7%, and the mean reduction in non-inflammatory lesion counts was 71.5% at day 29.

In summary, although reduction in total acne vulgaris lesion counts were observed with all CD5789 formulations and concentrations tested, the local tolerance for CD5789 50 µg/g cream appeared to be slightly better relative to CD5789 50µg/g gel.

Overall, the results from the Phase 2/exploratory studies support the dosing regimen used in the Phase 3 trials; i.e., once daily application over a treatment period of 12 weeks with CD5789 50µg/g cream.

Summary of results obtained in the pivotal Phase 3 studies – Co-primary end-points

In the Phase 3 studies, the CD5789 50 µg/g cream met the three co-primary end-points which investigated efficacy of the medicinal product proposed for marketing on acne vulgaris lesions on the face. The studies have identical design, and compared the percentage of subjects (ITT population) who achieved an IGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12 (co-primary end-point 1), absolute change in facial inflammatory lesion count from Baseline to Week 12 (co-primary end-point 2) and absolute change in facial non-inflammatory lesion count from Baseline to Week 12 (co-primary end-point 3).

The results of the co-primary efficacy variables showed highly significant ($p<0.001$) results in both pivotal studies. In study 18251, the IGA success rate at Week 12 was 29.4% in subjects who received CD5789 50 µg/g cream and 19.5% in those who received Vehicle Cream in the ITT population. A higher mean reduction in facial inflammatory lesion counts from Baseline to Week 12 was observed in CD5789 50 µg/g cream (Least squares [LS] mean of -19.0) compared with Vehicle Cream (LS mean of -15.4). Concerning non-inflammatory lesion counts, a higher mean reduction in facial non-inflammatory lesion counts from Baseline to Week 12 was observed in CD5789 50 µg/g cream (LS mean of -25.0) compared with Vehicle Cream (LS mean of -17.9) (see table below).

In study 18252, The IGA success rate at Week 12 was 42.3% in subjects who received CD5789 50 µg/g cream and 25.7% in those who received Vehicle Cream in the ITT population. A higher mean reduction in facial inflammatory lesion counts from Baseline to Week 12 was observed in CD5789 50 µg/g cream (Least squares [LS] mean of -24.2) compared with Vehicle Cream (LS mean of -18.7). Regarding non-inflammatory lesion counts, a higher mean reduction in facial non-inflammatory lesion counts from Baseline to Week 12 was observed in CD5789 50 µg/g cream (LS mean of -30.1) compared with Vehicle Cream (LS mean of -21.6) (see table below).

Table. Analysis of Success Rate of Investigator's Global Assessment at Week 12 (Multiple imputation) in Studies 18251 and 18252 (Intent-to-treat population)

	Study 18251		**Study 18252**	
	CD5789 50 µg/g cream (N=612)	**Vehicle Cream (N=596)**	**CD5789 50 µg/g cream (N=602)**	**Vehicle Cream (N=610)**
Success rate (%)	29.4	19.5	42.3	25.7
p-value	<0.001	-	<0.001	-
Difference in Success Rate from Vehicle (95%CI)	9.8 (4.8, 14.8)	-	16.6 (11.3, 22.0)	-

Cochran Mantel Haenszel; CI=confidence interval

Note: Success is defined as an IGA score of "Clear (0)" or "Almost Clear (1)" at Week 12 and a grade change of at least 2 from Baseline. Success rate is calculated as the number of subjects achieving success divided by the number of subjects with IGA data at Week 12. P-values are based on the general association statistic from a CMH test stratified by analysis center. CIs are based on the large-sample approximation method for binary data without the use of a continuity correction. Data source: ISE Table 2.1.1

Table. Analysis of facial lesion count absolute change from Baseline to Week 12 (Multiple imputation) in Studies 18251 and 18252 (Intent-to-treat population)

	Study 18251		Study 18252	
	CD5789 50 µg/g cream (N=612)	**Vehicle Cream (N=596)**	**CD5789 50 µg/g cream (N=602)**	**Vehicle Cream (N=610)**
Inflammatory Lesion Count				
Week 12 Change from Baseline, n	612	596	602	610
LS Mean (SE)	-19.0 (0.50)	-15.4 (0.51)	-24.2 (0.51)	-18.7 (0.51)
LS Means Difference from Vehicle (95% CI)	-3.6 (-4.9, -2.2)	-	-5.6 (-6.9, -4.3)	-
p-value	<0.001	-	<0.001	-
Non-inflammatory Lesion Count				
Week 12 Change from Baseline, n	612	596	602	610
LS Mean (SE)	-25.0 (0.87)	-17.9 (0.87)	-30.1 (0.71)	-21.6 (0.71)
LS Means Difference from Vehicle (95% CI)	-7.1 (-9.4, -4.8)	-	-8.5 (-10.3, -6.6)	-
p-value	<0.001	-	<0.001	-

ANCOVA= Analysis of Covariance; CI=confidence interval; LS=least squares; SE=standard error.
Note: P-values and CIs are based on an ANCOVA model with baseline lesion count, analysis center, and treatment as factors.
Data source: ISE Table 2.2.1, ISE Table 2.3.1

Overall, the vehicle response is fairly large, and largest in study 18252. The difference in IGA success rate from vehicle was 9.8% in study 18251 and 16.6% in study 18252.

Sensitivity analyses show consistent results which is expected given that the amount of missing data is relatively low. Overall, the results for the PP population were consistent with the ITT population.

Onset of effect was determined using post-hoc analysis of the change from Baseline in the three co-primary end-points, to week's two to four. The differences between active and vehicle cream increased thereafter over time (see table below).

Table. Summary of IGA Success Rate by visit in Studies 18251 and 18252 (Intent-to-treat population, Observed data)

	Study 18251		Study 18252	
	CD5789 50 µg/g cream (N=612)	**Vehicle Cream (N=596)**	**CD5789 50 µg/g cream (N=602)**	**Vehicle Cream (N=610)**
Week 1, n	584	567	595	597
No. of Subjects with Success	1	3	4	3
Success Rate (%)	0.2	0.5	0.7	0.5
Week 2, n	578	563	588	597
No. of Subjects with Success	13	10	18	11
Success Rate (%)	2.2	1.8	3.1	1.8
Week 4, n	582	573	587	595
No. of Subjects with Success	46	23	33	23
Success Rate (%)	7.9	4.0	5.6	3.9
Week 8, n	557	550	571	578
No. of Subjects with Success	90	52	118	61
Success Rate (%)	16.2	9.5	20.7	10.6
Week 12, n	543	539	563	573
No. of Subjects with Success	161	108	241	148

Success Rate (%)	29.7	20.0	42.8	25.8

IGA=Investigator's Global Assessment

Note: Success is defined as an IGA score of "Clear (0)" or "Almost Clear (1)" at the summarized visit and a grade change of at least 2 from Baseline. Success rate is calculated as the number of subjects achieving success divided by the number of subjects with IGA data at the summarized visit.

Data source: ISE Table 2.1.2

However, the size of the obtained efficacy level is considered modest. Nevertheless, the International Dermatology Consensus Groups (Asai 2016 p118; Nast 2016 p1261) has determined a threshold effect size of 10% to be clinically relevant for the treatment of facial and truncal acne. This opinion must be accepted (see section VI Benefit-risk assessment).

Pivotal Phase 3 studies - Secondary end-points

The CD5789 50 µg/g cream met the three co-secondary end-points which investigated efficacy of the medicinal product proposed for marketing on acne vulgaris lesions on the trunk. The percentage of subjects (ITTT population) who achieved an PGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12 (co-secondary end-point 1), absolute change in truncal inflammatory lesion count from Baseline to Week 12 (co-secondary end-point 2) and absolute change in truncal non-inflammatory lesion count from Baseline to Week 12 (co-secondary end-point 3) were investigated.

