25 August 2025
EMA/292571/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Winlevi

International non-proprietary name: Clascoterone

Procedure No. EMEA/H/C/006138/0000

Note

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

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List of abbreviations

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AHEG	Ad hoc expert group
ANCOVA	analysis of covariance
API	active pharmaceutical ingredient
AR	androgen receptor
ATC	Anatomical Therapeutic Chemical
ASR	Application site reaction
AUC	area under the plasma concentration curve
$AUC_{ss,0-12h}$	area under the plasma concentration curve from time 0 to 12 hours
BID	twice daily
BMI	body mass index
BOCF	Baseline Observation Carried Forward
CRF	Case Report Form
CRO	Contract Research Organization
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximal concentration
CST	Cosyntropin stimulation test
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of study
FDA	Food and Drug Administration
HPA	Hypothalamic-pituitary-adrenal
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
ILC	Inflammatory Lesion Count
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
LEC	Local Ethics Committee
LTF	Long term follow-up
LOCF	Last Observation Carried Forward
LSR	Local Skin Reaction
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NCT	National Clinical Trial
NILC	Non-Inflammatory Lesion Count
OTC	Over-the-Counter
P1	Primary efficacy endpoint 1
P2	Primary efficacy endpoint 2
P3	Primary efficacy endpoint 3
PK	Pharmacokinetic
PP	Per-Protocol
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
QD	Once daily

S1	Secondary efficacy endpoint 1
S2	Secondary efficacy endpoint 2
S3	Secondary efficacy endpoint 3
S4	Secondary efficacy endpoint 4
SAE	serious adverse event
SAS	Statistical Analysis Software
SOC	System Organ Class
SE	standard error
SMQ	standardized MedDRA query
SOC	system organ class
SPA	Special Protocol Assessment
STD	standard deviation
TEAE	treatment-emergent adverse event
TLC	Total Lesion Count
UPT	Urine Pregnancy Test
USAN	United States Adopted Name
VEH	Vehicle
WOCBP	Women of Childbearing Potential

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Cassiopea S.p.A. submitted on 6 October 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Winlevi, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2022.

The applicant applied for the following indication *'Winlevi is indicated for the topical treatment of acne vulgaris in adults, and adolescents aged 12 to 18 years.'*.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0076/2023 on the agreement of a paediatric investigation plan (PIP) and on the granting of a class waiver.

At the time of submission of the application, the PIP P/0076/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0076/2023.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.4.2. New active substance status

The applicant requested the active substance Clascoterone contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	6 October 2023
The procedure started on	26 October 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 January 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	26 January 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 February 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	8 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 November 2024
The CHMP agreed on a second list of outstanding issues to be sent to the applicant on	12 December 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 February 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	11 March 2025

to all CHMP and PRAC members on	
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	21 March 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	25 March 2025
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the Outstanding Issues following Oral explanation on	9 April 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Winlevi on	25 April 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	25 April 2025

1.7. Steps taken for the re-examination procedure

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

Rapporteur: Maria Grazia Evandri Co-Rapporteur: Edward Laane

The Applicant submitted written notice to the EMA, to request a re-examination of Winlevi CHMP opinion of 25 April 2025, on	6 May 2025
The CHMP appointed Maria Grazia Evandri as Rapporteur and Edward Laane as Co-Rapporteur on	22 May 2025
The PRAC Rapporteur Amelia Cupelli was appointed on	22 May 2025
The Applicant submitted the detailed grounds for the re-examination on	27 June 2025
The re-examination procedure started on	28 June 2025
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP and PRAC members on	15 July 2025
The CHMP Co-Rapporteur's assessment report was circulated to all CHMP and PRAC members on	15 July 2025
Expert group was convened to address questions raised by the CHMP on The CHMP considered the views of the Expert group as presented in the minutes of this meeting	25 July 2025
The PRAC had a plenary meeting on 31 July 2025 to agree on the PRAC Assessment Overview and Advice to CHMP. The PRAC outcome was adopted via written procedure on	5 August 2025

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the detailed grounds for re-examination to all CHMP and PRAC members on	7 August 2025
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	25 August 2025
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation on	25 August 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Acne is a chronic inflammatory skin condition of pilosebaceous glands that typically begins at puberty and may continue through adulthood with flares often coinciding with increasing serum androgens[1]. It is one of the most common dermatological disorders worldwide (AAD, 2019), with its incidence and severity influenced by genetics and environment (Arora, 2011). Acne vulgaris affects approximately 9% of the population worldwide and approximately 85% of those aged 12 to 24 years (Eichenfield, 2021). Acne is often the first sign of puberty in boys and girls, and this onset is thought to be secondary to hormonal surges leading to increased sebum production (Goldberg, 2011). Although the prevalence of acne is highest in adolescents and young adults, it can also occur in younger children. However preadolescent acne is a rare disease, affecting only 3.5% of patients (Frénard, 2021).

Endogenous androgens, particularly testosterone and dihydrotestosterone, mediate excess sebum production in the skin, and stimulate abnormal keratinisation and desquamation, leading to obstruction of the pilosebaceous duct that allows *Cutibacterium acnes* (formerly *Propionibacterium acnes*) to proliferate (Dréno, 2018; Lai, 2012). Proinflammatory mediators are released in response, triggering localised inflammation and exacerbation of acne lesion eruption (Lai 2012).

2.1.2. Epidemiology

The worldwide prevalence of acne vulgaris is 20.5%, depending on the study methodology and definitions used. Although the prevalence tends to decrease with age, a substantial number of adults, particularly women, have acne vulgaris.

The self-reported prevalence of acne is high in European adolescents and young adults.

According to the Global Burden of Disease Study, acne vulgaris is the eighth most common skin disease worldwide. The prevalence of acne vulgaris varies among different countries and age groups, with estimates ranging from 35 % to close to 100 % of adolescents experiencing acne vulgaris at some point (Vasam et al, 2023).

2.1.3. Aetiology and pathogenesis

Genetics, environmental variables (temperature, pollution, humidity, sun exposure, mineral oils/halogenated hydrocarbons), nutrition, hormonal state, stress, smoking, comedogenic medicines such as androgens, halogens, corticosteroids, bacteria, and cosmetics may cause, worsen, or exacerbate acne vulgaris. Acne vulgaris typically causes discomfort, emotional suffering, deformity, and possibly permanent scars. In addition to this, patients may have feelings of anxiety and embarrassment, both of which contribute to a mentally depressed state. Due to the aforementioned exposome factors, the pathogenesis of acne vulgaris is multifactorial. The excess production of sebum, hyper proliferation of the bacteria colonisation known as

[1] Arora, 2011; Taylor, 2011

Cutibacterium acnes (previously known as *Propionibacterium acnes*), abnormal hyperkeratinisation of the pilosebaceous follicles, and inflammatory mechanisms are the four primary causes for acne (Vasam et al, 2023).

A number of risk factors for vulgaris have been proposed, including genetic, hormonal and lifestyle factors such as diet and smoking. With respect to lifestyle, there is evidence of an association between a Western diet, in particular high glycaemic index foods, and acne. However, the relationship between acne and smoking remains unclear. Relatively few studies have specifically evaluated the effect of lifestyle factors on acne in European populations.

The data suggest the main risk factor for developing acne is heredity. An association between self-reported acne vulgaris and chocolate consumption, and an apparent inverse relationship with smoking, need to be confirmed by additional studies (Wolkenstein, JEADV 2018, 32, 298-306).

2.1.4. Clinical presentation, diagnosis

Acne vulgaris is the most prevalent form of acne, accounting for 99% of all acne cases. It is differentiated by two types of lesions: non-inflammatory, open and closed comedones, as well as inflammatory papules, pustules, nodules, and cysts. The comedones are of two types: a comedone that is closed is a whitehead, while another that is open is a blackhead type (Vasam et al, 2023).

Acne vulgaris nearly always affects the face (99 %), the back (60 %) and the chest (15 %). Seborrhoea is a frequent feature. Scarring and post inflammatory hyperpigmentation are frequently seen clinical signs in acne.

Its clinical picture embraces a spectrum of signs, ranging from mild comedonal acne, with or without sparse inflammatory lesions, mild to moderate papulopustular, severe papulopustular, moderate nodular, and severe nodular/ conglobate acne (EDF guidelines, 2016).

2.1.5. Management

The primary objective is to manage and treat existing lesions by controlling the sebum secretion, the abnormal hyperkeratinisation of the pilosebaceous follicles and the *Cutibacterium* infection. As a result, the main treatment options for acne include anti-inflammatory and antibacterial drugs administered either through topical or systemic or oral route of administration and by physical way by using non-drug treatments such as optical therapy, cryotherapy, comedones extraction or cyroslush therapy.

Numerous formulations of topical preparations include creams, gels, lotions, solutions, and washes. Mild to moderate acne is typically treated with topical medicines. Skin irritation is a common side effect of topically administered anti-acne medications. Topical treatment may last 6–8 weeks or continue for many years (M. Vasam et al, 2023).

2.2. About the product

Clascoterone, referred to as CB-03-01 and cortexolone-17α-propionate throughout development, is a new chemical entity, acting as an androgen receptor inhibitor with claimed local anti-androgenic activity.

The proposed indication for clascoterone 1% cream is the treatment of acne vulgaris in patients from 12 years of age and older. The proposed recommended dosing regimen is to apply a thin uniform layer of cream (1 g of cream) twice per day, in the morning and the evening, over the entire area prone to acne.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a cream containing 10 mg/g of clascoterone as active substance.

Other ingredients are: cetyl alcohol, citric acid monohydrate (E330, for pH-adjustment), glycerol monostearate 40-55 type I, liquid paraffin, polysorbate 80, propylene glycol (E1520), purified water, disodium edetate, all-*rac*-α-tocopherol (E307).

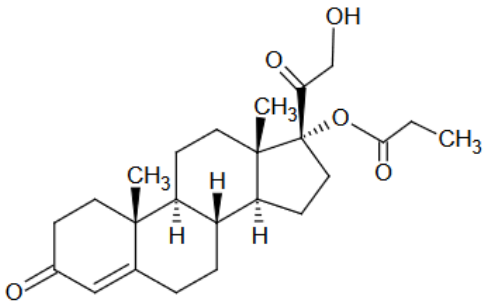
The product is available in an epoxy-lined aluminium tube with a polypropylene screw cap.

2.3.2. Active substance

General information

The chemical name of clascoterone is cortexolone-17α-propionate corresponding to the molecular formula $C_{24}H_{34}O_5$. It has a molecular mass 402.5 g/mol and the structure depicted in Figure 1.

Figure 1: clascoterone active substance structure



The chemical structure and solid-state properties of clascoterone were elucidated by the ASMF holder using UV spectroscopy, nuclear magnetic resonance spectroscopy (NMR) (^{1}H, ^{13}C, HMBC, HMQC and COSY), infrared spectroscopy (IR), mass spectrometry (MS), differential scanning calorimetry (DSC) and X-ray powder diffraction.

The active substance is a white or almost white powder, practically insoluble in water, very soluble in alcohols and soluble in ethanol /propylene glycol (1:1).

Clascoterone exhibits stereoisomerism due to the presence of 6 chiral centres. The absolute stereoconfiguration of the steroid skeleton of the active substance originates in the starting material which is obtained from phytosterols. A control by specific optical rotation is included in the active substance specifications.

Polymorphism has been observed for clascoterone. The controlled manufacturing conditions ensure that the desired form is consistently manufactured. The desired polymorphic form is controlled by XRPD at release and during shelf life

Manufacture, characterisation and process controls

A single manufacturer of active substance is used.

Clascoterone is synthesized in three main steps, using a well-defined starting material with acceptable specifications. The manufacturing steps include three chemical transformations and one purification. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

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

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

A risk assessment was conducted to determine which process solvents should be tested in the active substance. Only solvents, used in the last step, are routinely analysed for batch release. The carryover of impurities coming from the starting material is discussed and considered satisfactory.

Potential and actual impurities have been assessed for mutagenic potential as described the ICH M7. Impurities classified as Class 2 mutagenic impurities are controlled according to ICH M7 Option 4. It has been experimentally demonstrated that Class 2 impurities are routinely not present at or above 30% of the acceptable intake limit (30 ppm). The manufacturing process development is satisfactorily described in the restricted part of the ASMF.

The active substance is packaged in a container closure system which complies with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification includes tests for description (observation), identification (IR, X-ray), specific optical rotation (Ph. Eur.), melting point (capillary, Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC) and microbiological analyses (Ph. Eur.; also includes *Burkholderia cepacia complex* (BCC) tested in line with USP).

Limits for specified impurities are set.

During the procedure, the limit for one specified impurity was tightened based on historical data; the limit value is justified by the fact that the specified impurity is also a metabolite of clascoterone.

During the procedure, the CHMP did not agree with the proposed specification limit for one specified impurity as it was considered mutagenic based on the interpretation of non clinical data, resulting in a major objection (MO). In response the applicant provided further data and argumentation and agreed to tighten its limit. Such limit is therefore based on the non clinical assessment and the impurity is considered qualified at the proposed limit and its control strategy in the active substance can be accepted.

Limits for other impurities (individual and total) are in compliance with the ICH Q3A.

Residual solvent limits are in compliance with ICH Q3C.

A routine test for *Burkholderia cepacia* complex is included in the active substance specifications to mitigate a potential contamination risk.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented and it is satisfactory.

Batch analysis from production batches of active substance, manufactured at the proposed site, were provided. The results were within the specification limits and consistent from batch to batch.

Stability

Stability data from batches of the active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (5°C) and for up to 6 months under accelerated conditions (25 °C/60% RH), according to the ICH guidelines, were provided.

The following parameters were tested during stability studies: description, identification (IR, x-ray), specific optical rotation, melting point, loss on drying, related substances, and assay. The obtained results showed no significant changes, with a little or no variability or trending in any of the parameters tested at both storage conditions.

A photostability study was performed in line with ICH Q1B as part of the forced degradation study. Results under stress conditions, namely photostability (not less than 1.2 million lux hours), stability in solution, thermal stress, temperature and humidity, oxidative degradation, acid degradation, alkali degradation were also provided on one batch of the active substance to demonstrate the stability indicating nature of the analytical methods.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months when stored in the proposed container in well-closed containers protected from light at 5ºC ± 3ºC.

2.3.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a white to almost white homogeneous cream

Pharmaceutical development aimed at obtaining a semisolid formulation suitable for topical application of the active substance with adequate absorption at the administration site, also taking into consideration the intended patient population, proposed as adolescents over 12 years of age, and adults.

Solubility and stability of the active substance in different vehicles was investigated.

The selection and concentration of each excipient in the final formulation was based on the physicochemical characteristics of each excipient and their known properties in topical formulations. The functionality related characteristics of all the excipients were satisfactorily discussed. All excipients are well known pharmaceutical

ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and above. The compatibility of the active substance with the excipients has been evaluated and it is supported by stability data.

The formulation used during pivotal phase III clinical studies is the same as that intended for marketing.

No significant changes were detected demonstrating the stability of the formulation, throughout its proposed shelf-life including after opening. An *in vitro* release test was also used to indirectly evaluate the physiochemical and performance characteristics of the cream. The test results confirmed that the finished product does not change its characteristics over the shelf life.

The suitability of the proposed finished product formulation was also demonstrated with regards to the proposed patient population.

During the procedure the applicant was requested to define the quality target product profile (QTPP) and critical quality attributes (CQAs) of the finished product. The physical characterization of the finished product was not considered complete by CHMP as viscosity had not been discussed and the associated specification limit was not considered justified resulting in a MO. In response, the applicant provided additional information on the rheological characterisation of the finished product. The submitted rheograms, generated in line with the Ph. Eur. viscosity test, further support the equivalence between the clinical and commercial batches. The viscosity method development was included and the analytical method updated. The revised method and associated specification provide assurance of the rheological behaviour of the finished product and is considered acceptable. The MO is considered as satisfactorily resolved.

The manufacturing process is a conventional manufacturing process for an oil-in-water cream. The *in vitro* release testing confirmed that, the introduction of new equipment, used to manufacture a scaled-up batch size and the concurrent optimisation of the process parameters did not impact the performance of the finished product.

The primary packaging is an epoxy-lined aluminum tube, containing 10 g, 30 g or 60 g of cream, blind-ended, with a polypropylene screw cap closure. The materials comply with EC requirements. The choice of the container closure system has been validated by an extractables and leachables study and stability data. No leachables were identified that need to be controlled in the finished product specifications. The container closure system is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured, packaged, tested, and released by one manufacturer, Cosmo S.p.A., Milan, Italy. Satisfactory documentation confirming GMP compliance has been provided. The manufacturing process consists of five main steps. During the procedure, it has been demonstrated that the manufacturing process can be considered as standard. Two batch sizes are proposed.

Manufacturing process and equipment, as well as its control have been adequately described. Critical steps and IPCs are presented. The critical process parameters are controlled. The proposed bulk hold time for both proposed batch sizes is supported by physicochemical and microbiological data.

The manufacturing process has been validated using three batches for each of the two proposed bulk batch sizes. It has been demonstrated that the manufacturing process is capable of producing the finished product

of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release and end of shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), identification (HPLC and UV), identification polymorphic form (IR), assay (HPLC), related substances (HPLC), pH (Ph. Eur.), viscosity (Ph. Eur.), globular size (microscopic examination), particle size (microscopic examination), tube filling weight (in-house), microbiological analysis (Ph. Eur.) and *Burkholderia cepacia complex* (USP).

The tests for identification of polymorphic form, globular size, particles size and tube filling weight were added at the request of CHMP. During the procedure, the limits for specified impurities were tightened based on batch data. The proposed limits for specified impurities are acceptable based on non-clinical data.

The limit for any unspecified substance is in compliance with the ICH Q3B guideline.

As part of the response to the MO raised on the rheological properties of the finished product, an additional test for viscosity (pharmacopeial) was added to the specification. The specification limits have also been updated. The test for *Burkholderia cepacia* complex is included due to the potential risk of contamination of the non-sterile, water-based formulation.

The finished product specifications are considered adequate for this type of pharmaceutical form. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The potential presence of elemental impurities in the finished product has been assessed following a risk based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on nine batches were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for both batch sizes confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from production scale batches of finished product, covering both batch sizes and all proposed commercial packaging configurations stored for up to 36 months under long term conditions (5 ºC) and for up to six months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In-use stability studies on one batch confirmed that the product is stable from a chemical, physical and microbiological point of view, when the tube is opened and the product administered, for up to 6 months at 25 °C/60% RH. Based on the duration of therapy for the highest strength (60 g), a shelf-life of 1 month from the opening of the container is proposed.

Stress test studies (thermal, acid basic and oxidative degradation) demonstrated that the assay and related substances method are stability indicating.

A photostability study was also conducted in accordance with ICH Q1B.

Samples were tested in line with the shelf-life specifications.

A significant increase in one of the specified impurities was observed at under accelerated conditions and in the in-use study. However, levels formed remained below the updated limit Based on available stability data, the proposed shelf-life of 36 months (discarde the unused product 1 month after first opening) and the following storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable: Prior to dispensing: store in a refrigerator (2 °C - 8 °C). Once dispensed to patient: before opening, store in a refrigerator (2 °C – 8 °C). After the first opening, do not store above 25 °C. Do not freeze.

Adventitious agents

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

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure additional information on the viscosity properties of the finished product was provided and the analytical methods and specifications were updated accordingly. The results of tests carried out indicate the consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

A comprehensive nonclinical testing program was conducted to assess the pharmacologic, pharmacokinetic, and toxicologic properties of the molecule when administered both topically and systemically. As appropriate, and as indicated throughout the Nonclinical Summary, safety pharmacology, pharmacokinetic, and toxicology studies have been conducted in compliance with Good Laboratory Practice (GLP) ICH/EU guidelines. Studies examining primary and secondary pharmacodynamics, as well as safety pharmacology, have been conducted on clascoterone using various in *vitro* methods and nonclinical animal models. Where specific studies were not conducted as part of the nonclinical development program (e.g., juvenile toxicity and phototoxicity studies), this has been discussed.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The *in vitro* primary pharmacology studies showed that clascoterone exhibited high affinity for the human androgen receptor although being at least 10-fold less potent than the methyltrienolone selective ligand; and clascoterone inhibited DHT (dihydrotesterone)-induced AR transcriptional activity that leads to lipid synthesis as part of the cascade that produces sebum.

Clascoterone, administrated by topical route on the flank organ of the golden Syrian hamster, exhibited marked anti-androgenic activity; however, the effects from topical administration of the 1% clinical cream formulation were shown to be limited to the site of application.

2.4.2.2. Secondary pharmacodynamic studies

CB-03-01 did not exhibit off-target binding in a screening assay using 54 different receptors, did not affect binding at the Gonadotropin-Releasing Hormone (GnRH) receptor, and was not estrogenic in immature female mice. Using splenocytes from young castrated male rats treated with CB-03-01 and testosterone propionate (TP) or TP alone, the immunosuppressive effects of TP, as determined following *ex vivo* incubation with different mitogens, tended to be counteracted by CB-03-01. In a parabiotic rat model (castrated male, intact female), CB-03-01 administered subcutaneously (SC) did not inhibit the hypersecretion of gonadotropins produced by castration. A significant decrease in circulating corticosterone levels was reported in male rats following intravenous (IV) dosing for 3 days at 5 mg/day (approximately equivalent to about 25 mg/kg/day). Evidence of local anti-inflammatory activity was obtained in female rats where CB-03-01 (at 1 and 5 µM) produced a significant reduction in the size and amount of exudate produced by a croton oil-induced granuloma. The response at 5 µM was similar to that of betamethasone 17-benzoate at 0.1 µM (used as reference positive control). In immature female rabbits, CB-03-01 administered SC (1 mg/kg/day) produced an increase in uterine weight (approximately half the increase produced by progesterone) and

endometrial proliferation (progesterone produced very pronounced proliferation), indicating a potential progestational activity.

Furthermore, regarding the effects of clascoterone on the cytokine's levels in association with TP in castrated rats, the data showed that clascoterone acts as a functional anti-androgen through the mechanistic blockade of TP-induced cytokine level responses.

2.4.2.3. Safety pharmacology programme

The safety pharmacology studies reported that clascoterone can be considered a low-potency hERG-channel inhibitor, but the highest concentration tested is 1500 times higher than the highest plasma concentration measured in the clinical studies (7.65 ng/mL). The *in vivo* study conducted in dogs at a maximal dose of 250 mg/kg was negative. The results were negative for the effects on CNS and respiratory system.

2.4.2.4. Pharmacodynamic drug interactions

None

2.4.3. Pharmacokinetics

Pharmacokinetic evaluation of CB-03-01 via validated bioanalytical methods was carried out in order to assess the amount of systemic drug absorption and to associate the exposure in animals with the degree of toxicity in toxicological studies. Although topical application is the expected route of administration in clinical use, oral, subcutaneous, and intravenous routes of administration were employed in toxicologically relevant species, to assess the plasma concentrations related to any toxic effects after single and repeated administration. Systemic administration in mice, rats, and rabbits required the drug to be formulated differently from that intended for clinical use (using suspending vehicle SV17874, consisting of 0.4% (v/v) Tween 80, 0.5% (w/v) carboxy-methylcellulose (CMC), and 0.9% (v/v) benzyl alcohol in 0.9% physiological saline for injection). In minipigs, a preliminary study was conducted using topical application of the above formulation, whereas in long-term studies in the same species, the cream formulation was used. CB-03-01 and its main metabolite, cortexolone, were investigated in toxicokinetic studies. Aspects of distribution, metabolism, and enzyme induction were also assessed *in vitro.*

The systemic exposure in the subcutaneous toxicity study in rat was higher than in topical treatment. After SC administration, exposure to the drug was variable with respect to dose proportionality and was different from one study to another. After repeated administrations in some toxicity studies in rats and in minipigs, a significant accumulation was observed (e.g. in 9 months dermal in minipigs, the ratio of AUC ranged from 6.38 to 20.3), varying in extent depending on the doses and treatment duration.

The 6/9 months toxicity studies in minipigs showed that the systemic exposure is higher with the solution topical application than with the cream application for the same clascoterone concentration.

Pregnancy appears to increase systemic exposure in rats. A similar comparison cannot be made in rabbits due to the different dose routes used in the embryofetal study and the repeat-dose study.

Clascoterone is found to be moderately bound to plasma protein from all species evaluated. It exhibited similar plasma protein binding across species (mouse, rat, rabbit, minipig, and human; approximately 80% to 90%).

No distribution studies (e.g. quantitative whole-body autoradiography) were carried out in order to detect a possible target organ for toxicity and tissue retention.

The metabolism is only investigated in the *in vitro* study. The possible cutaneous metabolism was not investigated, therefore the possible metabolites emerged *in situ* are unknown.

Clascoterone is metabolised to cortexolone via hydrolysis of intermediate compound cortexolone 21-propionate.

Cortexolone is a human metabolite and an endogenous substance, (a metabolic intermediate of cortisol). In mice and rats, cortexolone concentration was much lower than the parent drug in most plasma samples, falling below the extrapolated lower limit of quantitation (LLOQ) of the method. In minipigs, cortexolone was sparsely detected after topical application for 9 consecutive months.

No specific studies were conducted to evaluate the excretion of clascoterone in animals.

2.4.4. Toxicology

The toxicology studies were conducted in compliance with Good Laboratory Practice (GLP) except for the 14-day dermal tolerability study in minipigs, and the 4-week cortexolone 21-propionate study in rats. No significant deviations occurred during the performance of the toxicology studies and none affected the integrity or interpretation of the data.

To evaluate the safety of clascoterone (CB-03-01), a range of toxicology studies have been conducted in rodents and non-rodent species, and by various routes of administration.

The vehicle (SV17874) tested in the SC and IV studies was composed of 0.4% (v/v) Tween 80, 0.5% (w/v) carboxymethylcellulose (CMC), and 0.9% (v/v) benzyl alcohol in 0.9% physiological saline. In the 13-week minipig study, the initial 1% and 5% clinical cream formulations were evaluated (identical to the Phase 3 clinical and commercial formulation, save the omission of citric acid monohydrate for pH optimization). The rabbit ocular irritation study was also carried out using the initial 1% clinical cream formulation.

2.4.5. Single dose toxicity

In both female mice and rats, a single IV administration of clascoterone produced a median lethal dose (LD50) of > 100 mg/kg and a single SC administration produced an LD50 of > 1000 mg/kg.

2.4.5.1. Repeat dose toxicity

Regarding clascoterone, the GLP pivotal repeat-doses toxicity studies were performed in two species, in rats and minipigs.

In all repeat doses toxicity studies in rats and minipigs, none of the deaths were considered to be treatment-related.

Following repeated SC administration of clascoterone to rats for either 28 days or 13 weeks, the main effects related to clascoterone were: a decrease in white blood cell and lymphocyte counts, a reversible microscopic changes in the liver (minimal to slight hypertrophy) and adrenal gland, lymph nodes, spleen, thymus and Peyer's patch (reported as minimal to moderate atrophy or lymphocyte depletion, and slight to marked atrophy of the adrenal glands), in the injection site reversible minimal to moderate acanthosis, parakeratosis,

scab/ulceration, inflammation, edema, and/or degeneration. The changes observed in the white blood cells population, in the adrenals and in the lymphoid organs (spleen, thymus) were probably related to the weak glucocorticoid activity of the clascoterone. In the 28-day toxicity study, a concomitant group of animals was tested for immunotoxicity. Variations in leukocyte populations were noted, including increased $CD3^+$ at 10 mg/kg/day and decreased $CD3^+$ at 50 mg/kg/day, decreased $CD3^+/CD4^+$ at 50 mg/kg/day, and increased $CD11b^+$ at 50 mg/kg/day; however, no difference in the primary immune response to sheep red blood cells was noted between the control rats and those treated with CB-03-01. Although the morphology of the leukocyte population changed, the function of this population did not.

In the SC 26 week toxicity study in rats, the effects were limited and for most of them, they were considered to be related to the SC route of administration at the site of injection or incidental, characteristic for Wistar rats of the same age.

In a dermal 13-week rat study, test article-related findings in males and females included decreases in the incidence of hair regrowth with minimal to slight atrophy of adnexal hair follicles at $\geq$ 0.1%, minimal to moderate atrophy of the skin and subcutaneous tissue at $\geq$ 1.5%, minimal to moderate atrophy of adnexal sebaceous glands at 5%. In addition, the increase of the weight of liver and the decrease adrenal weights were noted in males only at 5% (high dose).

In a dermal 13-week minipig study, the 1% and 5% cream formulations of clascoterone produced effects that were limited to the site of application. Microscopic examination of the treated skin also revealed reduced epidermal and dermal thickness in all clascoterone-treated animals, which was generally minimal in severity following application of 1% cream (once or twice per day) and mild following application of 5% cream (once per day). The severity of the epidermal changes decreased after a 4-week recovery period, but the severity of the dermal changes remained unaltered.

The test article-related microscopic findings in minipigs after 9 months daily dermal administration of clascoterone cream were present in the treated and untreated skin (thinning) and adrenal glands (weight reduction) of both sexes with 1% to 5% cream, and in the testes (hypertrophy) of one male with 5% cream. These findings were considered by the Applicant to be non-adverse due to the overall low magnitude and/or nature of the findings (consistent with expected pharmacologic effects with no associated inflammation or necrosis), and the near complete reversal of these changes following the recovery period. Furthermore, adrenal cortical atrophy observed in treated animals was not associated with any adverse clinical signs or alterations in traditional clinical pathology endpoints that may be impacted by altered adrenal function such as electrolytes, glucose, or lymphocyte counts. Thus, more sensitive indicators of adrenal function (cortisol and ACTH levels) were not assessed in the current study, a clascoterone impact on overall adrenal function could not be definitively ruled out. Indeed, the regions of the adrenal gland that were affected were the zona reticularis (responsible for androgenic hormone production) and the zona fasciculata (responsible for glucocorticoid production). Similar adrenal gland atrophy has been reported with administration of some anti-androgen compounds in rodents and is likely due to ACTH suppression in the pituitary gland. Therefore, the atrophic response produced in minipigs in the current study by clascoterone an anti-androgenic compound, may have been related to its pharmacologic activity. Therefore, the adrenal glands of both sexes treated with clascoterone 2.5% or 5% cream had test article-related bilateral cortical atrophy. The findings were dose dependent and ranged from mild to moderate severity in males and from minimal to mild severity in females in the affected dose groups. Cortical atrophy was characterised by a diffuse decrease in the thickness of the zonae fasciculata and reticularis.

In the dermal 26/39-week repeat doses toxicity study in minipigs performed with a clascoterone solution (up to 15%) systemic and dermal effects occurred: atrophy and organ weight reduction in the adrenal glands of

males receiving 5% and 15% and of females receiving 15%, reversible minimal thinning of the epidermis and/or dermis, minimal to mild hypertrophy of the interstitial cells (Leydig cells) of the testes considered as test article-related in males in the 5% and 15% groups. Indeed, the change was characterised by a slightly enlarged cytoplasm that was vacuolated in rare occasions. The number of interstitial cells did not appear to be increased in the affected testes. Similar changes have been described with androgen receptor antagonists. Based on the minimal to mild severity, the absence of changes in the seminiferous tubules, and the lack of effects on the testes weights, this finding was not considered adverse by the Applicant. The changes in the adrenal gland were considered minor and from a physiological standpoint in the study report: all animals were functionally normal.

Furthermore, hyperplasia of skin (injection site) was observed in the 13-week rat toxicity study, epidermal hyperplasia observed in non-GLP 5-Day Oral Bioavailability and 14-Day Subcutaneous Toxicity studies in mice and Toxicokinetic Study in ICR Mice, and hyperplasia of the seminal vesicles was observed in the 26/39-week minipig toxicity study. The hyperplasia at the injection may be due to injection procedure, and a reversible minimal hypertrophy/hyperplasia of seminal vesicles is a known high dose anti-androgen effect.

2.4.5.2. Genotoxicity

A battery of genotoxicity studies was performed in accordance with ICH S2.

Table 1: Overview of GLP genotoxicity studies on clascoterone

Type of test/study ID/GL		Concentrations/ Concentration range/ Metabolising system	Results positive/negative/equivocal
Gene mutations in bacteria	*Salmonella* strains: TA98, TA100 TA1535 TA1537 and *Escherichia coli* WP2 uvrA	+/- S9 (rat) Up to 5000µg/plate	A biologically significant increase (>2) in the number of revertants was observed in strain TA98 in the presence of S9 in the test with the pre-incubation method in the presence of S9 at the highest non-precipitating dose of 333 µg/plate. The applicant concluded that CB-03-01 did not produce structural aberrations in human lymphocytes.
Gene mutations in mammalian cells / *In vitro* Chromosome aberration test	Human Lymphocytes	+/- S9 (rat) 4h: up to 342.9 µg/ml 22h: up to 196 µg/ml 46h: up to 112 µg/ml	Negative for clastogenic potential

In vivo chromosomal aberrations	Rat, micronuclei in bone marrow	Up to 2000 mg/kg (SC)	Equivocal

In order to identify the mechanism of the putative genotoxicity/clastogenicity mechanism of action the study "3844-327 - Clascoterone: In vitro Human Lymphocyte Micronucleus Assay" has been conducted in response to question during the procedure.

In vitro Human Lymphocyte Micronucleus Assay-Study	Human peripheral blood lymphocytes	+/- S9 (rat) 3h 24h	Clascoterone showed no genotoxic potential in the *in vitro* micronucleus assay in human lymphocytes in primary culture in the absence of metabolic activation for a short time of 3h and a long time of 24h. Clascoterone induced a statistically significant and concentration-dependent increase in micronucleus frequency in the presence of S9 at 3 different concentrations between 140 and 220 µg/ml. According to the study director, these increases were within historical controls and he therefore considers this result to be equivocal, since 2 of the 3 positivity criteria were met. Analysis of the micronuclei formed by Clascoterone showed that a majority of micronuclei contained centromeres, indicating an aneugenic effect of Clascoterone with a threshold of 50 µg/mL.

2.4.5.3. Carcinogenicity

The results of a two-year carcinogenesis study in rats were provided.

Table 2: Overview of carcinogenicity studies

	Study details	No.Sex/ Group	Dose (mg/ml)	Exposure	Major (alt. Salient) findings
Species Duration Route GLP status Study ID	Sprague-Dawley CD rats 24 months Dermal application GLP compliant Initial age~ 6 weeks 15-2470	65/sex/group	0 (CB-03-01 Vehicle Cream, Group 2), 0.1, 1 or 5 CB-03-01 (Groups 3, 4 and 5) Group 1 was untreated and used as a negative control group	N/A	Mortality No CB-03-01 cream-related increase in the overall number of unscheduled decedents at the end of the dosing period in either males or females. The most common major factors related to death were pituitary adenoma (males and females), progressive cardiomyopathy (males), and mammary tumors (females), all of which are commonly observed in aged rats of this strain. Clinical signs Test item-related clinical observations were limited to the dermal dose site observations of abnormal color and translucent skin, which were noted in most animals (both sexes) between Week 51 and 99 following application of the 1% and 5% cream formulation. Tumors Increased incidence of skin tumors of sebaceous origin was present in male rats treated with 5% cream for up to 23 months; this occurred in four animals. Sebaceous cell adenomas in male rats with 5% cream were considered test article-related because they were: statistically significant (p = 0.049) compared to the vehicle control groups (as well as clinical research organization [CRO] historical control data) were not present in any control animals; were associated with multiplicity of sebaceous cell tumors: and were observed at a higher incidence than published historical control databases (Charles River 2013, Weber 2017,

					Zwicker 1992). As observed in this study, epithelial tumors of the skin have been reported to be more common in males than females (Zwicker 1992). Microscopic findings The non-neoplastic finding of atrophy of the skin and subcutis at the topical application site was dose-related in males and females and was considered to be related to dermal doses of the test article at ≥ 1% cream. This change was probably related to the mechanism of action of the test article. Increased incidences of adenomas and adenocarcinomas in the mammary gland of females administered 5% cream and periportal vacuolation in the liver of males administered 5% cream were considered spurious and not related to test article administration because these changes are common spontaneous changes in aged SD rats (McInnes 2012) and/or were similar to historical background incidences. No evidence of local carcinogenicity was noted in female rats or systemic carcinogenicity in male or female rats following topical administration of CB-03-01 cream at concentrations ranging from 0.1% to 5%. In male rats, a slight increase in sebaceous cell adenomas at the site of application was noted following topical application of CB-03-01 cream 5%.

2.4.5.4. Reproductive and developmental toxicity

A full programme of developmental and reproductive toxicity studies was conducted in rats and rabbits dosed subcutaneously once daily with clascoterone. In the rat fertility study, there were some findings on the male reproductive organ weights (increased testes and decreased seminal vesicle weights), sperm parameters (increased testicular but decreased caudal epididymis sperm counts), and an increase in preimplantation loss at the high dose level of 12.5 mg/kg/day. The NOAEL for fertility and early embryonic development was 2.5 mg/kg/day (4.7 to 8.0 times the human exposure based on AUC comparison). In an embryo-fetal development study performed in rats at doses of 0, 1, 5, 25 mg/kg/day, clascoterone induced fetal malformations at all dose levels tested (≥2.5 times the human exposure based on AUC comparison). In particular, omphalocele was noted in one fetus of each treated group. There were also two additional fetuses at 1 mg/kg/day with external malformations on one hand (small size, thin skin, protruding tongue) and visceral malformations on the other (severe dilation of the lateral and third cerebral ventricles). In the study

conducted in rabbits at dose levels of 0, 0.1, 0.4, 1.5 mg/kg/day, an increase in postimplantation loss (early resorptions) was reported at 1.5 mg/kg, in line with the 100% postimplantation loss noted in all females at ≥ 6 mg/kg in the dose range-finding study. In addition, a 16-18% decrease in fetal weight and delayed ossification (forelimbs, hindlimbs, pelvis, sternum and cranium) were reported at 1.5 mg/kg. No treatment-related effect on embryofetal development was observed at doses up to 0.4 mg/kg/day (3.7 times the human exposure based on AUC). Eventually, no effect on post-weaning development of F1 animals including sexual maturation, behavioral tests (learning and memory, locomotor activity), and mating performance and fertility was observed at subcutaneous doses up to 12.5 mg/kg/day in the pre-post-natal development toxicity study conducted in rats.

2.4.5.5. Toxicokinetic data

The pharmacokinetic part was based on toxicokinetic (TK) data as described in Table 3.

Table 3: TK of clascoterone and its metabolite, cortexolone, for the repeat-doses studies

			Clascoterone		Cortexolone	
Species (sex, n)	**Dose (mg/kg/day) at NOAEL**	**Study Design**	**C_{max} (ng/mL)**	**$AUC_{(0-24h)}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**$AUC_{(0-24h)}$ (ng.h/mL)**
RAT SUBCUTANEOUS						
Rat (M, 9)	**10**	**D1**	530	994	37	31.9
		D28	495	982	52.4	175
Rat (F, 9)	**10**	**D1**	650	1173	12.3	88.4
		D28	1131	1369	102	884
Rat (M, 9)	**1**	**D1**	30.52	40.99	ND	ND
		D91	45.19	66.98	ND	ND
Rat (F, 9)	**1**	**D1**	28.24	38.01	ND	ND
		D91	58.19	70.74	ND	ND
Rat (M, 9)	**2.5 (26 w study)**	**D1**	84.35	298.06	ND	ND
		D91	84.35	298.61	ND	ND
Rat (F, 9)	**2.5 (26 w study)**	**D1**	126.8	447.47	ND	ND
		D91	71.33	173.19	ND	ND
RAT DERMAL						
Rat (M, 3 to 6)	**Cream 5% 4 mg/cm2 10% BSA**	**D1**	24.7	133	0.69	0.77
		D90	57.2	308	231	11.8
Rat (F, 3 to 6)	**Cream 5% 4 mg/cm2 10% BSA**	**D1**	25.4	164	1.14	2.17
		D90	132	372	5.51	7.16
MINIPIG DERMAL						
Minipig (M, 4 to10)	**Solution 5% QD 6mg/cm2 to 10% BSA**	**D1**	4.98	49.9	ND	ND
		D181	12.7	184	ND	ND
		D272	21.9	139	ND	ND
Minipig (F, 4 to10)	**Solution 5% QD 6mg/cm2 to 10% BSA**	**D1**	4.15	48.5	ND	ND
		D181	19.6	206	ND	ND
		D272	28.5	145	ND	ND
Minipig (M, 4 to 6)	**Cream 5% 0.5ml/kg 10% BSA**	**D1**	5.36 (0.214(ng/ml)/ / (mg/kg/day)	42.5 1.70 (ng/ml).h/ / (mg/kg/day)	ND	ND
		D272	30.1 (1.21 (ng/ml)/ / (mg/kg/day)	401 16.0 (ng/ml.h)/ / (mg/kg/day)	ND	ND
Minipig (F, 4 to 6)	**Cream 5% 0.5ml/kg 10% BSA**	**D1**	4.32 (0.173 (ng/ml)/ / (mg/kg/day)	51.5 2.06 (ng/ml.h)/ / (mg/kg/day)	ND	ND
		D272	16.8 (0.670 (ng/ml)/ / (mg/kg/day)	269 10.8 (ng/ml.h)/ / (mg/kg/day)	ND	ND
		Ratio of AUC for D272/ D1		10.4 in males 9.09 in females	ND	ND

TK data from all repeat-dose toxicity studies were included in the report, except for the carcinogenicity study in rats which reported no TK data.