The results of the co-secondary efficacy variables showed highly significant ($p<0.001$) results in both pivotal studies. In study 18251, The PGA success rate at Week 12 was 35.7% in subjects who received CD5789 50 µg/g cream and 25.0% in those who received Vehicle Cream in the ITTT population. A higher mean reduction in truncal inflammatory lesion counts from Baseline to Week 12 was observed in CD5789 50 µg/g cream (Least squares [LS] mean of -21.4) compared with Vehicle Cream (LS mean of -18.8). Concerning non-inflammatory lesion counts, a higher mean reduction in truncal non-inflammatory lesion counts from Baseline to Week 12 was observed in CD5789 50 µg/g cream (LS mean of -21.9) compared with Vehicle Cream (LS mean of -17.8) (see table below).

In study 18252, The PGA success rate at Week 12 was 42.6% in subjects who received CD5789 50 µg/g cream and 29.9% in those who received Vehicle Cream in the ITTT population. A higher mean reduction in truncal inflammatory lesion counts from Baseline to Week 12 was observed in CD5789 50 µg/g cream (Least squares [LS] mean of -25.5) compared with Vehicle Cream (LS mean of -19.8). Regarding non-inflammatory lesion counts, a higher mean reduction in truncal non-inflammatory lesion counts from Baseline to Week 12 was observed in CD5789 50 µg/g cream (LS mean of -25.9) compared with Vehicle Cream (LS mean of -20.8) (see table below).

Table. Analysis of Success Rate of Physician Global Assessment at Week 12 in Studies 18251 and 18252 (Multiple imputation) (Intent-to-treat on the trunk population)

	Study 18251		**Study 18252**	
	CD5789 50°µg/g cream (N=600)	**Vehicle Cream (N=585)**	**CD5789 50°µg/g cream (N=598)**	**Vehicle Cream (N=609)**
Success rate (%)	35.7	25.0	42.6	29.9
p-value	<0.001	-	<0.001	-
Difference in Success Rate from Vehicle (95%CI)	10.7 (5.4, 16.1)	-	12.7 (7.2, 18.2)	-

CI=confidence interval;

Note: Success is defined as a PGA score of "Clear (0)" or "Almost Clear (1)" at Week 12 and a grade change of at least 2 from Baseline. Success rate is calculated as the number of subjects achieving success divided by the number of subjects with PGA data at Week 12. P-values are based on the general association statistic from a CMH test stratified by analysis center. CIs are based on the large-sample approximation method for binary data without the use of a continuity correction.
Data source: ISE Table 3.1.1

The difference in PGA success rate from vehicle was of similar magnitude, 10.7 in study 18251 and 12.7 in study 18252. CD57879 50 µg/g cream had a similar efficacy on non-inflammatory lesions in comparison with inflammatory lesions on the trunk.,

Sensitivity analyses show consistent results which is expected given that the amount of missing data is relatively low. Overall, the results for the PPT population were consistent with the ITTT population.

Onset of effect was determined using post-hoc analysis of the change from Baseline in the three co-primary end-points, to week's two to eight. The differences between active and vehicle cream increased thereafter over time (see table below).

Table. Summary of Physician Global Assessment Success Rate by visit in Studies 18251 and 18252 (Intent-to-treat population, Observed data)

	Study 18251		**Study 18252**	
	CD5789 50 µg/g cream (N=600)	**Vehicle Cream (N=585)**	**CD5789 50 µg/g cream (N=598)**	**Vehicle Cream (N=609)**
Week 1, n	572	556	591	596
No. of Subjects with Success	4	3	4	8
Success Rate (%)	0.7	0.5	0.7	1.3
Week 2, n	566	554	584	596
No. of Subjects with Success	18	25	24	18
Success Rate (%)	3.2	4.5	4.1	3.0
Week 4, n	571	564	583	594
No. of Subjects with Success	64	46	50	34
Success Rate (%)	11.2	8.2	8.6	5.7
Week 8, n	546	541	567	577
No. of Subjects with Success	127	78	127	83
Success Rate (%)	23.3	14.4	22.4	14.4
Week 12, n	533	530	559	572
No. of Subjects with Success	191	136	241	172
Success Rate (%)	35.8	25.7	43.1	30.1

PGA=Physician's Global Assessment
Note: Success is defined as a PGA score of "Clear (0)" or "Almost Clear (1)" at the summarized visit and a grade change of at least 2 from Baseline. Success Rate is calculated as the number of subjects achieving success divided by the number of subjects with PGA data at the summarized visit.
Data source: ISE Table 3.1.2

Analysis performed across trials

The Applicant has made an analysis across trials of the combined studies RD.03.SRE.18251 and RD.03.SRE.18252. The proportion of subjects with success for the co-primary efficacy endpoints showed results similar to those described above for the individual studies (see tables above). The results of the co-secondary efficacy parameters overall supported the co-primary efficacy parameters.

Subgroup analysis

Subgroup analyses for the 3 co-primary and 3 co-secondary efficacy endpoints on pooled data from the pivotal studies were conducted to assess the consistency of treatment effects across the subgroup categories using the ITT and ITTT populations, respectively.

Subgroup analyses for the 3 co-primary and 3 co-secondary efficacy endpoints were performed by gender (male and female), age group 1 (9 to 11 years, 12 to 17 years, and ≥18 years), age group 2 (<14 years, 14 to 17 years, and ≥18 years), ethnicity (Hispanic or Latino and not Hispanic or Latino), race (white, black or African American, Asian, and Other), skin phototype (I to III, and IV to VI), country and region.

No specific differences between the subgroups investigated were noted in the analysis performed.

Long-term follow-up studies

The long-term Phase 3 follow-up study RD.03.SRE.18580, aimed at investigating the long-term safety of CD57879 50 µg/g cream and to evaluate the maintenance of efficacy over 52 weeks in subjects with acne vulgaris on the face and trunk.

Over the course of the 1-year treatment with CD5789 50 µg/g cream, there was continuous improvement of acne vulgaris of the face and trunk with progressive success (Clear and Almost Clear) in IGA (from 26.6% at Week 12 visit to 65.1% at Week 52 visit) and progressive success (Clear and Almost Clear) in PGA (from 38.6% at Week 12 visit to 66.9% at Week 52 visit). Overall success (IGA and PGA success in the same subject) was 22.0% and 57.9% at Week 12 and Week 52, respectively.

Both IGA and PGA success rates were slightly greater in subjects aged ≥18 years than in subjects aged <18 years, and in females compared to males. At Week 52 visit, 233/350 (66.6%) subjects self-reported to have marked or complete improvement of facial acne.

Those numbers however seem to be based on observed cases and hence could be argued to overestimate the true long-term effect. If it is assumed that patients with poor response discontinue the study early, it would be expected that response rates based on observed cases increase over time. On the other hand, not only the response rates but also the numbers of responders increase over time. The Applicant has provided response rates over time for Study 18250 based on failure imputation for missing data (i.e. using the number of enrolled subjects in the denominator). The success rates still increase over time, but to a lesser degree than in the original analysis presenting observed cases. At week 52 the success rate is 50.1% for IGA and 50.5% for PGA. This is based on no-responder analysis, which takes account of missing values as non-responder.

The tolerability and safety profile were consistent with the known profile of topical retinoids.

Subjects with acne scaring

A study (RD.06.SRE.40187E) to investigate the effect of CD5789 on the physiopathology of acne scarring in scar prone and non-scar prone patients with acne vulgaris has been performed. CD5789 50 µg/g cream had no effects in terms of modulation of gene expression and quality of healing.