In general, dermal exposure in both sexes of rats and minipigs was comparable, or slightly but not significantly different. Pregnancy appears to increase exposure in female rats.

Administration of clascoterone by both SC and topical routes produced rapid absorption. The systemic exposure was time-dependent. The concentration of the main metabolite, cortexolone, was negligible. No significant gender differences were seen.

The absorption of clascoterone has been evaluated with different routes of administration in rats (SC, topical), rabbits (SC, topical), and minipigs (topical). Plasma protein binding and *in vitro* metabolism were also assessed in the different species. The main metabolite identified is cortexolone (an endogenous metabolic intermediate of cortisol), which has been quantified *in vivo*, in rats, rabbits, and minipigs.

Subcutaneous administration of clascoterone to rats and rabbits resulted in rapid absorption.

After SC administration, exposure to the drug was variable with respect to dose proportionality. After repeated administrations, some accumulation was observed in all species tested, varying in extent depending on the doses and treatment duration; however, this accumulation did not appear to correlate with toxicity. Topical treatment resulted in a much lower exposure than SC treatment, particularly in minipigs, but a similar behaviour with the two routes of administration was noted in terms of dose and time dependency.

The increase in the systemic exposure from the first dose to the last dose observed in studies 13-week in rats and 9-month in minipigs, assessed through the ratio of last dose/first dose AUC0-24, ranged from 2.27 to 5.50 and from 6.38 to 20.3, respectively.

The safety margin provided in this file, were 1.8 and 4.6 compared to systemic exposure at NOAEL for 13-week toxicity SC study and for 26-week SC toxicity study in rats, respectively. Regarding the 26-week dermal toxicity study in minipigs, the safety margin was 4.9. The safety margins were 8 for the dermal 13-week toxicity study in rats and 7 for dermal 39-week toxicity study in minipigs.

2.4.5.6. Local Tolerance

The potential irritation of CB-03-01 has been evaluated on the skin and in the eye of various animal species. Dermal irritation data were collected as part of the 28-day rabbit study, 14-day minipig study and 90-day minipig study.

Clascoterone 1% cream was found to be slightly irritating to the eyes of rabbits, with complete resolution of irritation by 72 hours.

In the contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test, the results show that clascoterone did not exhibit an ability to produce dermal sensitization in guinea pigs.

2.4.5.7. Other toxicity studies

Studies on impurities

Cortexolone 21-propionate was identified as the main degradation product. However, its concentrations were not found *in vivo* in human plasma.

The cortexolone-21-propionate genotoxicity was evaluated by an Ames test (study No. 1198500) and a Chromosome Aberrations test (study No. A3233) which were both negative. Moreover, 2 QSAR methods concluded that there was no positive prediction.

2.4.6. Ecotoxicity/environmental risk assessment

Table 4: Summary of main study results

Substance (INN/Invented Name): CLASCOTERONE Winlevi			
CAS-number (if available): 19608-29-8			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 Log Kow =2.9	Log Kow =2.9	Potential PBT: NO
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.9	not B
	BCF		not B
Persistence	DT50 or ready biodegradability	Readily biodegradable	not P
Toxicity	NOEC or CMR	No CMR	
PBT-statement :	Studies for aquatic toxicity pending. The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.1	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)	-	Endocrine active	Y
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =	To be conducted
Ready Biodegradability Test	OECD 301B	Clascoterone is rapidly hydrolysed tocortexolone 21-propionate. Human metabolite, Cortexolone is a natural steroid hormone which is readily biodegradable	Readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ =	Not required

		% shifting to sediment =			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	-	µg/L	To be conducted
Daphnia sp. Reproduction Test	OECD 211	NOEC	-	µg/L	To be conducted
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	-	µg/L	To be conducted
Activated Sludge, Respiration Inhibition Test	OECD 209	3-hour NOEC 3-hour EC_{10}	32 52.2	mg/L mg/L	-
Phase IIb Studies					
Chironomid toxicity (spiked sediment)	OECD 218	-	-	-	To be conducted
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	-	-	Not required
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	-	mg/kg	Not required
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	-	mg/kg	Not required
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	-	mg/kg	Not required
Collembolan (reproduction in soil)	OECD 232	-	-	-	Not required

2.4.7. Discussion on non-clinical aspects

Clascoterone is a novel androgen receptor inhibitor that has a chemical structure similar to dihydrotestosterone (DHT) and competes with thi s natural substrate for binding to androgen receptors in the skin. When applied topically to the skin, it acts locally, influencing multiple cellular and molecular acnegenic pathways with minimal systemic exposure. Once absorbed in the skin, clascoterone is rapidly hydrolysed by the skin and plasma esterases to cortexolone, a physiological component of the pool of endogenous corticosteroids, an intermediate in the synthesis of glucocorticoid steroids that only exhibits weak glucocorticoid properties. Although the exact mode of action of clascoterone in the treatment of acne vulgaris is unknown, the proposed mechanism is direct inhibition of testosterone and dihydrotestosterone binding to the androgen receptor in sebocytes.

Preclinical studies examining primary and secondary pharmacodynamics, as well as safety pharmacology, have been conducted on clascoterone using both *in vitro* and *in vivo* evaluations. These studies were performed in mice, rats, hamsters, rabbits, and dogs.

In vitro and *in vivo* pharmacology***:*** CB-03-01 is a new androgen receptor (AR) inhibitor with local anti-androgenic activity. *In vitro,* it binds strongly to human AR (IC50: 5×10^{-8} M) and inhibits DHT-induced lipid synthesis and inflammation in sebocytes, these are key mechanisms in acne pathogenesis. *In vivo*, its efficacy was shown in the hamster flank organ model, where topical application reduced testosterone-induced enlargement without systemic effects. Compared to standard anti-androgens, CB-03-01 showed similar local efficacy. In rats, SC administration did not affect androgen-dependent organs but reduced adrenal and thymus weights at high doses, suggesting a weak glucocorticoid activity.

Secondary pharmacology***:*** CB-03-01 showed high target specificity, with no off-target binding among 54 receptors and no estrogenic activity. It partially reversed immunosuppressive effects of testosterone in rats and did not alter gonadotropin secretion in a parabiotic model. It decreased corticosterone levels after IV dosing and showed local anti-inflammatory activity in a granuloma model, comparable to corticosteroids. A moderate progestational effect was observed in rabbits.

In safety pharmacology studies, no adverse effects were observed on the central or cardiovascular systems in rats and dogs at high doses. In a hERG assay, CB-03-01 showed low potential for cardiac risk (40% inhibition at the highest concentration tested).

In the single dose study, in both female mice and rats, a single IV administration of clascoterone produced a median lethal dose (LD50) of > 100 mg/kg and a single SC administration produced an LD50 of > 1000 mg/kg.

GLP-compliant repeat-dose toxicity studies were conducted in rats and minipigs via subcutaneous and dermal routes. No treatment-related deaths occurred in any of the studies.

In rats, repeated SC administration (28 days or 13 weeks) led to reduced white blood cells, reversible liver hypertrophy, and atrophy in adrenal glands and lymphoid tissues. Skin changes at the injection site included inflammation, ulceration, and degeneration, all reversible. These findings likely reflect clascoterone's weak glucocorticoid activity. An immunotoxicity assessment showed altered leukocyte profiles, but no change in immune response to sheep red blood cells.

A 26-week SC study in rats showed minimal systemic effects, mostly related to the local route of administration.

In a 13-week dermal rat study, findings included hair regrowth reduction and skin, sebaceous gland, and follicle atrophy, with liver weight increase and adrenal weight decrease at high dose.

In a dermal 13-week minipig study, the 1% and 5% cream formulations of clascoterone produced effects that were limited to the site of application. The severity of the epidermal changes decreased after a 4-week recovery period but the severity of the dermal changes remained unaltered.

A 9-month dermal study (daily dermal administration of clascoterone cream) in minipigs showed thinning of both treated and untreated skin, adrenal weight loss, and mild testicular changes. These were non-adverse due to low severity and reversibility. Adrenal cortical atrophy affected the zona fasciculata and reticularis, regions linked to glucocorticoid and androgen production. These effects were dose-dependent and likely due to clascoterone's pharmacological action. In a 26/39-week study with up to 15% dermal solution, adrenal atrophy and skin thinning were observed. Mild Leydig cell hypertrophy was also seen in males, but was non-adverse due to lack of structural or weight changes. All animals remained functionally normal despite adrenal effects. Some hyperplasia (skin, seminal vesicles) was observed in rats and minipigs. These findings suggest possible hormonal modulation effects.

Overall, the toxicological profile of clascoterone has been well characterized and the data suggest an anti-androgen glucocorticoid-type and response in the nonclinical species examined, at high doses and high systemic exposures. In the topical repeat-doses toxicity studies in rats and minipigs, dermal changes included dermal irritation, reductions in epidermal and dermal thickness. Given that the safety margin (AUC ratio) value, provided in the dossier and based on data of 26 week toxicity study in rats and minipigs, were around 4-5, therefore the effects observed in nonclinical species cannot be ruled out in patients with acne.

The genotoxic study battery on clascoterone is in accordance with the guideline ICH S2. The study report assessments have highlighted some remarkable findings which question the conclusion on the genotoxic potential.

Gene mutations in bacteria test: The GLP study to establish the mutagenic potential of clascoterone followed the recommendations of guideline 471 and showed the absence of mutagenic properties of clascoterone in strains TA1535, TA1537, TA100 and WP2 uvrA in the absence and presence of metabolic activation and in strain TA98 in the absence of S9. Although the results of experiment 1 with strain TA98 in the presence of S9 were negative, experiment 1 was carried out using the direct incorporation method, whereas experiment 2 was carried out using a pre-incubation method. However, it is clearly accepted that certain compounds can give positive results only in the pre-incubation method, in particular in the presence of S9, because the compound is more easily in contact with S9, which allows better detection of genotoxic metabolites.

However, several criteria do not support the conclusion:

- Clascoterone induced a significant increase in the number of revertants in strain TA98 in the presence of S9 in the pre-incubation method at the highest dose tested. (1)
- This biologically significant induction was observed for all 3 replicates and these 3 values were higher than historical control values from more than 150 studies. Therefore, this result cannot be considered as a chance-related biological response. (2)
- Only 3 doses were analysed in experiment 2, whereas a minimum of 5 doses should be analysed in the absence of precipitation and/or toxicity. Thus, a complementary study should be carried out on strain TA98 at doses between 333 and 1000 µg/plate in order to determine a potential dose effect. (3)

Thus, the results obtained on strain TA98 in the presence of S9 did not meet the 3 criteria that would allow the study to be classified as clearly positive. However, 2 criteria were met: (1) a significant increase in the number of revertants at least one dose and (2) an increase beyond the data from historical controls. The third criterion, relating to a dose effect, could not be met due to the presence of precipitates at the dose of 1000 µg/plate. In conclusion, on the basis of this study and in the absence of further data, clascoterone cannot be considered negative in the gene mutation test on prokaryotic cells, so in vitro mutagenic activity cannot be ruled out.

In vitro chromosome aberration test in human lymphocytes: The GLP study to establish the clastogenic potential of Clascoterone followed the recommendations of guideline 473. Also according to OECD guideline No. 473, a compound is considered to be clearly negative if under all experimental conditions studied: a) no test concentration shows a statistically significant increase compared with the concurrent control, b) an appropriate trend test shows that there is no concentration-related increase, c) all results fall within the distribution of historical negative control data. According to this study, criteria a/ and b/ are not met, so the test product, clascoterone, cannot be considered clearly negative in the human lymphocyte chromosome aberration assay. However, it should be noted that the most significant effects were weak and induced at

concentrations that exceeded the acceptable cytotoxicity levels defined by the guideline, i.e. 55%±5. Therefore, based on the data from this study, it can be considered that under the conditions of the study, clascoterone did not show any clastogenic potential *in vitro.*

In vivo rat bone marrow erythrocytes micronucleus test: The GLP study n° AD33DF.125M.BTL consisted of evaluating the clastogenic and/or aneugenic potential of clascoterone in male rats at the level of immature bone marrow erythrocytes following a single subcutaneous exposure of up to 2000 mg/kg bw. The results showed that the compound cannot be considered as clearly positive in the absence of a dose effect, however 2 out of 3 criteria are met: a condition with a statistically significant effect and an effect beyond the distribution of historical values. These results showed a weak clastogenic effect of the compound which was not found in all the animals tested. However, this *in vivo* study had some limitations, particularly in terms of experimental design. To maximise exposure of the target tissue in this study, bone marrow, a double administration over 24 hours would have been more appropriate than choosing to carry out an additional group 48 hours after administration. Furthermore, in this study, only 2,000 erythrocytes per animal were read, whereas the current guideline recommends that 4,000 erythrocytes per animal must be read, as this allows better detection of weak responses and also limits false-positive results. It would also have been judicious in this study to repeat the count on 4,000 erythrocytes to eliminate or not the uncertain nature of this result. On the basis of this study, it is not possible to rule out an *in vivo* genotoxic potential for clascoterone.

In vitro Human Lymphocyte Micronucleus Assay-Study was performed in response to questions about the procedure. GLP study 3844-327 was designed to determine the ability of Clascoterone to induce micronuclei in primary human lymphocytes in the presence or absence of rat S9 fraction and to determine its clastogenic or aneugenic potential. The results indicate that Clascoterone induced a statistically significant increase in the frequency of micronuclei only in the presence of rat liver S9 mix. In addition, FISH analysis of the micronucleus content indicated that the vast majority of micronuclei resulted from aneuploidy events.

On the basis of available *in vitro* studies, clascoterone can be considered negative in the prokaryotic cell gene mutation assay, and equivocal in *in vitro* the micronucleus test. Regarding the *in vivo* data, a bone marrow erythrocyte micronucleus test in male Sprague-Dawley rats after double subcutaneous administration up to 2000 mg/kg, showed a statistically significant increase in micronucleus frequency at the highest dose tested, so clascoterone can be considered genotoxic *in vivo* after subcutaneous administration. The results of study 3844-327 - Clascoterone: In vitro Human Lymphocyte Micronucleus Assay" (FISH) showed that clascoterone genotoxic mechanism is aneugenic. Clascoterone aneugenic effect is with a threshold of 50 µg/ml.

Considering the >100-fold margin identified at the NOGEL in *in vivo* genotoxicity study and that the latest study no. 3844-327 confirms a thresholded mechanism (aneugenicity), and in accordance with « *SWP/NcWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug* » (EMA/CHMP/SWP/74077/2020 rev. 1*), clascoterone could be considered as an active substance « *whose mechanism of genotoxicity is known to have a threshold which is not expected to be attained in patients* ». Consequently, contraception is required only for women of childbearing potential to prevent exposure during pregnancy, given the teratogenic risk (androgen receptor inhibition). The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with clascoterone and contraception should be implemented for women of childbearing potential during the treatment period and continued for at least up to 5 elimination half-lives, or 10 days after the last dose.

A carcinogenicity study assessed clascoterone cream (concentrations ranging from 0.1% to 5%), administered as a dermal application to Sprague Dawley rats for up to 23 months. No evidence of local

carcinogenicity was noted in female rats. In male rats, an increase in sebaceous cell adenomas at the site of application was noted following topical application of clascoterone cream 5%, only.

Concerning the neoplastic tumors, the sebaceous cell adenomas observed in male rats at 5% clascoterone cream were considered test related because they were statistically significant (p=0.049) compared to the vehicle control groups (as well as Envigo historical control data), were not present in any control animals, were associated with multiplicity of sebaceous cell tumors, and were observed at a higher incidence than published historical control databases (Weber, 2017; Charles River, 2013; Zwicker, et al.1992).

Regarding the reproductive and developmental toxicity, the applicant concluded that there was no evidence of effects on reproduction and fetal and pup development following administration of clascoterone, although cases of major malformations were found in embryofetal studies in rats and rabbits. It was pointed out that the frequency of malformations however, often followed an inverse dose relationship and that the effects in rats were not confirmed in fertility and pre- and postnatal studies, where the presence of the major malformations would have been detected. This conclusion is not fully endorsed since the absence of increased frequency with dose does not always alleviate concern for rare malformations. In addition, the occurrence of omphalocele should be regarded as treatment-related in view of the low incidence in historical controls and observation of this finding in 1 fetus per group and at a higher incidence at the top dose level of the less powered dose range-finding study. Regarding the historical control data, it is not clear why the applicant relies on Charles River data in a first approach instead of those of the test facility having conducted the study. Moreover, the absence of malformation in other studies conducted in another rat strain and in another testing facility is noted but is not fully unexpected especially for rare findings and/or in studies wherein treatment did not cover organogenesis. Finally, developmental effects seen at the high dose level of 1.5 mg/kg in rabbits (increased post-implantation loss, delayed ossification and decreased fetal weight) should be viewed as adverse since they occurred in absence of maternal toxicity. Indeed, there was no clear treatment-related maternal toxicity at any dose level and therefore the maternal NOAEL should be upgraded from 0.4 to 1.5 mg/kg/day. Given that a genotoxic risk cannot be excluded for patients treated with clascoterone, it is recommended that women of childbearing potential use effective contraception during treatment and at least 10 days after the last dose.

Toxicokinetic (TK) data from all repeat-dose toxicity studies were included, except for the rat carcinogenicity study, which lacked TK data. In both rats and minipigs, dermal exposure levels were similar across sexes, with no significant gender differences observed. However, pregnancy in female rats appeared to slightly increase systemic exposure.

Clascoterone was rapidly absorbed after both subcutaneous (SC) and topical administration. Topical administration produced significantly lower systemic exposure than SC dosing, especially in minipigs. Despite the route, systemic exposure showed similar time- and dose-dependent patterns. The main metabolite, cortexolone, was found at negligible concentrations. Plasma protein binding and *in vitro* metabolism were evaluated across species.

The increase in the systemic exposure from the first dose to the last dose observed in 13 week in rats and 9-month in minipigs studies, assessed through the ratio of last dose/first dose AUC0-24, ranged from 2.27 to 5.50 and from 6.38 to 20.3, respectively. It is considered that this increase can be attributed, at least in part, to reaching steady state during the study, similar to that observed in human PK studies. It cannot be established whether, in addition to the steady state effect, this increase in systemic exposure should be attributed to an increased absorption of clascoterone through the thinner skin, or to a slight drug accumulation following several weeks of application of clascoterone cream.

The safety margin provided in this file, were 1.8 and 4.6 compared to systemic exposure at NOAEL for 13-week toxicity SC study and for 26-week SC toxicity study in rats respectively. Regarding the 26-week dermal toxicity study in minipigs, the safety margin was 4.9. The safety margins were 8 for the dermal 13-week toxicity study in rats and 7 for dermal 39-week toxicity study in minipigs. In view of these exposure ratios, the occurrence risk of the effects noted in nonclinical species cannot be ruled out in patients with acne.

However, given that the Repeat-Dose Pharmacokinetic Study in Healthy Adult Subjects reports an inter-subject variability of Cmax and AUC of 73% and 58%, respectively and the total variability reported is very high, the CVs varying from 76.5% to 350%, and that accumulation of clascoterone over time is possible, the exposure ratio should be taken into account the highest exposure in patients with acne after a long-term administration at the maximal recommended posology.

The potential irritation of clascoterone has been evaluated on in the eye of rabbit: clascoterone 1% cream was found to be slightly irritating to the eyes of rabbits, with complete resolution of irritation by 72 hours.

In the contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test, the results show that clascoterone did not exhibit an ability to produce dermal sensitization in guinea pigs. As a 290 to 700 nm scan of the drug substance and drug product did not reveal absorption of light, in accordance with the ICH S10 guideline, a specific phototoxicity study is not warranted.

In the impurities study, cortexolone 21-propionate was identified as the main degradation product. However, its concentrations were not found *in vivo* in human plasma.

Given that the amount of cortexolone-21-propionate is equal to a 1 mg daily dose and given that the lack of a positive prediction in 2 (Q)SAR methods, per ICH M7, no additional data on the genotoxicity of cortexolone-21-propionate is required.

For the Ecotoxicity/environmental risk assessment: An assessment of the environmental relevance of two clascoterone transformation products, a hydrolysis product (cortexolone 21-propionate) and the human metabolite, cortexolone, including a consideration of their endocrine activity based on in vitro data should be taken into account. The environmental risk assessment is limited to the determination of log Kow, the calculation of PECSW, a ready biodegradation study and an Activated Sludge Respiration Inhibition Test:

- The results from an experimental OECD TG 107 study indicate that the mean log KOW for clascoterone is 2.9, which is below the trigger value of 4.5 for further PBT assessment. Clascoterone and its transformation products are not expected to persist in the environment and therefore are not considered Persistence, Bioaccumulative and Toxic (PBT).

- The PECSW of 0.1 µg/L calculated for clascoterone in this Phase I exposure assessment is greater than the trigger value of 0.01 µg/L. In accordance with the EMA (2024) guidance, a Phase II environmental fate and effects assessment of the active ingredient is required.

As clascoterone is endocrine active, tailored testing in fish is anticipated to be required for the Phase II ERA: a CHMP scientific advice was issued on the choice for the fish study, the use of the modified FLCTT study proposed by the Applicant was granted by the CHMP.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of clascoterone to the environment

2.4.8. Conclusion on the non-clinical aspects

The environmental risk assessment should take into account the endocrine activity of the two transformation products of clascoterone, a hydrolysis product (cortexolone 21-propionate) and the human metabolite, cortexolone. Moreover, the PECSW of 0.1 µg/L calculated for clascoterone in the Phase I exposure assessment is greater than the trigger value of 0.01 µg/L. In accordance with the EMA (2024) guidance, a Phase II environmental fate and effects assessment of the active ingredient clascoterone is required. Further, studies results are necessary to determine the final environmental risk assessment.

At high systemic exposure, the anti-androgenic and glucocorticoid effects were observed in rats and in minipigs. At the application site, dermal changes were observed included mainly dermal irritation, epidermal atrophy and dermal thickness. Regarding developmental and reproductive studies, clascoterone induced malformations in rats and embryo-lethality in rabbits. Some effects were also reported at the high dose level in the fertility study, whereas no effect on post-weaning development of F1 animals was observed at up to this dose in the pre- and postnatal development study. Clascoterone was found to be aneugenic in an *in vitro* micronucleus test with a threshold of 50 µg/mL. In the dermal 2 years carcinogenicity study in rats, sebaceous cell adenomas were statistically significant.

In conclusion, although the toxicological data have been sufficiently characterised, the environmental risk (phase 2) assessment is essential and should be provided to determine the final environmental risk assessment of clascoterone.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The clinical programme of Winlevi consisted of:

- 1 dose-escalation Phase 2 study (171-7151-201),
- 1 pilot Phase 2 study vs tretinoin as active comparator (CB-03-01/03)
- 2 Phase 3 studies of same design, 12 weeks (CB-03-01/25 and CB-03-01/26)
- 1 Phase 3 study with a long-term follow-up, 52 weeks (CB-03-01/27).

- **Tabular overview of clinical studies**

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
171-7151-201 13 sites in the US	11 Jun 2012 to 19 Feb 2014	**Phase 2**, double-blind, vehicle-	CB-03-01 cream: 0.1% BID: **72/58** 0.5% BID: **76/64**	**Subjects ≥ 12 years** old with facial acne vulgaris, **IGA**

		controlled, dose escalation	1% QD: **70/61** 1% BID: **70/59** Vehicle QD or BID: **75/62** Applied for 12 weeks	**score 2 to 4**, 20 to 75 ILC*, and 20 to 100 NILC*
CB-03-01/03 4 sites in Romania	13 Jan 2009 to 01 Sep 2009	**Phase 2**, randomized, double-blind, active-controlled	CB-03-01 1% cream: **30/27** Retin-A® 0.05% cream: **32/26** Vehicle: **15/14** QD (evening) for 8 weeks	**Adult males** (18 to 45 years) with facial acne vulgaris **IGA score 2 or 3**, 20 to 100 TLC, and 10 to 50 ILC
CB-03-01/25 45 sites in the US, 7 sites in Ukraine, 3 sites in Republic of Georgia	21 Jan 2016 to 11 Apr 2018	**Phase 3**, multicentre, randomized, double-blind, vehicle-controlled, parallel-group study	CB-03-01 1% cream: **353/287** Vehicle: **355/290** BID for 12 weeks	**Subjects ≥ 9 years** old with moderate or severe facial acne vulgaris, **IGA score 3 or 4**, 30 to 75 ILC, and 30 to 100 NILC
CB-03-01/26 12 sites in Poland 10 sites in the US 9 sites in Romania 8 sites in Bulgaria 6 sites in Republic of Georgia 3 sites in Serbia	16 Nov 2015 to 21 Feb 2018	**Phase 3**, multicentre, randomized, double-blind, vehicle-controlled, parallel-group study	CB-03-01 1% cream: **369/302** Vehicle: **363/282** BID for 12 weeks	**Subjects ≥ 9 years** old with moderate or severe facial acne vulgaris, **IGA score 3 or 4**, 30 to 75 ILC, and 30 to 100 NILC
CB-03-01/27 40 sites in the US 11 sites in Poland, 8 sites in Romania, 6 sites in Bulgaria, 4 sites in Ukraine, 3 sites in Serbia, 3 sites in Republic of Georgia	09 Mar 2016 to 31 Aug 2018	**Phase 3**, open-label, long-term follow-up with application on **face and trunk** to maximize exposure	CB-03-01 1% cream: **n=609** BID for up to 9 months	Subjects who completed Study CB-03-01/25 or CB-03-01/26

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Summary of Clinical Pharmacokinetic Studies

Study and Phase	Study Design	Study Objectives	Test Formulation/Dose	Subjects Receiving CB-03-01
CB-03-01/02	Phase 1, randomized, double-blind, placebo-controlled, single ascending dose	To evaluate single-dose PK of CB-03-01 1% cream vs control at increasing volumes (1, 2, or 4 mL) in healthy subjects	CB-03-01 1% cream: 1 mL (6), 2 mL (6), 4 mL (6) Single dose	18
CB-03-01/04	Phase 1, CB-03-01 on half of back, placebo on contralateral half	To evaluate 2-week repeat dose PK of CB-03-01 1% cream vs control at increasing volumes (4 mL or 8 mL) in healthy subjects	CB-03-01 1% cream: 4 mL (12), 8 mL (12) QD for 14 days	24
171-7151-203	Phase 1, open-label	To evaluate 6-week repeat-dose PK of CB-03-01 1% cream (6 grams daily) in subjects with acne vulgaris	CB-03-01 1% cream (6 grams) QD for 6 weeks	8
171-7151-202	Phase 2, open-label, sequential cohorts	To evaluate adrenal suppression potential and PK in adults and adolescents with acne vulgaris	CB-03-01 1% cream (6 grams or 4 grams for subjects < 18 years with BSA < 1.6 m^2) BID for 2 weeks	42
CB-03-01/28	Phase 2, open-label	Maximum use HPA/PK study to evaluate adrenal suppression potential and PK evaluation over 2 weeks in pediatric subjects with acne vulgaris of the face and trunk	CB-03-01 1% cream 2 grams to face and trunk Every 12 hours for 2 weeks	27
CB-03-01/33	Phase 1, double-blind, placebo-controlled	Thorough QT study including PK of CB-03-01 and metabolites cortexolone, 21-propionate and cortexolone	CB-03-01 7.5% solution BID to scalp and thighs on Days 1-3, once on Day 4	23

BID = *bis in die* (twice daily); BSA = body surface area; HPA = hypothalamic-pituitary-adrenal; QD = *quaque die* (once daily)

Absorption

Absorption has been evaluated in two *in vitro* studies. The results show that clascoterone in a 1% cream formulation does penetrate human skin.

In order to quantify the parent compound and metabolites, six bioanalytical methods have been developed and validated.

The two main Phase 1 human studies (CB-03-01/02 and CB-03-01/04), absorption has been evaluated using plasma and urine data.

Mean cumulative excretion (0-36 h), excretion rate and percent excreted fraction of the applied dose of cortexolone 17α-propionate calculated after application of 1, 2 and 4 mL of CB-03-01 1% A cream are summarised in the following Table 5.

Table 5: Mean cumulative excretion (0-36 h), excretion rate and percent excreted fraction of the applied dose of cortexolone 17α-propionate calculated after application of 1, 2 and 4 mL of CB-03-01 1% A cream for 8 h

CB-03-01 1% A cream		∑Xu (µg)	dXu/Δt (µg/h)	Excreted fraction (%)
1 mL	Mean	46.08	1.28	0.46
	SD	21.24	0.59	0.21
2 mL	Mean	78.06	2.17	0.39
	SD	40.84	1.13	0.20
4 mL	Mean	56.19	1.56	0.14
	SD	41.09	1.14	0.10

Results from study CB-03-01/02 show that in plasma, 11 of 18 subjects did not have quantifiable plasma concentrations of clascoterone. Urinary data have been provided on the basis of which the total urinary recovery can be estimated as 2.85% from a dose of 1mL of 1% cream (highest value). These results reflect the limited systemic exposure in as much as the total urinary recovery reflects the minimum parent compound that has been absorbed. No faecal elimination data has been provided, as a consequence of a proper mass balance study not having been performed. The applicant should have justified the absence of those data. Topically administered steroid hormone faecal elimination is likely to be negligible. Thus, faecal elimination data would not add much to the knowledge of clascoterone PK.

Judging from the data, as dose increases, % excreted decreases, which seems to be contradictory to the assumption of dose proportionality. Therefore, dose proportionality cannot be inferred from the data.

In study CB-03-01/04, results confirm the very low extent of absorption. Of note the increase in plasma concentration at 6 h from 1st to 14th day of administration in the 4 mL dose and from 10th to 14th day in the 8 mL dose. This concentration increase across the days of administration is consistent but not so evident in other times of collection and doses. But it can be speculated that there is an accumulation effect along the time. The meaning of this observation was discussed. The accumulation detected is only apparent. By averaging only the concentrations >LLOQ, the data shows that there is no sign of accumulation.

These findings indicate no difference in excretion of cortexolone and tetrahydrocortexolone (conjugated forms) between active and placebo treated subjects suggesting low systemic bioavailability of CB-03-01. This general conclusion has already been stated before. No quantitative measure of fraction absorbed has been estimated.

Distribution

A plasma protein binding of 84% to 89% in humans can be considered moderate to high and independent of concentrations as determined *in vitro*. No volume of distribution has been estimated due to scarcity of plasma data.

Metabolism

In vitro metabolism studies indicated that cortexolone 17α-propionate is metabolised to the main metabolite cortexolone via hydrolysis of the intermediate compound cortexolone 21-propionate. No unique metabolites for humans were found compared to tested species. The excreted fraction of the dose of cortexolone 17α-propionate, to which the subjects were exposed, was not higher than 0.5%. Excretion rate was quite constant, not varying with the dose.

Elimination

In vitro, in human hepatocytes, the primary metabolite was cortexolone, but glucuronide acid conjugates were also found, which is consistent with *in vivo* results. No unique human metabolites were observed and overall, the metabolic profile was similar between humans and the nonclinical species evaluated. Limited systemic exposure precludes a proper and complete PK perspective due to the lack of a proper mass balance study. Both cortexolone and tetrahydrocortexolone can be considered major metabolites, based on urinary excretion data.

In another *in vitro* study (B37653) in human plasma, cortexolone 21-propionate was identified as the main degradation product. However, cortexolone 21-propionate concentrations were not found *in vivo* in human plasma. Limited systemic exposure precludes a proper assessment of the *in vivo* pharmacokinetics of metabolites. The conversion of cortexolone to tetrahydrocortexolone has not been found in the study as presented. The applicant provided the following information: Cortexolone-21-propionate is an intermediate between clascoterone and cortexolone. Being an ester of a primary alcohol, cortexolone-21-propionate has the ester function that is more accessible to the active site of carboxylesterase than in the case of clascoterone.

PK was further approached in three studies (171-7151-203, 171-7151-203, and CB-03-01/28) analysing PK in the target population and giving a more complete information.

In study 171-7151-203, results confirm the accumulation of clascoterone after multiple dosing based on both Cmax and AUC. A long half-life is reported in study CB-03-01/33 as 26.80 hours confirming steady-state possibly being reached at 96 hours (study CB-03-01/04).

Results also confirm the low levels reached (Cmax on day 4 of 7.65 ng/mL). This study also confirms that cortexolone 21-propionate concentrations were not found *in vivo* in human plasma.

Genetic polymorphism: *In vitro* study CB-03-01/18 / Harlan 1389401 shows that polymorphic CYP450 enzymes (namely, CYP 2D6, 2C19, 2E1, 1A2) are possibly involved in clascoterone metabolism. Nevertheless, due to limited dermal absorption, the effect of polymorphism affecting CYP450 isozymes is probably negligible.

Plasma data from study CB-03-01/04: Repeat-Dose Pharmacokinetic Study in Healthy Adult Subjects reported under absorption section reports an **inter-subject variability** of Cmax and AUC of 73% and 58%, respectively. The **total variability** reported is very high, the CVs varying from 76.5% to 350%.

Dose proportionality and time dependencies

Plasma and urine data from study CB-03-01/04 do not support **dose proportionality**. The data reported from study CB-03-01/02: Single Ascending Dose-Ranging Pharmacokinetic Study in Healthy Adult Males (see above under Absorption) indicates that, as dose increases, % excreted in urine decreases, which seems to be contradictory to the assumption of dose proportionality.

Time dependency: Plasma data from study CB-03-01/04: Repeat-Dose Pharmacokinetic Study in Healthy Adult Subjects confirm the very low extent of absorption. Of note the increase in plasma concentration at 6 h from 1st to 14th day of administration in the 4 mL dose and from 10th to 14th day in the 8 mL dose. This concentration increase across the days of administration is consistent but not so evident in other times of collection and doses. But it can be stated that there is an accumulation effect along the time, taking into consideration that in other studies half-life is reported with values ranging from 9 to 26.80 hours. By averaging only the concentrations >LLOQ, the data shows that there is no sign of accumulation.

Table 6: Special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	0/142	0/142	0/142

There is only one study involving subjects 9 to <12 years of age.

Results from study CB-03-01/28 in patients aged 9 to <12 years of age showed that morning trough concentrations of CB-03-01 and cortexolone in plasma were generally below or near the LLOQ throughout the study with trough concentrations of CB-03-01 and cortexolone being similar on Days 7 and 14.

Pharmacokinetic interaction studies

In study CB-03-01/18 / Harlan 1389401: Evaluation of Inhibitory Effects of clascoterone (CB-03-01) on Human CYP450 Enzymes, the slight inhibition detected with isozymes CYP 1A2, 2C19, 2D6, 2B6 and 2E1, with an IC50 clearly exceeding the clascoterone concentrations in human plasma, suggests that an inhibitory interaction is unlikely.

The applicant has conducted an *in vitro* study to evaluate Clascoterone as inhibitor of the human ABC (efflux) transporters: BCRP and MDR1 and the human SLC (uptake) transporters: MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2. The results showed that clascoterone do not inhibit P-gp, BCRP, OAT1 and OATP1B3. A weak inhibition of MATEs, OATP1B1 and OCT2 with an IC50 > 7.87 Mm. Clascoterone is an in vitro inhibitor of OAT3 transporter with an estimated IC50 value of 8.15 µM.

Table 7: Inhibition Potential Results, Comparison of Co- and Pre-Incubation in Human Liver Microsomes

CB-03-01 (µM)	Activity Compared to Solvent Control (Mean of Three Replicates)			IC50 determination	
	Determined After Co-incubation (%)	Determined After Pre-incubation (%)	Ratio of Activity Co-incubation/ Pre-incubation	Pre-incubation	Co-incubation
CYP 2C8, amodiaquine as model substrate					
1	95.4	89.5	1.07	Moderate inhibition, IC_{50} ~41 µM	Slight inhibition at 50 µM, IC_{50} not determined
2	90.9	92.7	0.98		
5	65.2	95.8	0.68		
10	64.9	93.0	0.70		
25	56.7	83.1	0.61		
50	46.8	78.5	0.60		
CYP 2C9, diclofenac as model substrate					
1	109	92.1	nd	Slight inhibition at 50 µM, IC_{50} not determined	Slight inhibition at 25 and 50 µM, IC_{50} not determined
2	98.3	103	nd		
5	91.9	102	nd		
10	92.5	98.8	nd		
25	70.3	96.5	0.73		
50	56.9	71.6	0.79		
CYP 3A4, testosterone as model substrate					
1	94.3	115	nd	No inhibition	Slight inhibition, IC_{50} not determined
2	115	93.4	nd		
5	98.6	94.7	nd		
10	94.3	90.1	nd		
25	85.4	84.5	nd		
50	87.3	73.1	> 1.15		
CYP 3A4, midazolam as model substrate					
1	99.4	87.7	nd	Slight inhibition, IC_{50} not determined	Slight inhibition, IC_{50} not determined
2	88.2	93.3	nd		
5	90.1	91.3	nd		
10	81.3	95.4	nd		
25	71.4	86.4	0.83		
50	63.8	71.5	0.89		
CYP 3A4, midazolam as model substrate					
1	99.4	87.7	nd	Slight inhibition, IC_{50} not determined	Slight inhibition, IC_{50} not determined
2	88.2	93.3	nd		
5	90.1	91.3	nd		
10	81.3	95.4	nd		
25	71.4	86.4	0.83		
50	63.8	71.5	0.89		
CYP 2E1, chlorzoxane as model substrate					
1	87.7	86.1	nd	No inhibition	No inhibition
2	89.4	116	nd		
5	87.4	100	nd		
10	87.3	86.9	nd		
25	109	114	nd		
50	116	121	nd		

In study CB-03-01/16 / Harlan 1389402 Evaluation of Induction Properties of CB-03-01 on Human CYP1A2, 2B6 and 3A4 results showed that CB-03-01 up to 50 µM was not an inducer for the tested CYP enzymes.

Human plasma concentrations are far below 50 µM. Therefore, the applicant consider that an enzyme induction is unlikely.

The applicant has conducted an *in vitro* study to evaluate Clascoterone as inhibitor of the human ABC (efflux) transporters: BCRP and MDR1 and the human SLC (uptake) transporters: MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2. The results showed that clascoterone do not inhibit P-gp, BCRP, OAT1 and OATP1B3. A weak inhibition of MATEs, OATP1B1 and OCT2 with an IC50 > 7.87 Mm. Clascoterone is an in vitro inhibitor of OAT3 transporter with an estimated IC50 value of 8.15 µM. This result suggests that an inhibitory interaction is unlikely.

Given the *in vitro* results on inhibition and induction the applicant did not perform any *in vivo* interactions studies.

Pharmacokinetics using human biomaterials

The applicant performed eight studies using human biomaterials on dermal penetration, protein binding, metabolism and inhibition and inducing properties of clascoterone. These studies provided complementary valuable information due to the lack of a complete *in vivo* PK profile.