Conclusions on clinical efficacy

A significantly superior efficacy for Aklief (trifarotene 50 μg/g cream) compared with vehicle cream was demonstrated for the co-primary endpoints in the two pivotal phase 3 studies RD.03.SRE.18251 and RD.03.SRE.18252 when evaluated after 12 weeks of once daily treatment. The three co-primary efficacy endpoints investigated efficacy on facial acne vulgaris lesions. The three co-secondary efficacy endpoints which investigated efficacy on truncal acne vulgaris lesion also demonstrated significantly superior efficacy for Aklief (trifarotene 50 μg/g cream) compared with vehicle cream. Other endpoints investigated, including subject's preference, also supported the efficacy of Aklief.

The size of the obtained efficacy level when evaluated at week 12 (end of treatment in the pivotal Phase 3 studies) is considered modest. No active comparator was included in the pivotal clinical trials, therefore the place in therapy with other topical acne products cannot be assessed. An efficacy comparison has been made with adapalene (Differin®) and although difficult, it can be concluded that the efficacy of the two compounds is in the same range. In favour of the product proposed for marketing is that the efficacy increased over time. Overall success rate (IGA and PGA success in the same subject) increased considerably during 52 weeks of treatment, which indicates benefit considered of clinical relevance when both face and trunk are involved and treated in the same subject.

Clinical safety

The active substance, trifarotene is a retinoid and a new chemical entity. In total the Applicant conducted 31 clinical studies, in various indications, in the trifarotene development program. A total of 4825 subjects were enrolled in this program. 12 clinical studies were performed specifically in acne vulgaris. Of these, 8 studies assessed the to-be-marketed formulation and concentration (50 μg/g cream) and 6 of these had efficacy or disease assessment evaluations. Of the 4825 subjects, 3662 subjects were exposed to various formulations of trifarotene, either alone or in association. Out of these 3662 subjects were exposed to trifarotene, 1932 were exposed to the to-be-marketed formulation (i.e., trifarotene 50 μg/g cream). Aklief cream is applied to the affected areas of the face and/or trunk once a day, in the evening, on clean and dry skin. The duration of treatment should be determined by the doctor on the basis of the clinical condition.

The main safety information was derived from the 2 pivotal studies described above in the efficacy section where acne patients received Aklief- trifarotene 50 μg/g cream, once daily for 12 weeks including a long-term open label safety study (LTS) of one year. These data were pooled to one primary safety pool. Safety information was also retrieved from all phase 1 and phase 2 studies in healthy volunteers and acne patients. These data comprised an additional supportive safety pool. In Safety Pool 1 (Studies 18251 and 18252), the mean (SD) daily study drug usage was similar between trifarotene 50 μg/g cream (1.5 [1.03] g/day) and vehicle cream (1.6 [0.84] g/day). In the long-term Study 18250, the mean (SD) average daily usage was 1.1 (0.71) g/day (median of 1 g/day).

Safety assessments

Safety assessments were conducted for all subjects at screening and all subsequent visits until the week 12 visit for the pivotal studies.

Safety assessment generally included:

- Adverse events (AEs). Treatment-emergent adverse events were monitored throughout the course of the clinical studies, including serious TEAEs and treatment-emergent adverse events of special interest (AESIs). In the 3 Phase 3 studies (i.e., Studies 18250, 18251, and 18252) the events defined as AESI were the same. In all studies, relationship to the study drug and severity of the AEs were also assessed. In the majority of studies, signs and symptoms of skin irritation (such as erythema, scaling, dryness, and stinging/burning) assessed through local tolerability scales were also reported as TEAEs if they led to permanent treatment discontinuation or if they required concomitant treatment. The Phase 3 studies were all coded with MedDRA version 18.0. For cutaneous events reported on treated areas, PTs starting with "application site" were chosen for the Phase 3 studies.
- Local tolerability signs/symptoms (erythema, scaling, dryness and stinging/burning) expected with the use of a topical retinoid were collected separately from the AEs. In Safety Pool 1 and the LTS study, local tolerability parameters (erythema, scaling, dryness and stinging/burning) were evaluated at each scheduled visit using 4-point scales (ranging from 0 [none] to 3 [severe]). Local tolerability was assessed separately on the face and the trunk, and data were analyzed for the SAF and SAFT populations, respectively. Erythema as well as scaling and dryness were evaluated by the Investigator, while stinging/burning was recorded by the Investigator after discussion with the subject.
  The pivotal studies and the LTS study also included routine hematology and blood chemistry tests, urinalysis, vital signs measurements and general physical examination.

Primary Safety Pools:

- Safety Pool 1: This pool included the two 12-week Phase 3 pivotal studies (Study 18251 and Study 18252). Pooled data from these 2 pivotal studies comprised the primary safety data to characterize the safety profile of trifarotene 50 μg/g cream in the targeted indication.
- Long-term safety study (Study 18250): The results are presented as a stand-alone study.

The results of the 1-year, open-label, long-term safety (LTS) study provided the long-term safety data for trifarotene 50 μg/g cream. The safety findings in the LTS study up to Week 12 (84 days) were also presented for selected safety endpoints along the Week 12 data in Safety Pool 1 for comparison purposes.

Safety analyses

In the Phase 3 studies (Studies 18251, 18252, and 18250), the following populations were used for safety analyses: 1/ Safety (SAF) population, defined as all randomized subjects who applied/administered the study drug at least once. Except for the local tolerability parameters on the trunk, the SAF population was used for the analysis of all safety endpoints and was analyzed as per Statistical Analysis Plan (SAP).
2/ Safety Population on the Trunk (SAFT), defined as all subjects in the SAF population who also applied the study drug on the trunk region (i.e., upper trunk, middle and/or lower back areas) at least once. The SAFT population was used for the analysis of the local tolerability parameters on the trunk.

Table 7 4-point scale to assess local tolerability (overall clinical irritation)

Used in Studies 18251, 18252, 18250, 103813, 103918, 40128, 40196, 18223, 40129, 103918, 40182, 18237, 18213, 18214, 40126, and 40205E				
Grade	**Erythema**	**Scaling**	**Dryness**	**Stinging/burning**
0 (none)	No erythema	No scaling	No dryness	No stinging/burning
1 (mild)	Slight pinkness present	Barely perceptible shedding, noticeable only on light scratching or rubbing	Slight but definite roughness	Slight warm, tingling/stinging sensation, not really bothersome
2 (moderate)	Definite redness, easily recognized	Obvious but not profuse shedding	Moderate roughness	Definite warm, tingling/stinging sensation somewhat bothersome
3 (severe)	Intense redness	Heavy scale production	Marked roughness	Hot, tingling/stinging sensation that causes definite discomfort

Supportive Safety Pools:
In the supportive pools, data were presented separately for studies conducted in healthy subjects (Safety Pool 2) and for studies conducted in subjects with acne vulgaris (Safety Pool 3) due to the differing study populations.

Statistical methods of safety analyses
Pivotal studies: All safety analyses of the pivotal studies are descriptive, and no formal inferential testing will be performed. The frequency (N %) of each adverse experience in the trial is presented by system organ class and preferred term by treatment group using the SAF population. Only local tolerability (erythema, scaling, dryness, stinging/burning) worsened from baseline will be analyzed. For further details please refer to the clinical AR.

Patient exposure

Table 1 Exposure intervals for safety pools

Pool	Pool Description	Treatment Durations	Exposure Intervals in the ISS
Primary Safety Pool			
Safety Pool 1 + LTS study	Safety Pool 1: 2 Phase 3 studies	12 weeks	Week 12
	LTS study as stand alone	52 weeks	Week 13 Week 26 Week 39 Week 52
Supporting Safety Pools			
Safety Pool 2	Healthy volunteers	1 – 29 days	1 – 14 days 15 – 28 days ≥29 days
Safety Pool 3	Subjects with acne vulgaris	28 days – 52 weeks	1 – 28 days 29 – 84 days 85 – 182 days ≥183 days

ISS=integrated summary of safety; LTS=long-term safety.