Description	Test System	Dose or Concentration	Report Number
Absorption: Human Skin Penetration and Permeation			
Skin penetration/ permeation	Human cadaver skin	0.92 – 0.99%	Skin Penetration of CB-03-01
Skin penetration/ permeation	Dermatomed human skin	639.1, 901.5, 979.4, 3432.5, 10001.1 ng/mL	CPS/01
Distribution: Plasma Protein Binding			
Plasma Protein Binding	Plasma from mice, rats, rabbits, minipigs, humans	0.5 to 500 ng/mL	MC11M-0048
Metabolism (*In Vitro* Studies)			
Metabolism in human plasma	Human plasma	0.1 mg/mL	B37653
Hepatic metabolism	Hepatocytes from mice, rats, rabbits, minipigs, humans	10 µM	MC11M-0047
Drug-Drug Interactions			
Effects on cytochrome P450	Human hepatocytes	1, 2, 5, 10, and 50 µM	CB-03-01/16
Effects on cytochrome P450	Human liver microsomes	1, 2, 5, 10, 25, and 50 µM	CB-03-01/18
Effects on testosterone metabolism	Reconstructed human epidermis	10^{-3}, 10^{-4}, 10^{-5} M	GT050709

2.5.2.2. Pharmacodynamics

Mechanism of action

Clascoterone, (INN, ATC code D10AX06), chemical name cortexolone 17α-propionate and referred to as CB-03-01 throughout development with its anti-androgenic potential, offers a novel mechanism of action compared to current topical treatments for acne vulgaris.

Primary and Secondary pharmacology

The primary pharmacodynamics studies explored clascoterone effects on:

- in vitro binding property to androgen receptor in report 10631
- sebocyte lipid and inflammatory cytokine production in reports RD301-002, RD301-002a, Rosette 2019
- topical anti-androgenic activity in reports 04008, CB-03-01/01, 09006, 04010, Celasco 2004
- systemic anti-androgenic activity in report 04010.

Clascoterone did not exert in the model of Wistar rat any systemic anti-androgen properties and only a weak glucocorticoid like activity when administered in SC.

The secondary pharmacodynamics studies explored:

- systemic anti-androgenic and glucocorticoid activity, effect on gonadotropin hypersecretion and effect on plasma corticosterone in Celasco 2004
- off-target binding (screening assay) in report 13142
- GnRH (LH-RH) receptor binding assay in report 11161
- immunomodulatory effects in report 04011
- estrogenic activity in report CB-03-01/12
- anti-inflammatory activity in report 11R10-07012
- progestinic activity in report CB-03-01/11.

Clascoterone showed no effect on GnRH activity and binding, plasma corticosterone levels, oestrogen and progesterone activity, binding to 54 receptors (to address selectivity), immune functions ex vivo and inflammation. CB-03-01 decreased significantly the plasma corticosterone levels in rats but has no estrogenic activity.

The safety pharmacology studies assessed:

- K+ channel (hERG) assay in report 13142
- CNS (Irwin test, temperature) in report CB-03-01/03
- cardiovascular impact in report CB-03-01/14.

The pilot hERG Assay of CB-03-01 allowed to conclude that clascoterone can be considered a low-potency hERG-channel inhibitor. Clascoterone did not affect behaviour or body temperature at any dose or timepoint in the behavioural Irwin test after single subcutaneous administration in the rat. No pharmacodynamics drug interactions studies were performed.

Overall, no effects on blood pressure, heart rate, ECG, and body temperature and QTc interval duration were observed.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics (PK)

Winlevi is a locally applied, locally acting medicinal product intended for the treatment of acne vulgaris in adults and adolescents. For this reason, PK data is very limited. The clinical PK programme includes several studies encompassing healthy subjects and patients with acne vulgaris, including adolescents aged 12 and older. The applicant did not provide a study evaluating PK in patients treated according to the proposed dose recommendation scheme (2 g BID per day up to 5 g total daily dose), data for higher doses (i.e., 4 and 6 g BID) were presented instead. The posology is supported mainly by PD data.

Absorption has been evaluated in two *in vitro* studies. The results show that clascoterone in a 1% cream formulation does penetrate human skin. How this finding relates to the *in vivo* behaviour is hard to establish in a quantitative way. From human studies, it was found that clascoterone is absorbed in a very low, almost negligible extent even at the higher doses employed.

In order to quantify the parent compound and metabolites, six bioanalytical methods have been developed and validated. Bioanalytical methods were properly validated and stability of analytes as reported was appropriate. Bioanalytical methods were properly validated and stability of analytes as reported was appropriate. Stability of analytes as reported was appropriate to account for the time between sampling, storage and laboratory handling.

The PK data analysis methodology is standard. The scarcity of data did not allow a proper PK analysis and modelling to obtain the planned PK parameters.

Absorption has been evaluated to penetrate human skin in two *in vitro* studies. From human studies, it was found that clascoterone is absorbed in a very low extent. Urinary data have been provided on the basis of which the total urinary recovery can be estimated as 2.85% from a dose of 1mL of 1% cream (highest value). These results reflect the limited systemic exposure in as much as the total urinary recovery reflects the minimum parent compound that has been absorbed.

No quantitative measure of fraction absorbed has been estimated, due to the low plasma levels and absence of comparative data. These results confirm the very low extent of absorption. Of note, the increase of % excreted along time. This may raise the suspicion of high accumulation of parent and metabolites across the number of administrations. As it relates to safety in multiple dosing, the applicant provided the following comment: Despite the low percentage excretion in urine and low plasma exposure with multiple doses over a period of up to 6 weeks, neither systemic exposure nor an increase in urinary excretion of clascoterone and its metabolites led to serious safety concerns in treated patients. No proper mass balance study has been performed. The applicant has justified the absence of those data. Topically administered steroid hormone faecal elimination is likely to be negligible. Thus, faecal elimination data would not add much to the knowledge of clascoterone PK.

As for distribution, a plasma protein binding of 84% to 89% in humans can be considered moderate to high. No volume of distribution has been estimated due to scarcity of plasma data.

In vitro, in human hepatocytes, the primary metabolite was cortexolone, but glucuronide acid conjugates were also found. However, cortexolone 21-propionate concentrations were not found *in vivo* in human plasma.

Trough concentrations of CB-03-01 and cortexolone in plasma were generally below or near the LLOQ throughout multiple dosing.

Due to limited dermal absorption, the effect of genetic polymorphism affecting CYP450 isozymes is negligible.

A consistent increase of the concentration across the days of administration shows there is an accumulation effect over time. Steady-state has been reached after 96 hours of administration, consistent with half-life values ranging up to 26.80 hours.

Plasma and urine data from study CB-03-01/04 do not support **dose proportionality**. The data reported from study CB-03-01/02: Single Ascending Dose-Ranging Pharmacokinetic Study in Healthy Adult Males indicates that, as dose increases, percentage excreted in urine decreases, which seems to be contradictory to the assumption of dose proportionality. Therefore, dose proportionality cannot be inferred from the data. However, there are factors that can explain the lack of proportionality found. The applicant states that dose proportionality cannot be considered established and claimed in this study.

Inter-subject variability of Cmax and AUC of 73% and 58%, respectively. The total variability reported is very high, the CVs varying from 76.5% to 350%.

PK results in the target population confirm and is essentially similar to the findings in healthy human subjects.

PK parameters were not studied in special populations (e.g., subjects with impaired renal or hepatic function, sex, race, or weight) due to the low systemic bioavailability of clascoterone. Also, the effects of extrinsic factors (smoking, concomitant medication, diet) were not explored. Studies were not conducted in subjects 65 years of age and older, a population that is not generally affected by acne vulgaris. However, the impact of skin changes in the elderly on drug permeation warrants consideration, especially given the absence of instructions for this population. In subjects aged 12 to 18, the PK of cortexolone 17α-propionate did not significantly differ from adults.

Given the *in vitro* results on inhibition and induction the applicant did not perform any *in vivo* interactions studies.

In various clinical studies, a very low level of clascoterone and its metabolites is reported. This feature conditions most of the PK characterisation in this report and consequences thereof. In most of the clinical studies, plasma data did not reach LLOQ. The scarcity of data did not allow a proper PK analysis and modelling to obtain the planned PK parameters.

Issues were related to dose proportionality, lack of faecal data as a result of the lack of a proper mass balance study, several issues on accumulation effect along the time and steady-state evaluation as related to half-life values reported, as well as the conversion of cortexolone to tetrahydrocortexolone. They were responded to satisfactorily.

PK DDI

Regarding the PK interaction studies, the ability of clascoterone (CB-03-01) to be direct and/or time-dependant inhibitors, of CYP1A2, 2B6, CYP2C8, CYP2C9, 2C19, 2D6, 2E1 and 3A4 was assessed as part of three assays: CB-03-01/16 / Harlan 1389402, and CB-03-01/18 / Harlan 1389401.

The study setups were adequate with an appropriate system, human liver microsome (HLM), ranges of concentrations, from 1 up to 50 µM covering the worst expected at systemic level (i.e. 5.58 µM), control substrates and inhibitors. For the time-dependent inhibition (TDI), the experimental conditions are also fulfilled.

Results from these studies show that, at the highest tested concentrations of 50 µM clascoterone did not exert any direct or time-dependent inhibition on CYP1A2, CYP2C19, CYP2D6, CYP2B6, and CYP2E1. Only a slight reversible and/or time-dependent inhibition occurred on CYP2C8, CYP2C9 and CYP3A4 with IC50= ~41 µM (reversible inhibition of CYP2C8) and > 50 µM for the others. These IC50 values and their corresponding Ki or KI values are higher than the estimated systemic concentration of clascoterone, i.e. 5.58 µM. Then clinically relevant DDI due to the inhibition of CYP2C8, CYP3A4 and CYP2C9 by clascoterone (CB-03-01) can be ruled out.

Study CB-03-01/16 was carried out to assess clascoterone (CB-03-01) induction on CYP1A2, 2B6 and 3A4 in individual human cryopreserved hepatocytes of three individual donors. It was concluded that clascoterone does not induce the enzymatic activity of CYP1A2, 2B6, and 3A4 at concentrations up to 50 µM.

The applicant has conducted an in vitro DDI study to evaluate the potential inhibitory effect of Clascoterone (CB-03-01) on transporters P-gp, BCRP, OCT2, MATEs, OAT1/3, OATP1B1 and 1B3 in the range of 0.01-10 µM, covering the concentration expected at the worst-case scenario. The results showed that clascoterone do not inhibit P-gp, BCRP, OAT1 and OATP1B3. A weak inhibition of MATEs, OATP1B1 and OCT2 with an IC50 > 7.87 Mm. Clascoterone is an in vitro inhibitor of OAT3 transporter with an estimated IC50 value of 8.15 µM. However, based on these results the clascoterone is not expected to be a clinical inhibitor of these transporters since its IC50 values were not detected or are much higher than the concentration expected at the worst-case scenario. Therefore, the DDI risk of clascoterone with these transporters substrates could be ruled out.

In view of the reproductive toxicity and the recommendation for contraception, a clinical DDI study is considered necessary.

Pharmacodynamics (PD)

For **primary pharmacology** exploration, as one of the pathogenetic mechanisms of acne vulgaris is characterised by the accumulation of fatty acids and inflammation in the sebaceous glands, the effect of clascoterone (or CB-03-01) on the AR-dependent production of lipids and the stimulation of inflammatory pathways from cultured primary human sebocytes was evaluated. The hamster flank organ acne vulgaris model had been chosen which is acceptable as it composed of clusters of large sebaceous glands.

For **secondary pharmacology** exploration, clascoterone showed no effect on GnRH activity and binding, plasma corticosterone levels, oestrogen and progesterone activity, binding to 54 receptors (to address selectivity), immune functions ex vivo and inflammation. CB-03-01 decreased significantly the plasma corticosterone levels in rats but has no estrogenic activity.

For **safety pharmacology,** the pilot hERG Assay of clascoterone allowed to conclude that clascoterone can be considered a low-potency hERG-channel inhibitor.

Clascoterone did not affect behaviour or body temperature at any dose or timepoint in the behavioural Irwin test after single subcutaneous administration in the rat.

Overall, no effects on blood pressure, heart rate, ECG, and body temperature and QTc interval duration were observed.

PK/PD

Since the applicant claimed that this is a locally applied locally acting (LALA) product with no expected systemic efficacy, no data to assess the relationship between plasma concentration and effect was provided.

PD uncertainties regarding clascoterone mechanism of action, anti-androgenic effects and potential risks on HPA axis including its impact on corticotropic and gonadotropic activities should be overcome by clinical data.

2.5.4. Conclusions on clinical pharmacology

It is not clear how clascoterone acts on the androgen receptor (AR) and if the claimed mechanism of action on acne is primarily due to its antagonism on AR. The scarcity of PK data did not allow a proper PK analysis in particular regarding the systemic exposure of clascoterone when topically applied twice daily at the dose of 2 g per day for a long-term period. Plasma levels are extremely low and not quantifiable in several subjects leading to very wide variability margins. In addition, PK/PD relationship is also uncertain with possible accumulation in case of reiterated administration which could be non-proportional to the dose and PD uncertainties regarding its mechanism of action, anti-androgenic effects and potential risks on HPA axis including its impact on corticotropic and gonadotropic activities, which makes it difficult to predict clascoterone cream behaviour particularly in adolescents from 12 years to less than 18 years of age. They should be overcome by clinical data.

2.5.5. Clinical efficacy

Clascoterone is also called in the text as CB-03-01 or cortexolone 17α-propionate.

Description of Clinical Efficacy Studies of CB-03-01 for Acne

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
171-7151-201 13 sites in the US	11 Jun 2012 to 19 Feb 2014	**Phase 2**, double-blind, vehicle-controlled, dose escalation	CB-03-01 cream: 0.1% BID: **72/58** 0.5% BID: **76/64** 1% QD: **70/61** 1% BID: **70/59** Vehicle QD or BID: **75/62** Applied for 12 weeks	**Subjects ≥ 12 years** old with facial acne vulgaris, **IGA score 2 to 4**, 20 to 75 ILC*, and 20 to 100 NILC*
CB-03-01/03 4 sites in Romania	13 Jan 2009 to 01 Sep 2009	**Phase 2**, randomized, double-blind, active-controlled	CB-03-01 1% cream: **30/27** Retin-A® 0.05% cream: **32/26** Vehicle: **15/14** QD (evening) for 8 weeks	**Adult males** (18 to 45 years) with facial acne vulgaris **IGA score 2 or 3**, 20 to 100 TLC, and 10 to 50 ILC
CB-03-01/25 45 sites in the US, 7 sites in Ukraine,	21 Jan 2016 to 11 Apr 2018	**Phase 3**, multicentre, randomized, double-blind, vehicle-controlled,	CB-03-01 1% cream: **353/287** Vehicle: **355/290** BID for 12 weeks	**Subjects ≥ 9 years** old with moderate or severe facial acne vulgaris, **IGA score**

3 sites in Republic of Georgia		parallel-group study		**3 or 4**, 30 to 75 ILC, and 30 to 100 NILC
CB-03-01/26 12 sites in Poland 10 sites in the US 9 sites in Romania 8 sites in Bulgaria 6 sites in Republic of Georgia 3 sites in Serbia	16 Nov 2015 to 21 Feb 2018	**Phase 3**, multicentre, randomized, double-blind, vehicle-controlled, parallel-group study	CB-03-01 1% cream: **369/302** Vehicle: **363/282** BID for 12 weeks	**Subjects ≥ 9 years** old with moderate or severe facial acne vulgaris, **IGA score 3 or 4**, 30 to 75 ILC, and 30 to 100 NILC
CB-03-01/27 40 sites in the US 11 sites in Poland, 8 sites in Romania, 6 sites in Bulgaria, 4 sites in Ukraine, 3 sites in Serbia, 3 sites in Republic of Georgia	09 Mar 2016 to 31 Aug 2018	**Phase 3**, open-label, long-term follow-up with application on **face and trunk** to maximize exposure	CB-03-01 1% cream: **n=609** BID for up to 9 months	Subjects who completed Study CB-03-01/25 or CB-03-01/26

ILC: Inflammatory Lesion Count
NILC: Non Inflammatory Lesion Count

Table 8: Investigator's Global Assessment Scale

0	Clear	Absence of active disease with no inflammatory or non-inflammatory lesions.
1	Almost Clear	Rare non-inflammatory lesions with no more than one small inflammatory lesions.
2	Mild	Some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only; no nodular/cystic lesions).
3	Moderate	Up to many non-inflammatory lesions and may have some inflammatory lesions but no more than one nodular/cystic lesion.
4	Severe	Up to many non-inflammatory lesions and inflammatory lesions but no more than a few nodular/cystic lesions.

2.5.5.1. Dose response study

Study 171-7151-201

A multicentre, randomized, double-blind, vehicle-controlled, consecutive groups, dose escalation study in male and female subjects 12 years or older with acne vulgaris on the face.

Population: Selection of the dose was performed in the population targeted for the MA: adult and adolescent ≥12 years with facial acne vulgaris and an IGA score of 2 to 4 defining a mild to severe acne.

Main exclusion criteria:

- Subject had greater than 3 facial nodules/cysts (nodule/cyst is defined as an inflammatory lesion greater than or equal to 0.5 cm in size with or without cystic changes)

- Subject had facial hair that could have interfered with the study assessments in the opinion of the investigator
- Subject had used any of the following topical anti-acne preparations or procedures on the face:

  • Topical anti-acne treatments including but not limited to over-the-counter (OTC) acne cleaners or treatments, benzoyl peroxide, antibiotics, azelaic acid, sulfa based products, corticosteroids and salicylic acid within two (2) weeks of the initiation of treatment.

  • Retinoids, including tazarotene, adapalene, tretinoin, within four (4) weeks of the initiation of treatment.

  • Light treatments, microdermabrasion or chemical peels within eight (8) weeks of the initiation of treatment.
- Subject had used the following systemic anti-acne medications:

  • Corticosteroids (including intramuscular and intralesional injections) within four (4) weeks of the initiation of treatment. Inhaled, intranasal or ocular corticosteroids are allowed if use is stable (stable use is defined as dose and frequency unchanged for at least four weeks prior to the initiation of treatment).

  • Antibiotics within four (4) weeks of the initiation of treatment with the exception of five (5) days or less of antibiotic therapy during this period, BUT with no antibiotics use permitted within one (1) week prior to the initiation of treatment.

  • Spironolactone within eight (8) weeks of the initiation of treatment with the exception of five (5) days or less of spironolactone therapy during this period, BUT with no spironolactone use permitted within one (1) week prior to the initiation of treatment.

  • Retinoid therapy within six (6) months of the initiation of treatment.

  • Other systemic therapy which may materially affect the subject's acne in the opinion of the investigator.

Primary Endpoints:

• Proportion of subjects achieving success in each treatment group at Week 12/EOS (End of Study) using the dichotomized IGA with success defined as a score of "clear" or "almost clear" (IGA Score of 0 or 1) AND a two or more grade improvement from Baseline.

• Absolute change from Baseline in inflammatory AND non-inflammatory lesion counts in each treatment group at Week 12/EOS.

The IGA score is a well-known and generally accepted scale representing a static quantitative evaluation of overall acne severity.

Characteristics: Demographic data were generally comparable across all five treatment groups. At baseline, the majority of ITT subjects (247/363, 68.0%) had grade 3 = moderate acne.

Endpoints results: At 12 weeks, even if very modest the highest dosage of 1% BID dosage showed the highest rate of success: from 8.6 to 10.9% (NS).

Table 9: Dose escalation study

Population	**CB-03-01 0.1% BID**	**CB-03-01 0.5% BID**	**CB-03-01 1% QD**	**CB-03-01 1% BID**	**VEHICLE QD or BID**	P-value†
Proportion of subjects achieving success at Week 12: IGA Score of 0 or 1 AND a ≥ 2-grade improvement from Baseline						
PP	(N=57)	(N=64)	(N=52)	(N=55)	(N=59)	**0.4139**
Success	5 (8.8%)	3 (4.7%)	2 (3.8%)	6 (**10.9%**)	2 (3.4%)	-
Total Inflammatory Lesion Counts Change from Baseline at Week 12/EOS*						
PP	(N=57)	(N=64)	(N=52)	(N=55)	(N=59)	0.0468
Mean	-8.3	-5.8	-10.1	**-12.3**	-9.1	
Total NON-Inflammatory Lesion Counts Change from Baseline at Week 12/EOS*						
PP	(N=55)	(N=62)	(N=52)	(N=55)	(N=57)	0.0468
Mean	-8.7	-6.1	-8.4	**-15.5**	-6.7	

†Fisher's exact test (two-tailed)

*End of Study, †Rank Analysis of Covariance; ITT: 1% BID < 0.5%, 1% QD and VEHICLE; PP: 1% BID < 0.5% and VEHICLE.

Patients who had a baseline IGA of 4:

- Clascoterone 0.1% BID: 6
- Clascoterone 0.5% BID: 8
- Clascoterone 1% QD: 11
- Clascoterone 1% BID: 20
- Vehicle: 11

2.5.5.2. Main studies

The two pivotal Phase 3 Studies CB-03-01/25 and CB-03-01/26 had the same design, endpoints, hypotheses and titles:

A Phase 3, Multicentre, Randomised, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Cortexolone 17α-Propionate (CB-03-01) Cream, 1% Applied Twice Daily for 12 Weeks in Subjects with Facial Acne Vulgaris.

Methods

Patients were randomised 1:1 to twice-daily treatment of the whole face with clascoterone or vehicle to be applied for up to 12 weeks.

- **Study Participants**

Main inclusion criteria

- Subject male or non-pregnant female, 9 years of age or older.
- Subject had an IGA score of 3 or 4 [0 (clear) to 4 (severe) scale].
- Subject had facial acne vulgaris, (which may have included the nose), with at least 30 to a maximum of 75 inflammatory lesions (papules, pustules, and nodules) and 30 to a maximum of 100 non-inflammatory lesions (open and closed comedones).
- Subject used the same type and brand of make-up, other facial products (exclusive of prescription/over-the-counter [OTC] acne cleansers) and hair products (e.g., shampoo, gel, hair spray, mousse, etc.) for at least one month prior to the Baseline Visit and agreed to continue his/her other general skin and hair care products and regimen for the entire study.

Main exclusion criteria

- Subject was pregnant, lactating, or was planning to become pregnant during the study.
- Subject had any skin pathology or condition that could have interfered with the evaluation of the test products or required the use of interfering topical or systemic therapy.
- Subject had greater than two facial nodules.
- Subject had nodulocystic acne.
- Subject had facial hair that could have interfered with the study assessments in the opinion of the investigator.
- Subject had the need or planned to be exposed to artificial tanning devices or excessive sunlight during the trial.
- Subject used any of the following topical anti-acne preparations or procedures on the face
    - Topical anti-acne treatments including, but not limited to, OTC acne cleansers or treatments, benzoyl peroxide, antibiotics, azelaic acid, sulfa based products, corticosteroids and salicylic acid within two (2) weeks of the initiation of treatment.
    - Retinoids, including tazarotene, adapalene, tretinoin, within four (4) weeks of the initiation of treatment.
    - Light treatments, microdermabrasion, or chemical peels within eight (8) weeks of the initiation of treatment.
- Subject had used the following systemic anti-acne medications:
    - Corticosteroids (including intramuscular and intralesional injections) within four (4) weeks of the initiation of treatment. Inhaled, intranasal or ocular corticosteroids were allowed if use was stable (stable use was defined as dose and frequency unchanged for at least four (4) weeks prior to the initiation of treatment).

- Antibiotics within four (4) weeks of the initiation of treatment with the exception of five (5) days or less of antibiotic therapy during this period, BUT with no antibiotics use permitted within one (1) week prior to the initiation of treatment.
- Spironolactone within eight (8) weeks of the initiation of treatment with the exception of five (5) days or less of spironolactone therapy during this period, BUT with no spironolactone use permitted within one (1) week prior to the initiation of treatment.
- Retinoid therapy within six (6) months of the initiation of treatment.
- Other systemic therapy which could materially affect the subject's acne in the opinion of the investigator.

- **Treatments**

Eligible subjects were randomised (1:1) to CB-03-01 cream, 1% or Vehicle cream.

At the first visit, the subjects were instructed to wash their entire face (the area to be treated) with mild soap and water and then dry the area gently. The first application of cream was to be applied in the office at Visit 1 under supervision of the study staff.

About 1 gram of the cream was dispensed onto a fingertip and applied to the face by dabbing small amounts gently on multiple regions of the face (e.g., forehead, nose, cheeks, and chin). Using a fingertip, the cream was spread to provide a thin, uniform layer of the cream over the entire face.

- **Objectives**

Primary objective: to determine the safety and efficacy of CB-03-01 cream, 1% versus the vehicle cream applied twice daily for 12 weeks in subjects with facial acne vulgaris.

Superiority hypothesis vs vehicle cream with the following size of effect for each primary endpoint:

- An IGA success rate of (continuity corrected) 14.00% for CB-03-01 cream and 2.17% for vehicle cream (odds ratio=7), sample size was estimated to be 202 subjects per treatment group.
- A mean absolute change from Baseline in NILC of -22 for CB-03-01 cream and -1 for vehicle cream (standard deviation=17), sample size was calculated to be 19 subjects per treatment group.
- A mean absolute change from Baseline in ILC of -14 for CB-03-01 cream and -11 for vehicle cream (standard deviation=17), sample size was calculated to be 334 subjects per treatment group.

- **Outcomes/endpoints**

The primary efficacy endpoints (hierarchical) were:

- P1: Proportion of subjects in each treatment group achieving "success" at Week 12, with "success" defined as an IGA score of "clear (score=0)" or "almost clear (score=1)" AND at least a two-point reduction in IGA compared to Baseline.
- P2: Absolute change from Baseline in NILC in each treatment group at Week 12.
- P3: Absolute change from Baseline in ILC in each treatment group at Week 12.

The secondary efficacy endpoints (hierarchical) were:

- S1: Absolute change from Baseline in total lesion count (TLC) in each treatment group at Week 12.

- S2: Percent change from Baseline in TLC in each treatment group at Week 12.
- S3: Percent change from Baseline in NILC in each treatment group at Week 12.

S4: Percent change from Baseline in ILC in each treatment group at Week 12.

- **Sample size**

Assumptions used for sample size calculation for studies CB-03-01/25 and CB-03-01/26 were estimated from the dose escalation study (171-7151-201), using a subset of subjects with 30 to 75 inflammatory lesions and 30 to 100 non-inflammatory lesions at baseline. Sample size calculations were performed on the basis of the formulas for testing superiority in terms of mean differences and odds ratio of Wang. It was determined that at least 350 subjects in each treatment group were to be included in each Phase 3 study to provide 90% power with the chosen primary endpoints.

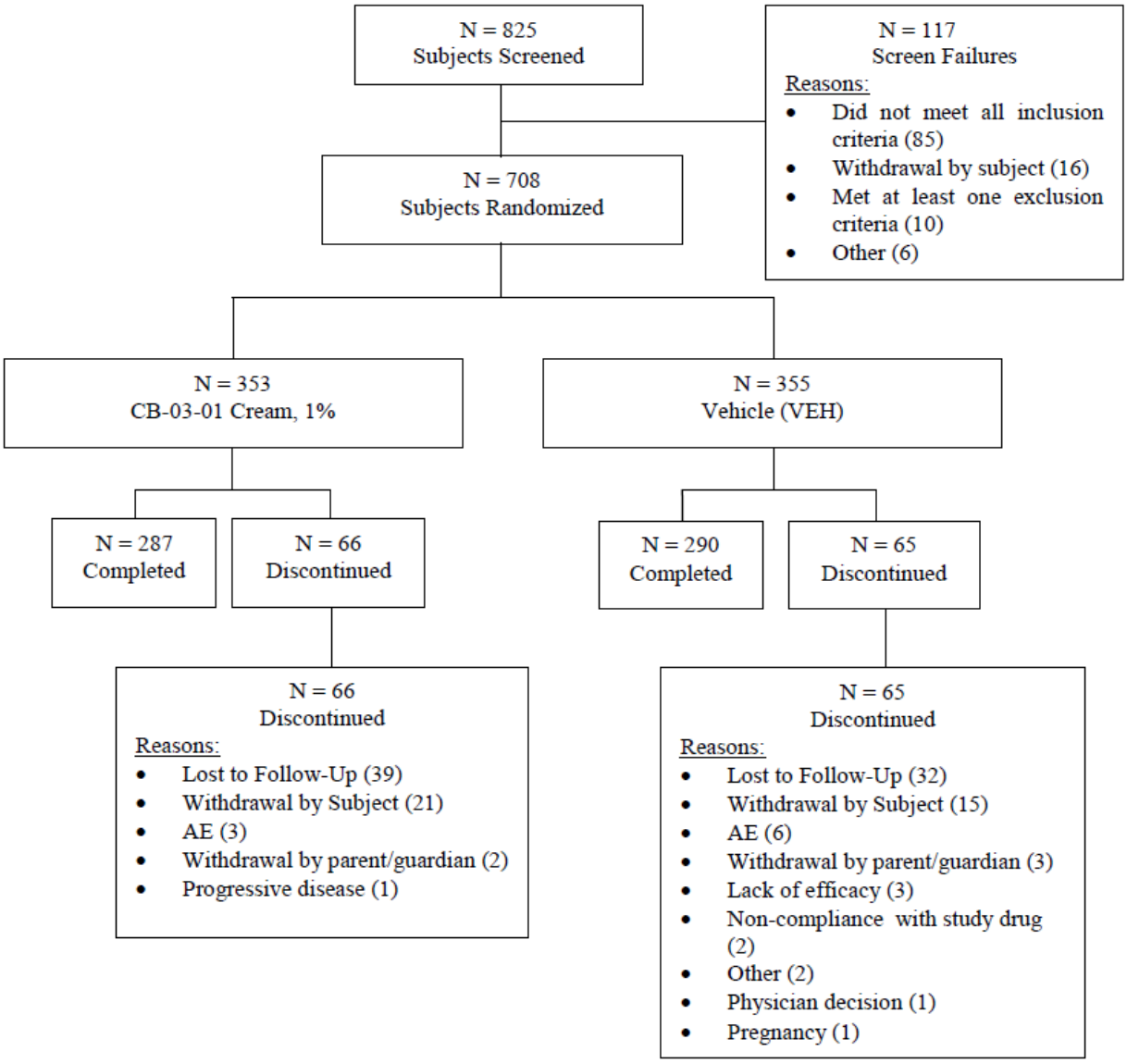
- **Randomisation and blinding (masking)**

Patients were randomised 1:1 to twice-daily treatment of the whole face with clascoterone or vehicle to be applied for up to 12 weeks.

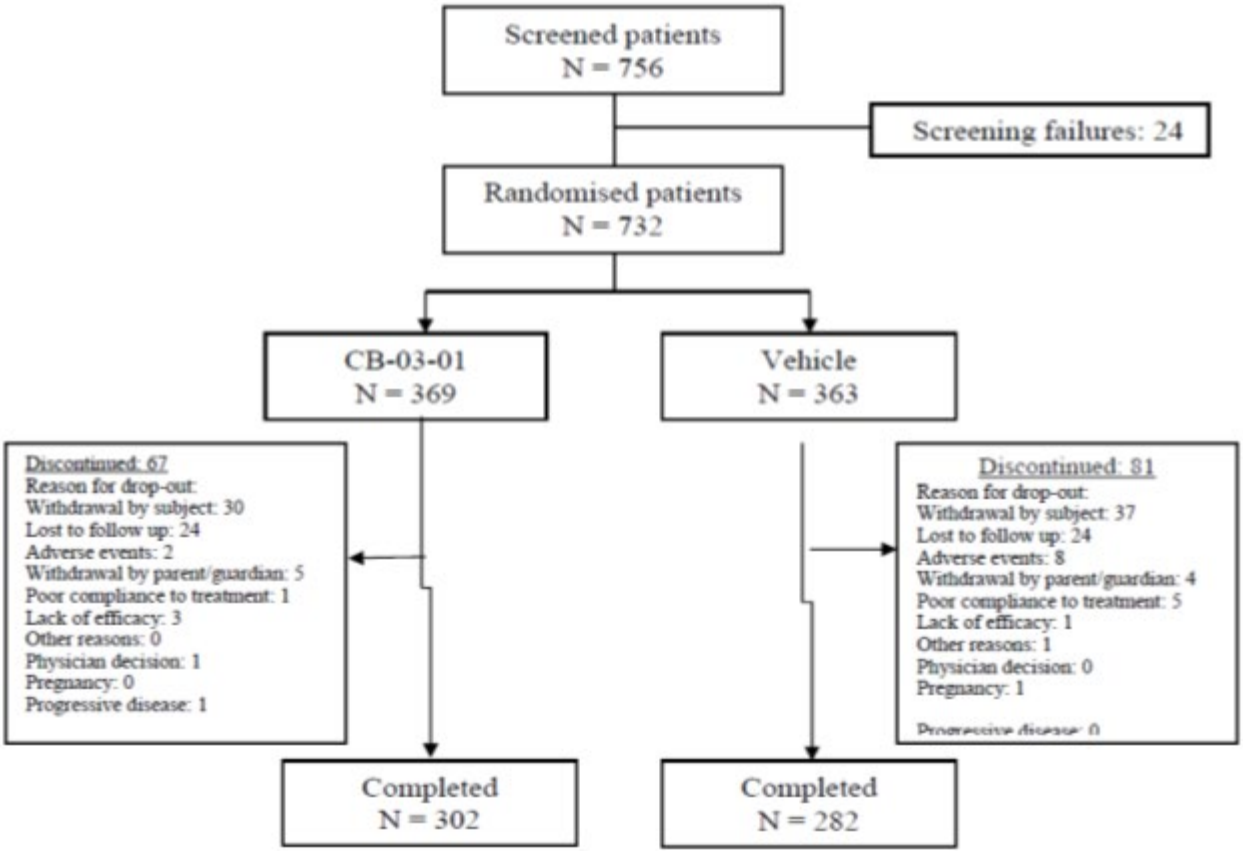
The randomisation of subjects and management of the drug supply was supported by the software Datatrak One to receive CB-03-01 cream or vehicle cream in a 1:1 ratio and it generated a randomised study drug container list with a block size of 4.

- **Participant flow**

Study CB-03-01/25: 708 subjects were randomised with 353 in the clascoterone (CB-03-01) group and 355 in the vehicle group.


N = 825
Subjects Screened
N = 117
Screen Failures
Reasons:
Did not meet all inclusion criteria (85)
Withdrawal by subject (16)
Met at least one exclusion criteria (10)
Other (6)
N = 708
Subjects Randomized
N = 353
CB-03-01 Cream, 1%
N = 355
Vehicle (VEH)
N = 287
Completed
N = 66
Discontinued
N = 290
Completed
N = 65
Discontinued
N = 66
Discontinued
Reasons:
Lost to Follow-Up (39)
Withdrawal by Subject (21)
AE (3)
Withdrawal by parent/guardian (2)
Progressive disease (1)
N = 65
Discontinued
Reasons:
Lost to Follow-Up (32)
Withdrawal by Subject (15)
AE (6)
Withdrawal by parent/guardian (3)
Lack of efficacy (3)
Non-compliance with study drug (2)
Other (2)
Physician decision (1)
Pregnancy (1)

Study CB-03-01/26: 732 subjects were randomised with 369 in the CB-03-01 group and 363 in the vehicle group.



- **Recruitment**

Dates defining the periods of recruitment and follow-up:

- Study CB-03-01/25: 21 January 2016 to 11 April 2018
- Study CB-03-01/26: 16 November 2015 to 21 February 2018

- **Conduct of the studies**

Study CB-03-01/25: A post-hoc analysis of P3 was performed by adding Fitzpatrick skin type as fixed effect based on the results of the analysis of the centre by treatment interaction for absolute change from Baseline in ILC at Week 12.

Study CB-03-01/26: No protocol amendments were implemented.

In order to investigate the impact of data collected during anticipated visit 4 on the efficacy endpoints, additional post-hoc sensitivity analyses were conducted on the primary and secondary efficacy endpoints excluding data from anticipated visit 4 of discontinued subjects. The data of discontinued subjects who underwent an anticipated visit 4 (before Day 70) were treated as missing data supposing that they were not indicative of the treatment effect at week 12.

- **Baseline data**

Summary of Demographic and Baseline Characteristics in Phase 3 Pivotal Studies

Characteristic	Study CB-03-01/25		Study CB-03-01/26		Total	
	CB-03-01 N = 353	Vehicle N = 355	CB-03-01 N = 369	Vehicle N = 363	CB-03-01 N = 722	Vehicle N = 718
Age (years)						
Mean (SD)	20.0 (6.65)	19.9 (6.77)	19.3 (5.63)	19.0 (5.39)	19.6 (6.16)	19.4 (6.12)
Median	18.0	18.0	18.0	18.0	18.0	18.0
Min, Max	10, 58	9, 50	10, 50	11, 42	10, 58	9, 50
Sex, n (%)						
Male	132 (37.4)	140 (39.4)	126 (34.1)	142 (39.1)	258 (35.7)	282 (39.3)
Female	221 (62.6)	215 (60.6)	243 (65.9)	221 (60.9)	464 (64.3)	436 (60.7)
Race, n (%)						
Caucasian	298 (84.4)	297 (83.7)	357 (96.7)	348 (95.9)	655 (90.7)	645 (89.8)
Black	31 (8.8)	38 (10.7)	7 (1.9)	6 (1.7)	38 (5.3)	44 (6.1)
Asian	9 (2.5)	10 (2.8)	0	4 (1.1)	9 (1.2)	14 (1.9)
Other[a]	15 (4.2)	10 (2.8)	5 (1.4)	5 (1.4)	20 (2.8)	15 (2.1)
Ethnicity, n (%)						
Hispanic or Latino	94 (26.6)	80 (22.5)	20 (5.4)	9 (2.5)	114 (15.8)	89 (12.4)
Not Hispanic or Latino	259 (73.4)	275 (77.5)	349 (94.6)	354 (97.5)	608 (84.2)	629 (87.6)
BMI, kg/m^2						
Mean (SD)	24.47 (6.487)	24.66 (6.361)	22.13 (4.049)	22.03 (3.943)	23.28 (5.503)	23.33 (5.436)
Median	23.10	23.00	21.20	21.20	22.10	22.00
Min, Max	13.6, 77.1	11.9, 57.9	13.2, 39.8	15.5, 40.6	13.2, 77.1	11.9, 57.9
Fitzpatrick skin type, n (%)[b]						
I	7 (2.0)	7 (2.0)	7 (1.9)	12 (3.3)	14 (1.9)	19 (2.6)
II	111 (31.4)	111 (31.3)	122 (33.1)	107 (29.5)	233 (32.3)	218 (30.4)
III	122 (34.6)	121 (34.1)	170 (46.1)	166 (45.7)	292 (40.4)	287 (40.0)
IV	63 (17.8)	64 (18.0)	57 (15.4)	54 (14.9)	120 (16.6)	118 (16.4)
V	27 (7.6)	23 (6.5)	7 (1.9)	21 (5.8)	34 (4.7)	44 (6.1)
VI	23 (6.5)	29 (8.2)	6 (1.6)	3 (0.8)	29 (4.0)	32 (4.5)
Investigator's Global Assessment (IGA), n (%)						
Moderate	292 (82.7)	291 (82.0)	305 (82.7)	313 (86.2)	597 (82.7)	604 (84.1)
Severe	61 (17.3)	64 (18.0)	64 (17.3)	50 (13.8)	125 (17.3)	114 (15.9)
Inflammatory Lesion Count						
Mean (SD)	42.4 (11.77)	42.9 (12.31)	42.9 (12.20)	41.3 (10.96)	42.6 (11.99)	42.1 (11.67)
Median	38.0	39.0	39.0	37.0	39.0	38.0
Min, Max	30, 83	30, 75	30, 75	30, 74	30, 83	30, 75
Non-Inflammatory Lesion Count						
Mean (SD)	59.1 (22.19)	60.7 (22.09)	62.8 (21.37)	63.3 (20.52)	61.0 (21.84)	62.0 (21.33)
Median	53.0	57.0	61.0	63.0	58.0	59.0
Min, Max	30, 100	30, 144	30, 177	30, 100	30, 177	30, 144
Total Lesion Count						
Mean (SD)	101.5 (25.12)	103.6 (26.13)	105.7 (25.76)	104.6 (24.18)	103.6 (25.52)	104.1 (25.15)
Median	98.0	101.0	103.0	103.0	101.0	102.0
Min, Max	60, 170	61, 196	60, 241	60, 170	60, 241	60, 196

BMI = body mass index; SD = standard deviation

a "Other" includes American Indian or Alaska native, native Hawaiian or other Pacific Islander, those reported as "other," and those reported as multiple.

b I - Always burns easily; never tans (sensitive)
II - Always burns easily; tans minimally (sensitive)
III - Burns moderately; tans gradually (light brown) (normal)
IV - Burns minimally; always tans well (moderate brown) (normal)
V - Rarely burns minimally; tans profusely (dark brown) (insensitive)
VI - Never burns; deeply pigmented (insensitive)

Table 10: Baseline characteristics of the study population of studies CB-03-01/25 and CB-03-01/26

	Study CB-03-01/25		Study CB-03-01/26	
	Clascoterone 1% cream (N = 353)	**Vehicle (N = 355)**	**Clascoterone 1% cream (N = 369)**	**Vehicle (N = 363)**
IGA - n, (%)				
3-Moderate	292 (82.7%)	291 (82.0%)	305 (82.7%)	313 (86.2%)
4-Severe	61 (17.3%)	64 (18.0%)	64 (17.3%)	50 (13.8%)
Lesion count – mean (SD)				
Non-inflammatory lesions	59.1 (22.2)	60.7 (22.1)	62.8 (21.4)	63.3 (20.5)
Inflammatory lesions	42.4 (11.8)	42.9 (12.3)	42.9 (12.2)	41.3 (11.0)

- **Numbers analysed**

Subject Disposition by Treatment in Studies CB-03-01/25 and CB-03-01/26 (ITT/Safety Population)

Disposition, n (%)	Study CB-03-01/25		Study CB-03-01/26		Total	
	CB-03-01 N = 353	Vehicle N = 355	CB-03-01 N = 369	Vehicle N = 363	CB-03-01 N = 722	Vehicle N = 718
Completed?						
Completed the study	287 (81.3)	290 (81.7)	302 (81.8)	282 (77.7)	589 (81.6)	572 (79.7)
Withdrew	66 (18.7)	65 (18.3)	67 (18.2)	81 (22.3)	133 (18.4)	146 (20.3)
Reason for withdrawal						
Withdrawal by subject[a]	23 (6.5)	18 (5.1)	35 (9.5)	41 (11.3)	58 (8.0)	59 (8.2)
Lost to follow-up	39 (11.0)	32 (9.0)	24 (6.5)	24 (6.6)	63 (8.7)	56 (7.8)
Physician decision	0	1 (0.3)	1 (0.3)	0	1 (0.1)	1 (0.1)
Noncompliance with study drug	0	2 (0.6)	1 (0.3)	5 (1.4)	1 (0.1)	7 (1.0)
Adverse event	4 (1.1)[b]	6 (1.7)	3 (0.8)[b]	8 (2.2)	7 (1.0)	14 (1.9)
Pregnancy	0	1 (0.3)	0	1 (0.3)	0	2 (0.3)
Lack of efficacy	0	3 (0.8)	3 (0.8)	1 (0.3)	3 (0.4)	4 (0.6)
Others	0	2 (0.6)	0	1 (0.3)	0	3 (0.4)

a For the pooled analyses, withdrawal by subject included both withdrawal by subject and withdrawal by parent/guardian as reported in the individual clinical study reports.
b In the CB-03-01/25 and CB-03-01/26 clinical study reports, one of these subjects was counted as discontinuing for progressive disease. For the pooled analysis, that reason was counted as an adverse event.