Table 13 Extent of exposure in the primary and supportive safety pools – Safety population

Safety Pools	Subjects exposed to trifarotene	Subjects exposed to vehicle
Primary Safety Pool		
Safety Pool 1 (2 pivotal Phase 3 studies)	1220	1200
Long-term safety	453	NA
Supportive Safety Pools		
Safety Pool 2: Healthy volunteers	224	116
Safety Pool 3: Subjects with acne vulgaris	1983	1261

ISS=integrated summary of safety; NA=not applicable; SAF=safety population; SAFT=safety population on the trunk.
Data source: ISS Table 1.3.1, ISS Table 1.3.3, ISS Table 1.1.2, and RD.06.SRE.18250, Table 14.1.1.1.
Note: In Study 18251, 5 subjects (Subjects 5812-006, 8135-006, 8168-008, 8580-001, 8580-003) randomized to Vehicle Cream, received CD5789 50 ug/g cream at or after Baseline. Subjects 5812 007 and 8135 005, randomized to CD5789 50 ug/g cream, received Vehicle Cream at or after Baseline. All these subjects were treated as CD5789 50 ug/g in the SAF and SAFT populations. In Study 18252, Subjects 5770-011 and 5778-012 were randomized to CD5789 50 µg/g cream but received Vehicle Cream at or after Baseline. Subject 8208-003 was randomized to Vehicle Cream but received CD5789 50 µg/g cream. These 3 subjects were treated as CD5789 50 µg/g cream in the SAF and SAFT populations.

Table 15 Treatment duration and number of applications, Safety population – Study 18250

	trifarotene 50 µg/g cream (N = 453)	
	Face	Trunk[a]
Treatment Duration (days), n	453	446
Mean (SD)	298.2 (121.41)	281.6 (125.19)
Median	364.0	363.0
Min, Max	1, 391	1, 391
1 to 89 days, n (%)	71 (15.7)	78 (17.5)
90 to 179 days, n (%)	17 (3.8)	25 (5.6)
180 to 269 days, n (%)	21 (4.6)	38 (8.5)
≥270 days, n (%)	344 (75.9)	305 (68.4)
Total Applications, n	453	446
Mean (SD)	284.6 (120.29)	269.2 (124.12)
Median	352.0	343.5
Min, Max	1, 388	1, 388

Max=maximum; Min=minimum; N=number of subjects; SD=standard deviation.
a) Trunk included chest, shoulders, upper, middle and/or lower back (if applicable).

The LTS of 52 weeks in which 453 patients were exposed to trifarotene is considered to sufficiently cover the likelihood of detecting any long-term adverse reactions related to this topical therapy. According to table 15 above 305-344 patients were treated for more > 270 days and the detailed number of patients being exposed for 1 year (completed full study) was requested in the Day 70 AR. The applicant has presented the requested figures. Apparently 589 patients were exposed to trifarotene 50 µg/g either in the face or the trunk for at least 360 days and 191 patients for at least 365 days. These figures are considered sufficient. However, the number of included patients aged 9-11 is limited.

Adverse events

In Safety Pool 1, there were 331 (27.1%) subjects in the trifarotene 50 µg/g cream group who reported 587 TEAEs compared with 240 (20.0%) subjects in the Vehicle Cream group who reported 338 TEAEs. Of the 331 trifarotene 50 µg/g cream-treated subjects who had any TEAE in Safety Pool 1, 144 subjects had a TEAE related to study drug, while 18 of 240 subjects in the Vehicle Cream group had a TEAE related to study drug.
In the long-term study overall, 218/453 (48.1%) subjects reported 468 TEAEs. Of these, 154/453 (34.0%) subjects reported TEAEs during the first quarter of the study.

More subjects in the trifarotene 50 µg/g cream group had cutaneous TEAEs (188 [15.4%] subjects in Safety Pool 1) compared with subjects in the Vehicle Cream group (48 [4.0%]

subjects). Of the 188 subjects in the trifarotene 50 µg/g cream group who had cutaneous TEAEs, 143 subjects in Safety Pool 1 had cutaneous TEAEs related to trifarotene 50 µg/g cream, while 14 of 48 subjects in the Vehicle Cream group had cutaneous TEAEs related to Vehicle Cream.

In the long-term study, cutaneous TEAEs in general were the most common, with a total of 107/453 (23.6%) subjects reporting those events. Cutaneous TEAEs which were considered related to the study drug accounted for all TEAEs related to the study drug and were reported by a total of 57/453 (12.6%) subjects. Most cutaneous TEAEs considered related to the study drug were reported during the first quarter of the study.

Table 10 Overall summary of treatment-emergent adverse events, Safety population – Safety Pool 1

	Safety Pool 1 (Studies 18251 and 18252)		LTS Study Up to Week 12
	CD5789 50 µg/g cream (N = 1220)	Vehicle Cream (N = 1200)	CD5789 50 µg/g cream (N = 453)
Number of TEAEs	587	338	236
Subjects with any TEAE, n (%)	331 (27.1)	240 (20.0)	152 (33.6)
Subjects with any TEAE related to study drug, n (%)	144 (11.8)	18 (1.5)	45 (9.9)
Subjects with any cutaneous TEAE, n (%)	188 (15.4)	48 (4.0)	79 (17.4)
Subjects with any cutaneous TEAE related to study drug, n (%)	143 (11.7)	14 (1.2)	45 (9.9)
Subjects with any AESI, n (%)	25 (2.0)	4 (0.3)	11 (2.4)
Subjects with any serious TEAE, n (%)	6 (0.5)	6 (0.5)	3 (0.7)
Subjects with any serious TEAE related to study drug, n (%)	0	0	0
Subjects with any severe TEAE, n (%)	12 (1.0)	8 (0.7)	4 (0.9)
Subjects with any severe TEAE related to study drug, n (%)	8 (0.7)	0	1 (0.2)
Subjects with any TEAE leading to discontinuation, n (%)	24 (2.0)	2 (0.2)	11 (2.4)
Subjects with any TEAE leading to discontinuation related to study drug, n (%)	19 (1.6)	0	11 (2.4)
Subjects with any TEAE leading to death, n (%)	0	0	0
Subjects with any TEAE leading to death related to study drug, n (%)	0	0	0

AESI=adverse events of special interest; LTS=long-term safety; ISS=Integrated Summary of Safety; N=number of subjects; TEAE=treatment-emergent adverse events.
Note: The long-term safety study data was presented as stand-alone. The long-term safety summary included events that occurred within the first 84 days of exposure.

Table 24 Summary of treatment-emergent adverse events with incidence of ≥1% by System Organ Class and Preferred Term, Safety population – Safety Pool 1

System Organ Class/Preferred Term	trifarotene 50 µg/g cream (N=1220)	Vehicle Cream (N=1200)
Number of TEAEs with incidence ≥1%	297	140
Subjects with any TEAE with incidence ≥1%, n (%)	206 (16.9)	116 (9.7)
General disorders and administration site conditions	107 (8.8)	14 (1.2)
Application site irritation	84 (6.9)	4 (0.3)
Application site pruritus	29 (2.4)	10 (0.8)
Infections and infestations	79 (6.5)	89 (7.4)
Nasopharyngitis	50 (4.1)	56 (4.7)
Upper respiratory tract infection	19 (1.6)	16 (1.3)
Influenza	11 (0.9)	18 (1.5)
Injury, poisoning and procedural complications	33 (2.7)	6 (0.5)
Sunburn	33 (2.7)	6 (0.5)
Nervous system disorders	16 (1.3)	16 (1.3)
Headache	16 (1.3)	16 (1.3)

ISS=integrated summary of safety; MedDRA=Medical dictionary for regulatory activities; N=number of subjects; TEAE=treatment-emergent adverse events.
Note: This table only included preferred terms which occurred in at least 1% of all subjects. Adverse events were coded using MedDRA version 18.0. System organ classes were sorted by frequency in the trifarotene 50 µg/g cream 50 µg/g group. Preferred terms were sorted by frequency in the trifarotene 50 µg/g cream 50 µg/g cream treatment group within each system organ class.

Table 25 Treatment-emergent adverse events reported by ≥1% of subjects by System Organ Class and Preferred Term, by quarter and overall, Safety population – Study 18250

System Organ Class/Preferred Term	trifarotene 50 µg/g cream (N = 453)				
	Q1 (M = 453)	Q2 (M = 384)	Q3 (M = 368)	Q4 (M = 351)	Overall (N = 453)
Number of TEAEs	249	91	85	43	468
Subject with any TEAE, n (%)	154 (34.0)	68 (17.7)	62 (16.8)	36 (10.3)	218 (48.1)
Infections and infestations	**61 (13.5)**	**41 (10.7)**	**30 (8.2)**	**18 (5.1)**	**116 (25.6)**
Nasopharyngitis	23 (5.1)	21 (5.5)	11 (3.0)	8 (2.3)	48 (10.6)
Upper respiratory tract infection	8 (1.8)	5 (1.3)	1 (0.3)	0	13 (2.9)
Influenza	2 (0.4)	3 (0.8)	2 (0.5)	2 (0.6)	9 (2.0)
Infectious mononucleosis	1 (0.2)	2 (0.5)	1 (0.3)	1 (0.3)	5 (1.1)
Tonsillitis	3 (0.7)	0	2 (0.5)	0	5 (1.1)
General disorders and administration site conditions	**47 (10.4)**	**7 (1.8)**	**8 (2.2)**	**2 (0.6)**	**57 (12.6)**
Application site pruritus	20 (4.4)	2 (0.5)	4 (1.1)	2 (0.6)	23 (5.1)
Application site irritation	20 (4.4)	1 (0.3)	1 (0.3)	0	22 (4.9)
Injury, poisoning and procedural complications	**32 (7.1)**	**8 (2.1)**	**10 (2.7)**	**6 (1.7)**	**50 (11.0)**
Sunburn	22 (4.9)	2 (0.5)	3 (0.8)	2 (0.6)	27 (6.0)
Ligament sprain	1 (0.2)	3 (0.8)	1 (0.3)	1 (0.3)	6 (1.3)
Skin and subcutaneous tissue disorders	**16 (3.5)**	**4 (1.0)**	**4 (1.1)**	**2 (0.6)**	**25 (5.5)**
Acne[a]	4 (0.9)	0	1 (0.3)	0	5 (1.1)
Respiratory, thoracic and mediastinal disorders	**14 (3.1)**	**2 (0.5)**	**4 (1.1)**	**3 (0.9)**	**23 (5.1)**
Oropharyngeal pain	6 (1.3)	2 (0.5)	1 (0.3)	0	9 (2.0)
Nervous system disorders	**6 (1.3)**	**3 (0.8)**	**0**	**2 (0.6)**	**10 (2.2)**
Headache	4 (0.9)	1 (0.3)	0	1 (0.3)	6 (1.3)
Gastrointestinal disorders	**12 (2.6)**	**3 (0.8)**	**4 (1.1)**	**0**	**19 (4.2)**
Diarrhoea	4 (0.9)	0	1 (0.3)	0	5 (1.1)

M=number of subjects at risk; N=number of subjects; PT=preferred term; Q=quarter; TEAE=treatment-emergent adverse event.
a) PT of acne refers to worsening of acne. In addition to the events coded as acne, 1 PT of application site acne (= acne nodule on left shoulder) was reported by 1 (0.2%) subject.

In the pivotal studies treatment-emergent adverse events which were reported in at least 1% of subjects in the trifarotene group (at the preferred term level) were, by decreasing frequency: application site irritation, nasopharyngitis, sunburn, application site pruritus, upper respiratory tract infection, and headache.
Additional adverse reactions that were reported in more than 1 patient treated with trifarotene cream (and at a frequency < 1%) included application site pain, skin irritation, application site dryness, application site discoloration, application site rash, application site swelling, application site erosion, acne, dermatitis allergic, and erythema.
In the LTS the most frequently reported TEAE was nasopharyngitis (in a total of 48 [10.6%] subjects), followed by the cutaneous TEAEs of sunburn (in 27 [6.0%] subjects), application site pruritus (in 23 [5.1%] subjects) and application site irritation (in 22 [4.9%] subjects). Notably, the number of subjects with cutaneous TEAEs significantly decreased over time. The TEAEs also occurred in consistent proportions between the trifarotene 50 µg/g cream-treated subjects in Safety Pool 1 and the LTS study at Week 12.
In the LTS study at Week 12, there were 75 drug-related TEAEs reported in 45 (9.9%) trifarotene 50 µg/g cream-treated subjects. The TEAEs in the General disorders and administration site conditions SOC were considered related to the study drug most often (37 subjects, 8.2%). The most commonly reported treatment-related TEAEs over the entire study- see table 26 below- were application site pruritus [21 (4.6%) subjects], application site irritation [19 (4.2%) subjects], and sunburn [8 (1.8%) subjects].

Table 27 **Summary of treatment-emergent adverse related to the study drug by System Organ Class and Preferred Term, Safety population – Safety Pool 1**

System Organ Class/Preferred Term	Safety Pool 1 (Studies 18251 and 18252)		LTS Study Week 12
	trifarotene 50 µg/g cream (N = 1220)	Vehicle Cream (N = 1200)	trifarotene 50 µg/g cream (N = 453)
Number of TEAEs related to study drug	222	21	75
Subjects with any TEAE related to study drug, n (%)	144 (11.8)	18 (1.5)	45 (9.9)
General disorders and administration site conditions	112 (9.2)	11 (0.9)	37 (8.2)
Application site irritation	79 (6.5)	2 (0.2)	15 (3.3)
Application site pruritus	28 (2.3)	9 (0.8)	19 (4.2)
Application site pain	8 (0.7)	0	2 (0.4)
Application site dryness	4 (0.3)	0	1 (0.2)
Application site discolouration	2 (0.2)	0	0
Application site erosion	2 (0.2)	0	0
Application site rash	2 (0.2)	0	0
Application site swelling	2 (0.2)	0	0
Application site erythema	1 (0.1)	0	2 (0.4)
Application site urticaria	1 (0.1)	0	0
Application site vesicles	1 (0.1)	0	0
Injury, poisoning and procedural complications	21 (1.7)	0	6 (1.3)
Sunburn	15 (1.2)	0	5 (1.1)
Drug administered at inappropriate site	3 (0.2)	0	1 (0.2)
Incorrect dosage administered	2 (0.2)	0	0
Accidental overdose	1 (0.1)	0	0
Skin and subcutaneous tissue disorders	19 (1.6)	2 (0.2)	5 (1.1)
Skin irritation	8 (0.7)	0	0
Acne	3 (0.2)	1 (0.1)	3 (0.7)
Dermatitis allergic	3 (0.2)	0	0
Erythema	2 (0.2)	0	0