- **Outcomes and estimation**

Analysis of Co-Primary Efficacy Endpoints by Study and Pooled (ITT Population)

	Study CB-03-01/25		Study CB-03-01/26		Pooled	
	CB-03-01 N = 353	Vehicle N = 355	CB-03-01 N = 369	Vehicle N = 363	CB-03-01 N = 722	Vehicle N = 718
Proportion of subjects with a ≥ 2-point reduction in IGA and IGA score of 0 or 1 at Week 12 – logistic regression[a], MI under MAR						
n (%)	57 (16.1)	25 (7.0)	69 (18.7)	17 (4.7)	126 (17.5)	42 (5.8)
Adjusted proportions	18.4%	9.0%	20.3%	6.5%	19.5%	7.7%
Adjusted odds ratio						
Point estimate	2.3		3.7		2.9	
95% Confidence limits	1.38, 3.78		2.16, 6.25		2.04, 4.18	
Two-sided p-value for treatment effect	0.0006		< 0.0001		< 0.0001	
Absolute change from baseline in NILC at Week 12 – ANCOVA[b], MI under MAR						
LS mean	-19.4	-13.0	-19.4	-10.8	-19.3	-11.8
LS mean difference						
Point estimate	-6.4		-8.6		-7.5	
95% CI of difference	-10.26, -2.62		-12.34, -4.92		-10.20, -4.82	
Two-sided p-value for treatment effect	0.0009		< 0.0001		< 0.0001	
Absolute change from baseline in ILC at Week 12 – ANCOVA[b], MI under MAR						
LS mean	-19.3	-15.5	-20.0	-12.6	-19.8	-13.9
LS mean difference						
Point estimate	-3.8		-7.4		-5.9	
95% CI of difference	-6.36, -1.27		-9.80, -5.05		-7.55, -4.17	
Two-sided p-value for analysis centre effect	0.0027		< 0.0001		< 0.0001	

ANCOVA = analysis of covariance; CI = confidence interval; IGA = Investigator's Global Assessment; ILC = inflammatory lesion count; ITT = intent-to-treat; MI under MAR = multiple imputation under missing at random assumption; n = the number of subjects who fulfilled the analysis criterion in the raw dataset; the denominator for calculating the proportions is the number of subjects in the intent-to-treat set of each treatment group; NILC = non-inflammatory lesion count

a A logistic regression model with treatment and pooled analysis centres as fixed effects was used to compare the proportion of subjects with at least a 2-point reduction in IGA compared to baseline and an IGA score of 0 or 1 at Week 12. The null hypothesis to be rejected was H0 : Adjusted Odds Ratio (CB-03-01 vs. Vehicle) ≤ 1. To avoid quasi-complete separation of data points, pooled analysis centres were used.

b An ANCOVA with treatment and analysis centres as fixed effects and the baseline NILC or ILC as covariate was used to compare the absolute change from baseline in NILC or ILC at Week 12. The null hypothesis to be rejected was H0: μNILC CB-03-01 - μNILC Vehicle ≥ 0 or H0: μILC CB-03-01 - μILC Vehicle ≥ 0.

Table 11: Analysis of Secondary Efficacy Endpoints by Study and Pooled (ITT Population)

	Study CB-03-01/25		Study CB-03-01/26		Pooled	
	CB-03-01 N = 353	Vehicle N = 355	CB-03-01 N = 369	Vehicle N = 363	CB-03-01 N = 722	Vehicle N = 718
Absolute change from baseline in TLC at Week 12 – ANCOVA[a], MI under MAR						
LS mean	-39.1	-28.8	-40.0	-23.6	-39.5	-26.3
LS mean difference						
Point estimate	-10.3		-16.4		-13.2	
95% CI of difference	-15.69, -4.89		-21.84, -10.96		-17.03, -9.45	
Two-sided p-value for treatment effect	0.0001		< 0.0001		< 0.0001	
Percent change from baseline in TLC at Week 12 – ANCOVA[a], MI under MAR						
LS mean	-37.0	-28.4	-37.3	-22.1	-37.2	-25.2
LS mean difference						
Point estimate	-8.6		-15.2		-12.0	
95% CI of difference	-13.91, -3.31		-20.52, -9.93		-15.72, -8.32	
Two-sided p-value for treatment effect	0.0012		< 0.0001		< 0.0001	
Percent change from baseline in NILC at Week 12 – ANCOVA[a], MI under MAR						
LS mean	-30.6	-21.6	-29.3	-15.6	-29.8	-18.4
LS mean difference						
Point estimate	-9.0		-13.7		-11.4	
95% CI of difference	-15.84, -2.24		-19.93, -7.56		-15.95, -6.79	
Two-sided p-value for treatment effect	0.0086		< 0.0001		< 0.0001	
Percent change from baseline in ILC at Week 12 – ANCOVA[a], MI under MAR						
LS mean	-44.8	-36.5	-46.9	-29.6	-46.2	-32.7
LS mean difference						
Point estimate	-8.3		-17.2		-13.5	
95% CI of difference	-14.17, -2.41		-22.94, -11.55		-17.40, -9.55	
Two-sided p-value for treatment effect	0.0048		< 0.0001		< 0.0001	

ANCOVA = analysis of covariance; CI = confidence interval; ILC = inflammatory lesion count; ITT = intent-to-treat; MI under MAR = multiple imputation under missing at random assumption; NILC = non-inflammatory lesion count; TLC = total lesion count

a An ANCOVA with treatment and analysis centres as fixed effects and the baseline TLC as covariate was used to compare the absolute change from baseline in TLC at Week 12. The null hypothesis to be rejected was μTLC CB-03-01 - μTLC Vehicle ≥ 0. Similar analyses were performed for percent change from baseline for TLC, NILC, and ILC.

Post-hoc analyses demonstrated that there was a statistically significant (p = 0.0035) effect of skin type on absolute change from Baseline in ILC at Week 12:

- in subjects with Fitzpatrick Skin Type I, II, or III (white skin), treatment group differences were statistically significant and in favour of CB-03-01 compared to vehicle (-18.2 vs -14.2, respectively; p

= 0.0168)

- in subjects with Fitzpatrick Skin Type IV, V, or VI (dark skin), treatment group differences for P3 were no longer statistically significant (-19.1 CB-03-01, -21.4 vehicle; p = 0.2329).

- **Ancillary analyses**

N/A

- **Summary of main efficacy results**

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

Table 12: Summary of Efficacy for trial CB-03-01/25

Title: A Phase 3, Multicentre, Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Cortexolone 17α-Propionate (CB-03-01) Cream, 1% Applied Twice Daily for 12 Weeks in Subjects with Facial Acne Vulgaris			
Study identifier	CB-03-01/25		
Design	Phase III, multicentre, randomized, double-blind, vehicle-controlled		
Hypothesis	Superiority		
Treatments groups	CB-03-01 cream 1% (clascoterone)		N=353/708 randomised
	Vehicle		N=355/708 randomised
Endpoints and definitions	Primary endpoints (hierarchical)	P1, P2, P3, P4	- P1: Proportion of subjects in each treatment group achieving "success" at Week 12, with "success" defined as an IGA score of "clear (score=0)" or "almost clear (score=1)" AND at least a two-point reduction in IGA compared to Baseline. - P2: Absolute change from Baseline in Non-Inflammatory Lesions Count (NILC) in each treatment group at Week 12. - P3: Absolute change from Baseline in Inflammatory Lesions Count (ILC) in each treatment group at Week 12.

	Secondary	S1, S2, S3, S4	• S1: Absolute change from Baseline in total lesion count (TLC) in each treatment group at Week 12. • S2: Percent change from Baseline in TLC in each treatment group at Week 12. • S3: Percent change from Baseline in NILC in each treatment group at Week 12. • S4: Percent change from Baseline in ILC in each treatment group at Week 12.
	Safety endpoint	AEs	• Local and systemic AEs at every visit (Baseline, Weeks 4, 8, and 12). • Local Skin Reactions (LSRs): telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus scored by frequency and severity at every visit (Baseline, Weeks 4, 8, and 12). • Urine Pregnancy Test in all WOCBP at every visit (Baseline, Weeks 4, 8, and 12). • Material changes from Baseline in ECGs at Week 12.

Primary endpoints **ITT set at Week 12**	**CB-03-01** **N=353**	**VEH** **N=355**	**Comparison between Treatments** **(95% CI of the difference)** **p-value (two sided)**
P1: Proportion of subjects with at least 2-point IGA reduction from baseline AND IGA =0 or 1 Adjusted proportions	**57** 16.1% **18.8%**	**25** 7.0% **8.9%**	9.1% 9.9% (1.43, 3.88) 0.0008
P2: Proportion of subjects with absolute Change from Baseline in NILC	**-19.4**	**-13.1**	-6.3 (-10.2,-2.4) 0.0016
P3: Proportion of subjects with absolute Change from Baseline in ILC	**-19.4**	**-15.5**	-3.9 (-6.5,-1.3) 0.0029

Secondary endpoints **ITT set at week 12**	**CB-03-01** **N=353**	**VEH** **N=355**	**Comparison between Treatments** **(95% CI)** **p-value (two sided)**

S1: Absolute Change from Baseline in TLC	-39.2	-28.9	-10.3 (-15.7,-5.0) 0.0002
S2: Percent Change from Baseline in TLC	-37.1	-28.5	-8.7 (-14.0,-3.3) 0.0016
S3: Percent Change from Baseline in NILC	-30.7	-21.9	-8.8 (-15.9,-1.8) 0.0141
S4: Percent Change from Baseline in ILC	-44.8	-36.6	-8.3 (-14.3,-2.3) 0.0070

Table 13: Summary of Efficacy for trial CB-03-01/26

<table>
<tr><td colspan="4">Title:

A Phase 3, Multicentre, Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Cortexolone 17α-Propionate (CB-03-01) Cream, 1% Applied Twice Daily for 12 Weeks in Subjects with Facial Acne Vulgaris</td></tr>
<tr><td>Study identifier</td><td colspan="2">CB-03-01/256</td><td></td></tr>
<tr><td>Design</td><td colspan="3">Phase III, multicentre, randomized, double-blind, vehicle-controlled</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">CB-03-01 cream 1% (clascoterone)</td><td>N=369/732 randomised</td></tr>
<tr><td colspan="2">Vehicle</td><td>N=363/732 randomised</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoints
(hierarchical)</td><td>P1, P2, P3, P4</td><td>- P1: Proportion of subjects in each treatment group achieving “success” at Week 12, with “success” defined as an IGA score of “clear (score=0)” or “almost clear (score=1)” AND at least a two-point reduction in IGA compared to Baseline.
- P2: Absolute change from Baseline in Non-Inflammatory Lesions Count (NILC) in each treatment group at Week 12.
- P3: Absolute change from Baseline in Inflammatory Lesions Count (ILC) in each treatment group at Week 12.</td></tr>
</table>

	Secondary	S1, S2, S3, S4	• S1: Absolute change from Baseline in total lesion count (TLC) in each treatment group at Week 12. • S2: Percent change from Baseline in TLC in each treatment group at Week 12. • S3: Percent change from Baseline in NILC in each treatment group at Week 12. • S4: Percent change from Baseline in ILC in each treatment group at Week 12.
	Safety endpoint	AEs	• Local and systemic AEs at every visit (Baseline, Weeks 4, 8, and 12). • Local Skin Reactions (LSRs): telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus scored by frequency and severity at every visit (Baseline, Weeks 4, 8, and 12). • Urine Pregnancy Test in all WOCBP at every visit (Baseline, Weeks 4, 8, and 12). • Material changes from Baseline in ECGs at Week 12.

Primary endpoints ITT set at Week 12	**CB-03-01 N=369**	**VEH N=363**	**Comparison between Treatments (95% CI of the difference) p-value (two sided)**
P1: At least 2-point IGA reduction from baseline AND IGA =0 or 1	**20.8%**	**6.5%**	14.3% (2.19,6.43) <0.0001
P2: Absolute Change from Baseline in NILC	**-19.4**	**-10.9**	-8.4 (-12.4,-4.5) <0.0001
P3: Absolute Change from Baseline in ILC	**-20.0**	**-12.6**	-7.4 (-9.8,-5.0) <0.0001

Secondary endpoints ITT set at week 12	**CB-03-01 N=353**	**VEH N=355**	**Comparison between Treatments (95% CI) p-value (two sided)**
S1: Absolute Change from Baseline in TLC	-40.3	-23.7	-16.6 (-22.0,-11.1) <0.0001
S2: Percent Change from Baseline in TLC	-37.7	-22.2	-15.6 (-20.9,-10.3)

			<0.0001
S3: Percent Change from Baseline in NILC	-29.3	-15.8	-13.5 (-19.8,-7.1) <0.0001
S4: Percent Change from Baseline in ILC	-47.0	-29.8	-17.2 (-22.9,-11.5) <0.0001

2.5.5.3. Clinical studies in special populations

N/A

2.5.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

The efficacy pooled data from studies /25 and /26 consisted in 1440 patients, 722 treated by clascoterone cream and 718 by vehicle.

In the pooled data from CB-03-01/25 and CB-03-01/26 studies at Week 12, the primary efficacy endpoints were in a hierarchical order:

- IGA "success" was 19.5% for clascoterone group compared to 7.7% for VEH group (p<0.0001)
- Absolute change from baseline of non-inflammatory lesions count was -19.3 vs -11.8 (p<0.0001)
- Absolute change from baseline of inflammatory lesions count was -19.8 vs -13.9 (p<0.0001).

The secondary efficacy endpoints were in a hierarchical order:

- Absolute change from baseline in total lesions count was -39.5 vs -26.3. (p<0.0001)
- Percent change from baseline of total lesions count was -37.2 vs -25.2 (p<0.0001)
- Percent change from baseline of non-inflammatory lesions count was -29.8 vs -18.4 (p<0.0001)
- Percent change from baseline of inflammatory lesions count was -46.2.0 vs -32.7 (p<0.0001).
- Analysis of Co-Primary Efficacy Endpoints Pooled (ITT Population)

	Pooled results	
	CB-03-01 **N = 722**	**Vehicle** **N = 718**
Proportion of subjects with a ≥ 2-point reduction in IGA and IGA score of 0 or 1 at Week 12 – logistic regression[a], MI under MAR		
n (%)	126 (17.5)	42 (5.8)
Adjusted proportions	19.5%	7.7%
Adjusted odds ratio: Point estimate and 95% confidence limits	2.9 (2.04, 4.18)	
Two-sided p-value for treatment effect	< 0.0001	

Absolute change from baseline in NILC at Week 12 – ANCOVA[b], MI under MAR		
LS mean	-19.3	-11.8
LS mean difference: Point estimate and 95% confidence limits	-7.5 (-10.20, -4.17)	
Two-sided p-value for treatment effect	< 0.0001	
Absolute change from baseline in ILC at Week 12 – ANCOVA[b], MI under MAR		
LS mean	-19.8	-13.9
LS mean difference: Point estimate and 95% confidence limits	-5.9 (-7.55, -4.17)	
Two-sided p-value for treatment effect	< 0.0001	

- ANCOVA = analysis of covariance; CI = confidence interval; IGA = Investigator's Global Assessment; ILC = inflammatory lesion count; ITT = intent-to-treat; MI under MAR = multiple imputation under missing at random assumption; n = the number of subjects who fulfilled the analysis criterion in the raw dataset; the denominator for calculating the proportions is the number of subjects in the intent-to-treat set of each treatment group; NILC = non-inflammatory lesion count
- a A logistic regression model with treatment and pooled analysis centres as fixed effects was used to compare the proportion of subjects with at least a 2-point reduction in IGA compared to baseline and an IGA score of 0 or 1 at Week 12. The null hypothesis to be rejected was H0: Adjusted Odds Ratio (CB-03-01 vs. Vehicle) ≤ 1. To avoid quasi-complete separation of data points, pooled analysis centres were used.
- b An ANCOVA with treatment and analysis centres as fixed effects and the baseline NILC or ILC as covariate was used to compare the absolute change from baseline in NILC or ILC at Week 12. The null hypothesis to be rejected was H0: μNILC CB-03-01 - μNILC Vehicle ≥ 0 or H0: μILC CB-03-01 - μILC Vehicle ≥ 0.

- Efficacy results by age:

The success rate in adolescents was 14.9% in clascoterone group vs 3.7% in vehicle group and in adults, the success rate was 19.6% vs 7.5%.

Proportion of subjects achieving treatment success (IGA 0 or 1 and at least 2-point reduction in IGA from baseline) in the age subgroups 12 to <18 years and 18 to 65.

	Age 12 to <18 (Pooled data)		Age 18 to 65 (Pooled data)	
	CB-03-01 (N=316)	Vehicle (N=325)	CB-03-01 (N=393)	Vehicle (N=387)
n (%)	47 (14.9)	12 (3.7)	77 (19.6)	29 (7.5)
Adjusted odds ratio Point estimate	4.3		2.4	
95% C.I.	2.21, 8.39		1.55, 3.84	
2-sided p-value	<0.0001		0.0002	

N = total number of subjects in each subgroup

- Efficacy results by the severity of acne

The success rate in IGA=3 was 18.9% in clascoterone group vs 6.6% in vehicle group and in IGA=4, the success rate was 10.4% vs 1.8%.

Subgroup analysis of treatment success rate (co-primary endpoint P1) by baseline IGA in studies CB-03-01/25 and CB-03 -01/26 (baseline IGA = 3 vs baseline IGA = 4)

a) Baseline IGA = 3

	CB-03-01/25		CB-03-01/26		Pooled data	
	CB-03-01 (N=292)	Vehicle (N=291)	CB-03-01 (N=305)	Vehicle (N=313)	CB-03-01 (N=597)	Vehicle (N=604)
Patients achieving success – n (%)	52 (17.8)	25 (8.6)	61 (20.0)	15 (4.8)	113 (18.9)	40 (6.6)
Adjusted Odds Ratio Point estimate	2.1		3.8		2.8	
95% C.I.	1.22, 3.47		2.16, 6.75		1.92, 3.99	
2-sided p-value	0.0070		<0.0001		<0.0001	

N: Number of subjects with baseline IGA of 3

b) Baseline IGA = 4

	CB-03-01/25		CB-03-01/26		Pooled data	
	CB-03-01 (N=61)	Vehicle (N=64)	CB-03-01 (N=64)	Vehicle (N=50)	CB-03-01 (N=125)	Vehicle (N=114)
Patients achieving success – n (%)	5 (8.2)	0 (0.0)	8 (12.5)	2 (4.0)	13 (10.4)	2 (1.8)
Adjusted Odds Ratio Point estimate	N.A.		3.3		7.4	
95% C.I.	N.A.		0.55, 20.21		1.56, 35.18	
2-sided p-value	N.A.		0.1912		0.0119	

N: Number of subjects with baseline IGA of 4; N.A.: Not able to be estimated from the logistic regression due to quasi-complete separation of the outcome variable by the predictor variables, thus the maximum likelihood estimate does not exist.

2.5.5.6. Supportive studies

Were considered as supportive the following studies:

- a Phase 2 active-controlled study: CB-03-01/03

- a long-term follow-up (LTF) study: CB-03-01/27

- 2 clinical PK studies: 171-7151-202 and CB-03-01/28.

Active-controlled, pilot Phase 2 study CB-03-01/03

Clascoterone applied QD for 8 weeks in adults was statistically superior to vehicle at each visit (week 2, 4, 6 and 8) but not to Retin-A (tretinoin) 0.05% cream for any of the primary endpoints.

Table 14: Total lesion count, inflammatory lesion count, success rate by IGA and acne severity index in the Clascoterone 1% cream group, Retin-A group and vehicle group

	CB-03-01 N = 28	**Retin-A N = 30**	**Vehicle N = 14**
Total Lesion Count (TLC) at Week 8, Mean (SD)			
Baseline	46.2 (15.0)	48.5 (17.2)	50.6 (15.9)
Week 8	16.3 (17.3)[a]	24.4 (19.4)[b]	31.2 (17.4)
% Improvement	**65.7 (31.4)**	**52.5 (25.7)**	**37.0 (33.3)**
p-value vs vehicle	*0.0017*	0.0805	
p-value CB-03-01 vs Retin-A	0.0899		
Inflammatory Lesion Count (ILC) at Week 8, Mean (SD)			

Baseline	28.5 (11.1)	29.1 (10.4)	33.5 (11.4)
Week 8	9.3 (10.5)a	14.4 (10.9)b	20.6 (14.0)
% Improvement	**67.3 (32.0)**	**50.7 (34.5)**	**39.0 (33.2)**
p-value vs vehicle	*0.0134*	0.2754	
p-value CB-03-01 vs Retin-A	0.0944		
IGA Success at Week 8[c]	6/27 (22.2%)	3/26 (11.5%)	1/14 (7.1%)
Acne Severity Index (ASI), Mean (SD)			
Baseline	45.7 (17.4)	48.2 (17.1)	51.4 (19.0)
Week 8	14.7 (16.6)a	23.0 (17.6)b	30.9 (20.7)
% Improvement	**68.4 (30.6)**	**53.1 (33.5)**	**39.5 (31.6)**
p-value vs vehicle	*0.0090*	0.1985	
p-value CB-03-01 vs Retin-A	0.1085		

a N = 27, b N = 26, c Percent of success was calculated on the available data by treatment group; at Week 8 (Visit 4), 5 frequencies were missing.

Long-Term Follow-Up study CB-03-01/27

The aim of this open study was to determine the long-term safety of clascoterone, 609/1440 patients rolled over from the 2 Phase 3 pivotal studies (CB-03-01/25 and CB-03-01/26) for treatment by 1% cream applied twice daily on face and trunk for an additional 9 months for a total treatment of up to 12 months.

In addition to facial acne, treatment of truncal acne which was not treated in the Phase 3 pivotal studies, was discussed by the investigator and subject.

In the ITT population from 609 patients rolling over both pivotal studies, only 123 were assessed at 12 months for the face and 49 at 9 months for the trunk (since only the face was treated the first 3 months).

For the face, IGA 2 was observed in:

- 48.3% of subjects at 1 month
- 42.3% of subjects at 3 months
- 30.0% of subjects at 6 months
- 26.5% of subjects at 9 months

For the face, IGA score 0 or 1 was 32.2% (Investigator's last assessment) and 56.1% (at 12 months).

For the trunk, IGA score 0 or 1 was 40.2% (Investigator's last assessment) and 59.2% (at 9 months).

Clinical PK studies 171-7151-202 and CB-03-01/28

Study 171-7151-202*: An Open Label Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Cortexolone 17α-Propionate (CB-03-01) Cream Applied Every 12 Hours for Two Weeks in Subjects with Acne Vulgaris*

Although the primary objective of this study was safety, the overall severity of each subject's facial acne at the end of the study was documented using the Investigator's Global Assessment.

65% (13/20) and 64% (14/22) of subjects in Cohorts 1 (adult) and 2 (paediatric subjects), respectively, had no change at Day 14/EOS in their facial acne severity from Baseline. Six subjects each in Cohort 1 (30%) and

Cohort 2 (27%) had a 1-grade improvement in their facial acne at Day 14/EOS from Baseline. One subject (Subject 03- 204 from Cohort 2) had a 2-grade improvement in her facial acne at Day 14/EOS from Baseline. One subject in each cohort had a worsening in their facial acne by 1 grade at Day 14/EOS from Baseline.

At Day 14/EOS, 41 of the 42 subjects still had significant acne (IGA score ≥2), showing the slow onset or the apparent lack of clascoterone effect even at doses x 3 compared to claimed posology in adult or paediatric subject.

Study CB-03-01/28*: An Open Label Evaluation of the Adrenal Suppression Potential and Trough Plasma Concentrations of Clascoterone (CB-03-01) Cream Applied Every 12 Hours for Two Weeks in Subjects 9 to <12 Years of Age with Acne Vulgaris*

No efficacy assessments were planned for this study. However, the overall severity of each facial acne at the end of the study was documented by the investigator or designee using the IGA score. The IGA was performed at Screening, Day 1 and Day 14 (EOS).

All subjects had moderate facial acne vulgaris (Grade 3) as determined by the IGA at Screening and Day 1. By Day 14/EOS, 20 subjects (20/27, 74.1%) had moderate facial acne vulgaris (Grade 3) as determined by the IGA with the remainder having mild acne (Grade 2; 6/27, 22.2%) or were almost clear (Grade 1; 1/27, 3.7%).

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical programme consisted of:

- 1 dose-escalation Phase 2 study during 12 weeks (171-7151-201),
- 1 pilot Phase 2 study vs tretinoin as active comparator (topical retinoid) during 8 weeks (CB-03-01/03)
- 2 Phase 3 studies of same design during 12 weeks (CB-03-01/25 and CB-03-01/26)
- 1 Phase 3 study with a long-term follow-up, 52 weeks (CB-03-01/27).

The population enrolled comprised adults, adolescents and children≥ 9 years with different levels of severity of acne with IGA score:

- from 2 (mild) to 4 (severe) as inclusion criterion in the dose-escalation phase 2 study

- from 2 (mild) to 3 (moderate) as inclusion criterion in the pilot phase 2 study

- and from 3 (moderate) to 4 (severe) as inclusion criterion in the phases 3 studies.

The co-primary endpoints were for dose-escalation study and both pivotal studies:

- P1: Proportion of subjects in each treatment group achieving "success" at Week 12, with "**success**" defined as an IGA score of "clear (score=0)" or "almost clear (score=1)" AND at least a two-point reduction in IGA compared to Baseline.
- P2: Absolute change from Baseline in NILC in each treatment group at Week 12
- P3: Absolute change from Baseline in ILC in each treatment group at Week 12.

The Investigator's Global Assessment (IGA) score was used as a primary endpoint to grade acne severity at baseline and at week 12. It is one of the grading systems mostly used in acne clinical trials (Zarchi, 2012: Severity assessment and outcome measures in acne vulgaris). IGA score was also completed with lesions counting measures: non-inflammatory lesions counting (NILC), inflammatory lesions counting (ILC) and total lesions counting (TLC).

The 3 co-primary efficacy endpoints IGA score, NILC and ILC counts are acceptable. European guidelines recommend a grading technique associated to a counting technique of non-inflamed and inflamed lesions, including superficial papules and pustules, deep inflamed lesions and macules with photography support (Nast A et al. European Dermatology Forum. S3-Guideline for the treatment of acne - Update 2016- http://www.euroderm.org/edf/index.php/edf-guidelines/category/4-guidelines-acne).

It is to be noted that in European guidelines topical therapies as monotherapy are recommended only in the treatment of mild to moderate acne and not in severe acne (Nast A et al. European Dermatology Forum. S3-Guideline for the treatment of acne - Update 2016- http://www.euroderm.org/edf/index.php/edf-guidelines/category/4-guidelines-acne).

In both pivotal studies, post-hoc analyses were performed according to Fitzpatrick Skin Type which is the most commonly measure of skin type used to identify any difference in terms of efficacy in patients with darker skin (FST IV–VI) when compared to lighter skin patients (FST I–III).

Efficacy data and additional analyses

Dose-response study (171-7151-201)

The dose escalation study showed that clascoterone at the strength of 1% applied twice a day had the highest rate of success in adult and adolescent ≥12 years with mild to severe acne (68% of moderate acne at baseline): at 12 weeks success was 10.9% in PP population with no statistically significant differences among treatments but with statistically significant differences ($p<0.05$) observed for total lesion counts. The limited number of patients in each group of strengths could explain the lack of statistical significance and why the 0.5% group of patients had lower efficacy result than 0.1% group.

Post-hoc analyses according to acne severity at baseline and change in total lesion counts confirmed that 1% BID of clascoterone led to highest success in terms of lesion clearance. No exposure/response relationship was performed.

Placebo effect was high with results similar to 0.5% BID. This seems to be usual in clinical trials testing a new drug in acne in which the effect of the vehicle can be high as shown by Chiou in article "Low intrinsic drug activity and dominant vehicle (placebo) effect in the topical treatment of acne vulgaris" (Chiou, 2012 - Int J Clin Pharmacol Ther. 2012 Jun;50(6):434-7. doi:10.5414/cp201694).

The rationale of the different doses tested was missing. The dose of 1% of clascoterone was selected based on the non-clinical study result which showed that 0.8% of clascoterone inhibited the effects of testosterone propionate (TP) and dihydrotestosterone (DHT) in hamsters.

Percent Change in Inflammatory and Non-Inflammatory Lesion Counts at Weeks 8 and 12/EOS was evaluated as a 4th Secondary Endpoint. The mean percent change from Baseline at Week 8 in inflammatory and non-inflammatory lesions was greatest for subjects treated with CB-03-01 1% BID (-43.1 and -33.3, respectively). However, it is noted that in a vehicle group the mean percent change from Baseline at Week 8 in inflammatory and non-inflammatory lesions were -31.9 and -23.8, respectively. Therefore, the overall effect size is considered very limited. The applicant explained that the low change in NIL and IL lesion counts

in the 1% group is mainly due to the higher severity of acne in this group. This is probably also due to the high rate of success in the vehicle group.

Active-controlled, pilot phase 2 study (CB-03-01/03)

This pilot study is rather interesting and not only **supportive** as clascoterone 1% applied once daily was compared to an **active comparator**, tretinoin 0.05% (Retin-A) and vehicle in 72 adults (n=28 vs 30 vs 14 respectively) with mild to moderate acne (IGA 2 to 4) at 8 weeks.

The European guidelines recommend adapalene among topical retinoids to be preferred over topical isotretinoin and tretinoin as adapalene has the best tolerability/ safety profile for the treatment of comedonal acne and mild to moderate papulopustular acne. The applicant explained for the choice of Retin-A as active comparator that all benzoyl peroxide formulations in commercial distribution were gels with clear appearance. Therefore, it would have been impossible to make it undistinguishable from the clascoterone 1% cream or the clascoterone vehicle. It would be immediately clear, for the study staff, to understand the treatment allocation of the subjects (e.g., when drug accountability and compliance checks were performed), and therefore the blind in the study would have been lost. This is understood but the choice of the active comparator was not appropriate according to European guidelines.

In this study clascoterone showed statistically significant difference compared to vehicle at each visit (week 2, 4, 6 and 8) but not compared to Retin-A for any of the primary endpoints. Moreover, Retin-A failed also to show efficacy vs the placebo cream. This casts also doubt on the way in which the study was carried out.

Regarding the percent of success of IGA (0 or 1), comparison between 3 arms are missing as no p-value is provided to assess the differences CB-03-01 vs vehicle and CB-03-01 vs Retin-A. The lack of statistically significance compared to the vehicle can be explained by the low number of subjects in each group. Due to the lower magnitude of effect of Retin-A as compared to clascoterone 1% cream, the sample size of the group did not have enough power to reach statistical significance.

The number of missing frequencies at each visit, especially 5 frequencies missing at week 8 (primary endpoint) were due to patients who did not attend study visits.

Assessing efficacy at week 8 was unusual in the treatment of acne for topical therapies, timepoint at 12 weeks would have been preferable since the efficacy of tretinoin was demonstrated at 12 weeks. This could explain the rather poor results vs tretinoin. Besides as the claimed pharmacological effect is an anti-androgenic effect, 8 weeks seems rather too early to obtain full effect, 24 weeks would have been more appropriate.

The design of this study could have provided interesting data to assess this topical drug compared to a well-established topical anti-acneic drug but due to differences from pivotal studies in terms of timepoint (8 instead of 12 weeks), frequency of application (once vs twice daily) and acne severity (mild to moderate vs moderate to severe patients), no solid data was obtained from this study. No firm conclusion can be drawn.

Pivotal Phase 3 studies (CB-03-01/25 and CB-03-01/26)

Two clinical multicentre, randomized, double-blind, vehicle-controlled, parallel-group comparison studies evaluated the safety and efficacy of CB-03-01 cream, 1% applied twice daily for 12 weeks in subjects, 9 years of age or older with moderate to severe acne vulgaris on the face.

No active comparator was included which would have been of interest in both pivotal studies. However, comparison with vehicle cream in the pivotal studies is accepted according to guidelines.

Success was defined as an IGA score of "clear (score=0)" or "almost clear (score=1)" AND at least a two-point reduction in Investigator's Global Assessment (IGA) compared to Baseline.

IGA scores at baseline were IGA 3 (moderate acne) = 82.7% and IGA 4 (severe acne) = 17.3%.

Fitzpatrick Skin Type Assessment used for clinical evaluation at baseline is also acceptable. It is the most commonly used measure of skin type. Here it was used to identify any difference in terms of efficacy in patients with darker skin (FST IV–VI) when compared to lighter skin patients (FST I–III). Most of the subjects had a skin Fitzpatrick type of II and III (white skin phototype).

There was no heterogeneity between groups in terms of demographic characteristics.

The applicant provided the number of patients with prior, concomitant and follow up anti-androgenic medications. The drugs used were oral combined hormonal contraceptives of progestogens and oestrogens. The purpose of this question was to evaluate if prior or concomitant anti-androgenic medications had an impact on clascoterone efficacy results and safety. The efficacy and safety results in these patients have not been provided. Therefore, information about the impact of previous anti-androgenic medications on clascoterone effect is still not known.

The pooled efficacy results showed a modest clascoterone effect with an IGA 'success' at week 12 of 19.5% vs 7.7% for the vehicle. Further, it is not known if the effect in moderate acne vulgaris (IGA 3 at baseline) is similar compared to severe acne (IGA 4). Although statistical significance was achieved in both pivotal studies, the overall proportion of subjects achieving treatment success (at least a 2-Point reduction in IGA) was rather low and the absolute changes in number of inflammatory and non-inflammatory lesions are considered limited.

- The size effect of clascoterone cream is modest in both pivotal studies, which included moderate and severe patients: success rate (pooled data) in the clascoterone group: n=126/722 (17.5%) versus n=42/718 (5.8%) in the vehicle group. The effect of clascoterone was mainly due to moderate patients' success: 18.9% vs 6.6% with 113/597 and 40/604 patients, respectively.
- In these studies, few patients with severe acne were included (success rate in the clascoterone group: n=13/125 (10.4%) versus n=2/114 (1.8%) in the vehicle group), which jeopardises the robustness of the results in this population.
- Assessment of the effect of clascoterone in mild patients was issued from a phase II study (n=18, in whom treatment success was 0%), which also jeopardises the robustness of the results in this population.
- Specifying in the labelling of the indication that clascoterone is intended to treat moderate and severe acne would give an advantage to this cream over other topical drugs in severe acne. This is not considered justified taking into account the low number of patients with success in the severe subgroup. To date, there is no topical treatment indicated in severe acne.
- The positioning of medicines in the management of acne is addressed in the frame of national/European guidelines.

Moreover, it is noted that in sensitivity analysis effect of study centre was demonstrated for P2 and P3, showing that the primary efficacy results for P2 and P3 were driven by extreme centres in Study CB-03-01/25. In the analysis excluding centres with the highest impact, statistical significance was no longer observed for P3. The subgroup of subjects 9 to < 12 years did not show a statistically significant treatment effect; interpretation in that subgroup is not possible due to the very small sample size (19 subjects in total,

of whom 13 were randomized to CB-03-01 and 6 to vehicle). The effect of skin type, particularly the appearance of a lack of effect of CB-03-01 on lesion count for skin types IV, V, or VI, may be attributed to acne post-inflammatory hyperpigmentation that is more prominent in darker skin types which may make acne lesion counts more difficult for investigators to evaluate. While there is no known biologic differences in acne between various skin types the challenges of evaluating darker skin types is confounded by the presence of post-inflammatory hyperpigmentation left by inflammatory acne lesions. This is acceptable.

The power calculations were based on expected large clinical benefits. The chance of achieving a clear or almost clear acne was expected 7-fold higher in the treated arm as compared to the control. Expectations were high as well for key secondary endpoints where the reduction of the number of lesions was anticipated to be much higher under clascoterone treatment. The Applicant indicated that expectations were based on observations from previous subgroups of patients responding very favourably to the active treatment. In addition, the control arm's responses were higher than expected. Although it is understandable, expectations should be based on more substantial data providing more accurate, realistic and conservative results, otherwise the relevance of the clinical observed results could be at stake even though statistically significant.

The Applicant's response when focusing on the active group results is rather convincing and treatment effects appear to keep some noticeable clinical relevance, though lower than expected.

In the new analysis provided on the CHMP request, in both adults and adolescents, clascoterone 1% cream was statistically superior to placebo in the baseline IGA=3 subgroups; in the baseline IGA=4 subgroups, a trend favouring clascoterone 1% cream was observed.

In the per-subject results in the IGA=4 subgroup in both adolescents and adults randomized to clascoterone 1% cream achieved a reduction in NILC and ILC. In adolescents clascoterone 1% cream was statistically superior in the absolute change from baseline in both ILC and NILC (difference in NILC vs placebo: -13.9, p-value: 0.0123; difference in ILC vs placebo: -10.7, p-value: 0.0106), whereas, in adults, clascoterone 1% cream was statistically superior in the absolute change from baseline in ILC and showed a positive trend in the absolute change from baseline in NILC (difference in ILC vs placebo: -6.4, p-value: 0.0458; difference in NILC vs placebo: -6.7, p-value: 0.1268;). Comparable effects were observed in the comparisons of total lesion counts and in the percent change in ILC and NILC.