Table 27 continued

System Organ Class/Preferred Term	Safety Pool 1 (Studies 18251 and 18252)		LTS Study Week 12
	trifarotene 50 µg/g cream (N = 1220)	Vehicle Cream (N = 1200)	trifarotene 50 µg/g cream (N = 453)
Eczema asteatotic	1 (0.1)	0	0
Seborrhoeic dermatitis	1 (0.1)	0	0
Skin burning sensation	1 (0.1)	0	1 (0.2)
Skin fissures	1 (0.1)	0	0
Skin hyperpigmentation	1 (0.1)	0	0
Mechanical urticaria	0	1 (0.1)	0
Rash	0	0	1 (0.2)
Infections and infestations	2 (0.2)	1 (0.1)	0
Herpes simplex	1 (0.1)	0	0
Tinea versicolour	1 (0.1)	0	0
Oral herpes	0	1 (0.1)	0
Blood and lymphatic system disorders	1 (0.1)	0	1 (0.2)
Lymphadenopathy	1 (0.1)	0	1 (0.2)
Eye disorders	1 (0.1)	0	0
Eyelid exfoliation	1 (0.1)	0	0
Eyelid oedema	1 (0.1)	0	0
Gastrointestinal disorders	1 (0.1)	0	0
Cheilitis	1 (0.1)	0	0
Psychiatric disorders	1 (0.1)	0	0
Insomnia	1 (0.1)	0	0
Vascular disorders	1 (0.1)	0	0
Flushing	1 (0.1)	0	0
Investigations	0	4 (0.3)	0
Blood creatinine increased	0	3 (0.3)	0
Liver function test abnormal	0	2 (0.2)	0
Blood bilirubin increased	0	1 (0.1)	0
Metabolism and nutrition disorders	0	1 (0.1)	0
Hyperuricaemia	0	1 (0.1)	0

Table 13 **Summary of treatment emergent adverse related to the study drug System Organ Class and Preferred Term, by quarter and overall, Safety population – Study 18250**

System Organ Class/Preferred Term	CD5789 50 µg/g cream (N = 453)				
	Q1 (M = 453)	Q2 (M = 384)	Q3 (M = 368)	Q4 (M = 351)	Overall (N = 453)
Number of TEAEs related to the study drug	80	10	11	2	103
Subjects with any TEAE related to the study drug, n (%)	46 (10.2)	8 (2.1)	9 (2.4)	2 (0.6)	57 (12.6)
General disorders and administration site conditions	**40 (8.8)**	**6 (1.6)**	**6 (1.6)**	**2 (0.6)**	**47 (10.4)**
Application site pruritus	19 (4.2)	2 (0.5)	3 (0.8)	2 (0.6)	21 (4.6)
Application site irritation	17 (3.8)	1 (0.3)	1 (0.3)	0	19 (4.2)
Application site dryness	1 (0.2)	2 (0.5)	0	0	3 (0.7)
Application site erythema	3 (0.7)	1 (0.3)	0	0	3 (0.7)
Application site pain	2 (0.4)	0	1 (0.3)	0	2 (0.4)
Application site eczema	0	0	1 (0.3)	0	1 (0.2)
Injury, poisoning and procedural complications	**6 (1.3)**	**1 (0.3)**	**2 (0.5)**	**0**	**9 (2.0)**
Sunburn	5 (1.1)	1 (0.3)	2 (0.5)	0	8 (1.8)
Drug administered at inappropriate site	1 (0.2)	0	0	0	1 (0.2)
Skin and subcutaneous tissue disorders	**5 (1.1)**	**1 (0.3)**	**0**	**0**	**6 (1.3)**
Acne	3 (0.7)	0	0	0	3 (0.7)
Rash[a]	1 (0.2)	0	0	0	1 (0.2)
Skin burning sensation	1 (0.2)	0	0	0	1 (0.2)
Skin irritation	0	1 (0.3)	0	0	1 (0.2)
Blood and lymphatic system disorders	**1 (0.2)**	**0**	**0**	**0**	**1 (0.2)**
Lymphadenopathy[b]	1 (0.2)	0	0	0	1 (0.2)
Infections and infestations	**0**	**0**	**1 (0.3)**	**0**	**1 (0.2)**
Skin candida	0	0	1 (0.3)	0	1 (0.2)

M=number of subjects at risk; N=number of subjects; Q=quarter; TEAE=treatment-emergent adverse event.

a) This event of intermittent exanthema on the face, decolette of the chest and upper trunk was reported in Subject 5549-005 on Study Day 64, on treated areas. It was mild, led to temporary discontinuation of the study drug (for 10 days) and resolved 11 days after its onset.

b) This event of lymphadenopathy was reported in Subject 5572-009 on Study Day 55. It was mild and resolved 41 days after its onset without changing the study drug dose and, it was concomitant to an extensive flare of eczema which presented with swollen cervical lymph nodes related to eczema.

Note: Events were summarized by quarter based on study day of onset date: Q1 = 1 to 89, Q2 = 90 to 179, Q3 = 180 to 269, and Q4 = 270 to 391. A subject was considered at risk if their date of last study drug application was during or after the summarized period. Events with missing onset dates were not included in quarterly summaries but were counted in the overall column.

In Safety Pool 1 and the LTS study, local tolerability parameters (erythema, scaling, dryness, and stinging/burning) were evaluated at each scheduled visit (Baseline, Week 1, Week 2, Week 4, Week 6, Week 8, and Week 12 in the placebo-controlled studies 18251 and 18252 and at Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 20, Week 26, Week 38, and Week 52 for the LTS study

Table 31 Summary of local tolerability parameters worsened from Baseline on the face (final and worst post-Baseline), Safety population – Safety Pool 1

	trifarotene 50 µg/g cream (N = 1220)	Vehicle Cream (N = 1200)
Erythema		
Final, n	1214	1194
Mild (1)	257 (21.2)	103 (8.6)
Moderate (2)	88 (7.2)	22 (1.8)
Severe (3)	13 (1.1)	1 (0.1)
Worst Post-Baseline, n	1214	1194
Mild (1)	371 (30.6)	251 (21.0)
Moderate (2)	345 (28.4)	81 (6.8)
Severe (3)	75 (6.2)	10 (0.8)
Scaling		
Final, n	1214	1194
Mild (1)	263 (21.7)	107 (9.0)
Moderate (2)	90 (7.4)	18 (1.5)
Severe (3)	7 (0.6)	2 (0.2)
Worst Post-Baseline, n	1214	1194
Mild (1)	455 (37.5)	283 (23.7)
Moderate (2)	329 (27.1)	71 (5.9)
Severe (3)	59 (4.9)	4 (0.3)
Dryness		
Final, n	1214	1194
Mild (1)	300 (24.7)	153 (12.8)
Moderate (2)	88 (7.2)	18 (1.5)
Severe (3)	10 (0.8)	2 (0.2)
Worst Post-Baseline, n	1214	1194
Mild (1)	473 (39.0)	357 (29.9)
Moderate (2)	360 (29.7)	81 (6.8)
Severe (3)	58 (4.8)	9 (0.8)
Stinging/burning		
Final, n	1214	1194
Mild (1)	167 (13.8)	50 (4.2)
Moderate (2)	51 (4.2)	12 (1.0)
Severe (3)	13 (1.1)	1 (0.1)
Worst Post-Baseline, n	1214	1194
Mild (1)	432 (35.6)	190 (15.9)
Moderate (2)	250 (20.6)	45 (3.8)
Severe (3)	72 (5.9)	6 (0.5)

N=number of subjects; ISS=integrated summary of safety.

Note: Percentages were calculated out of the number of subjects in each category. A subject's final data was the last data observed during the post-Baseline period.

These local reactions are well-known common to very common superficial cutaneous irritations during topical retinoid therapy and usually mild to moderate in severity, resolving within the first couple of weeks.

The absolute number of reported *serious* TEAEs was the same for trifarotene 50 µg/g cream and Vehicle Cream; 7 serious TEAEs were reported by 6 (0.5%) subjects in each treatment group. None of the serious TEAEs were considered to be related to study drug. Except for the serious TEAEs of ligament sprain and facial bones fracture, all these events resolved during the study. Please refer to table 29 below.

Table 29 Summary of serious treatment-emergent adverse events by System Organ Class and Preferred Term, Safety population – Safety Pool 1

System Organ Class/Preferred Term	trifarotene50 µg/g cream (N=1220)	Vehicle Cream (N=1200)
Number of serious TEAEs	7	7
Subjects with any serious TEAE, n (%)	6 (0.5)	6 (0.5)
Injury, poisoning and procedural complications	3 (0.2)	0
Facial bones fracture	1 (0.1)	0
Ligament sprain	1 (0.1)	0
Procedural dizziness	1 (0.1)	0
Infections and infestations	2 (0.2)	3 (0.3)
Cellulitis	1 (0.1)	0
Infectious mononucleosis	1 (0.1)	0
Appendicitis	0	1 (0.1)
Atypical pneumonia	0	1 (0.1)
Sinusitis	0	1 (0.1)
Psychiatric disorders	1 (0.1)	1 (0.1)
Suicide attempt	1 (0.1)	1 (0.1)
Major depression	1 (0.1)	0
Congenital, familial and genetic disorders	0	1 (0.1)
Hereditary angioedema	0	1 (0.1)
Renal and urinary disorders	0	1 (0.1)
Urinary tract infection	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (0.1)
Asthma	0	1 (0.1)

ISS=integrated summary of safety; MedDRA=Medical dictionary for regulatory activities; N=number of subjects; TEAE=treatment-emergent adverse events.
Note: Adverse events were coded using MedDRA version 18.0. System organ classes were sorted by frequency in the trifarotene 50 µg/g cream 50 µg/g group. Preferred terms were sorted by frequency in the trifarotene 50 µg/g cream 50 µg/g cream treatment group within each system organ class.

A total of 12 *serious* TEAEs were reported by 10 (2.2%) subjects in the LTS study. All SAEs resolved during the study expect Crohn's disease (in Subject 5189-004). None were assessed by the Investigators as related to the study drug.
No *deaths* were reported in any of the studies.
Laboratory findings: Overall, there were no clinically meaningful changes in mean values from Baseline in hematology or blood chemistry parameters for subjects in Safety Pool 1 or the long-term Study 18250.
For direct bilirubin, a shift in reference category at the last post-Baseline visit compared with the Baseline visit was observed in 69 of 413 subjects for direct bilirubin. These changes were not associated with any clinical sign or symptom and/or changes in associated laboratory parameters and were considered as non-clinically significant. There were 5 subjects in the CD5789 50 mikrog/g cream group who had clinically significant urinary results that included out-of-range urinary results for leukocytes or proteins at Week 12. Three of these subjects were considered TAEs not related to the study treatment and in two subjects these findings were not recorded as TEAEs.

Safety in children aged 9-11 years old
There were no TEAEs leading to discontinuation in the 9 to 11 years old subgroup population No deaths occurred. No SAEs occurred in the 9 to 11 years of age. This is reassuring. It is noted though that a total of 4 (21.1%) subjects ages 9 to 11 years old in the trifarotene cream

treatment arm reported 5 related-TEAEs while for the 12 -17 years of age had 123 TEAEs related to trifarotene cream in 79 (13.7%) subjects and for the ≥ 18 years of age and older there were a total of 94 TEAEs with 61 (9.7%) subjects with TEAEs related to trifarotene cream. However, as the total number of patients aged 9 to 11 years old reporting related-TEAS is very limited (4), these specific figures expressed as percentages between the grown-up population and patients ages 9 to 11 years old are difficult to conclude on and data presently considered insufficient.
Safety in special populations: Studies assessing the effect of trifarotene 50 μg/g cream in special populations (subjects with hepatic and renal impairments) have not been conducted by the Sponsor. The low systemic exposures observed in clinical studies make it unlikely that new safety issues would be anticipated with the use of trifarotene 50 μg/g cream in these special patient populations. There was no meaningful impact of age, gender, race, or skin phototype on local facial and truncal tolerability profiles though interpretation of the data was limited due to the small sample size in some of the subgroups in Safety Pool 1. Overall, in the long-term Study 18250, in the age, gender, age and gender, race, ethnicity, and skin phototype subgroups, the frequency of TEAEs was similar to that observed in the overall SAF population.

The applicant did not conduct specific evaluations of extrinsic factors such as food, alcohol, or tobacco consumption during the clinical development program for trifarotene 50 μg/g cream.

In a randomised, double-blind vehicle controlled, parallel group thorough *QTc study* in healthy subjects, the ECG results showed that trifarotene 100 microg/g gel did not have an effect on cardiac repolarization.
Four studies were conducted that evaluated *phototoxicity* (Study 40208), cumulative irritation potential (Study 40209), *photosensitization* potential (Study 40189), and *sensitization* potential (Study 40190). An additional *cumulative irritation* study was conducted with CD5789 gel (Study 40055E). No potential for sensitization, phototoxicity, and photosensitization was observed in these studies. Still a caution of excessive exposure to sunlight, including sunlamps or phototherapy during the treatment and use of sun protection (products, clothing) is recommended. A dose-dependent cumulative irritancy potential was observed in Study 40209.

Twelve pregnancies were reported since the beginning of the development program despite a highly effective contraception method being required per protocol. This resulted in 5 miscarriages, 4 normal deliveries, 1 elective abortion and 2 pregnancies with an unknown outcome. All miscarriages were considered as not related to the study drug considering the limited systemic absorption of the product, the risk factors of the study subject (e.g., concomitant genital infection and/or previous gynecological history) and/or the concomitant contraceptive treatment. Due to the low number and the presence of confounding factors, the number of miscarriages is difficult to interpret. Trifarotene cream should not be used during pregnancy. The potential teratogenicity of topical retinoids has recently been thoroughly reviewed in an article 31 procedure by EMA. The submitted finally proposed SmPC is in line with the outcome of the article 31 procedure completed by EMA in March 2018 on updated measures for pregnancy prevention during retinoid use. No data are available regarding the presence of trifarotene in human milk.

Safety related to drug-drug interactions and other interactions: The pharmacokinetic interaction potential of topically administered trifarotene, either as victim or perpetrator, is expected to be low -please refer to section IV.2 Pharmacokinetics for a detailed description. However, as during the development studies, neither topical nor systemic anti acne preparations were allowed, there is no clear knowledge about this risk.

Discontinuation due to AES
A total of 26 TEAEs leading to study drug discontinuation were reported by 24 (2.0%) subjects in the trifarotene 50 microg/g cream group and 2 TEAEs leading to study drug discontinuation were reported by 2 (0.2%) subjects in the Vehicle Cream group in safety pool 1. TEAEs that led to study drug discontinuation were generally of cutaneous nature, including skin irritation, and were considered to be related to study drug (qualified as AESIs by protocol-specified definition). This is not a surprising finding for a topical retinoid. Still, the total number of study drug discontinuation is not very high.

Proposals for post authorisation follow up (post marketing surveillance-
Please refer to the RMP section for a detailed description. Routine Pharmacovigilance activities are proposed. For follow-up reports of pregnancies and lactation, specific follow-up questionnaire are used as part of routine pharmacovigilance. No additional Pharmacovigilance activities are proposed to be conducted with Aklief 50 microgram/g cream.