Long-Term Follow-Up study (CB-03-01/27)

The aim of this open study was to determine the long-term safety of clascoterone 1% cream applied twice daily on face and trunk in 609/1440 patients rolled over from the 2 Phase 3 pivotal studies for an additional 9-month treatment with a total treatment duration up to 12 months. However, IGA scores were also noted by investigators: the % of subjects with an IGA clear or almost clear at investigator's last assessment was 32.2% (face area) and 40.2% (trunk area).

Interpretation of results is difficult as there is no controlled group and the efficacy endpoint differs from those used in pivotal studies.

Moreover, at the end of the study it was not known how many patients who were initially treated for 3 months by clascoterone were still treated at 12 months. The global number of 123 patients assessed for facial acne at 12 months and 49 for the trunk did not explain if these patients were previously treated by clascoterone or not. The applicant provided the efficacy results of patients, especially children and adolescents treated but not their number taking into account the initial double-blinded arms (clascoterone/clascoterone and vehicle/clascoterone). The efficacy results showed an increase of the rate of success with time but the number of adolescents in each group is not provided although requested.

It is not explained why the success rate at 6 months of treatment in patients (adolescents 17.2% vs 12.8% and adults 24.4% vs 14.4%) who had been treated for 3 months with vehicle did not reach that of patients treated with clascoterone from the start.

During the additional 9-month period of treatment, the overall mild acne rate decreased over time from month 1 to month 9 but moderate acne rate decreased and increased at 9 months. The applicant explained this rise in scores between the 6-month and 9-month visits by the missing data during this open-label extension study. This can explain the discrepancies in efficacy results in moderate acne.

Besides, the rebound effect of acne after clascoterone treatment stopping was not assessed in this study, this adds to the difficulty of recommending an appropriate duration of treatment in acne for clascoterone. As clascoterone has glucocorticoid properties, an exacerbation could be expected at the time of treatment discontinuation with a reactivation of lesions with greater intensity than their pre-treatment state. A warning in section 4.4 of the SmPC and PL has been recommended.

Assessment of paediatric data on clinical efficacy

The current application is seeking approval for the treatment of acne vulgaris in adults, and adolescents aged 12 to 18 years. Children aged 9 to < 12 years old are not included in this application.

The age criterion for inclusion in both pivotal studies was 9 years or older. By age group in the pooled population, 1.3% (19/1440) of subjects were 9 to < 12 years, 44.5% (641/1440) were 12 to < 18 years, and 54.2% (780/1440) were 18 to < 65 years; no subjects were ≥ 65 years old.

In pooled 9-12 years group, the primary endpoint P1 (proportion of subjects in each treatment group achieving "success" at Week 12, with "success" defined as an IGA score of "clear (score=0)" or "almost clear (score=1)" AND at least a two-point reduction in IGA compared to Baseline), was not statistically significant in clascoterone group 15.4% (13/19) vs the vehicle group 16.7% (6/19).

In pooled adolescents group, the success rate was 14.9% (316/641) vs 3.7% (325/641) and in pooled adults group, 19.6% (393/780) vs 7.5% (387/780).

2.5.7. Conclusions on the clinical efficacy

Although the effect is considered modest, clascoterone 1% cream twice daily applied on face was superior to the vehicle cream (17.5% vs 5.8%, adjusted proportions 19.5% vs 7.7%) at 12 weeks, mostly in patients with moderate facial acne vulgaris.

The post-hoc subgroup analysis by acne vulgaris severity at baseline showed a success rate of 18.9% in moderate and 10.4% in severe acne vulgaris and the post-hoc subgroup analysis by age showed a success rate of 14.9% in adolescents and 19.6% in adults.

Although pivotal clinical studies have only focused on facial acne vulgaris, open-label long-term follow-up study data on trunk acne vulgaris have shown a similar effect. It is therefore acceptable not to restrict the indication to only facial acne vulgaris.

Taking into account the 10% improvement, considered as clinically relevant by international guidelines, the overall effect was modest, and the requested sub-analyses showed that the global results were driven mainly by the response of patients with moderate acne. The study was not powered to compare the effect observed in moderate to severe acne patients and it is not known what would have been the sub-group results if a higher number of patients with severe acne was available.

Overall, taking account all data presented, the CHMP considers that the efficacy of clascoterone for the treatment of acne vulgaris has been demonstrated in the adolescent and adult populations.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Two sets of pooled data were analysed for AEs (adverse events) and LSRs (local skin reactions):

- Pool A was composed of Phase 3 pivotal studies (CB-03-01/25 and CB-03-01/26) and included 722 subjects treated with clascoterone cream 1% BID for 3 months.
- Pool B was composed of Pool A and Phase 2 Study 171-7151-201 (only clascoterone 1% cream BID and Vehicle BID groups) and included 792 subjects treated with clascoterone cream 1% BID for 3 months.

Long term follow-up (LTF) study CB-03-01/27 included 123 subjects treated with clascoterone for 12 months.

In total, 339 subjects aged 12-<18 years were treated with clascoterone cream 1% BID in Pool B.

An additional pool of all studies was analysed and included 1467 subjects treated with clascoterone cream.

2.5.8.2. Adverse events

Overview of Adverse Events

Table 15: Overall Summary of Treatment-Emergent Adverse Events in Phase 3 Pivotal Studies (Pool A, Safety Population)

Category, n (%)	**CB-03-01/25**		**CB-03-01/26**		**Total**	
	CB-03-01 N = 353	**Vehicle N = 355**	**CB-03-01 N = 369**	**Vehicle N = 363**	**CB-03-01 N = 722**	**Vehicle N = 718**
All TEAEs	40 (11.3)	41 (11.5)	42 (11.4)	50 (13.8)	82 (11.4)	91 (12.7)
Serious TEAE	0	1 (0.3)	0	1 (0.3)	0	2 (0.3)
TEAE related to study drug	4 (1.1)	9 (2.5)	8 (2.2)	13 (3.6)	12 (1.7)	22 (3.1)
Serious TEAE related to study drug	0	0	0	0	0	0
TEAE leading to dose modification	3 (0.8)	3 (0.8)	3 (0.8)	4 (1.1)	6 (0.8)	7 (1.0)
TEAE leading to discontinuation of study drug	3 (0.8)	4 (1.1)	2 (0.5)	8 (2.2)	5 (0.7)	12 (1.7)
TEAE leading to death	0	0	0	0	0	0

In Pool B, results were similar. In the clascoterone cream 1% BID group, one subject had a serious TEAE, not related to study drug (Right Ankle Fracture) and a TEAE leading to discontinuation of study drug for another subject.

Common Adverse Events

Table 16: Treatment-Emergent Adverse Events Reported for ≥ 1% of Subjects in Either Treatment Group in Phase 3 Pivotal Studies (Pool A, Safety Population)

Preferred Term	Study CB-03-01/25		Study CB-03-01/26		Total	
	CB-03-01 N = 353	Vehicle N = 355	CB-03-01 N = 369	Vehicle N = 363	CB-03-01 N = 722	Vehicle N = 718
Nasopharyngitis	6 (1.7)	13 (3.7)	4 (1.1)[a]	7 (1.9)	10 (1.4)	20 (2.8)

In Pool B, the SOCs in which TEAEs were the most commonly reported (≥ 1%) were Infections and infestations (5.8% in clascoterone group, 5.8% in vehicle group), Respiratory, thoracic and mediastinal disorders (1.9% in clascoterone group, 1.4% in vehicle group), General disorders and administration site conditions (1.1% in clascoterone group, 3.5% in vehicle group), Gastrointestinal disorders (1.1% in clascoterone group, 1.4% in vehicle group), Nervous system disorders (1.0% in clascoterone group, 1.0% in vehicle group), and Skin and subcutaneous tissue disorders (0.9% in clascoterone group, 1.0% in vehicle group).

In Pool B, TEAEs reported in ≥ 1% of subjects were Nasopharyngitis (1.4% clascoterone, 2.6% vehicle) and Upper respiratory tract infection (0.6% clascoterone, 1.0% vehicle).

In Pool A or B, no TEAEs were reported for ≥ 1% of clascoterone-treated subjects and twice as many in vehicle-treated subjects.

In the all-studies pool, TEAEs were more reported in clascoterone group (15.6%) than placebo group (13.6%). Most of the SOCs were higher in clascoterone group than placebo group. The most represented SOCs were Infections and infestations (6.5% vs 5.7%, respectively), Respiratory, thoracic and mediastinal disorders (2.0% vs. 1.5%, respectively), Skin and subcutaneous tissue disorders (1.6% vs. 1.5%, respectively), Gastrointestinal disorders (1.6% vs. 1.3%, resp.), Nervous system disorders (1.6% vs 1.0%, respectively), Injury, poisoning and procedural complications (1.3% vs. 0.7%). The TEAEs the most frequent in clascoterone group were Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain and Headache.

Adverse Events with Long-Term Exposure

Table 17: Overall Summary of Subjects with Treatment-Emergent Adverse Events by Treatment Sequence from Parent Study

	CB-03-01 N=317 n (%) [#]	Safety Set Vehicle N=290 n (%) [#]	Overall N=607 n (%) [#]
Treatment-emergent Adverse Events	58 (18.3) [106]	52 (17.9) [85]	110 (18.1) [191]
Relationship			
Related	12 (3.8) [17]	2 (0.7) [2]	14 (2.3) [19]
Not related	47 (14.8) [89]	50 (17.2) [83]	97 (16.0) [172]
Severity			
Mild	36 (11.4) [57]	36 (12.4) [53]	72 (11.9) [110]
Moderate	28 (8.8) [42]	23 (7.9) [29]	51 (8.4) [71]
Severe	4 (1.3) [7]	3 (1.0) [3]	7 (1.2) [10]
Leading to discontinuation	9 (2.8) [9]	0 (0.0) [0]	9 (1.5) [9]
Serious Treatment-emergent Adverse Events	3 (0.9) [4]	3 (1.0) [3]	6 (1.0) [7]
Relationship			
Related	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Not related	3 (0.9) [4]	3 (1.0) [3]	6 (1.0) [7]
Leading to discontinuation	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
Leading to death	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Note: Subjects are summarised overall and according to the original product they actually received in the studies CB-03-01/25 and CB-03-01/26
Subjects are summarised according to the each level of relationship and severity reported in each treatment group and overall
The number and the proportion of subjects with any adverse event and the number of adverse events for each classification level are reported
The denominator for calculating the proportions is the number of subjects in the safety set of each treatment group and overall
The adverse events with relationship 'Definitely related', 'Probably related' and 'Possibly related' are deemed related to the IMP

The most frequently reported TEAEs (≥ 1%) in either treatment by PT were Nasopharyngitis (1.9% clascoterone, 3.4% vehicle), Upper respiratory tract infection (2.2% clascoterone, 0.3% vehicle), Respiratory tract infection viral (0.3% clascoterone, 1.4% vehicle), Application site acne (1.3% clascoterone, 0.0% vehicle).

In subjects treated with clascoterone during 12 months (Phase 3 and long term studies), the TEAEs observed at 12 months (at the end of long term study) were similar to those observed in Phase 3 studies (at the end of phase 3 study). The SOC 'Infections and infestations' was the most represented.

There was a total of 14 (2.3%) subjects who had a total of 19 study drug related TEAEs, including 17 TEAEs in the clascoterone group (Table 18) with the number of subjects with related TEAEs and number of related TEAEs being higher in subjects originally assigned to treatment with clascoterone versus vehicle (3.8% vs. 0.7% subjects) in the Phase 3 pivotal study. Most TEAEs were mild in severity and most LSRs and treatment-emergent LSRs were trace/minimal or mild in severity.

Table 18: Subjects with treatment-emergent adverse events related to the IMP by system organ class and preferred term

System Organ Class [1] Preferred Term [1]	CB-03-01 N=317 n (%) [#]	Vehicle N=290 n (%) [#]	Overall N=607 n (%) [#]
Treatment-emergent Adverse Events related to the IMP	12 (3.8) [17]	2 (0.7) [2]	14 (2.3) [19]
Skin and subcutaneous tissue disorders	6 (1.9) [6]	1 (0.3) [1]	7 (1.2) [7]
Acne	1 (0.3) [1]	1 (0.3) [1]	2 (0.3) [2]
Acne conglobata	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
Acne cystic	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
Dermatitis contact	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
Hair colour changes	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
Pruritus	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
General disorders and administration site conditions	5 (1.6) [9]	1 (0.3) [1]	6 (1.0) [10]
Application site acne	2 (0.6) [2]	0 (0.0) [0]	2 (0.3) [2]
Application site pain	1 (0.3) [1]	1 (0.3) [1]	2 (0.3) [2]
Application site dryness	1 (0.3) [2]	0 (0.0) [0]	1 (0.2) [2]
Application site erythema	1 (0.3) [2]	0 (0.0) [0]	1 (0.2) [2]
Application site pruritus	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
Application site swelling	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
Gastrointestinal disorders	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
Dysgeusia	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
Injury, poisoning and procedural complications	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]
Sunburn	1 (0.3) [1]	0 (0.0) [0]	1 (0.2) [1]

Note: Subjects are summarised overall and according to the original product they actually received in the studies CB-03-01/25 and CB-03-01/26
The number and the proportion of subjects with any related adverse event and the number of related adverse events for each classification level are reported
The denominator for calculating the proportions is the number of subjects in the safety set of each treatment group and overall
The adverse events with relationship 'Definitely related', 'Probably related' and 'Possibly related' are deemed related to the IMP
Note 1: MedDRA version 18.1

Adverse Events by Severity

In Pool A, no subject had a TEAE reported as severe in the clascoterone group and three subjects had events reported as severe in the vehicle group (application site acne, hematoma, and pneumonia).

In Pool B, mild AEs were reported for 9.0% of subjects treated with clascoterone 1% cream and for 8.9% of subjects treated with vehicle, moderate AEs were reported for 2.8% of subjects treated with clascoterone 1% cream and for 4.5% of subjects treated with vehicle, and severe AEs were reported for 0.3% of subjects treated with clascoterone 1% cream (ankle fracture and upper limb fracture, both not related, in population age 12-<18 years) and for 0.4% of subjects treated with vehicle.

In LTF CB-03-01/27 study, 72 subjects had 110 TEAEs that were mild, 51 subjects had 71 TEAEs that were moderate, and 7 subjects had 10 TEAEs that were severe. The 10 severe TEAEs included gastroenteritis eosinophilic, nephrolithiasis, pancreatitis, sciatica, pruritus, dizziness, suicide attempt, coronary artery dissection, toothache, and fatigue. The distribution of severity scores was similar in subjects originally treated with clascoterone versus vehicle in the pivotal studies.

Adverse drug reactions

In Pool A or B, no TEAEs were considered related to study drug in ≥ 1% of subjects treated with clascoterone 1% cream. The only related TEAE reported for more than one subject treated with clascoterone was Application site dryness, which was reported for two subjects (0.3%) in each treatment group.

In Pool A, TEAEs related to study drug were reported for 1.7% (12 TEAEs) of subjects in the clascoterone group and 3.1% (22 TEAEs) of subjects in the vehicle group (Table 18). In study 171-7151-201, there was no TEAE related to study drug reported.

In Pool B, TEAEs related to study drug were reported for 1.5% (12 TEAEs) of subjects in the clascoterone group and 2.8% (22 TEAEs) of subjects in the vehicle group.

2.5.8.3. Serious adverse event/deaths/other significant events

Serious AEs

Across all studies, serious TEAEs were reported for 10 subjects treated with clascoterone and two subjects who received vehicle. No serious TEAEs were considered related to study drug.

Table 19: Listing of SAEs across all studies by treatment

Study Subject[a]	Treatment	Sex/ Age/ Race	MedDRA Preferred Term (verbatim if different)	Intensity	Relationship to Study Drug	Outcome
Subjects with acne vulgaris						
171-7151-201 [redacted] narrative	CB-03-01 0.5% BID	F/21/W	Spontaneous abortion (Miscarriage)	Severe	Not related	Recovered
171-7151-201 [redacted] narrative [ISS [redacted]]	CB-03-01 1% BID	M/17/AI	Ankle fracture	Severe	Not related	Resolved with sequelae
CB-03-01/25 [redacted] narrative [ISS [redacted]]	Vehicle	F/19/W	Pneumonia	Severe	Not related	Resolved
CB-03-01/26 [redacted] narrative [ISS [redacted]]	Vehicle	M/17/W	Hematoma	Severe	Not related	Resolved
CB-03-01/27 [redacted] narrative	CB-03-01 1% BID	M/17/W	Depression (Major depressive disorder, recurrent unspecified)	Moderate	Not related	Resolved
CB-03-01/27 [redacted] narrative	CB-03-01 1% BID	M/14/W	Gastroenteritis eosinophilic	Severe	Not related	Resolved
CB-03-01/27 [redacted] narrative	CB-03-01 1% BID	F/14/W	Dizziness[b] Suicide attempt[b]	Severe Severe	Not related Not related	Resolved Resolved
CB-03-01/27 [redacted] narrative	CB-03-01 1% BID	F/25/B	Abortion induced	Moderate	Not related	Resolved
CB-03-01/27 [redacted] narrative	CB-03-01 1% BID	F/37/W	Coronary artery dissection (Spontaneous coronary artery dissection)	Severe	Not related	Resolved with sequelae
CB-03-01/27 [redacted] narrative	CB-03-01 1% BID	M/16/W	Fatigue (Exhaustion of the body)	Severe	Not related	Resolved
Healthy subjects						
CB-03-01/32 [redacted] narrative	CB-03-01, vehicle, saline	F/56/B	Hiatal hernia	Mild	Not related	Recovered[b]
CB-03-01/32 [redacted] narrative	CB-03-01, vehicle, saline	F/56/W	Atrial fibrillation	Moderate	Not related	Recovered[b]

A = Asian; AI = American Indian or Alaska native; B = Black/African-American; F = female; M = male; W = White/Caucasian
a Linked to subject narrative
b The SAE led to withdrawal of study drug and discontinuation from the study.
Source: Individual CSRs

In LTF study, there were 6 subjects who experienced 7 serious TEAEs and these included moderate depression, severe gastroenteritis eosinophilic, severe dizziness, severe suicide attempt, moderate abortion induced, severe coronary artery dissection, and severe fatigue all of which were deemed not related to study drug with 1 of the serious TEAEs leading to study discontinuation (severe suicide attempt).

AEs of special interest

Local skin reactions

In Pool A, the most frequent treatment-emergent LSRs after Day 1 were erythema (12.2% clascoterone, 15.3% vehicle) and scaling/dryness (10.5% clascoterone, 10.3% vehicle) (3.3.7.3.2). Most of the treatment-emergent LSRs were no or trace/mild in severity.

Table 20: Number (Percentage) of Subjects with Treatment-Emergent (New or Worsening) Local Skin Reactions After Day 1 by Severity in Pooled Phase 3 Pivotal Studies (Safety Population)

Reaction	**CB-03-01 1% cream N=687[a]**				**Vehicle N=662[a]**			
	Trace/Mild[b]	**Moderate**	**Severe**	**Total**	**Trace/Mild[b]**	**Moderate**	**Severe**	**Total**
Oedema	22 (3.2)	3 (0.4)	0	25 (3.6)	22 (3.3)	1 (0.2)	0	23 (3.5)
Erythema/reddening	73 (10.6)	11 (1.6)	0	84 (12.2)	88 (13.3)	12 (1.8)	1 (0.2)	101 (15.3)
Pruritus	36 (5.2)	14 (2.0)	2 (0.3)	52 (7.6)	37 (5.6)	15 (2.3)	3 (0.5)	55 (8.3)
Scaling/ dryness	70 (10.2)	2 (0.3)	0	72 (10.5)	67 (10.1)	1 (0.2)	0	68 (10.3)
Skin atrophy	10 (1.5)	1 (0.1)	0	11 (1.6)	16 (2.4)	1 (0.2)	0	17 (2.6)
Stinging/ burning	23 (3.3)	3 (0.4)	2 (0.3)	28 (4.1)	23 (3.5)	3 (0.5)	2 (0.3)	28 (4.2)
Striae rubrae	17 (2.5)	0	0	17 (2.5)	10 (1.5)	0	0	10 (1.5)
Telangiectasia	8 (1.2)	0	0	8 (1.2)	10 (1.5)	2 (0.3)	0	12 (1.8)

a The denominators for calculating the percentages were the 687 of 722 patients treated with WINLEVI cream and 662 of 718 patients treated with vehicle in these studies who had local skin reaction results reported after Day 1.

B Minimal or mild for oedema, erythema, and scaling/dryness; minimal for stinging/burning; and mild for pruritus

In LTF CB-03-01/27 study, the number and proportion of subjects with at least one LSR of any severity on the face was <24.2% throughout the study. The most frequently reported LSRs on the face throughout the study were erythema (24.2%), scaling/dryness (16.6%), pruritus (8.7%), and skin atrophy (8.1%). In general, there was a higher proportion of subjects who received clascoterone as original product with treatment emergent LSRs on the face throughout the study compared to subjects who received VEH as original product.

Similar to what was observed with LSRs for the face, the number and proportion of subjects, overall, with at least one LSR of any severity on the trunk was < 16% throughout the study. The most frequently reported LSRs on the trunk throughout the study were erythema (16.0%), scaling/dryness (9.6%), pruritus (3.6%), and edema (2.4%). There was a higher proportion of subjects who received clascoterone as original product with treatment emergent LSRs on the trunk through Day 29 and at Day 85 (erythema only) compared to subjects who received VEH as original product with the proportions being similar between groups at Day 183. By Day 274, there was a higher proportion of subjects who received VEH as original product with treatment emergent LSRs on the trunk compared to subjects who received clascoterone as original product.

Hypersensitivity/Drug Reactions

Three subjects had TEAEs identified as hypersensitivity or drug reaction, one of them was probably related to clascoterone and led to discontinuation, the others were not related.

Hypothalamic pituitary adrenal (HPA) axis suppression

HPA axis suppression were not performed in the Phase 3 studies.

The action of clascoterone on the HPA axis (cosyntropin stimulation test [CST]) was tested in two studies:

- Studies 171-7151-202 (An Open Label Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Cortexolone 17α-Propionate (clascoterone) Cream Applied Every 12 Hours for Two Weeks in Subjects with Acne Vulgaris)
- CB-03-01/28 (An Open Label Evaluation of the Adrenal Suppression Potential and Trough Plasma Concentrations of Clascoterone Cream Applied Every 12 Hours for Two Weeks in Subjects 9 to <12 Years of Age with Acne Vulgaris).

In both studies, HPA axis response to CST was assessed by measurement of serum cortisol concentrations after stimulation of the adrenal cortex with CST at screening and Day 14/EOS.

In study 171-7151-202, subjects were instructed to apply, to the face and trunk BID for 2 weeks, 6 grams or 4 grams of the cream per application. Forty-two subjects were enrolled, including 20 adults (cohort 1) and 22 adolescents (cohort 2).

Three (3/42, 7.1%) subjects, 1 adult (1/20, 5.0%) and 2 adolescents (2/22, 9.1%), had abnormal HPA axis response at Day 14/EOS under maximal use conditions as documented by a 30-minute post-stimulation serum cortisol level of < 18 µg/dL. All "suppressed" subjects returned to normal HPA axis function (as assessed by CST) at their initial follow-up visit approximately 4 weeks after Day 14/EOS (Table 21).

Table 21: Subjects who had Adrenal Suppression at Day 14/EOS

Cohort	Subject #	Total Test Article used (grams)	EOS Post-CST Cortisol (µg/dL)	Follow-Up (~4 weeks after EOS) Post-CST Cortisol (µg/dL)
Cohort 1	PI	167.9	17.7†	23.4
Cohort 2	PI	158.6	17.0†	19.5
	PI	105.8	14.9†	22.3

*Data from Listings 16.2.7.1 and 16.2.5.2.
†All three of these abnormal CST results were documented as AEs.

These 3 TEAEs of ACTH stimulation test abnormal were deemed related to clascoterone 1% cream.

The mean total amount of test article applied by the three subjects that suppressed was 144.1 grams vs. 153.48 grams for subjects who did not suppress over the 2-week treatment period.

The average post-CST cortisol level (mcg/dL) at Day 14/EOS was 26.7 (adults) and 22.8 (adolescents) with a range of 17.7 to 42.6 (adults) and 14.9 to 28.0 (adolescents).

Although the mean clascoterone maximum, average, and minimum steady-state plasma concentrations in subjects with adrenal suppression tended to be higher than in subjects with no adrenal suppression, there was significant overlap in the mean and range of exposures in subjects with and without adrenal suppression and there was no clear relationship between adrenal suppression and clascoterone exposure. Analysis of the

PK data indicated that clascoterone plasma concentrations were at steady state by Day 5 and during the assessment of adrenal suppression potential on Day 14.

In study CB-03-01/28, subjects (9 to <12 Years of Age) were instructed to apply, to the face and trunk BID for 2 weeks a total of 4 grams daily. Twenty-seven subjects were enrolled in the study.

Two (2/23, 8.7%) subjects from the evaluable population (N=23) had abnormal HPA axis response at Day 14/EOS under maximum use conditions as documented by a 30-minute post-stimulation serum cortisol level of ≤ 18 μg/dL. Both "suppressed" subjects returned to normal HPA axis function approximately 4 weeks after Day 14/EOS. None of the subjects demonstrated any clinical signs/symptoms associated with adrenal suppression.

There were 4 (4/27, 14.8%) TEAEs of ACTH stimulation test abnormal (including the 2 subjects mentioned above), all deemed to be related to clascoterone 1% cream and resolved by the end of the study.

Table 22: Subjects who had Adrenal Suppression at Day 14

Subject #	Screening/Baseline Post-CST Cortisol (μg/dL)	Day 14 Post-CST Cortisol (μg/dL)	Follow-Up (~4 weeks after Day 14) Post-CST Cortisol (μg/dL)	Total Test Article Used (grams)
PI	19.5	18.0*	23.0	50.69
PI	18.2	16.1*	30.5	55.95

Source: Listing 16.2.7.
* These abnormal CST results were documented as AEs.

In total, 7 subjects (7/69, 10.1%) had TEAEs of ACTH stimulation test abnormal in the HPA axis suppression studies (study 171-7151-202 and study CB-03-01/28). All TEAEs were deemed to be related to clascoterone 1% cream.

Deaths

No deaths were reported during any of the studies of clascoterone.

2.5.8.4. Laboratory findings

Five subjects experienced laboratory-related AEs during the studies (Table 23), none of which were SAEs. A subject discontinued study drug due to elevated liver function tests and completed the study.

Table 23: Laboratory-related Adverse Events

Study	Subject ID Treatment	Adverse Event (Preferred Term): Severity, Relationship, Outcome	Reported Values[a]
CB-03-01/28	[redacted] CB-03-01 1% BID	Leukopenia: mild, not related, resolving	Leukocytes [5.0-24.5 x 10^3/µL]: 11.7 (screening), 2.7 (Day 14)
171-7151-201	[redacted] CB-03-01 1% BID	Liver function test abnormal: mild, not related, drug withdrawn (subject completed the study), resolving	ALT [5-30 U/L]: 116 (BL), 31, 188, 142, 49 (EOS) AST [0-41 U/L]: 18 (BL), 42, 138, 81, 44 (EOS) AP [180-700 U/L]: 68 (BL), 69, 101, 112, 80 (EOS)
171-7151-201	[redacted] CB-03-01 1% BID	Blood creatine phosphokinase increased: mild, not related, ongoing ALT increased; mild, not related, ongoing AST increased; mild, not related, ongoing	CK [35-232 U/L]: 5097 (EOS) ALT [5-30 U/L]: 16 (BL), 14, 19, 35 (EOS) AST [0-41 U/L]: 17 (BL), 16, 16, 90 (EOS)
171-7151-201	[redacted] CB-03-01 0.5% BID	WBC count increased: moderate, not related, resolving Neutrophil count increased; moderate, not related, resolved	WBC [3.5-10.5 x 10^3/µL]: 11.0 (BL), 8.8, 13.7, 11.3, 11.1 (EOS) Neutrophils [2.1-7.8 x 10^3/µL]: 5.9 (BL), 4.6, 10.2, 7.5, 7.8 (EOS)
CB-03-01/27	[redacted] CB-03-01 1% BID	Anaemia: mild, not related, ongoing	Laboratory values not reported

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BL = baseline; CK = creatine kinase; EOS = end of study; WBC = white blood cell
a Shown as analyte [reference range]: all reported values

In addition, seven subjects (10%) had AEs of ACTH stimulation test abnormal in the HPA axis suppression studies (cf. section 2.5.9).

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.5.8.6. Safety in special populations

An overall summary of TEAEs is presented in Table 24 by age, gender, race and baseline IGA for clascoterone 1% Cream BID group in Pool A.

Table 24: Overall Summary of Treatment-Emergent Adverse Events by Subgroups of Age, Gender, Race, and Baseline Investigator's Global Assessment (IGA) for CB-03-01 1% Cream BID Group in Pooled Phase 3 Pivotal Studies (Safety Population)

	Age[a]			Gender		Race		Baseline IGA[b]		Total
	9 - < 12 N = 13	12 - < 18 N = 316	≥ 18 N = 393	Male N = 258	Female N = 464	White N = 655	Non-White N = 67	Moderate N = 597	Severe N = 125	All N = 722
All TEAEs	3 (23.1)	34 (10.8)	45 (11.5)	27 (10.5)	55 (11.9)	77 (11.8)	5 (7.5)	68 (11.4)	14 (11.2)	82 (11.4)
Serious TEAE	0	0	0	0	0	0	0	0	0	0
TEAE related to study drug	0	5 (1.6)	7 (1.8)	4 (1.6)	8 (1.7)	11 (1.7)	1 (1.5)	10 (1.7)	2 (1.6)	12 (1.7)
Serious TEAE related to study drug	0	0	0	0	0	0	0	0	0	0
TEAE leading to dose modification	1 (7.7)	1 (0.3)	4 (1.0)	0	6 (1.3)	6 (0.9)	0	4 (0.7)	2 (1.6)	6 (0.8)
TEAE leading to discontinuation of study drug	0	2 (0.6)	3 (0.8)	2 (0.8)	3 (0.6)	5 (0.8)	0	4 (0.7)	1 (0.8)	5 (0.7)
TEAE leading to death	0	0	0	0	0	0	0	0	0	0

TEAE = treatment-emergent adverse event
a No subjects were ≥ 65 years old.
b All subjects had baseline IGA of 3 (moderate) or 4 (severe).

Age

The current application is seeking approval for the treatment of acne vulgaris in adults, and adolescents aged 12 to 18 years. Children aged 9 to < 12 years old are not included in this application.

The most common SOCs in subjects aged 12 to < 18 years were Infections and infestations (5.4%) and Nervous system disorders (1.3%).

No subject were ≥ 65 years old.

Table 25: TEAEs by age range in Pool A

	Active			Comparator		
MedDRA Terms	9-<12a n (%)	12-<18a n (%)	18-<65a n (%)	9-<12a n (%)	12-<18a n (%)	18-<65a n (%)
Total AEs	3 (23.1)	34 (10.8)	45 (11.5)	0 (0.0)	46 (14.2)	45 (11.6)
Infections and infestations	0 (0.0)	17 (5.4)	23 (5.9)	0 (0.0)	27 (8.3)	12 (3.1)
General disorders and administration site conditions	1 (7.7)	2 (0.6)	6 (1.5)	0 (0.0)	7 (2.2)	19 (4.9)
Skin and subcutaneous tissue disorders	0 (0.0)	3 (0.9)	4 (1.0)	0 (0.0)	3 (0.9)	4 (1.0)
Nervous system disorders	0 (0.0)	4 (1.3)	3 (0.8)	0 (0.0)	1 (0.3)	4 (1.0)
Psychiatric disorders	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Genders, race categories, disease severity at baseline

The proportion of subjects who experienced TEAEs was similar between genders, race categories, and whether subjects had moderate or severe disease at baseline (IGA score). There were no notable differences among the subgroups in the nature of the TEAEs.

In Pool B, no TEAE in population aged 9-<12 years were considered related to study drug.

Five (1.5%) TEAEs related to study drug were reported in population aged 12-<18 years, none were serious.

Use during pregnancy

Clinical data on exposure to clascoterone during pregnancy is very limited, with only 3 cases described (Two others cases was an exposure to a vehicle).

Use during breastfeeding

There is no data on exposure during breastfeeding. Concerning exposure during breastfeeding, a risk cannot be excluded for the breastfed infant, therefore breastfeeding should be discontinued during treatment as precautionary measure.

2.5.8.7. Immunological events

N/A

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

Formal drug-drug interaction studies have not been conducted with clascoterone cream. *In vitro* studies of human cryopreserved hepatocytes showed that clascoterone did not induce cytochrome oxidases 1A2, 2B6, and 3A4 (CB-03-01/16). In pooled human liver microsomes, clascoterone did not inhibit CYP 1A2, 2B6, 2C19, 2D6, 2E1, or 2C9 to any significant degree as IC50 values could not be determined. There was slight to moderate inhibition of CYP 2C8 with an IC50 of 41 µM (CB-03-01/18). This finding is not likely to have any clinical significance since peak plasma levels of clascoterone average 6.7 µM in subjects treated with clascoterone after 6 weeks.

2.5.8.9. Discontinuation due to adverse events

TEAEs leading to study drug withdrawal and/or study discontinuation.

In Pool A and B, TEAEs led to dose modification, which was an interruption in dosing, for 6 subjects (0.8%) with CB-03-01 and 7 subjects (1.0%) with vehicle. The TEAEs that led to dose interruption in the CB-03-01 group were application site dryness, bronchitis, dry skin, furuncle, oropharyngeal pain, and pyrexia.

TEAEs considered at least possibly related to clascoterone in Pool A were Application Site Hypersensitivity, Oropharyngeal Pain, Dermatitis Contact, and Hair Colour Changes. None of these TEAEs were serious or severe.

In Pool A, 5 subjects (0.7%) in clascoterone group had TEAEs that led to discontinuation of study drug and 12 (1.7%) in vehicle group. In study 171-7151-201, one TEAE leading to discontinuation of study drug was reported (Infectious mononucleosis) in clascoterone cream 1% BID group.

In LTF study CB-03-01/27, there were 9 subjects in clascoterone cream 1% group who experienced 9 TEAEs (2.8% in clascoterone group vs 0.0% in vehicle group) that led to study discontinuation and these included moderate application site swelling, moderate application site dryness, moderate acne cystic, moderate application site acne, mild polycystic ovaries, severe suicide attempt, and moderate hair colour changes.

2.5.8.10. Post marketing experience

A total of 1,342 AEs of Winlevi (as a suspected drug) were retrieved between 26 August 2021 and 25 May 2023 in the US. All of the 1,342 AEs were reported spontaneously. Of these 1,342 AEs, eight cases were reported as serious: 1 adrenal suppression, 1 hypothalamic pituitary adrenal axis suppression, 1 cyst, 1 inflammation, 1 haemorrhage, 1 burning sensation, 1 hypertension and 1 product contamination microbia.

2.5.9. Discussion on clinical safety

A total of 1757 subjects were exposed to at least one application of clascoterone in all studies, including 352 healthy subjects and 1405 subjects with acne. The Applicant provided a **Pool A** set of patients treated for 3 months issued from Phase 3 pivotal studies that included 1440 adolescents and adults subjects (722 were treated with clascoterone cream 1% BID and 718 with vehicle cream), and a **Pool B** set of patients issued from Pool A and patients treated with clascoterone cream 1% BID in Phase 2 Dose Escalating Study 171-7151-201 (792 adolescents and adults subjects with acne were treated with clascoterone 1% cream BID and 773 subjects treated with vehicle cream BID for 12 weeks).

An additional pool of all studies was analysed and included 1467 subjects treated with clascoterone cream. The majority of the patients were treated >84 days. No meaningful differences between study groups in terms of study duration were observed, median of patient 12-<18 years and ⩾18 years in pooled Phase 3 and LTF study was 95 days which seems insufficient to observed long term AEs. This is particularly lacking in adolescent population, where an effect on HPA axis could have a serious clinical impact.

In Pool A, a total of 316 subjects aged 12-<18 years old were treated with clascoterone Cream 1% BID and 325 subjects with vehicle.

The number of patients exposed to CB-03-01 for longer period of time is overall very limited. In the LTF study, the number of patients treated with clascoterone 1% cream BID for 6 months is 236. Additionally, 123 patients were treated with clascoterone for 12 months (long term follow up study, LTF) which, according to ICH Guideline E1, is acceptable. Few paediatric patients were treated with clascoterone for 12 months (n=66), which raises concerns about long-term effects that may occur in this population. Indeed, clascoterone has glucocorticoid properties and long-term exposition in paediatric patients could lead to retardation of growth and/or an impact on sexual maturation.

Clinical laboratory tests were conducted in the Phase 2 studies but not in the Phase 3 studies.

In pool A, 81.6% in the CB-03-01 group and 79.7% in the vehicle group completed the 12-week studies. The most frequent reasons for discontinuation were withdrawal by the subject and lost to follow-up.

Overview of TEAEs

Over 12 weeks of treatment, TEAEs were low and seem similar between clascoterone cream 1% BID and vehicle in Pool A (11.4% vs. 12.7%, respectively) and in Pool B (12.0% vs. 13.8%, respectively). The incidence of TEAEs from long term follow up study (CB-03-01/27) up to 12 months are also similar between clascoterone cream 1% BID group and vehicle group (18.3% vs. 17.9%, respectively). Overall, these clinical data seem reassuring.

In Pool A, SOCs in which TEAEs were the most commonly reported were:

- Infections and infestations (5.5% in clascoterone group, 5.4% in vehicle group),

- Respiratory, thoracic and mediastinal disorders (1.8% in clascoterone group, 1.3% in vehicle group),
- General disorders and administration site conditions (1.2% in clascoterone group, 3.6% in vehicle group),
- Gastrointestinal disorders (1.1% in clascoterone group, 1.1% in vehicle group),
- Nervous system disorders (1.0% in clascoterone group, 0.7% in vehicle group).

There was no clear pattern for these SOCs.

The most commonly reported TEAEs were Nasopharyngitis (1.4% in clascoterone group, 2.8% in vehicle group), Oropharyngeal pain (0.8% in clascoterone group, 0.7% in vehicle group), Headache (0.8% in clascoterone group, 0.6% in vehicle group). The occurrence of the other TEAEs in clascoterone group were < 0.8%.

In the studies pool, TEAEs were more reported in clascoterone group (15.6%) than placebo group (13.6%). Most of the SOCs were higher in clascoterone group than placebo group. The most represented SOCs were Infections and infestations (6.5% vs 5.7%, respectively), Respiratory, thoracic and mediastinal disorders (2.0% vs. 1.5%, respectively), Skin and subcutaneous tissue disorders (1.6% vs. 1.5%, respectively), Gastrointestinal disorders (1.6% vs. 1.3%, resp.), Nervous system disorders (1.6% vs 1.0%, respectively), Injury, poisoning and procedural complications (1.3% vs. 0.7%). The TEAEs the most frequent in clascoterone group were flu-like symptoms (PTs Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain and Headache) and the incidence was relatively low and similar (1.0% to 1.6%).

The incidence of TEAEs related to clascoterone were low and similar to placebo except for the PT ACTH stimulation test abnormal (n=7, 0.5% in clascoterone group vs. 0 in placebo group). This issue is discussed below.

In total, the analysis of this new pool is consistent with Pool A and B.

Across all studies 12 subjects experienced **serious TEAEs** (10 subjects treated with CB-03-01 and two subjects who received vehicle). No cases of serious TEAE related to study drug were reported.

There was comparable number of **TEAEs leading to dose modification** between both pivotal studies and between both groups and the number of **TEAEs leading to discontinuation** of the study drug was lower in CB-03-01 group, compared to Vehicle (0.7% vs 1.7%). The most frequently reported TEAEs were acne worsening and application site events.

No **deaths** were reported during any of the studies of clascoterone.