Conclusions on clinical safety
The active substance, trifarotene is a retinoid and a new chemical entity for the treatment of acne. A thin layer of Aklief cream is applied to the affected acne areas of the face and/or trunk once a day. In total the Applicant conducted 31 clinical studies, in various indications, in the trifarotene development program with a total of 4825 subjects were enrolled in this program. Twelve clinical studies were related to acne vulgaris.
The main safety information was derived from the 2 pivotal studies where acne patients received Aklief- trifarotene 50 µg/g cream- once daily for 12 weeks and in a long-term open label safety study (LTS) of one year. These data were pooled to one primary safety pool (safety pool 1 + LTS). In Safety Pool 1, there were 331 (27.1%) subjects in the trifarotene 50 µg/g cream group who reported 587 TEAEs compared with 240 (20.0%) subjects in the Vehicle Cream group who reported 338 TEAEs. Of the 331 trifarotene 50 µg/g cream-treated subjects who had any TEAE in Safety Pool 1, 144 subjects were considered to have a TEAE related to study drug, while 18 of 240 subjects in the vehicle cream group had a TEAE related to study drug.
In the long-term study overall, 218/453 (48.1%) subjects reported 468 TEAEs. Of these, 154/453 (34.0%) subjects reported TEAEs during the first quarter of the study. As expected, the majority of adverse events of the pivotal studies was dermatological. There was no active comparator study submitted so it is not possible to evaluate the extent of local skin reactions with other approved retinoids. However, overall data of safety pool 1 demonstrate cutaneous adverse reactions to be 10-11% more frequent in the trifarotene group compared to the vehicle group, a figure that is not unreasonably high considering previous experiences of other topical retinoids. The most common dermatologic PTs were application site irritation, application site

pruritus a and sunburn occurring in a frequency > 1 %. A slightly better local tolerability profile was observed on the trunk compared to the face.

In the long-term 12-month study these events occurred mostly in the first 3 months, with the incidence decreasing in the latter periods of the study. This is also in line with previous experience of topical retinoids and local adverse reactions; tolerability improves some weeks after initiation of treatment. Serious adverse events occurring during the phase III studies and the long-term study were all considered unrelated to study treatment and there were no deaths reported. The LTS of 52 weeks in which 453 patients were exposed to trifarotene is considered to sufficiently cover the likelihood of detecting any common long-term adverse reactions related to this topical therapy. A total of 9 severe TEAEs were reported in 9 (2.0%) subjects, of which 3 events in 3 subjects were considered related to the study drug by the investigator (i.e. application site irritation, application site pruritus, and application site erythema) during the LTS. Treatment with trifarotene is contraindicated during pregnancy and in women planning a pregnancy. The potential teratogenicity of topical retinoids has recently been thoroughly reviewed in an article 31 procedure by EMA and relevant wordings in the submitted PI concerning trifarotene and pregnancy are in line with the outcome of the article 31 procedure completed by EMA in March 2018 should be followed.
To conclude, overall, the safety documentation presented for trifarotene 50 μg/g cream is considered adequate for ages 12 years and older.

IV.5 Risk Management Plans

The MAH has submitted a risk management plan version 1.3 with data lock point 14 March 2018 and signed off 09December 2019, 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 Aklief (trifarotene 50 μg/g) cream.

The submitted RMP includes part I with a product overview including information that trifarotene is a terphenyl acid derivative with retinoid-like activity, intended for the cutaneous treatment of acne vulgaris of the face and/or the trunk in patients from 12 years of age and older, when many comedones, papules and pustules are present.

Safety Specification
Part II comprises a section on epidemiology of the indication(s) and target population(s) and a summary of therapeutic recommendations.
The RMP also includes Part II: Module SII - Non-clinical part of the safety specification.

Module SIII - Clinical trial exposure
A total of 4825 subjects were enrolled in the trifarotene clinical development program. Thirty-one (31) studies were conducted during the development program. Twelve (12) of the 31 studies were conducted in healthy subjects, 12 were conducted in subjects with acne vulgaris, and 7 were conducted for other indications. Of the 4825 subjects, 3662 subjects were exposed to various formulations of trifarotene, either alone or in association. Out of these 3662 subjects exposed to trifarotene, 1932 were exposed to the to-be-marketed formulation (i.e., trifarotene 50 μg/g cream).

Table SIII. 1: Duration of exposure

Duration of exposure (person time)		
Cumulative for all indications (person time)	**Patients**	**Person time (person-months)**
<1 m	2124	9057.83
1 to <3 m	463	4700.33
3 to <6 m	369	4387.07
≥6 m	326	3968.53
Total person time for all indications	10223.17 person-months	

Cumulative for Acne Vulgaris (person time)	**Patients**	**Person time (person-months)**
<1 m	1760	8227.03
1 to <3 m	462	4687.97
3 to <6 m	368	4374.70
≥6 m	325	3956.17
Total person time for acne vulgaris indication	8658.23 person-months	

Relevant sections relating to duration of exposure, age and gender, dose, and ethnic group are included.

Summary of safety concerns

Summary of safety concerns	
Important identified risks	- None
Important potential risks	- Teratogenicity: safety during pregnancy
Missing information	- Use longer than 1 year - Use with concomitant acne medications

Pharmacovigilance Plan

No additional pharmacovigilance activities are proposed. Only routine pharmacovigilance is suggested by the applicant. This is endorsed.

Part IV: Plans for post-authorisation efficacy studies

It is not planned to initiate any PAES (Post Authorisation Efficacy Study).

Risk minimisation measures

Routine risk minimisation is suggested including the use of a targeted follow-up questionnaire concerning pregnancy and lactation; no additional risk minimisation activities are proposed by the applicant, which is endorsed

Summary of the RMP

The submitted Risk Management Plan, version 1.3 with data lock point 14 March 2018 and signed off 09 December 2019, is considered acceptable.

Routine pharmacovigilance activities are considered sufficient. There is no need of additional risk minimisation activities. The summary of the RMP presented within the submitted RMP document includes a summary consistent with the information presented in the proposed RMP part II modules SVII, SVIII and RMP parts III, IV and V.

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

Importance of favourable and unfavourable effects

The significantly superior efficacy of Aklief compared with vehicle cream on acne vulgaris lesions both on the face and trunk in the same individual is considered a favourable effect. The size of the obtained efficacy level (active cream minus vehicle cream) when evaluated at week 12 (end of treatment in the pivotal Phase 3 studies) is considered modest. However, the International Dermatology Consensus Groups has determined a threshold effect size of 10% to be clinically relevant for the treatment of facial and truncal acne. This level of efficacy was obtained in the performed pivotal studies, and has been accepted by the RMS.
Moreover, the clinical efficacy of Aklief increased over time which is considered an important favourable effect. Overall success rate (IGA and PGA success rate in the same subject) increased considerably up to 52 weeks of treatment, which indicates a clinically relevant efficacy when both face and trunk are involved and treated in the same subject.

The safety profile of trifarotene 50 μg/g cream is dominated by local skin reactions. This is not unexpected considering previous experiences of other topical retinoids and the low systemic exposure observed after administration Aklief cream. The incidence of these local reactions are decreasing in the latter periods of the long-term study, this also in line with previous experience of topical retinoids and local adverse reactions; tolerability improves some weeks after initiation of treatment. Serious adverse events occurring during the Phase 3 studies and the long-term study were all considered unrelated to study treatment and there were no deaths reported. The potential teratogenicity of topical retinoids has recently been thoroughly reviewed in an article 31 completed by EMA in March 2018. Relevant wordings are included in the Product Information for trifarotene in relation to pregnancy.

Balance of benefit and risks

The pivotal Phase 3 studies meet their co-primary and co-secondary endpoints; that several subjects could achieve clear or near clear results on their acne vulgaris lesions on the face and trunk and get a reduction in inflammatory and non-inflammatory lesions. The safety profile of trifarotene 50 μg/g cream is dominated by local skin reactions, the incidence of those decreasing by time. This is in line with previous experience of other topical retinoids. There

were no serious adverse events considered drug related, and no deaths reported within the primary safety pool.

Overall, the efficacy and safety documentation presented for Aklief is considered adequate.

The benefit/risk ratio is considered positive and Aklief, 50 μg/g, cream, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Aklief, 50 μg/g, cream, was positively finalised on 2019-12-18.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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