Long term TEAEs (up to 12 months of treatment) were mild or moderate. Four subjects had 7 severe TEAEs (Gastroenteritis eosinophilic, Pancreatitis, Pruritus, Dizziness, Sciatica, Suicide attempt, Nephrolithiasis).

SOCs that had an occurrence of long term TEAEs higher in clascoterone group compared to vehicle group and had an occurrence higher than 1% were:

- Infections and infestations (7.6% vs 6.9%, respectively),
- Gastrointestinal disorders (3.5% vs 2.8%),
- Skin and subcutaneous tissue disorders (3.5% vs 2.1%),
- General disorders and administration site conditions (2.8% vs 1.4%),

- Psychiatric disorders (1.3% vs 0.7%).

In Pool B and LTF study, the following cases were reported in the clascoterone group: suicide attempt (1), depression (3), mood swings (1), libido decreased (1).

Serious TEAEs of Suicide attempt and Dizziness occurred in a 14-year-old female. Although suicide attempt is a known comorbidity of acne disease, there is no information regarding the context of this TEAE (medical history, etc.)**.** The physician assessed the TEAE as not correlated to the study drug.

The only serious TEAE of depression was confounding by the patient's medical history (ongoing attention deficit/hyperactivity disorder and ongoing bipolar disorder) and causality to the study drug is unlikely. In addition, two non-serious TEAEs of depression of moderate severity were reported. One of them had a short time-to-onset and for the other the patient had no comorbidity, depression occurred 2.5 months after initiation of clascoterone, and he was treated during 12 months with clascoterone. However, the physician who evaluated multiple times this patient (8 visits in total) considered it not related to clascoterone.

In subjects treated with clascoterone during 12 months (Phase 3 and long-term studies), the TEAEs observed at 12 months (at the end of long-term study) were similar than those observed in Phase 3 studies (at the end of phase 3 study). 'Infections and infestations' was the most frequently reported SOC.

The overall number of **TEAEs related to study drug** was lower in CB-03-01 group, compared to Vehicle (1.7% vs 3.1%). They were mostly related to acne and application site reactions. Dryness is proposed as an ADR by the Applicant in Winlevi SmPC section 4.8 which is acceptable.

TEAEs at least possibly related to clascoterone and leading to discontinuation were mostly related to acne (worsening) and application site events. None of these TEAEs were serious or severe.

AEs of special interest

Local Skin Reactions

The reporting rate of subjects experiencing LSR was similar between clascoterone cream 1% BID group and vehicle BID group. The most frequent treatment-emergent LSRs were erythema and scaling/dryness and most of them were mild in severity. The number of subjects with at least one new or worsening LSR on face after day 1 was similar between clascoterone group (24.9%) and placebo (27.3%). The only LSR with significant difference is Striae rubrae (2.4% vs. 1.4%) which is a known side-effect of corticosteroid treatments and Cushing Disease. However, the causal relationship with clascoterone cannot be established at this time. LSR will be monitored in routine pharmacovigilance via PSURs.

Hypersensitivity/Drug Reactions

In total, 5 subjects had TEAEs identified as or related as hypersensitivity or drug reactions. One of them was reported as probably related to study drug and resolved (mild allergic reaction in a 15-year-old male). Further information (e.g. symptoms, time-to-onset, corrective treatment) were not provided in the narrative and thus, causality cannot be assessed.

Effect on hypothalamic-pituitary-adrenal (HPA) axis

HPA axis suppression was studied in two Phase 2 studies and perturbations were observed in some patients with clascoterone at supratherapeutic doses during 2 weeks. Seven subjects (7/69, 10%) had abnormal ACTH stimulation tests at D14, which returned to normal 4 weeks after stopping the clascoterone cream (> 18 µg/dL). Although abnormal HPA axis suppression tests were close to the lower limit, it seems more elevated with decreased of age (5% of adult subjects, 9.1% of adolescent subjects, and 14.8% of paediatric

subjects 9 years to 11 years). The fact that all subjects with abnormal HPA axis test returned to normal 4 weeks after stopping the clascoterone cream questions about a potential systemic passage and systemic effects. In both studies, reduced HPA axis response was not associated with clinical signs or symptoms.

It is questioned whether these perturbations could be higher with long term duration at therapeutic dose since it is known that the effect of glucocorticoid agonists on suppression of the corticotropic HPA axis is greater and lasts longer after discontinuation, the higher the cumulative doses are and the longer the duration of exposure is.

Moreover, cases of 'Adrenal suppression' and 'Hypothalamic pituitary adrenal axis suppression' were reported post marketing in USA, where clascoterone cream is marketed since 2021. Two serious cases reported HPA axis suppression and one serious case reported adrenal suppression. All cases were reported by healthcare professionals. Assessment of these cases are difficult because there is limited information and cortisol level was not available. The risk of HPA axis suppression is considered an important identified risk.

This major safety concern on potential systemic effect, in particular its impact on corticotropic and gonadotropic activities is reinforced by the lack of clear and robust data on systemic passage (see clinical pharmacology section). Indeed, the scarcity of PK data did not allow a proper PK analysis in particular regarding the systemic exposure of clascoterone when topically applied twice daily at the dose of 2 g per day for a long-term period.

During the procedure, the Applicant proposed a set of measures to address the CHMP concern on the risk of HPA axis suppression:

- limitation of the daily dose in adolescents to 2 g/day, thereby reducing the adolescent maximum dose by more than half the adult maximum dose, consequently reducing the potential for systemic exposure whilst still enabling treatment of acne in the adolescent patient population. This dose is aligned with the dose proven efficacious in the Phase 3 trials. This reduced dose would mean a reduction in the area of skin that could be treated, not a reduction in efficacy.

- Additionally, a routine RMM, early morning cortisol measurements every three months of treatment, alongside assessment of treatment success and condition of the treated skin, is proposed.

- Commitment to conduct a post-approval safety study in adolescents to formally assess impact on HPA axis function in the clinical setting. The design of this study is proposed to be discussed with CHMP through a Scientific Advice procedure.

Reducing the dose maximum daily dose in adolescents from 5 to 2 grams would represent 1/5 of the surface area initially identified in the claimed indication. This would limit the skin area to be treated. Although this in itself might reduce a safety risk, consequently additional (concomitant) treatment may become necessary to satisfactorily treat the condition, with its inherent risks. Also, patients (adolescents in particular) might not comply with a limited dose / treatment area.

It is considered that carrying out a cortisol test every 3 months for the entire duration of the treatment would represent a significant burden for the patients to treat a non-life-threatening condition. It is not deemed appropriate to impose routine cortisol tests on all patients aged 12 to 18 every 3 months to mitigate a risk that was not sufficiently characterised during the clinical studies.

In the absence of satisfactory data confirming there is no risk of HPA axis suppression with clascoterone use in adolescents, the potential impact of clascoterone on the HPA axis cannot be ruled out and is deemed detrimental to the safety profile of clascoterone in the adolescent population. Therefore, the CHMP is of the

view that the risk of HPA axis suppression in adolescents should be addressed with a well-conducted clinical trial on a representative sample of adolescents with acne prior to authorising clascoterone in this population to ensure its safe use.

Potential effect on the gonadotropic activity

The Applicant did not give reassuring data concerning a potential effect on gonadotropins, which is a safety concern as regards sexual and endocrine functions during puberty in adolescents. Indeed, cases of dysmenorrhoea were reported during clinical development (2 cases in pool A and 1 case in LTF study) and a few cases relating to menstrual disorders (amenorrhoea, irregular menstruation, menstrual bleeding) were also reported as part of post-marketing surveillance in the United States, which questioned the effect of clascoterone on gonadotropins.

Moreover, following FDA approval in 2020, a search was conducted in the FDA Adverse Event Reporting System (FAERS) on 27-DEC-2023. Most of the cases were reported in female patients. Some cases relative to menstrual disorders (amenorrhea, menstruation irregular, menstrual bleeding) were reported. Additionally, during clinical development, 2 cases of dysmenorrhoea were reported in Pool A and 1 case of amenorrhoea was reported in LTF study. In total, there were 13 TEAEs of sexual, endocrine and menstrual disorders, 2 were considered as unlikely related to clascoterone: one case of amenorrhea which occurred in a patient aged 16 years which is an age range of highest prevalence of secondary amenorrhea, and one case of polycystic ovaries which does not seem to correspond to clascoterone mechanism of action (anti-androgen). For both of these cases, the events led to drug withdrawal.

Considering the above and that gonadotropic effects of clascoterone has not been explored in the clinical trials, the negative impact of clascoterone on sexual maturation in adolescents cannot be ruled out.

Safety in special populations

Overall summary of TEAE by age, gender, race and baseline IGA is poorly documented as only data from Pool A was provided. The overall number of TEAEs was comparable between subgroups in subjects treated with CB-03-01 1% Cream BID in both pivotal studies.

The most common SOC in subjects aged 12-<18 years were Infections and infestations (5.4%), mostly TEAEs of Nasopharyngitis (2.1% in clascoterone group vs 4.6% in vehicle group), and Nervous system disorders (1.3%) with 4 (1.2%) TEAEs of headache in clascoterone group and 1 (0.6%) in vehicle group.

No subjects were ≥ 65 years old. This is acceptable taking into account that the prevalence of acne progressively decreases with increasing age of male and female, affecting approximately 7% and 15% of patients aged 50 years and older, respectively (Collier, 2008).

Although gender (258 males vs. 464 females), race (655 white vs. 67 non-white), and baseline IGA (597 IGA 3 vs. 125 IGA 4) subgroups are not equally distributed, there is no evidence of harmful effects depending on subgroups.

Pregnancy and breastfeeding

Clinical data on exposure to clascoterone during pregnancy is very limited. Based on its mechanism of action (androgen receptor inhibition) and a reproductive toxicity observed in animal studies (rats and rabbits) at all dose level tested and/or at non-maternotoxic doses without safety margin, clascoterone can cause fetal harm. The risk of reproductive toxicity is considered an important potential risk. Based on non-clinical studies results, clascoterone should be contraindicated during pregnancy and up to 10 days following treatment discontinuation. Additional risk minimisation measures are considered necessary in order to enhance

awareness of the prescribers of the important potential risk of reproductive toxicity (e.g., healthcare professional guide) and to facilitate that prescribers communicate to female patients the specific requirements for contraception and support the patients' adherence to these measures (e.g.,+ patient card).

There is no data on exposure during breastfeeding. As precautionary measure, breastfeeding should be discontinued during treatment as precautionary measure.

Drug-drug interactions

No formal drug-drug interaction studies have been performed and the use of clascoterone cream 1% in combination with other topical medicinal products used to treat acne has not been evaluated.

No clinical data are available on the concomitant use of clascoterone 1% cream with other topical products. A precaution for use is recommended regarding the risk of local irritation in case of concomitant topical anti-acneic drug.

Laboratory findings

No notable laboratory trends were noted in any of the treatment groups, similarly laboratory changes from baseline were generally unremarkable.

Adverse drug reactions

There were few TEAEs related to study drug in Pool A and in Pool B with clascoterone cream 1% BID (12 TEAEs). The most common TEAEs were related to application site reactions. The only related TEAE reported for more than one subject treated with clascoterone was application site dryness, which was reported for two subjects in each treatment group. Application site dryness was reported as an AE for 3 (0.4%) patients in clascoterone cream 1% BID in Pool A and B, and in 2 patients (0.3%) in vehicle group.

LSRs were collected independently of adverse events (AEs). Only LSRs that required medical intervention (e.g., prescription medication) or required withholding the application of study drug were to be documented as AEs. The most common treatment-emergent local skin reactions (LSRs) were erythema, scaling/dryness, and pruritus. New or worsening LSRs after day 1 that were more reported in clascoterone group than in vehicle group, in Pool A, were Striae Rubrae (2.4% vs 1.4%), Edema (3.5% vs 3.2%), and Scaling/Dryness (10% vs 9.5%).

Although reporting rate of some LSRs are higher in vehicle group than clascoterone group, they are considered as ADRs because of the route of administration (topical cream) and the mechanistic plausibility (anti-androgen). Excipients could also explain LSRs observed in vehicle group (cetyl alcohol, propylene glycol).

Hyperkalaemia could be expected based on mechanism of action of clascoterone (anti-androgen). This was mainly observed in patients aged between 9 and 12 years. This population is not included in the applied indication of clascoterone cream. The proportion of adolescent subjects was lower in the clascoterone group than in the vehicle group (3.3% vs. 5.4%) and slightly higher in the adult subjects treated with clascoterone compared to the vehicle group (3.9% vs. 3.0%), after excluding haemolysed samples. No clinical signs related to elevated serum potassium were observed in clinical trials and no issues were reported in the post-marketing experience in the US.

Assessment of paediatric data on clinical safety

The median duration of treatment of patient 12-<18 years and ≥18 years in pooled Phase 3 and LTF study was 95 days which seems insufficient to observed long term AEs. This is particularly lacking in adolescent population, where an effect on HPA axis could have a serious clinical impact.

Few paediatric patients were treated with clascoterone for 12 months (n=66), which raises concerns about long-term effects that may occur in this population. Indeed, clascoterone has glucocorticoid properties and long-term exposition in paediatric patients could lead to retardation of growth and/or an impact on sexual maturation.

In Pool A, a higher proportion of subjects aged 9 to < 12 years experienced TEAEs (23.1%) compared to those 12 to < 18 years (10.8%) or 18 to < 65 years (11.5%).

The most common SOCs in subjects aged 12 to < 18 years were Infections and infestations (5.4%) and Nervous system disorders (1.3%).

HPA axis suppression was studied in paediatric in two Phase 2 studies and perturbations were observed in some patients with clascoterone at supratherapeutic dosesduring 2 weeks. Two adolescents (2/22, 9.1%) had abnormal ACTH stimulation tests at D14 (17.0 µg/dL, 14.9 µg/dL), which returned to normal 4 weeks after stopping clascoterone cream (> 18 µg/dL). Although abnormal HPA axis suppression tests were close to the lower limit, it seems more elevated with decreased of age (5% of adult subjects, 9.1% of adolescent subjects, and 14.8% of paediatric subjects 9 years to 11 years). The fact that all subjects with abnormal HPA axis test returned to normal 4 weeks after stopping the clascoterone cream questions about a potential systemic passage and systemic effects. In both studies, reduced HPA axis response was not associated with clinical signs or symptoms.

It is questioned whether these perturbations could be higher with long term duration at therapeutic dose since it is known that the effect of glucocorticoid agonists on suppression of the corticotropic HPA axis is greater and lasts longer after discontinuation, the higher the cumulative doses are and the longer the duration of exposure is. In case of long-term exposition in adolescents, it could lead to a retardation of growth and/or an impact on sexual maturation both considered as major concerns.

2.5.10. Conclusions on the clinical safety

The safety profile of clascoterone in the treatment of acne vulgaris for the adult population is considered sufficiently characterised. With regard to the adolescent population from 12 years of age, major safety concerns about the effect of clascoterone on the HPA axis and gonadotropic activity have been identified. Long-term exposition in adolescents could lead potentially to a retardation of growth and/or an impact on sexual maturation. Therefore, the safety profile of clascoterone in the treatment of acne vulgaris in adolescents from 12 years to less than 18 years of age is not considered favourable.

2.6. Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

N/A

2.8. Product information

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the product information cannot be agreed at this stage.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Acne vulgaris is a chronic inflammatory skin condition of pilosebaceous glands that typically begins at puberty and may continue through adulthood with flares often coinciding with increasing serum androgens (Arora, 2011; Taylor, 2011). It is one of the most common dermatological disorders worldwide (AAD, 2019) with its incidence and severity influenced by genetics and environment (Arora, 2011).

Acne is a waxing and waning, inflammatory skin disease that develops as a result of hypersensitivity of the sebaceous glands to normal levels of circulating androgens (Motosko, 2019) and its pathophysiology is multifactorial involving increased androgen-induced sebum production, altered keratinization (including plugging of the pilosebaceous unit), changes in the skin's natural flora with increased bacterial colonization of hair follicles by Cutibacterium acnes (C. acnes), and the consequential immune and inflammatory response (Admani, 2013; Dréno, 2018; Lai, 2012).

The condition commonly manifests with papules, pustules, or nodules primarily on the face, although it can also affect the upper arms, trunk, and back. The pathogenesis of acne vulgaris involves the interaction of multiple factors that ultimately lead to the formation of its primary lesion, which is known as "comedo". The severity of this condition can vary, ranging from a mild presentation with only a few comedones to more severe forms characterized by disfiguring inflammatory manifestations, which can lead to hyperpigmentation, scarring, and adverse psychological effects (Sutaria, 2023).

Acne vulgaris affects approximately 9% of the population worldwide and approximately 85% of those aged 12 to 24 years (Eichenfield, 2021). Acne is often the first sign of puberty in boys and girls, and this onset is thought to be secondary to hormonal surges leading to increased sebum production (Goldberg, 2011).

Although the prevalence of acne is highest in adolescents and young adults, it can also occur in younger children. However preadolescent acne is a rare disease, affecting only 3.5% of patients (Frénard, 2021).

Drugs that are able to reduce androgen production or to antagonize androgen interaction with the specific sebaceous glands' androgen receptors may be beneficial in the treatment of acne.

3.1.2. Available therapies and unmet medical need

The treatment armamentarium for acne vulgaris includes both topical and systemic products. Treatments target one or more of the primary pathogenic factors: sebaceous gland hypersecretion stimulated by androgen production, bacterial proliferation, and abnormal keratinization with resultant follicular obstruction and inflammation. Therefore, it is considered there is no unmet medical need.

Numerous formulations of topical preparations include creams, gels, lotions, solutions, and washes. Mild to moderate acne is typically treated with topical medicines. Skin irritation is a common side effect of topically administered anti-acne medications. Topical treatment may last 6–8 weeks or continue for many years. For the management of severe acne, the European guidelines recommend to combine a topical therapy with a systemic therapy (M. Vasam et al, 2023: Acne vulgaris: A review of the pathophysiology, treatment, and recent nanotechnology-based advances).

3.1.3. Main clinical studies

Pivotal Phase 3 studies CB-03-01/25 and CB-03-01/26

These 2 clinical trials were Phase III, multicentre, randomized, double-blind, vehicle-controlled, parallel-group comparison studies of the safety and efficacy of CB-03-01 cream, 1% applied twice daily for 12 weeks in male and female subjects, 9 years of age or older with moderate to severe acne vulgaris on the face.

Eligible subjects must have acne vulgaris of the face (which can include the nose) with an Investigator's Global Assessment (IGA) score of 3 or 4, at least 30 to a maximum of 75 inflammatory lesions (papules, pustules, and nodules), and at least 30 to a maximum of 100 non-inflammatory lesions (open and closed comedones).

The 3 co-primary Efficacy endpoints were (hierarchical) at week 12:

- P1: Proportion of subjects in each group achieving "success" defined as an IGA score of "clear (score=0)" or "almost clear (score=1)" AND at least a two-point reduction in IGA compared to Baseline.
- P2: Absolute change from Baseline in Non-inflammatory Lesions Count (NILC) in each group
- P3: Absolute change from Baseline in Inflammatory Lesions Count (ILC) in each group.

The secondary efficacy endpoints were (hierarchical) at week 12:

- S1: Absolute change from Baseline in total lesion count (TLC) in each group
- S2: Percent change from Baseline in TLC in each group
- S3: Percent change from Baseline in NILC in each group
- S4: Percent change from Baseline in ILC in each group

3.2. Favourable effects

The efficacy endpoints used in pivotal Phase 3 studies showed the superiority of clascoterone cream applied twice daily on the face versus vehicle after a 3-month period of treatment:

- "success" (Proportion of subjects with a ≥ 2-point reduction in IGA and IGA score of 0 or 1) was 19.5% for clascoterone group compared to 7.7% for VEH group ($p<0.0001$)
- absolute change from baseline of non-inflammatory lesions count was -19.3 vs -11.8 ($p<0.0001$)
- absolute change from baseline of inflammatory lesions count was -19.8 vs -13.9 ($p<0.0001$)
- in moderate acne, the repeated analysis of the IGA success with logistic regression showing an efficacy for clascoterone of 21.3% vs vehicle 8.9% as pooled data, i.e. 12.4% of absolute difference;
- a new analysis of IGA responders (patients achieving an IGA score of 0 or 1 and at least 2-point reduction in IGA) among the European patients with moderate acne (IGA=3 at baseline), with results of 26.2% for clascoterone vs 8.5% for the vehicle, i.e. 17.7% of absolute difference.

Adolescents (12 - 18 years) are part of the applied indication and represented 44.5% (n=641) of the total study population in pivotal studies (n=1440). Analyses of IGA score with at least 2-point reduction and a score of 0 or 1 at 12 weeks showed a marginal effect of clascoterone in adolescents (14.9%).

3.3. Uncertainties and limitations about favourable effects

The claimed new mechanism of action could not be fully elucidated to ensure that clascoterone has a peripheral anti-androgenic effect only. Thus, only human data could provide reassurance on lack of central anti-androgenic effect.

The effect of clascoterone cream on acne vulgaris is considered modest (19.5% from pooled data) in both pivotal studies. The absolute changes in NILC and ILC are also considered limited. However, it is recognised that the effect has been satisfactorily demonstrated compared to vehicle based on the primary endpoint (IGA score 0 or 1)

The follow-up study including subjects from the 3-month pivotal studies and treated for an additional 9-month period aimed giving safety data. Thus, efficacy beyond 3 months is poorly documented and makes difficult interpretation of results concerning the long-term effect.

Evaluation of clascoterone on the trunk is also poorly documented. Only percentage of patients with IGA score 0 or 1 issued from the open-label study were provided: 40.2% (Investigator's last assessment) and 59.2% (at 9 months).

A potential rebound effect has not been evaluated during the clinical studies. As clascoterone has glucocorticoid properties, an exacerbation could be expected at the time of treatment discontinuation with a reactivation of lesions with greater intensity than their pre-treatment state. A warning advising on caution and seeking medical advice in these cases or considering other treatment options was recommended.

3.4. Unfavourable effects

The main unfavourable effect is the risk of HPA axis suppression in adolescents.

Clascoterone acts as an androgen antagonist and is hydrolysed to cortexolone, a physiological component of the pool of endogenous corticosteroids, an intermediate in the synthesis of glucocorticoid steroids. HPA axis suppression was studied in two Phase 2 studies and perturbations were observed in some patients with clascoterone at supratherapeutic dosesduring 2 weeks. Seven subjects (7/69, 10%) had abnormal cosyntropin stimulation tests at D14. Although abnormal HPA axis suppression tests were close to the lower limit, it seems more elevated with decreased of age (5% of adult subjects, 9.1% of adolescent subjects, and 14.8% of paediatric subjects 9 years to 11 years). The fact that all subjects with abnormal HPA axis test returned to normal 4 weeks after stopping the clascoterone cream questions about a potential systemic passage and systemic effects. In both studies, reduced HPA axis response was not associated with clinical signs or symptoms. It is questioned whether these perturbations could be higher with long term duration at therapeutic dose since it is known that the effect of glucocorticoid agonists on suppression of the corticotropic HPA axis is greater and lasts longer after discontinuation, the higher the cumulative doses are and the longer the duration of exposure is. In long-term exposure, this risk could lead to a retardation of growth and/or an impact on sexual maturation both considered as major concerns.

Cases of 'Adrenal suppression' and 'Hypothalamic pituitary adrenal axis suppression' were reported post-marketing in USA, where clascoterone cream has been marketed since 2021. At this stage, the frequency of this event is difficult to estimate from the available data as the dose of clascoterone in the Phase 2 study evaluating HPA suppression was different from the one proposed by the Applicant.

The risk of HPA axis suppression in adolescents has not been studied in the phase 3 studies and thus cannot be ruled out.

Gonadotropic effects of clascoterone have not been explored either. As a result, the negative impact on sexual maturation in adolescents cannot be ruled out.

Therefore, it is necessary to clarify the uncertainty concerning the impact on the HPA axis suppression with a well-conducted clinical trial in a representative sample of adolescents with acne to support a safe use and a favourable safety profile of clascoterone in the adolescent population pre-approval.

Local skin reactions (LSRs) are also observed: oedema, erythema/redness, pruritus, scaling/dryness, skin atrophy, stinging/burning, striae rubrae, telangiectasia.

The excipients cetyl alcohol and propylene glycol may also cause local skin reactions. The proportion of subjects in clinical trials experiencing these local skin reactions was similar between the treatment groups. The intensity of each LSR during the studies was no or trace/mild for most subjects. The most common treatment-emergent LSRs were erythema, scaling/dryness, and pruritus. New or worsening LSRs after day 1 that were more reported in clascoterone group than in vehicle group, in Pool A, were Striae Rubrae (2.4% vs 1.4%), Oedema (3.5% vs 3.2%), and Scaling/Dryness (10% vs 9.5%). Three clascoterone-treated subjects reported hypersensitivity of mild or moderate intensity. One of these subjects was discontinued from the study due to this event. These events all resolved without intervention.

Use during pregnancy

Clascoterone induced fetal malformations at all dose levels tested in rats and post-implantation loss and embryotoxicity at non-maternotoxic doses in rabbits.

Although it is considered low, there is a systemic exposure after administration of WINLEVI which can be quantifiable.

Based on its mechanism of action (androgen receptor inhibition), WINLEVI can cause fetal harm.

Clascoterone is therefore contraindicated during pregnancy. Considering the >100-fold margin identified at the NOGEL in previous genotoxicity studies, with the latest study no. 3844-327 confirming a thresholded mechanism (aneugenicity), and in accordance with « *SWP/NcWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug* » (EMA/CHMP/SWP/74077/2020 rev. 1*), clascoterone could be considered as an active substance « *whose mechanism of genotoxicity is known to have a threshold which is not expected to be attained in patients* ». Consequently, contraception is required only for women of childbearing potential to prevent exposure during pregnancy, given the teratogenic risk (androgen receptor inhibition). The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with clascoterone and contraception should be implemented for women of childbearing potential during the treatment period and continued for up to 5 elimination half-lives, or 10 days.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties on unfavourable effects are grounded on limited data on the systemic passage. Thus, uncertainties on the anti-androgen effects of clascoterone are raised, especially with regards to the mood disorders, pregnancy, carcinogenicity and mutagenicity of impurity.

Mood disorders

Taking into account the effects of anti-androgenic drug on mood, the potential risk of depression cannot be ruled out during long term treatment. However, current clinical data do not support a causal relationship with clascoterone and this risk is considered as theoretical at this stage.

Carcinogenicity of active substance

Based on the data presented the risk of skin tumour cannot be excluded. However, as the results showed benign proliferations the CHMP considered that there is no need to have additional pharmacovigilance activities or other additional risk minimisation measures.

Table 26: Effects Table for clascoterone cream 1% BID for topical treatment of acne vulgaris

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Refs
Favourable Effects						
Lesion clearance at week 12	Proportion of subjects with a ≥ 2-point reduction in IGA and IGA score of 0 or 1	N (%) Adjusted proportion Point estimate	N=126 (17.5%) 19.5% 2.9	N=42 (5.8%) 7.7%	p<0.0001 in both pivotal studies, sensitivity analyses showed similar results. Clinically relevant outcome.	Pooled data from Studies CB-03-01:25 and /26
	Absolute change from baseline in NILC	LS mean Point estimate	-19.3 -7.5	-11.8		
	Absolute change from baseline in ILC	LS mean Point estimate	-19.3 -5.9	-13.9		
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Refs
LSR	Treatment-Emergent (New or Worsening) Local Skin Reactions After Day 1	N	687	662	LSRs were observed during the 12-week treatment and occurred in a similar percentage of subjects treated with vehicle. The excipients cetyl alcohol and propylene glycol may also cause LSRs.	Pool A
	- erythema	N (%)	84/687 (12.2%)	101/662 (15.3%)		Pool A
	- scaling and dryness	N (%)	72/687 (10.5%)	68/662 (10.3%)		Pool A
	- pruritus	N (%)	52/687 (7.6%)	55/662 (8.3%)		Pool A
HPA axis suppression			7/69 (10.1%)	62/69 (89.9%)	Although no clinical signs or symptoms of HPA axis suppression were observed, abnormal HPA axis suppression tests were close to the lower limit and it seems more elevated with decreased of age. It is questioned whether these perturbations will be higher with long term duration at therapeutic dose.	Phase 2 studies 171-7151-202 and CB-03-01/28

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Favourable effect

In both pivotal studies the co-primary endpoints were statistically met after a 3-month period of treatment. The proportion of responders (defined as the proportion of subjects with a ≥ 2-point reduction in IGA and IGA score of 0 or 1 on a 4-point scale) was 19.5% (compared to 7.7% in the vehicle group).

In the new analysis provided on the CHMP request:

- In the subgroup of adolescents, the success rate was 14.9% and 19.6% in adults.
- In the subgroup of baseline IGA=3, the success rate was 18.9% and 10.4% in IGA=4.

The efficacy of clascoterone for the treatment of acne is considered demonstrated in adults and adolescents from 12 years of age and older.

Unfavourable effect

The major safety issue is linked to the mechanism of action of clascoterone, an androgen antagonist which could suppress the Hypothalamic-pituitary-adrenal (HPA) axis when applied twice daily for a long period of time and concerns the adolescent population.

It is of major concern that 7 patients (10%) had abnormal cosyntropin stimulation test in a study dedicated to exploring the HPA axis suppression in 65 acne subjects treated for 2 weeks. This was more frequent with younger age (5% of adult subjects, 9.1% of adolescent subjects, and 14.8% of paediatric subjects 9 years to 11 years). Data for longer treatment are not available. Moreover, cases of 'Adrenal suppression' and 'Hypothalamic pituitary adrenal axis suppression' were reported post marketing in USA, where clascoterone cream is marketed since 2021.

During the procedure, the Applicant proposed a set of risks minimisation measures and additional pharmacovigilance activity in order to address the CHMP concern on the risk of HPA axis suppression in adolescents:

- a reduction of the daily dose in adolescents from 5 g/day to 2 g/day;

- an early morning cortisol measurements every three months of treatment in adolescents, alongside assessment of treatment success and condition of the treated skin;

- a commitment to conduct a post-approval safety study in adolescents to formally assess impact on HPA axis function in the clinical setting.

These measures were not considered appropriate by the CHMP to satisfactorily address the risk of HPA axis suppression. Reducing the maximum daily dose in adolescents from 5 g to 2 g might reduce the safety risk but may lead to compliance issue and additional concomitant treatment to be taken by adolescent patients exposing them to safety risks inherent to the supplementary medication. Imposing early morning cortisol monitoring test every 3 months for the entire duration of the treatment would represent a significant burden for these patients. It is not deemed appropriate to impose such a burden to mitigate a risk that was not sufficiently characterised during the clinical studies to treat a non-life-threatening condition.

In the absence of satisfactory clinical data confirming that there is no risk of HPA axis suppression with clascoterone use in adolescents, the potential impact of clascoterone on the HPA axis cannot be ruled out and is deemed detrimental to the safety profile of clascoterone in the adolescent population. This risk could lead to a retardation of growth and/or an impact on sexual maturation. Therefore, the CHMP is of the view that the risk of HPA axis suppression in adolescents should be addressed with a well-conducted clinical trial on a representative sample of adolescents with acne prior to authorising clascoterone in this population to ensure its safe use.

3.6.2. Balance of benefits and risks

Acne vulgaris a benign chronic inflammatory skin condition of pilosebaceous glands that typically begins at puberty and may continue through adulthood. No unmet medical use is identified as numerous formulations of topical preparations intended to treat mild to moderate acne include creams, gels, lotions, solutions, and

washes. For the management of severe acne, the European guidelines recommend combining a topical and a systemic therapy.

Clascoterone cream could represent a new class in the topical armamentarium of acne with a local anti-androgen activity.

Results from pivotal studies showed evidence of efficacy of clascoterone compared to a vehicle at 3-month to treat acne vulgaris on the face. Although considered modest (i.e. proportion of subjects achieving treatment success at week 12: 19.5% for clascoterone vs 7.7% for the vehicle), the effect is statistically significant and clinically relevant. Open-label long-term follow-up study data on trunk acne vulgaris have shown a similar effect. It is therefore acceptable not to restrict the indication to only facial acne vulgaris.

However, the risk of HPA axis suppression linked to the systemic passage of clascoterone, even if low, is an important identified risk and is deemed detrimental to the safe use of clascoterone in the adolecent population from 12 years to less than 18 years of age. The lack of adequate clinical data confirming the absence of HPA axis suppression does not allow to conclude on a favourable safety profile of clascoterone in adolecents. HPA axis suppresion could lead to retardation of growth and/or have an impact on sexual maturation. As such, this risk is considered key to the benefit/risk profile of clascoterone in adolescents (i.e. from 12 years to less than 18 years of age). Although efficacy has been demonstrated, considering that acne vulgaris is a non-life-threatening condition and that adolescents might develop detrimental effects of HPA axis suppression, the CHMP considers that the risks of clascoterone outweighs its benefits in the adolescent population from 12 years to less than 18 years of age.

Further, the CHMP considers that the safety profile of clascoterone in the adult population is well-characterised. Considering that the efficacy is demonstrated, and that the safety profile is considered acceptable in adults, the CHMP was of the view that the benefit-risk balance of clascoterone is positive in a restricted indication for the treatment of acne vulgaris in the adult population. However, as the claim to seek an indication covering both the adult and adolescent populations was maintained by the Applicant, the CHMP concluded that the benefit/risk balance is negative in the sought indication of treatment of acne vulgaris in patients from 12 years of age and older.

3.7. Conclusions

The benefit/risk balance of Winlevi in the treatment of acne vulgaris in patients 12 years and older is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Winlevi 10 mg/g cream in the treatment of acne vulgaris in patients from 12 years of age and older, the CHMP considers that the safety of the above-mentioned medicinal product is not sufficiently demonstrated in adolescents from 12 years to less than 18 years of age. Therefore, the CHMP recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product in the sought indication "*treatment of acne vulgaris in patients from 12 years of age and older*".

The CHMP considers that:

- Winlevi (clascoterone) is a topical drug with claimed local anti-androgenic activity, representing the first in a new class with this mechanism of action. The product also expresses a glucocorticoid effect which is associated with an identified risk of hypothalamic-pituitary-adrenal (HPA) axis suppression. In 2 studies dedicated to explore the HPA axis suppression in acne subjects treated for 2 weeks, 7 patients (10%) in total had abnormal cosyntropin stimulation test;
- There are uncertainties with respect to the consequences of the risk of hypothalamic-pituitary-adrenal (HPA) axis suppression when Winlevi will be used for long-term treatment of adolescents (i.e., from 12 years to less than 18 years of age) with acne, e.g. with respect to potential risks of retardation of growth and/or an impact on sexual maturation;
- The risk minimisation measures proposed by the Applicant are not considered appropriate by CHMP to satisfactorily address the risk of HPA axis suppression in adolescents (i.e., from 12 years to less than 18 years of age).

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is reflected in Appendix 8.1.

5. Re-examination of the CHMP opinion of 25 April 2025

Following the CHMP conclusion that Winlevi was not approvable in adolescents due to the risk of HPA axis suppression and potential impact on sexual maturation and growth, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented in writing the following grounds for examination.

Ground #1

"Winlevi (clascoterone) is a topical drug with claimed local anti-androgenic activity, representing the first in a new class with this mechanism of action. The product also expresses a glucocorticoid effect which is associated with an identified risk of HPA axis suppression. In 2 studies dedicated to explore the HPA axis suppression in acne subjects treated for 2 weeks, 7 patients (10%) in total had abnormal cosyntropin stimulation test."

The Applicant's response to Ground 1 starts stating that during the initial CHMP procedure the risk of HPA axis suppression was reclassified from important potential risk to important identified risk, although based on only laboratory data from 3 adult/adolescents participating in two dedicated maximum-dose studies. In its view this interpretation likely represents an overestimation of the HPA axis suppression risk, which does not correspond to a clinically relevant adrenal insufficiency, as explained in detail below.

The Applicant states that, based on laboratory data (i.e., transient borderline lower 30-minute cortisol levels post-ACTH stimulation) in 3 adult/adolescents, there is no proper mechanistic and evidentiary basis to

support the contention that the risk of glucocorticoid-induced adrenal insufficiency associated with hypothalamic-pituitary-adrenal (HPA) axis suppression exists following topical treatment with Winlevi. To support its position the following arguments concerning the glucocorticoid properties of clascoterone, and its metabolite, are addressed:

1. Clascoterone's mechanism of action is exerted locally
2. Clascoterone has a negligible systemic absorption following topical application
3. Clascoterone has a weak glucocorticoid activity
4. Nonclinical evidence of adrenal cortical atrophy is observed at exposures clinically nonrelevant in humans and not associated with effect on growth or sexual maturation
5. Laboratory values indicative of HPA axis suppression were borderline, did not translate into clinical signs and symptoms and should be evaluated in light of the technical limitations of the ACTH test and the latest European Endocrinology guidelines
6. There is no evidence of pathological adrenal insufficiency documented in the clinical programme and post marketing
7. In its intended use, clascoterone has high safety margins

When describing HPA axis suppression, the Applicant focuses on the known risk factors associated with the development of HPA axis suppression. Reference is made to the current European Society of Endocrinology and Endocrine Society Joint Clinical Guideline on diagnosis and therapy of glucocorticoid-induced adrenal insufficiency (Beuschlein et al., 2024) supported by the expert position paper provided.

The risk factors are related to: potency, dose, duration and overall exposure to glucocorticoids. Prolonged application on large surface areas or areas of increased absorption and use of occlusive dressing (not indicated for Winlevi), further increase the risk of percutaneous absorption primarily by increasing skin hydration which is known to facilitate the diffusion of drug molecules through the skin.

1. Clascoterone's antiandrogen mechanism of action is well characterised and exerted locally.

Contrary to the conclusion of the CHMP's assessment report (EMA/CHMP/85894/2025, 25 April 2025) stating that "*It is not clear how clascoterone acts on the androgen receptor (AR) and if the claimed mechanism of action on acne is primarily due to its antagonism on AR"*, the inhibitory activity of clascoterone on AR is well characterised and the mechanism of action is supported by extensive nonclinical and clinical pharmacology studies.

This was addressed in response to Day 120 Question 77 and considered resolved by the CHMP (EMEA/H/C/006138, 23 September 2024). Therefore, there is no proper basis for this issue to be reactivated or otherwise re-considered in this re-examination procedure.

For completeness, data elucidating the mechanism of action of clascoterone are reiterated below, with the inclusion of clinical data demonstrating the *in vivo* effect of clascoterone 1% cream on sebum production.

The biological actions of androgens are primarily mediated through binding to the ARs, which are expressed in several types of cells within the skin, but primarily in sebocytes. The binding of androgens to an AR induces a conformational change that allows the receptor to translocate to the sebocyte nucleus, where the androgen/AR complex binds to androgen response elements within target genes to regulate transcription (Harper, 2006).

In vitro studies showed that clascoterone acts on the acne pathogenesis by directly binding to the AR in human sebocytes and reduces AR controlled transcription of genes responsible for increased sebum production, sebum lipid composition and inflammatory cytokines, with an IC_{50} = 1.6 µM. Clascoterone effectively inhibits dihydrotestosterone (DHT)-induced lipid synthesis across multiple DHT concentrations in sebocytes. Furthermore, clascoterone also significantly reduces proinflammatory cytokine (interleukin-1-β, interleukin-6, and interleukin-8) secretion from sebocytes obtained from multiple donors. Clascoterone potently antagonises the effects of androgens in primary human sebocytes to reduce sebum production and accumulation and inflammatory mediators (Rosette et al., 2019). As such, its mechanism of action acts on two well-known drivers of the acne pathogenesis (Cong et al., 2019).

Non-clinical and clinical data elucidating clascoterone's mechanism of action

The Golden Syrian Hamster animal model has been extensively used to evaluate anti-seborrheic mechanisms through modulation of sebum production and sebocyte proliferation; this animal model closely replicates the pathogenic mechanism involved in acne. In an *in vivo* study (1H14008), clascoterone, administered topically, clearly showed anti-androgenic activity, inhibiting the effects of testosterone in the hamster flank organ in a dose-dependent manner. Clascoterone activity was similar to that of cyproterone acetate, which was used as the study's positive control. Importantly, the observed anti-androgenic activity was topical, with no systemic effect observed on the animals' contralateral gland. The above nonclinical evidence is substantiated by interim data from a currently ongoing clinical study investigating the *in vivo* effect of clascoterone 1% cream on sebum production in 40 patients aged 12 years or older with mild or moderate acne vulgaris (study DCS-67-22). This study is being conducted in the US.

The 12-week interim data (already presented in response to Question 4 in the second D180 list of outstanding issues, EMEA/H/C/006138, 19 February 2025) showed that, after applying clascoterone cream 1% twice daily to their entire face only for 12 weeks, patients had an improvement from baseline through Week 6 to Week 12 in the investigator's global assessment (IGA) score, non-inflammatory lesion count (NILC), and inflammatory lesion count (ILC) (Table 27), which correlates with the decreased *in vivo* in sebum production and secretion. This study provides scientific evidence on the mechanism of action of clascoterone 1% cream and links the pharmacodynamic of clascoterone to the clinical effects (Draelos et al., 2025).

Table 27: Change from Baseline in IGA Score, NILC, and ILC From Baseline Through Week 12 in Subjects Treated with Clascoterone (Study DCS-67-22)

		Baseline (N = 40)	Week 6 (N = 40)	Week 12 (N = 40)
IGA	**Mean % CFB (±SD)**	-	-0.38 (±0.59)**	-0.70** (±0.56)**
	0 or 1	0%	22.5%	37.5%
	2	57.5%	50.0%	47.5%
	3	42.5%	27.5%	15.0%
	4	0%	0%	0%
NILC	**Mean CFB (±SD)**	-	-4.44 (±2.55)**	-3.70 (±3.18)**
	Mean % CFB	-	-40%	-34%
ILC	**Mean CFB (±SD)**	-	-4.04 (±3.70)**	-4.55 (±3.75)**
	Mean % CFB	-	-48%	-54%
Sebumeter	**Mean CFB (±SD)**	-	-25.37 (±48.71)*	-31.07 (±51.61)**
	Mean % CFB	-	-22%	-27%

Abbreviations: CFB = change from baseline; IGA = investigator's global assessment; ILC = inflammatory lesion count; N = number of patients evaluated; NILC = non-inflammatory lesion count; SD = standard deviation
* p-value: <0.01.
** p-value: <0.001

2. Clascoterone has a negligible systemic absorption following topical application

Systemic adverse effects, such as HPA axis suppression, can only develop if systemic absorption of clascoterone following application on the skin produces levels high enough to trigger pharmacological effects.

Several studies (CB-03-01/02, CB-03-01/04, 171-7151-202, 171-7151-203, CB-03-01/28, CB-03-01/33) were conducted to evaluate the pharmacokinetics (PK) and safety profile of clascoterone; the studies were conducted both in healthy volunteers and in patients (adolescents and adults) with acne vulgaris. In most of the early clinical studies (CB-03-01/02 and CB-03-01/04), clascoterone plasma concentration was below lower limit of quantification (LLOQ) (2.50 ng/mL). In the subsequent clinical studies (171-7151-202, 171-7151-203, CB-03-01/28, CB-03-01/33), a more sensitive method was developed, with a lower limit of quantitation (0.25 ng/mL) for clascoterone, in an attempt to decrease the occurrence of samples below LLOQ.

All clinical studies where clascoterone blood levels were quantified, independently of the study population (healthy subjects vs acne patients), the applied dose (ranging from 4 g to 14 g daily), the frequency of application (*quaque die* (once daily) [QD] vs *bis in die* (twice daily) [BID]), or the duration of treatment (ranging from 14 days up to 6 weeks), showed that the circulating levels of the drug are very low, with a mean maximal concentration (C_{max}) <5 ng/mL and area under the plasma concentration curve $(AUC)_{0-t}$ of <50 ng*h/mL, with a lack of proportionality with the applied dose. This minimal bioavailability is constant across all the studies. Based on the cumulative urinary excretion data of clascoterone in the Phase 1 PK studies, it can be estimated that a clascoterone fraction <0.5% of the total administered dose is absorbed and excreted with urine.

In regard to cortexolone, the main metabolite of clascoterone, plasma concentrations were generally below the LLOQ in both adult and adolescent subjects, and therefore a PK assessment could not be made.

In maximum-usage study (study 171-7151-202), in which clascoterone was administered to the entire face, shoulders, upper chest and upper back at supratherapeutic doses (mean daily amounts of 11.3 g in adults and 9.3 g in adolescents), for 2 weeks, the systemic levels/exposure of clascoterone at steady state were still negligible. In this study, drug quantities were ~6- and 5-fold higher than the amounts used in pivotal Phase 3 (studies CB-03-01/25 and CB-03-01/26) for adults and adolescents, respectively. In adolescents (n=22), at steady state (Day 14), the mean highest observed exposure C_{max} was 4.61 ng/mL, corresponding to 11.5 nM and the mean AUCτ was 30.97 ng·mL/h. In adult subjects with moderate to severe acne vulgaris (n=20), systemic concentrations of clascoterone were at steady state by Day 5. On Day 14, the mean C_{max} was 4.46 ng/mL, the mean AUCτ was 37.14 ng·mL/h and the mean plasma concentration (C_{avg}) was 3.10 ng/mL.

Human Subjects	Mean						
	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	T_{min} (h)	C_{avg}	AUCτ (h×ng/mL)	Accumulation Ratio
Adults	4.46	3.69	1.40	4.43	3.10	37.14	2.11
Adolescents	4.61	3.63	1.21	3.62	2.58	30.97	1.81

The Table 28 below summarises the PK data in Phase 1 and Phase 2 multiple dose studies in healthy subjects or acne patients.

Table 28: PK data in Phase 1 and Phase 2 multiple dose studies in healthy subjects or acne patients

Clinical Study Number	*Population*	*Treatment Areas*	*Acne Severity*	*Treatment and Daily Amount*	*Clascoterone PK Data at Steady State*		*Cortexolone (Metabolite) PK Data at Steady State*		*Key Findings*
					C_{max} (ng/mL)	*AUC τ*	*C_{max} (ng/mL)*	*AUC τ*	
CB-03-01/04	*Healthy subjects, 18- 64 years old (N=24)*	*Rectangular area 15x20 cm in one half of the back*	*NA*	*4 mL (N=12) 8 mL (N=12) Once daily for 14 days*	*Not calculated; most of values were BLQ (2.50 ng/mL)*		*Not calculated; most of values were BLQ (2.50 ng/mL)*		*Systemic exposure to clascoterone was limited. Clascoterone was absorbed and reached quantifiable levels in some but not all subjects. An estimated fraction lower than 1% of the applied dose was excreted in urine.*
171-7151-203	*Adult patients (19-36 years old) with acne vulgaris (N=8)*	*Whole face, chest and/or back*	*IGA 3 or 4 ≥20 IL ≥20 NIL*	*6 g once daily for 6 weeks*	*2.71*	*33.45*	*Not calculated; most of values were BLQ (0.5 ng/mL)*		*On Day 42, systemic exposure was low with a mean maximum clascoterone plasma concentration of 2.71 ng/mL. Unchanged cortexolone in plasma and urine and tetrahydrocortexolone in urine were BLQ.*
171-7151-202	*Cohort 1: Adults ≥18 years with acne vulgaris (N=20)*	*Face, shoulders, upper chest, and upper back*	*IGA 3 or 4 ≥20 IL ≥20 NIL*	*6 g BID (12 g daily) for 14 days*	*4.46*	*37.14*	*Not calculated; most of values were BLQ (0.5 ng/mL)*		*CB-03-01 plasma concentrations were at steady state at Day 5. Systemic exposure was similar between adults and adolescents.*
	Cohort 2: Adolescents 12-17 years with acne vulgaris (N=22)			*4 g BID (8 g daily) for patients <18 years with a body surface area <1.6 m^2 for 14 days*	*4.61*	*30.97*	*Not calculated; most of values were BLQ (0.5 ng/mL)*		
CB-03-01/28	*Paediatric patients (9 to <12*	*Face and trunk*	*At least moderate facial*	*2 g BID (4 g daily)*	*Average trough concentration of 0.577 on D7*		*Average trough concentration of 0.418 on D7*		*Morning trough plasma concentrations of*

	years old) with acne vulgaris (N=27)		*acne vulgaris and obvious acne on the trunk*	*for 14 days*	*and of 0.606 on D14*	*and of 0.398 on D14*	*CB-03-01 and cortexolone were generally near or below the LLOQ on Days 7 and 14. These trough levels indicate that steady state was reached by Day 7.*

The PK profile of clascoterone 1% cream is similar in healthy volunteers and in patients with acne vulgaris. In fact, in study CB-03-01/04 in healthy subjects, following the administration of 4 mL and 8 mL of cream QD (which correspond 4 g and 8 g, considering a density of 1.0 g/mL), the peaks in plasma concentrations on D15 were 2.42 ng/mL (at the 6th hour) and 2.13 ng/mL (at the 8th hour), respectively (study CB-03-01/04).

These data overlap with the PK data of study 171-7151-203 in patients with moderate to severe acne, where the peak plasma concentration at week 6, following the administration of 6 g of cream QD, was 2.71 ng/mL. The results of study 171-7151-202 show a slightly higher C_{max} in both adolescents and adults following the exposure to high supratherapeutic doses of cream, whereas the AUC$_T$ did not differ from that of study 171-7151-203. Taken together, these data demonstrate that the systemic absorption of clascoterone from the 1% cream is minimal across healthy subjects and patients with acne vulgaris and is not influenced by the presence of inflammatory lesions.

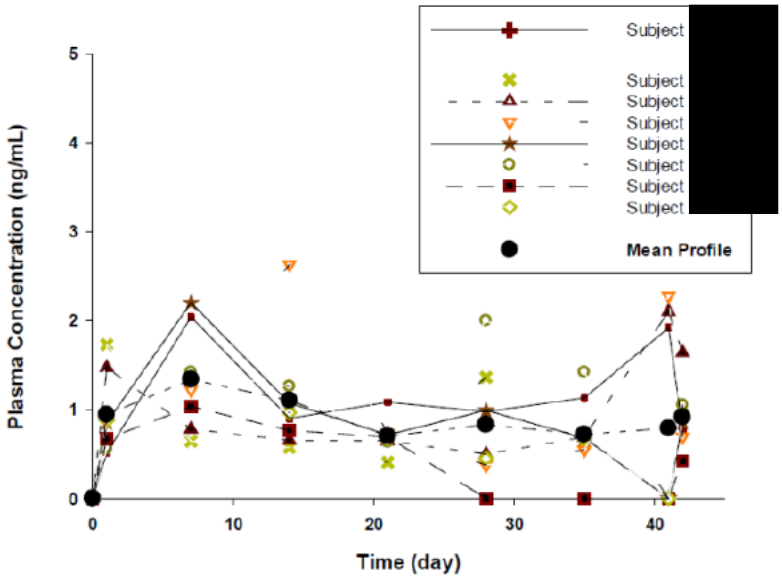
The PK data from Study 171-7151-203, in which clascoterone 1% cream was administered at a high dosage (6 grams daily) for 6 consecutive weeks, demonstrate that the absorption profile of the active substance remains consistent over the treatment duration. These findings indicate that prolonged use does not influence systemic absorption and effectively rule out accumulation of the active compound. As reported in the study report, results based on the observed trough plasma concentration-time profile and the observed urinary recovery-time profiles are consistent; based on urinary excretion of clascoterone, steady state is achieved within the first week of treatment (i.e., no increase in urinary recovery is observed upon multiple dosing). Table 29 shows that, except for the pre-dose sampling time, the observed trough clascoterone plasma concentrations upon multiple dosing were not statistically significant over the treatment period by the one-way repeated-measures analysis of variance (ANOVA), up to last sampling timepoint (Day 42).

Table 29: Statistical Assessment of Observed Trough Clascoterone Plasma Concentrations upon Multiple Dosing

Timepoint	P-value
Day 1 Predose	<0.0001
Day 2	0.9644
Day 8 / Week 1	0.0948
Day 15 / Week 2	0.3177
Day 22 / Week 3	0.3358
Day 29 / Week 4	0.9032
Day 36 / Week 5	0.5266
Day 42 / Week 6	0.9780

The individual and mean free clascoterone trough plasma concentration versus time profiles show a flat shape, with no signs of accumulation or trend for increase in plasma concentration over time (Figure 2).

Figure 2: Clascoterone Plasma Concentration Profile



On Day 42, after the last dose, the full 24-hour PK curve confirmed the very low systemic absorption, with an average C_{max} of 2.71 ng/mL and AUCт of 33.45 ng*h/mL.

Also, the 24-hour urine excreted amounts of clascoterone and its metabolites remained stable over the treatment period, with no evidence of a trend of increase in the excreted amount, which might be indicative of an increased systemic absorption, as shown in Table 30.

Table 30: Mean Urinary Recoveries Over 24h for Clascoterone (Unconjugated and Conjugated), Cortexolone (Conjugated) and Tetrahydrocortexolone1 (Conjugated)

Day	Conjugated clascoterone (µg)	Conjugated tetrahydrocortexolone (µg)	Conjugated cortexolone (µg)	Free Clascoterone (µg)
Day 0 Predose	0	44.51	0.268	0
1	305.1	81.26	1.369	0.977
7	344.5	98.13	1.250	1.040
14	313.9	100.07	1.261	0.905
21	237.2	77.40	1.364	0.547
28	245.1	83.18	1.474	0.807
35	245.1	84.32	1.459	0.656
42	291.7	88.29	0.797	0.431

[1] Tetrahydrocortexolone is a urinary metabolite of cortexolone (11-deoxycortisol).

Urinary recovery of total clascoterone and metabolites on Day 42 was extremely low with a maximum mean urinary recovery of 292 µg (compared to 60 mg dose applied daily for 42 days), over 24 hours collection interval, accounting for less than 0.5% of the applied dose.

The above PK data highlights that, following administration of clascoterone 1% cream, the systemic absorption of the active substance is negligible, with levels <5 ng/mL; these characteristics are constant across different studies, subject population, doses and treatment durations.

In the worst-case scenario of topical supratherapeutic dose (application of 6-9 g BID for 2 weeks, as in study 171-7151-202), systemic exposure to clascoterone is still minimal (C_{max} = 4.61 ng/mL, AUC = 30.61 ng·h/mL). C_{max} of 4.61 ng/mL corresponds to 11.5 nM.

Clascoterone binds to human plasma protein in the range 84-89%; thus, concentration of unbound clascoterone (free to bind to receptors) ranges from 1.8 to 1.3 nM.

The IC_{50} of clascoterone on human AR is 5 x 10^{-8} M (50 nM), this is 28 to 38 times higher than the highest unbound clascoterone concentration detected in the clinical worst-case scenario.

At dose levels closer to the intended use (application of 6 g once a day, as in study 171-7151-203), the margins are even larger: clascoterone mean C_{max} of 2.71 ng/mL corresponds to 6.7 nM, which makes the IC_{50} of clascoterone on human AR 45 to 68 times higher than the concentration of unbound clascoterone.

These data support systemic exposure of clascoterone with minimal likelihood of pharmacological activity on peripheral ARs. The safety margins with respect to the IC50 will be even higher when clascoterone is administered according to the recommended dosing regimen of 1 g of cream twice per day for adolescents as per SmPC (section 4.2).

Consistent with these PK findings, the clinical safety database, in particular from the two Phase 3 studies (CB-03-01/25 and CB-03-01/26) and the long-term safety (LTS) study CB-03-01/27 (with long-term treatment duration), did not show any adverse drug reactions linked to systemic endocrine effects, e.g., antiandrogen or glucocorticoid effects; in particular, no clinical signs or symptoms of HPA axis suppression were recorded (see point "No pathological adrenal insufficiency has been documented in the clinical development programmes and in the post-approval safety dataset from two countries'' below).

3. Clascoterone has a weak glucocorticoid activity

Cassiopea sponsored a vasoconstrictor assay study in 33 healthy volunteers (study CB-03-01/39). This assay is considered the gold standard to evaluate the potency of topical glucocorticoids *in vivo*. In the study, clascoterone 1% cream and clascoterone 5% solution were compared to their respective vehicles (negative controls) and to three commercial topical corticosteroid medicines approved in some European Union (EU) countries: ClobeGalen® Creme 0.05% (clobetasol propionate 0.05% cream, class IV), BetaGalen® Creme 0.1% (betamethasone valerate 0.1% cream, class III) and HydroGalen Creme 1% (hydrocortisone 1% cream, class I). 41 subjects were screened, out of whom 33 subjects (14 males and 19 females) were assessed with healthy skin in the area of the test fields and showed blanching response in the screening test and were therefore randomised and treated with a single dose of each investigational products. All eligible subjects received the same treatments: 7 single topical treatments with the investigational products (IPs) (single topical occlusive application of approximately 200 µL of each formulation) at the clinical study centre applied by a qualified person on Day 1. The 7 treatments were randomly allocated to 7 test fields measuring approximately 2.5 cm² on the volar surface of the forearms. One untreated test field on one volar forearm also served as negative control. The skin blanching was assessed by chromametric measurement (primary variable) pre-dose at baseline (Day 1) within 1 hour prior to IP application and 1 hour, 3 hours, 6 hours (Day 2), and 24 hours (Day 3) after the end of treatment period and after IP removal. The primary variable was the redness value (a*-value) by the measurement of skin colour (chromametry), to evaluate the degree of skin blanching (vasoconstriction properties) in the test fields using a chromameter (L*a*b system).

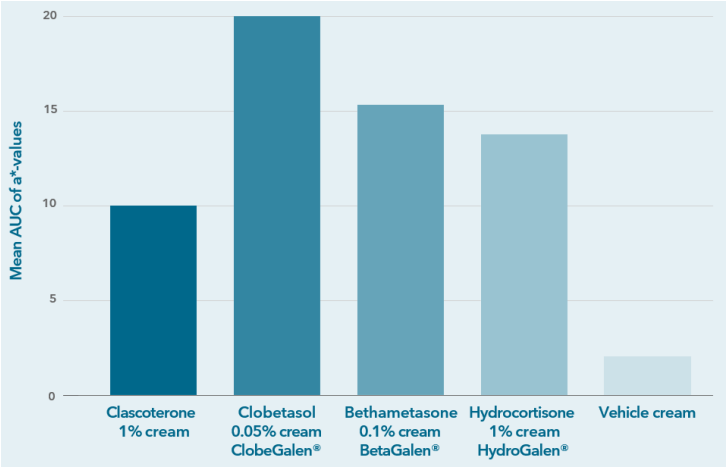
The main study endpoint was the comparison of the two topical anti-androgenetic formulations clascoterone 1% cream and clascoterone 5% solution with three topical marketed corticosteroid formulations and with the corresponding vehicles (cream and solution) with respect to the mean AUC of baseline-corrected, untreated control site-corrected a-values (a*- values) of each IP, where a-values are skin redness values measured by chromametry.

The results of the primary pharmacodynamic analysis showed that the mean AUCs of the a*- values:

- were smaller for both clascoterone 1% cream and clascoterone 5% solution when compared to the three comparator products
- were larger for both clascoterone 1% cream and clascoterone 5% solution when compared to the corresponding vehicle formulations
- was larger for clascoterone 1% cream than for clascoterone 5% solution

The following Figure 3 shows to the mean AUC of baseline-corrected, untreated control site-corrected a-values (a*- values) of each product.

Figure 3: Mean AUC of a*-values



*a-values are skin redness values measured by chromametry

The active comparators performed as expected according to their ranking in terms of glucocorticoid activity.

In conclusion, clascoterone 1% cream was found to have a vasoconstrictor activity which is well below that of the three positive controls; the study demonstrated that both clascoterone formulations (1% cream and 5% solution) had lower vasoconstrictive effects than the lowest steroid potency class (hydrocortisone 1% cream, low potency class I) in the vasoconstrictor assay. This indicates that clascoterone is less potent than hydrocortisone, which carries minimal risks of adrenal suppression even with extended use, is well tolerate in children and is used as replacement therapy for adrenal insufficiency at 15-25 mg dose that is considered equivalent to average daily cortisol production (see expert position paper provided).

4. Nonclinical evidence of adrenal cortical atrophy is observed at exposures clinically nonrelevant in humans and not associated with effect on growth or sexual maturation

Adrenal cortical atrophy in animal models is closely linked to glucocorticoid production.

Repeated-dose toxicity studies were conducted in rats and minipigs to assess the potential adrenal effects of clascoterone, focusing on adrenal gland weight reduction as a marker of HPA axis suppression.

Nonclinical Studies Completed with Clascoterone in Rats (6-7 Weeks of Age)

Study	Route/Dose of Administration	NOAEL*	Cmax (M/F) ng/ml	AUC (M/F) ng.h/ml
28 days toxicity study	**Subcutaneous** 2, 10 and 50 mg/kg/day	2 mg/Kg/day	244/154	248/130
13 weeks toxicity	**Subcutaneous** 1, 5 and 25 mg/kg/day	1 mg/Kg/day	45.19/58.19	66.98/70.74
26 weeks toxicity	**Subcutaneous** 0.1, 0.5 and 2.5 mg/kg/day	0.5 mg/Kg/day#	33.42/41.32	51.95/37.42
13 weeks dermal toxicity	**Dermal/Topical cream** 0.1, 1.5 and 5%	1.5% ##	8.42/25.9	57.2/132

* NOAEL (No Observed Adverse Effect Level) was determined based for adrenal weight reduction
# NOAEL underestimated since at 2.5 mg/Kg/day there was an adrenal reduction in males only (with no microscopic findings)
underestimated since at 5% there was an adrenal reduction in male, only (with no microscopic findings)

Nonclinical Studies Completed with Clascoterone in Minipigs (4.5 Months of Age)

Study	Route of Administration	Time of Analysis	NOAEL*	C_{max} (M/F) ng/ml	AUC (M/F) ng.h/ml
6/9 months toxicity study	**Dermal/Topical solution** 5% and 15%	26 weeks interim sacrifice	5%	12.7/19.6	184/206
		39 weeks *Final*	-	21.9/22.2	139/145
9 months toxicity study	**Dermal/Topical cream** 1%, 2.5%, 5%	39 weeks	5%	30.1/16.8	401/269

* NOAEL (No Observed Adverse Effect Level) was determined based on adrenal weight reduction

Main findings

Adrenal gland weight reduction was dependent on treatment duration, regardless of administration route. NOAELs (No Observed Adverse Effect Levels) decreased over time: longer treatments showed lower thresholds for adrenal effects.

The most conservative NOAELs (i.e., no adrenal weight loss in either sex) were used, even if in some cases effects were observed only in males—suggesting the NOAELs might be underestimated.

In rats AUC values at conservative NOAELs were ~2 to >8 times higher than the AUC (30.97 ng·h/mL) observed in study 171-7151-202, where clascoterone was applied topically at 4–6 times the clinical dose.

In minipigs, at 39 weeks, adrenal gland weight reduction occurred at all doses, so no NOAEL could be established. However, at interim sacrifice at 26 weeks, established NOAEL was 5%.

In a follow-up 9-month study using lower doses, a 5% NOAEL was identified, with systemic exposure ~9 to 14 times higher than in study 171-7151-202.

Safety margins

The IC50 of clascoterone on human AR is 5 x 10^{-8} M (50 nM), this is 28 to 38 times higher than the highest unbound clascoterone concentration detected in the clinical worst-case scenario.

At dose levels closer to the intended use (application of 6 g once a day, as in study 171-7151-203), the margins are even larger: clascoterone mean Cmax of 2.71 ng/mL corresponds to 6.7 nM, which makes the IC50 of clascoterone on human AR 45 to 68 times higher than the concentration of unbound clascoterone.

These data support a systemic exposure of clascoterone with minimal likelihood of pharmacological activity on peripheral ARs. The safety margins with respect to the IC50 will be even higher when clascoterone is administered according to the recommended dosing regimen of 1 g of cream twice per day for adolescents as per SmPC (section 4.2).

5. Laboratory values indicative of HPA axis suppression were borderline, did not translate into clinical signs and symptoms and should be evaluated in light of the technical limitations of the ACTH test and the latest European Endocrinology guidelines.

Following the FDA's recommendation 2 targeted studies were designed to explore the effect on HPA axis in supratherapeutic dosing of clascoterone cream in subjects of different age groups, studies CB-03-01/28 and 171-7151-202, which were conducted in 2012.

In order to test the function of the HPA axis, a cosyntropin stimulation test (CST; also known as ACTH test) was used.

Study 171-7151-202 assessed the potential for HPA axis suppression of clascoterone in a population representative of the intended use of the product, i.e. in patients with acne vulgaris in adults (≥18 years old; Cohort 1) and adolescents (12-17 years old; Cohort 2) with moderate to severe acne. Clascoterone 1% cream was applied under maximal usage conditions to the entire face, shoulders, upper chest and upper back of acne patients, corresponding to mean daily amounts of 11.3 g (adults) and 9.3 g (adolescents). These drug quantities were ~5.7- and 4.7-fold higher than the amounts used in pivotal Phase 3 (studies CB-03-01/25 and CB-03-01/26) for adults and adolescents, respectively and exceeded the mean daily amounts in the LTS study CB-03-01/27. Laboratory evidence of HPA axis suppression was detected in one out of 20 adult subjects (5%) and two out of 22 adolescent subjects (9%). In all these subjects, the 30-minute post-stimulation serum cortisol levels were just below the 18.0 µg/dL cut-off value (14.9; 17.0 and 17.7 µg/dL) and coincided with clascoterone 1% cream usage of 167.9 g (one adult), 105.8 g and 158.6 g (two adolescents) over 14 days.

This observed small shift in post-stimulation cortisol did not result in any clinically evident sign or symptom, or in significant adverse events or changes in other laboratory results in the three affected patients. In particular, none of the subjects experienced any findings in vital signs or laboratory results indicative of

adrenal suppression, for example hypotension, hypoglycaemia or hyponatremia. Laboratory parameters are sensitive to cortisol levels and would be impacted by clinically significant abnormal values.

Study CB-03-01/28 assessed the potential for clascoterone 1% cream to induce HPA suppression in 27 paediatric acne patients aged 9 to <12 years, which is not the intended population to be treated with clascoterone 1% cream.

Patients were instructed to apply to the face and trunk BID for 2 weeks a total of 4 grams daily (double the recommended therapeutic dose in the revised section 4.2 of the SmPC). As explained in in the response to Question 156 in the D120 list of outstanding issues (EMEA/H/C/006138, 30 July 2024), 2 subjects with ACTH stimulation test abnormal at Day 14 were excluded from the evaluable population for the following reasons:

One subject was excluded because he had a body mass index of 24.14 which put him in the 96th percentile for his age group (exclusion criterion #2)

One subject was excluded because he had insufficient washout of medications (antihistamine) (exclusion criterion #3)

Within the evaluable population, two out of 23 (8.7%) subjects, both aged 10 years old, demonstrated biochemical evidence of abnormal HPA axis response at Day 14 under maximum use conditions as documented by a 30-minute post-stimulation serum cortisol level of ≤18 µg/dL. In both cases, the subjects had borderline post-stimulation levels of cortisol, i.e., very close to the lower limit (18.0 and 16.1 µg/dL, respectively), coinciding with clascoterone 1% cream usage of 50.7 g and 56.0 g over 14 days. Both subjects returned to normal HPA axis function approximately 4 weeks after Day 14/end of study. None of the subjects demonstrated any clinical signs/symptoms associated with adrenal suppression, nor any findings in vital signs or laboratory results indicative of adrenal suppression (e.g., hypotension, hypoglycaemia, and hyponatremia).

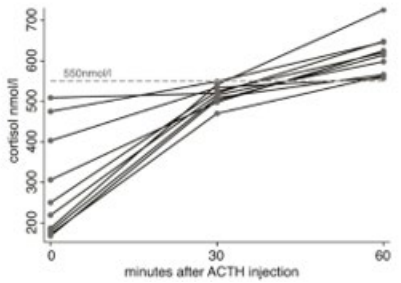
To fully evaluate the cases observed in adult and adolescents, the Applicant has sought an opinion from an expert who provided an independent evaluation of the results (see position paper provided). In light of his assessment, the Applicant requests consideration of the following points:

- In study 171-7151-202, patients were treated with supra-therapeutic doses (>9 g daily) (largely exceeding the recommended daily dose of clascoterone 1% cream in adolescents of 2 g as per the SmPC) and over large body surface area (face, trunk, shoulders, and back) rather than just the face (as in the revised SmPC).
- No correlation was observed between blood levels of clascoterone and HPA axis suppression: analysis of the PK data from study 171-7151-202 indicated that clascoterone plasma concentrations were at a PK steady state by Day 5 and remained so during assessment of adrenal suppression potential on Day 14. As such, no clear PK-pharmacodynamics (PD) correlation as regards the HPA axis suppression can be established. Cortexolone plasma levels were generally below the limit of detection.
    - The cosyntropin test (ACTH test) applied in the studies is not a screening test but a diagnostic test used in presence of symptoms presumptive of adrenal insufficiency; it has been criticised for producing a significant number of false-positive results (Lindholm, 2015; Mushtaq et al., 2008) and has shown great variability in the diagnostic accuracy of adrenal insufficiency due to several technical aspects (Burgos et al., 2019) (see expert position paper provided).

- Specifically, the single timepoint testing at 30 minutes, considered appropriate at the time of the study conduct (2012), is susceptible to the risk of false-positive diagnoses of adrenal insufficiency (Birtolo et al., 2023; Butt et al., 2020; Chitale et al., 2013).

These findings have been confirmed in subsequent independent studies. For example, Butt et al. conducted a study in 849 subjects and found that 35% of subjects who failed at 30 minutes passed at 60 minutes (Butt et al., 2020). Another study by Zueger showed that 10 out of 73 patients (with suspected adrenal insufficiency for different reasons including use of corticosteroids), who would be classified as adrenal insufficient post-30-minute stimulation test were sufficient at 60 minutes, with cortisol level above 500 nM, i.e. 18 µg/dL (Zueger et al., 2014). These subjects had borderline values at 30 minutes and were subsequently classified as adrenal sufficient at 60 minutes (Figure 4).

Figure 4: Discrepant Adrenal Response at 30 and 60 Minutes after injection of ACTH



- Consistently, the latest European Society of Endocrinology and Endocrine Society Joint Clinical Guideline recommend assessing adrenal response to synthetic ACTH at 30 and 60 minutes after administration (Beuschlein et al., 2024). Use of single assessment timepoint (30 min) in the study (standard practice at that time) has likely led to overestimation of cases of HPA axis suppression (testing at 30 and 60 min might have led to excluding HPA axis suppression in borderline cases). As such, study 171-7151-202 can be considered a worst-case scenario in the estimation of the risk HPA axis suppression.
- The traditional cut-off value of the ACTH test (500 nM, i.e. 18 µg/dL) has been questioned and is based on old polyclonal-based immunological methods, which were characterised by low specificity due to cross-reactivity with other serum steroids. Possibly due to the inter- and intra-assay variability, the choice of a cortisol cut-off of 18 µg/dL has been demonstrated to be associated to a false rate of positive results up to 15% (Stewart et al., 1988).
- A recent study by Michaelidou et al. classified post-stimulation cortisol levels as follows: a 30- and/or 60-min cortisol of ≥450 nM (16 µg/dL) indicated sufficient adrenal reserve, values between 350 nM and 449 nM (12.7- 16 µg/dL) were considered borderline, and values <350 nM (12.7µg/dL) were considered indicative of adrenal insufficiency (Michaelidou et al., 2021). If Michaelidou's criterion is applied to study 171-7151-202, two subjects (02-107 and 01-206) would be considered adrenally sufficient, while one subject (03-203) would still be classified as borderline.
- The proposed cut-off of morning serum cortisol for likelihood of adrenal insufficiency has been recently reviewed to ≤10 µg/dL in the latest European Society of Endocrinology and Endocrine Society Joint Clinical Guideline on diagnosis and therapy of glucocorticoid-induced adrenal insufficiency (Beuschlein et al., 2024). Given consideration to the results of several studies showing that morning cortisol levels above this threshold predicted normal adrenal function with 100%

sensitivity (Sagar et al., 2021; Sbardella et al., 2017), and taking into account that there is substantial variability in the calibration between different cortisol assays, a cut-off of morning serum cortisol of 10 µg/dL (>300 nmol/L) is considered appropriate to rule out adrenal insufficiency, when confirming recovery of the HPA axis (Beuschlein et al., 2024). The recommended interpretation of serum cortisol values is the following:

->300 nmol/L (>10 µg/dL): strongly suggests intact adrenal function; glucocorticoid replacement therapy may be safely discontinued

-150–300 nmol/L (5–10 µg/dL): indeterminate range; retesting is recommended

-<150 nmol/L (<5 µg/dL): consistent with suppressed HPA axis; maintenance of glucocorticoid replacement therapy is recommended

- Importantly, the observed mild shift in cortisol levels did not result in any clinically evident sign or symptom, or in significant adverse events or changes in safety measures attributable to HPA axis suppression. Vital signs and laboratory findings indicative of potential adrenal insufficiency (e.g., hypotension, hypoglycaemia, and hyponatremia) were not observed in any patients. Altered biochemistry values and clinical manifestations are instrumental to, and more important than, cortisol levels for an accurate diagnosis of adrenal insufficiency. Considering the clinical and technical factors that can affect cortisol values and diagnostic accuracy of this test, clinicians evaluating patients with suspected adrenal insufficiency give consideration to the clinical presentation (likelihood of adrenal insufficiency before testing) when interpreting the results of the ACTH stimulation test. In absence of signs of symptoms of hypoadrenalism, the interpretation of ACTH results is disputable and the clinical significance irrelevant.
- Lastly, the CHMP stated that "The fact that all subjects with abnormal HPA axis test returned to normal 4 weeks after stopping the clascoterone cream questions about a potential systemic passage and systemic effects". Taking into account the high coefficient of variation associated with the test (up to 12.8%), it is not possible to exclude that the normalisation of values observed 4 weeks after treatment discontinuation in all cases may be reflective of the assay variation rather than of the treatment discontinuation's effect. It is also not possible to exclude that normalisation of values could have occurred even in presence of treatment, if continued, as ACTH-stimulated cortisol levels have been reported to spontaneously return to normal within few weeks of treatment with class I–IV topical corticosteroids, despite continuous therapy in some patients (Levin et al., 2014).
- To assess whether there is a significant trend of association of the event of HPA axis suppression with age, a Cochran-Armitage trend test was conducted, using the safety population of study CB-03-01/28 as a worst-case scenario (i.e., including the two subjects with laboratory evidence of HPA suppression who were excluded from the evaluable population due to major protocol violations). The 2-sided p-value of the test was >0.05, indicating no statistically significant association between the HPA suppression and the age. When the statistical test was repeated comparing the adolescents and the adults (thus excluding the population 9-11 years) using the Fisher's exact test; the p-value was confirmed to be not statistically significant.

6. There is no evidence of pathological adrenal insufficiency documented in the clinical programme and post-marketing

Four cases of HPA axis suppression/adrenal suppression that mention Winlevi (clascoterone), have been submitted to FDA and are listed in the FDA Adverse Event Reporting System (FAERS).

Of these, only one case submitted by the marketing authorisation holder (MAH) of Winlevi in US was reported by a health care professional (HCP) and presents a potential causal relationship between the experienced event HPA axis suppression and the use of Winlevi. This case involved a 20-year-old female patient, who used Winlevi twice daily for three months on facial, chest, and back areas. There is no additional information on how the diagnosis was made. As relates to the other three cases, all of them are not considered to be related to the use of Winlevi.

Notably, it is important to emphasise that none of the collected cases from the post marketing surveillance include clinical signs or laboratory evidence consistent with HPA axis suppression.

Assessment of these cases is difficult because of the limited information available, which includes no cortisol level information. Other endocrine conditions cannot be excluded.

Notably, among the post-market HPA axis suppression cases where patient's age was specified, there were no cases involving adolescents. The narrative of these cases is provided:

Case #1

This spontaneous case was collected by the marketing authorization holder in US and reported by health care professional and concerns a 20-Year-old female patient from US.

No medical history was reported. On an unknown date, the patient started treatment with Winlevi (Clascoterone) cream 1% twice a day, for an unknown indication, at unknown dosage.

No concomitant medications were reported. On an unspecified date the patient experienced the event "Hypothalamic pituitary adrenal axis suppression"

Action taken with Winlevi (clascoterone) was unknown. The dechallenge and rechallenge were not applicable. The outcome of the event was unknown.

The reporter assessed the causality of the event as unknown to Winlevi.

The case is deemed serious (medically significant).

As per report, the reporter stated that one of her patients, a female woman of 20 years old, was using Winlevi twice a day for 3 months on her face, chest, & back and was experiencing HPA Axis suppression. The previous month the patient had been using the product in the same area but once a day. A blood analysis was to be ordered. No further information on follow-up is available.

Cassiopea medical reviewer's assessment, in agreement with the marketing authorization holder, confirms the pharmacological plausibility of suspect medication that suggests its propensity for the occurrence of reported event. Thus, causality cannot be ruled out.

Case #2

This spontaneous case was collected by the marketing authorization holder and reported by a female consumer of unknown age from US.

No medical history was reported. The patient was started on Company suspect: Winlevi (clascoterone) cream 1 % with unknown formulation, route of administration, frequency and for an unknown indication. No Concomitant medications were reported.

On an unspecified date the patient experienced "Adrenal suppression".

Action taken with Winlevi (clascoterone) (company suspect) was unknown. The dechallenge and rechallenge was not applicable. The outcome of the event was reported as unknown.

The reporter assessed the causality of the event as unknown to Winlevi.

The case is deemed serious (medically significant).

As per report, consumer stated the following: "I am having Adrenal suppression while taking this medicine Winlevi; It is very, very bad. I want to know if it is something that is permanent issue. If I stop using it what will happen?"

Cassiopea medical reviewer's assessment, in agreement with the marketing authorization holder, is that reported event occurred in an unspecified duration and unknown time frame of Clascoterone usage. The causality with clascoterone is thus not suspected due to insufficient information.

Case #3

This spontaneous case was collected by the marketing authorization holder and reported by female consumer of unknown age from US. The initial information received was very vague and it was not clear whether it was a general question or whether everything reported had happened.

In fact, the subject, with the medical history of Down syndrome (Trisomy 21), referred Down Syndrome Regression Disorder (DSRD), Hypothalamic pituitary adrenal axis suppression, Malaise and Anxiety and became worried about it and called the marketing authorization holder to ask if clascoterone could have triggered it.

The case was reported because the subject was administered at unknown dosage unknown route of administration: Winlevi (clascoterone) cream 1 % for an unknown indication; no concomitant medications were reported.

The additional information that the marketing authorization holder was able to collect, was of a subject who referred to be: "very sick, very, very sick", who called that "autoimmune", who thought "it was DSRD due to an autoimmune response that attacks the brain", triggered by Winlevi.

The subject asked for "any information can provide to her about what Winlevi had found with autoimmune issues … Which was the same thing as HPA axis suppression"

Cassiopea medical reviewer's assessment, in agreement with the marketing authorization holder, based on all the above, is that the subject had no clinical signs or symptoms indicative of HPA axis suppression nor developed HPA axis suppression.

The above description suggested that it could be a possible DSRD (in fact the attending physicians are investigating further: … seeing neurologists, getting spinal taps, getting MRIs…), the subject has also transferred the information to the HPA (perhaps having read about HPA in the leaflet) and wanted to have more information about the potential risks of the product for an autoimmune response that could impact on HPA and Down syndrome.

Case #4

This is a Spontaneous case received directly at FDA on 02 November 2023 and reported by a consumer, that concerned a female patient of 31-year-old age from unspecified country.

We are citing but not describing this case because it is in the FDA database, but it does not refer to our formulation of Clascoterone, much less to a formulation approved by the FDA, in fact, in the FAERS database, the column of the compounded drug has been selected for this case.

We reported here below, for clarity, the US FDA website, definition of Human drug compounding:

"Compounding is generally a practice in which a licensed pharmacist, a licensed physician or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.

Compounded drugs are not FDA approved, which means the agency does not verify their safety, effectiveness or quality before they are marketed. Although compounded drugs can serve an important medical need for certain patients, they also may pose a risk to patients.

FDA's compounding program aims to protect patients from poor-quality compounded drugs, while preserving access to lawfully marketed compounded drugs for patients who have a medical need for them" *(References: Human Drug Compounding | FDA; Compounding and the FDA: Questions and Answers | FDA)*

Cassiopea medical reviewer's assessment: We are sure, due to the above, not only that the case is not referring to our product, but above all, we have no data to be sure if the same active ingredient was used or if the final compound contained other active ingredients.

The Applicant calculated the patient exposure in terms of Patient Treatment Days (PTD) considering a treatment duration of 3 months (90 days). Based on the total units of Winlevi sold in the US and Canada up to December 2024, the incidence of HPA axis suppression related to study drug reported during the post-market surveillance can be estimated as 0.27 in 100,000 people years

Because the incidence of HPA axis suppression is less than 1 in 10,000 people, according to the EMA definition of frequencies, this event can be classified as "very rare".

From a clinical perspective (see expert position paper provided), a distinction can be made between physiological and pathological adrenal suppression associated with topical steroid use. While the former is identified by laboratory evidence of cortisol levels below the normal range with a capacity of full recovery, the latter is a clinically significant state of adrenal insufficiency, adrenal crisis or persistent laboratory evidence of adrenal suppression without prompt recovery.

Moreover, the estimation of exposure would require more than 7 Winlevi tubes of 60 g (i.e., 7 times the intended prescribed monthly dose), each delivering 600 mg of clascoterone, to be used by a patient per day in order to bring about the equivalent potential risk of symptomatic HPA axis suppression observed with 14 g/day clobetasol 0.05% cream.

No pathological adrenal insufficiency has been documented in the clinical development programmes and in the post-approval safety dataset from two countries.

7. In its intended use, clascoterone has high safety margins

The cumulative dataset supports the contention that the systemic absorption of clascoterone is negligible and that the true risk of HPA axis suppression is very low. However, as a further risk minimisation measure to reduce the potential effect of systemic passage of clascoterone following topical application in adolescents, the Applicant has revised the SmPC to include two controlling measures in adolescents:

A) Lower dose: a recommended dose of 2 g (4 fingertip units), which provides a safety margin of 4 to 6 fold as compared to the doses used in the maximum-dose HPA suppression studies where laboratory values indicative of HPA axis suppression were observed (studies CB-03-01/28 and 171-7151-201); and

B) Restriction to the face: a limitation of the area to be treated to the face only (this will minimise the risk of overuse over large skin surfaces). This second limitation is aligned with the main Phase 3 studies and will limit the topical exposure as opposed to the Phase 1 HPA suppression study 171-7151-202, where patients were treated with supratherapeutic doses of the product on the entire face, shoulders, upper chest and upper back.

These indications add to the specification that clascoterone is to be used without occlusive dressings (section 4.2 of the SmPC), as this too may result in an increased systemic absorption.

Two grams of a 1% cream formulation corresponds to a maximum of 20 mg/day of clascoterone applied on the skin. Even assuming this entire dose is absorbed, this could be considered within the cortisol replacement daily dose equivalent of 15-25 mg hydrocortisone, which was also found to be more potent than clascoterone in a vasoconstrictor assay (see study CB-03-01/39). However, the PK data described in previous sections (point 2) show that <0.5% of the dose is actually absorbed (study 171-7151-203), which means <0.1 mg of clascoterone are absorbed per day.

Ground #2

"There are uncertainties with respect to the consequences of the risk of hypothalamic-pituitary-adrenal (HPA) axis suppression when Winlevi will be used for long-term treatment of adolescents (i.e., from 12 years to less than 18 years of age) with acne, e.g. with respect to potential risks of retardation of growth and/or an impact on sexual maturation."

The Applicant refers here also to the response to the first ground for refusal.

Scientific evidence from the literature

Adrenal suppression is a very rare complication of mild-potency topical glucocorticoids, even when used in young children; this is supported by extensive literature evidence (see expert position paper provided).

Meta-analyses of studies conducted in very young children, including infants under one year of age with atopic dermatitis — a condition that typically affects large areas of the body — showed very low incidence of biochemical evidence of mild adrenal suppression (reversible and with no clinical signs) with low-potency topical glucocorticoids (Fishbein et al., 2019; Wood Heickman et al., 2018). This is young population particularly sensitive to glucocorticoids and more prone to adverse effects. Therefore, the low incidence of mild adrenal suppression observed, despite the high-dose topical glucocorticoid use over extensive body surface areas, is reassuring. This is especially relevant when considering the typical use of Winlevi, which is intended for an older population (12 years and above), applied in low doses, and limited to small areas of the body.

No association between topical glucocorticoids and growth abnormalities or sexual maturation has been found in children in published reports (see expert position paper provided). In the few studies that have assessed the effect of topical glucocorticoids on growth rates in the paediatric population no effect on height, height velocity and bone growth was reported, even with use of high-potent glucocorticoids.

Iatrogenic Cushing syndrome, the most common clinical form of hypercortisolaemia, has been reported only from prolonged (>1 month) misuse of clobetasol (very potent topical glucocorticoid) in children and adults

(Decani et al., 2014; Sahıp et al., 2016; Tempark et al., 2010). In children developing Cushing's syndrome, the amount of clobetasol used was reported to range between 75 g and 600-1,200 g (Tempark et al., 2010).

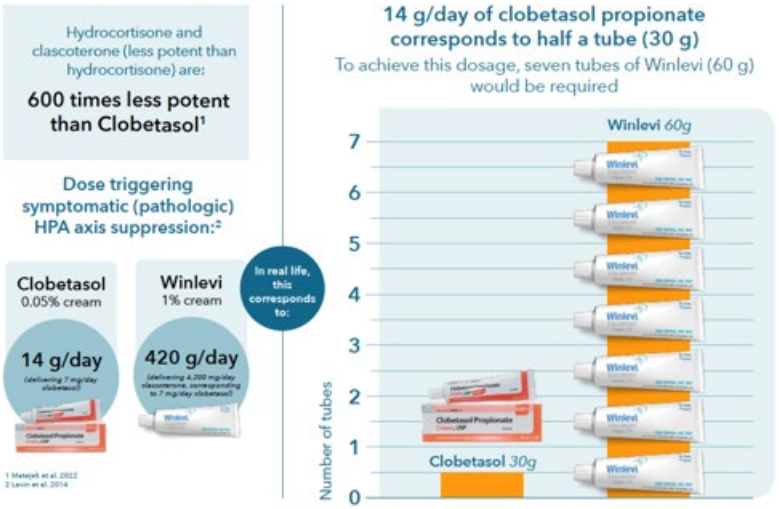
This is consistent with the high risk of adrenal suppression that has been identified in patients using more than 50 g of clobetasol propionate per week (Erdem et al., 2024). In children, high dose of potent topical glucocorticoids, such as clobetasol propionate 0.05%, have also been reported to cause HPA suppression and adrenal insufficiency (Güven, 2020).

The potency of clobetasol is estimated to be 600 times more than hydrocortisone, meaning that 1 mg clobetasol can be considered equivalent to 600 mg hydrocortisone (Matejek et al., 2022).

Even under the conservative assumption that clascoterone is as potent as hydrocortisone — which is not supported by available data, as vasoconstrictor assays have shown that clascoterone 1% cream is less potent than hydrocortisone 1% cream — a total of 60 g of clascoterone 1% cream (equivalent to 600 mg of clascoterone), corresponding to the typical monthly prescription, would be required to approach the documented risk potential of 1 mg of clobetasol propionate.

A daily dose corresponding to 7 x 60 g Winlevi tubes should be used to trigger the symptomatic HPA axis suppression observed with 14 g/day clobetasol 0.05% cream (half of a 30 g tube) (Figure 5).

Figure 5: Estimation of Winlevi Amount Needed to Trigger a Pathological HPA axis Suppression Similar to That Reported with Clobetasol



Clascoterone effect on gonadotropins

The submitted evidence supports that the effect of clascoterone on gonadotropins is negligible. As described below, in vitro and in vivo secondary pharmacology studies show that clascoterone has no gonadotropin or estrogenic effects. In adolescents, no effect on sexual maturation or growth impairment has been identified in clinical studies and post marketing surveillance. Moreover, the potential safety concern regarding clascoterone's gonadotropic effects is inherently linked to its systemic activity, which would require sufficient systemic bioavailability for the compound to reach a concentration high enough to activate the relevant receptors. As outlined in Section 4.1, systemic bioavailability of clascoterone following topical administration is negligible, thereby further decreasing the likelihood of such effects.

Nonclinical evidence

At doses approximating the intended clinical use, clascoterone showed a safety margin of approximately 45- to 68-fold compared to its IC_{50} for inhibition of the human androgen receptor (AR).

In vitro studies demonstrated no significant binding of clascoterone to the rat gonadotropin-releasing hormone (GnRH) receptor at concentrations ranging from 10^{-10} to 10^{-5} M. Based on the estimated free clascoterone concentration near clinical exposure levels (6.7 nM), the safety margin relative to GnRH receptor binding exceeded 1,400-fold.

No estrogenic activity was detected in the in vivo uterotrophic assay in immature mice following subcutaneous administration.

In a broad receptor screening panel (54 receptors and K^+ channels), clascoterone did not exhibit significant off-target binding.

In an in vivo study in parabiotic rats, subcutaneous administration of clascoterone at 1 and 5 mg (approximately 20 and 100 mg/kg, respectively) did not suppress the castration-induced increase in gonadotropin secretion, unlike the positive control (progesterone).

In repeated-dose toxicity studies (up to 9 months) conducted in rats and minipigs at an age corresponding to adolescence in humans, no adverse effects on growth or sexual maturation were observed following subcutaneous or topical administration.

Clinical evidence

During the clinical development, which includes the open-label LTS study CB-03-01/27 (treatment for up to 1 year), no cases with clinical signs of sexual maturation or growth impairment in adolescents were documented.

The only sexual, endocrine and menstrual disorders identified in clinical studies and considered as unlikely related to study drug were amenorrhea (1 case) and polycystic ovaries (1 case).

In addition, the following cases were reported in the clinical programme: there were 5 cases of dysmenorrhea (menstrual pain or cramps), 4 occurring in the clascoterone cream group (any dose) and 1 in the placebo group, 1 case of ovarian cyst occurring in a subject randomised to vehicle who received clascoterone 1% cream during the LTS, and 2 cases of polycystic ovaries in subjects randomised to vehicle who received clascoterone 1% cream. All these events were considered unrelated to study treatment, did not lead to drug withdrawal, and resolved within a few days following treatment with analgesics or anti-inflammatory drugs.

Narratives are provided.

Post-marketing, 18 cases of menstrual disorders have been submitted to FDA and are listed in the FDA Adverse Event Reporting System (FAERS). Of these, one was related to a compounded drug and is therefore not applicable to Winlevi.

Out of the remaining 17 cases (age information available only for three: two adults and one adolescents), 6 cases (35.3%) were related to amenorrhea, 2 cases (11.8%) to menstruation delayed, 3 cases (17.6%) to intermenstrual bleeding, 3 cases (17.6%) to irregular menstruation (17.6%), 2 cases (11.8%) to heavy menstrual bleeding and 1 case (5.9%) to menstrual disorder. All these cases occurred in US and were non-serious; there was no sufficient information to establish a clear causal relationship with the use of Winlevi.

The incidence calculated for clascoterone (7.3 cases per year) is notably lower than the background prevalence of menstrual disorders in the general female population with acne vulgaris.

Menstrual irregularities are often associated with acne vulgaris.

Hormonal imbalances, e.g., androgen and oestrogen fluctuations, play a crucial role in the development of acne vulgaris, and also contribute to the high prevalence of menstrual irregularities in female patients with acne vulgaris. Androgens, particularly testosterone, stimulate sebaceous gland activity, leading to increased sebum production and acne. Elevated levels of androgens, such as testosterone, are commonly observed in women with acne (Darley et al., 1983); this increased androgen production plays a major role in inducing the sebum alterations that participate to the pathogenesis of adult acne in females (Carmina et al., 2022).

The association between irregular menstrual cycles and acne is further supported by another more recent study in >17,000 women, reporting that acne prevalence was 24.9% in women with irregular menses vs 19.2% in women with regular menses ($p<0.001$) (Zouboulis et al., 2025).

The correlation between acne vulgaris and amenorrhea is also well-documented, with both conditions often co-occurring in the context of PCOS. A cross-sectional study of 40 women with acne found that 27.5% had PCOS, characterised by menstrual irregularities, hyperandrogenism, and polycystic ovaries (Begum et al., 2017). Another study on 447 PCOS patients reported that 40.6% had acne vulgaris, further supporting the association between these conditions (Aljefri et al., 2021).

Overall, these data indicate that the prevalence of menstrual disorders in women with acne vulgaris is high and often linked to underlying hormonal imbalances, particularly hyperandrogenism.

At present, there is no causal link that can be established between menstrual disorders and clascoterone 1% cream treatment.

Moreover, as per expert endocrinologist's opinion (see expert position paper), the wide safety margins with respect to the IC_{50} of clascoterone on human AR (>65 times higher than the concentration of unbound clascoterone at the recommended daily dose) indicate a low systemic activity that is unlikely to be able to inhibit the pulsatile secretion of GnRH and thus the synthesis and secretion of gonadotropins, as well as the ovarian and uterine development even when clascoterone is used long-term.

A clinically relevant effect of clascoterone on the HPA axis function has not been established by available evidence, making the risk of its consequences on retardation of growth and/or an impact on sexual maturation purely theoretical or otherwise hypothetical.

The expert position paper provided concludes with the following:

"In light of its negligible systemic exposure, low glucocorticoid potency, dose and treatment area limitations as per usage instructions, it is possible to conclude that the overall risk of clinically relevant HPA axis suppression in adolescents treated with clascoterone is lower than that of hydrocortisone and therefore minimal. Gonadal axis impairment and growth impairment are highly unlikely and not supported by literature or clinical evidence. The CHMP safety concerns about the potential for clascoterone 1% cream to cause HPA axis suppression and have long-term effects (e.g., growth impairment and sexual maturation issues) are deemed theoretical and totally disproportionate to the actual risk of HPA axis suppression occurring after topical use of clascoterone 1% cream in the adolescent population."

The Applicant concludes that CHMP safety concerns about the potential for clascoterone 1% cream to have long-term effects secondary to HPA axis suppression is therefore deemed not evidence-based, rendering the unfavourable benefit-risk assessment in the adolescent population inappropriate and not data-driven.

Ground #3

"The risk minimisation measures proposed by the Applicant are not considered appropriate by CHMP to satisfactorily address the risk of HPA axis suppression in adolescents (i.e., from 12 years to less than 18 years of age)."

The Applicant states that the submitted body of evidence does not support the characterisation that HPA axis suppression occurs following treatment with clascoterone 1% cream. Such evidence is derived from the non-clinical and clinical development, the post-marketing surveillance, scientific literature, European guidelines and the expert opinion provided.

Nevertheless, in line with the labelling of this product in other countries, the current version of the SmPC includes a specific warning regarding the potential risk of HPA suppression, as a precautionary measure. Additionally, the following aspects have been specified in the SmPC: Indication (section 4.1): Winlevi is indicated for the treatment of acne vulgaris in adult and adolescent patients (12 years and older). In adolescents its use must be limited to the face (see section 4.2). Posology (section 4.2): A thin uniform layer of cream should be applied to the affected area twice a day, in the morning and the evening, with at least eight hours between applications. Two (2) fingertip units of cream (corresponding to approximately 1 g of cream) will cover an area of about 28 x 22 cm (approximately 600 cm2 of skin). To achieve the therapeutic effect, it is recommended to treat for three months. After three months of treatment, it is recommended that the physician evaluates the continued improvement of the patient. Thereafter, regular assessment of the skin and of the status of the patient should determine if continued use of the product is needed taken into account the status of the disease and the safety profile of the treatment (see section 4.8). The product must be applied without using occlusive dressing; use of occlusive dressings may increase the risk for systemic side effects (see section 4.4).

The Applicant maintains that during the initial CHMP procedure the risk of HPA axis suppression was reclassified from important potential risk to important identified risk, although based on only laboratory data from 3 adult/adolescents participating in two dedicated maximum-dose studies. In its view this interpretation likely represents an overestimation of the HPA axis suppression risk, which does not correspond to a clinically relevant adrenal insufficiency.

The Applicant proposes the following routine risk minimization measures included in PI in order to mitigate the risk of HPA axis suppression.

For section 4.1 - indication: use limited to face in adolescent.

For section 4.2 - posology:

For all patients:

- application of 2 fingertips units of cream by a thin uniform layer twice a day with at least eight hours between applications (morning and evening), covering an area of about 28 x 22 cm (approximately 600 cm2 of skin);

- regular assessment of the skin and of the status of the patients in order to monitor efficacy and safety of treatment;

- recommendation not to use occlusive dressing;

For adolescents:

- recommendation not to exceed a daily dose of 4 fingertips units (approximately 2 g/day)

- recommendation to applied on face only.

Report from the Ad-hoc expert group

Following a request from the applicant at the time of the re-examination, the CHMP convened an Ad Hoc expert Group (AHEG) inviting the experts to provide their views on the following list of questions, taking into account the applicant's response.

The following questions are raised to the AHEG in view of the grounds for re-examination:

1. Winlevi (clascoterone) is a topical drug with local anti-androgenic effect. Its main metabolite cortexolone has a weak glucocorticoid effect. Please discuss the potential risk of HPA axis suppression with prolonged clascoterone treatment in adolescents (including impact on growth and sexual maturation) taking into account available evidence on ACTH-stimulated serum cortisol levels (in particular in the two dedicated studies) and post-marketing data.

All experts agreed that the risk of HPA axis suppression is low, however, certain individuals, for instance, those with a sensitive glucocorticoid receptor can be more susceptible. Notably, adrenal suppression or disturbance of the HPA axis due to the treatment is not the same as the clinical syndrome of adrenal insufficiency. The risk is associated with the dose, duration and precise timing (nocturnal glucocorticoid effect leads to an increased risk) of treatment. Application of Winlevi at night could increase the risk of HPA axis suppression (circadian rhythm effects) but it is recognised by the experts that the product must be administered every 12 hours. Further, it is considered that certain vulnerable patients are more prone to the risk even though low and it's not necessarily possible to identify such patients in advance. They referred to some examples from other medicines and other medical conditions e.g. corticosteroid eye drops, steroid inhalers, especially in acute stress. This is further substantiated by the Cmax & AUC which showed significant inter-individual variability, which would lead to some concern regarding potential for HPA axis suppression in certain patients, and variability in response to this product from a safety perspective.

It is noted that there is a lack of relevant real world use data to help inform on the exact risk of HPA axis suppression with the Winlevi's long-term use. As it was difficult to quantify the exact risk, some experts agreed that a post-marketing registry study (independent of the MAH) may be most robust, given the wide variability in baseline cortisol levels in adolescents in general. Yearly measurement of height and weight, measurement of early morning plasma cortisol levels and potential adverse reaction to the skin at 3 months and 12 months in such a study (as it would be more informative than measuring cortisol after 1 month) should also be measured as part of this registry study. Moreover, other studies to measure compliance and adverse reactions were proposed.

2. Can the AHEG provide their scientific views on ACTH stimulation test cut-off thresholds and sampling time in relation of HPA axis suppression diagnosis in adolescent 12-18 years old population?

It is not known how well the ACTH test preforms in adolescents with acne being treated with a medicine such as Winlevi. They cannot draw very strong conclusions based on the time-point that the test was done in the Winlevi studies. But overall, the actual results found did not cause alarm.

The ACTH test has its place in clinical practice; it is safer than an insulin-induced hypoglycaemia test in investigating HPA axis disturbance. However, the group's opinion was that the ACTH test should be used only for patients with clear clinical symptoms of adrenal insufficiency or for those having evidence of low morning baseline plasma cortisol.

In patients with evident risk factors (such as reduced longitudinal growth during treatment) or mild symptoms of potential adrenal insufficiency (such as nausea early in the morning), morning baseline cortisol should be measured first in accordance with the joined Endocrine Society and European Society of Endocrinology practice guideline. Plasma cortisol sampling should be done around 8 am and the experts agreed with the threshold of less than 8-10 mcg/dL (220-275 nmol/L) indicating further evaluation by endocrinologist with a low-dose ACTH test.

A low-dose (tetracosactrin 1 μg) ACTH test is considered suitable for any patient with an abnormal basal plasma cortisol level (see above) or for any patient showing clear clinical symptoms of adrenal insufficiency. The cortisol thresholds of the test are usually local as they are dependent of the cortisol assay used, but a stimulated value ≥ 15 μg/dL or 450 nmol/L indicates a normally functioning HPA axis. Collecting two stimulated samples at different timings instead of 30 min only improves the specificity of the test.

3. Please, comment on the appropriateness, feasibility and usefulness of the proposed measures for minimisation of the potential risk of HPA axis suppression in particular for adolescents:

a. Restriction of treatment to facial acne vulgaris in adolescents

b. Medicinal product subject to restricted medical prescription by a dermatologist with experience in the diagnosis and treatment of acne vulgaris

c. Daily dose limited to four (4) fingertip units (corresponding to approximately 2 g of cream in adolescents

d. Follow-up visits: 1 month after treatment initiation and then every 3 months

e. Warning on HPA axis suppression with recommendation to refer patients for endocrinological evaluation if adrenal insufficiency is suspected

f. Educational materials for HCPs (checklist) and patients (patient card)

Can the experts think of further measures not listed above to minimize the risk?

a) The experts agreed to the restriction of treatment to facial acne vulgaris in adolescents

b) The majority agreed to restrict the medical prescription to dermatologists as it is a first-in-class medicine until further post-marketing data collected in a study are generated. They were of the opinion that, at a later stage, paediatricians and GPs having experience in the disease could also prescribe, once the risk has been further characterised.

c) All experts agreed on the daily dose limit to 4 fingertips units (i.e. 2 g of cream) based on the clinical studies data.

d) The experts all agreed that a follow-up after 3 months is needed but not after 1 month. Some experts mentioned that the 1-month visit could be optional. Some experts also suggested a mandatory visit once a year for long-term growth, BMI, pubertal development and menstruation, or other dysregulations to be monitored by paediatrician or a GP.

e) The experts agreed that a warning on HPA axis suppression with recommendation to refer patients for endocrinological evaluation if adrenal insufficiency is suspected is needed, even if the risk is low, it cannot be ruled out and therefore should be mentioned.

f) For a diagnosed chronic condition, the patient card was not considered useful for information on HPA axis suppression as the symptoms are general and it would unduly worry the patients. The experts all agreed that

educational materials for HCPs (checklist) are needed, for example, to ensure patients are well informed of the need to keep to the posology and the risk of HPA axis suppression. Further, the experts suggested to consider the effect of sun exposure in summer, and the impact of concomitant glucocorticoid treatment regardless of the administration form for another disease (e.g. asthma, atopic dermatitis, chronic rhinitis).

Additional efficacy and safety data submitted by the Applicant

Efficacy

The Applicant has performed further subgroup analyses within the adolescent patient group (12 - <18 years of age) to investigate efficacy and safety of clascoterone in two age subsets, who might be at different stages of sexual maturation and growth.

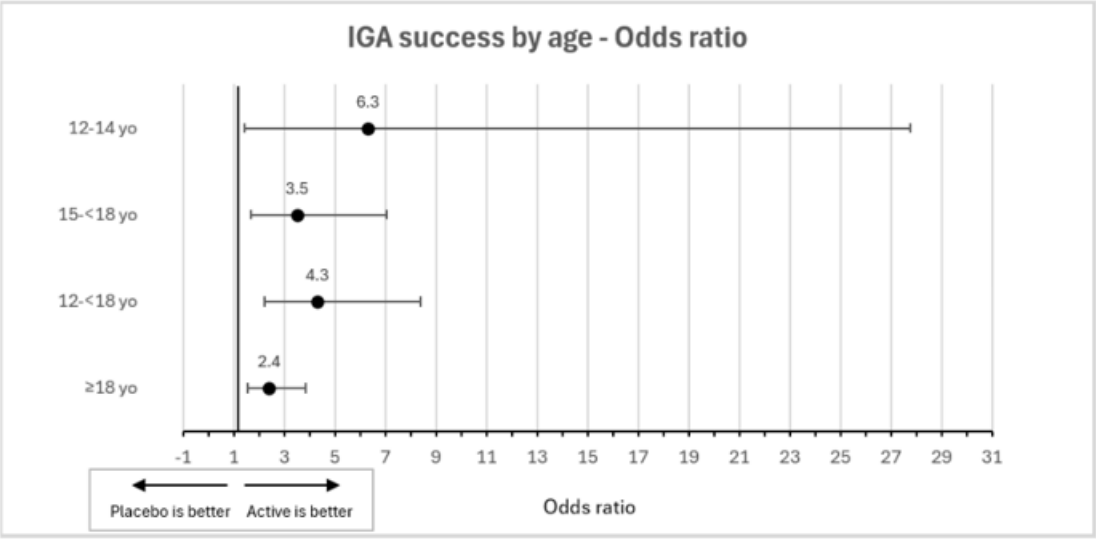
For analyses, the adolescent patient group of the clinical studies were grouped according to the following:

- 12 to 14 years of age (puberty)

- 15 to <18 years of age (post-puberty)

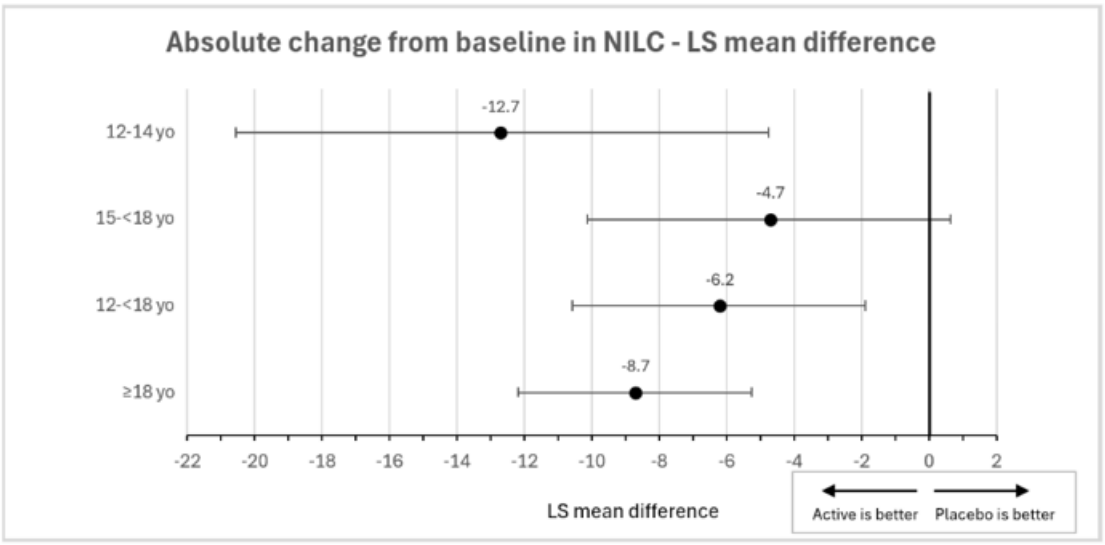
While subgroup analyses must be interpreted with appropriate caution due to smaller sample sizes compared to the primary dataset, the data clearly demonstrate a consistent treatment effect of clascoterone across all age groups and for all study endpoints (See Figures 6-9). This consistency supports a favourable benefit-risk profile for clascoterone in both adolescent subgroups (encompassing puberty and post-puberty) and adults.

Figure 6: IGA Success Rate (Percent Of Patients Achieving Treatment Success, Defined as an IGA Score of 0 or 1 at Least 2 Grades of Improvement in IGA Scale) at Week 12 (Co-Primary Endpoint P1) – Subgroup Analysis by Age (12-14; 15-<18; 12-<18 yr; ≥18 yr)



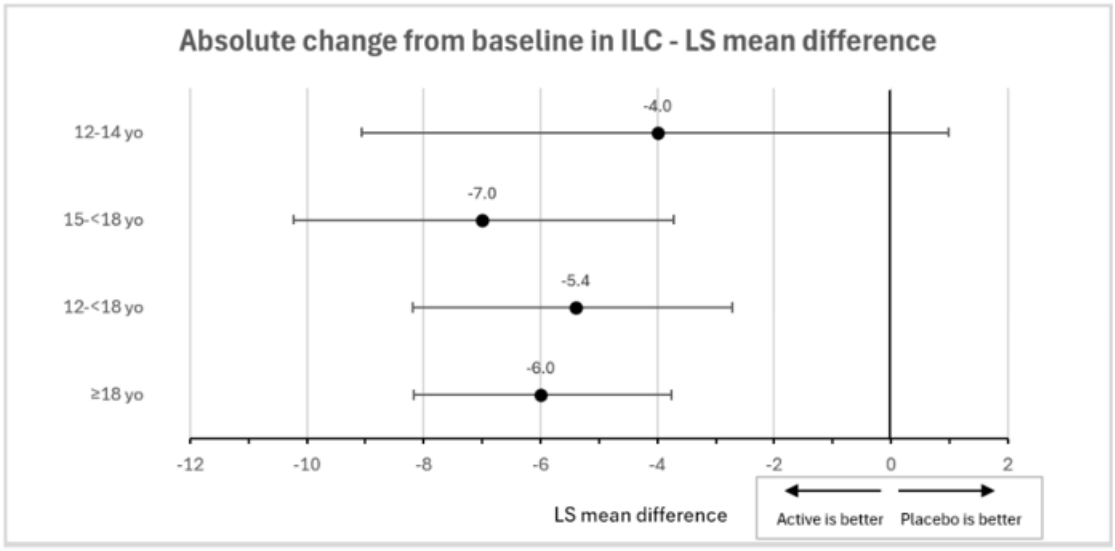
Abbreviations: IGA = investigator's global assessment

Figure 7: Absolute Change from Baseline in NILC at Week 12 (Co-Primary Endpoint P2) – Subgroup Analysis by Age (12-14; 15-<18; 12-<18 yr; ≥18 yr)



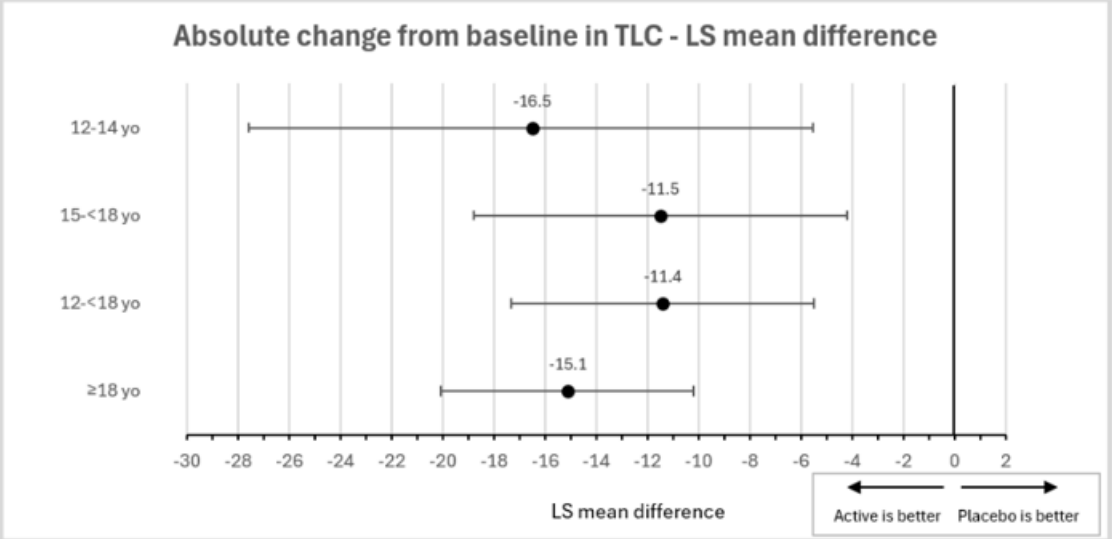
Abbreviations: NILC = non-inflammatory lesion count; LS = least squares

Figure 8: Absolute Change from Baseline I ILC at Week 12 (Co-Primary Endpoint P3) – Subgroup Analysis by Age (12-14; 15-<18; 12-<18 yr; ≥18 yr)



Abbreviations: ILC = inflammatory lesion count; LS = least squares

Figure 9: Absolute Change from Baseline in Total Lesion Count (TLC) at Week 12 (Secondary Endpoint S1) – Subgroup Analysis by Age (12-14; 15-<18; 12-<18 yr; ≥18 yr)



Abbreviations: TLC = total lesion count; LS = least squares

Safety

In adolescents, the incidence of TEAEs related to study drug in all the clinical studies was comparable to vehicle treatment and the reported safety profile for adults.

Table 31: Incidence of Treatment Emergent Adverse Events Related to Study Medication in Subjects 12 - <18 Years Old

	Phase 1 & 2 PK/Safety [1]		Phase 2 & 3 Controlled [2]			Total [3]		Phase 3 LTE [4]
Body System Organ Class Preferred Term, n (%)	CB-03-01 (N=22)	Placebo (N=0)	CB-03-01 (N=444)	Placebo (N=362)	Retin-A® 0.05% (N=0)	CB-03-01 (N=466)	Placebo (N=362)	CB-03-01 (N=302)
Subjects with Any TEAEs	2 (9.1)	0	6 (1.4)	6 (1.7)	0	8 (1.7)	6 (1.7)	7 (2.3)
General disorders and administration site conditions	0	0	2 (0.5)	3 (0.8)	0	2 (0.4)	3 (0.8)	4 (1.3)
Application site acne	0	0	0	1 (0.3)	0	0	1 (0.3)	2 (0.7)
Application site dermatitis	0	0	0	1 (0.3)	0	0	1 (0.3)	0
Application site dryness	0	0	0	1 (0.3)	0	0	1 (0.3)	1 (0.3)
Application site erythema	0	0	0	0	0	0	0	1 (0.3)
Application site hypersensitivity	0	0	1 (0.2)	0	0	1 (0.2)	0	0
Application site pain	0	0	1 (0.2)	0	0	1 (0.2)	0	1 (0.3)
Skin and subcutaneous tissue disorders	0	0	2 (0.5)	2 (0.6)	0	2 (0.4)	2 (0.6)	3 (1.0)
Acne	0	0	1 (0.2)	1 (0.3)	0	1 (0.2)	1 (0.3)	1 (0.3)
Skin irritation	0	0	0	1 (0.3)	0	0	1 (0.3)	0
Acne conglobata	0	0	0	0	0	0	0	1 (0.3)
Acne cystic	0	0	0	0	0	0	0	1 (0.3)
Dermatitis contact	0	0	1 (0.2)	0	0	1 (0.2)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (0.3)	0	0	1 (0.3)	0
Rhinorrhoea	0	0	0	1 (0.3)	0	0	1 (0.3)	0
Eye disorders	0	0	1 (0.2)	0	0	1 (0.2)	0	0
Eye irritation	0	0	1 (0.2)	0	0	1 (0.2)	0	0
Infections and infestations	0	0	1 (0.2)	0	0	1 (0.2)	0	0
Nasopharyngitis	0	0	1 (0.2)	0	0	1 (0.2)	0	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	0	1 (0.3)
Sunburn	0	0	0	0	0	0	0	1 (0.3)
Investigations	2 (9.1)	0	0	0	0	2 (0.4)	0	0
ACTH stimulation test abnormal	2 (9.1)	0	0	0	0	2 (0.4)	0	0
Nervous system disorders	0	0	1 (0.2)	0	0	1 (0.2)	0	0
Headache	0	0	1 (0.2)	0	0	1 (0.2)	0	0

Abbreviations: ACTH = adrenocorticotropic hormone; LTE = long-term extension; TEAE = Treatment-emergent adverse events.
Placebo = Vehicle cream.
[1] Phase 1 healthy subjects with planned treatment duration <=14 days: CB-03-01/02 (SAD), CB-03-01/04 (MAD), CB-03-01/33 (tQT).
Phase 1 healthy subjects with planned treatment duration 14-56 days: CB-03-01/05 (skin irritation intra-subject control) and CB-03-01/32 (skin irritation intra-subject control).
Phase 1 acne vulgaris subjects with planned treatment duration 14-56 days: 171-7151-203 (steady state PK).
Phase 2 acne vulgaris subjects with planned treatment duration 14-56 days: 171-7151-202 (maximum use PK) and CB-03-01/28 (maximum use PK).
[2] Phase 2 acne vulgaris subjects vehicle-controlled: CB-03-01/03 and 171-7151-201.
Phase 3 acne vulgaris subjects vehicle-controlled: CB-03-01/25 and CB-03-01/26.
[3] Phase 3 LTE: CB-03-01/27 was not included in this column.
[4] Phase 3 acne vulgaris subjects LTE: CB-03-01/27 (subjects rolled over from CB-03-01/25 and CB-03-01/26).

In pooled analysis of all the studies, TEAEs related to study medication were reported for 1.7% of the 466 adolescent subjects treated with clascoterone and 1.7% of the 362 subjects treated with placebo; in the LTS study, TEAEs related to study medication were reported for 2.3% of the 302 subjects. In terms of events from the pooled analysis, their incidence was very low across the groups, and there was no single event reported for more than 1.0% of subjects.

As already outlined above, 2 adolescent subjects (9.1%) participating in the dedicated supratherapeutic Phase 2 study had *ACTH-stimulation test abnormal.*

Most TEAEs related to the study medication were associated with administration site reactions and disorders of the skin and subcutaneous tissue. Among non-dermatologic TEAEs that occurred more frequently in the clascoterone 1% cream group compared to placebo, the following were noted:

- 1 case of eye irritation, related to improper use of the product; section 4.2 of the SmPC mentions a warning to avoid applying the cream to the eyes to minimise such risk
- 1 case of nasopharyngitis – this case was erroneously judged to be related to study drug, as agreed in the initial procedure
- 1 case of headache
- 2 cases of ACTH stimulation test abnormality (HPA axis suppression test)

The adolescent group was further divided into two further subsets, 12-14 and 15-<18 years of age (see tables below).

Age Subgroup: 12-14 Yrs

	Phase 1 & 2 PK/Safety [1]		Phase 2 & 3 Controlled [2]			Total [3]		Phase 3 LTE [4]
Body System Organ Class Preferred Term, n (%)	CB-03-01 (N=8)	Placebo (N=0)	CB-03-01 (N=155)	Placebo (N=134)	Retin-A® 0.05% (N=0)	CB-03-01 (N=163)	Placebo (N=134)	CB-03-01 (N=105)
Subjects with Any TEAEs Related to Study Medication	2 (14.3)	0	4 (1.4)	3 (1.3)	0	6 (2.0)	3 (1.3)	6 (3.0)
General disorders and administration site conditions	0	0	1 (0.3)	2 (0.9)	0	1 (0.3)	2 (0.9)	3 (1.5)
Application site acne	0	0	0	1 (0.4)	0	0	1 (0.4)	1 (0.5)
Application site dermatitis	0	0	0	1 (0.4)	0	0	1 (0.4)	0
Application site dryness	0	0	0	0	0	0	0	1 (0.5)
Application site erythema	0	0	0	0	0	0	0	1 (0.5)
Application site pain	0	0	1 (0.3)	0	0	1 (0.3)	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (0.4)	0	0	1 (0.4)	0
Rhinorrhoea	0	0	0	1 (0.4)	0	0	1 (0.4)	0
Eye disorders	0	0	1 (0.3)	0	0	1 (0.3)	0	0
Eye irritation	0	0	1 (0.3)	0	0	1 (0.3)	0	0
Infections and infestations	0	0	1 (0.3)	0	0	1 (0.3)	0	0
Nasopharyngitis	0	0	1 (0.3)	0	0	1 (0.3)	0	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	0	1 (0.5)

Injury, poisoning and procedural complications (cont'd)								
Sunburn	0	0	0	0	0	0	0	1 (0.5)
Investigations	2 (14.3)	0	0	0	0	2 (0.7)	0	0
ACTH stimulation test abnormal	2 (14.3)	0	0	0	0	2 (0.7)	0	0
Nervous system disorders	0	0	1 (0.3)	0	0	1 (0.3)	0	0
Headache	0	0	1 (0.3)	0	0	1 (0.3)	0	0
Skin and subcutaneous tissue disorders	0	0	1 (0.3)	0	0	1 (0.3)	0	2 (1.0)
Acne	0	0	0	0	0	0	0	1 (0.5)
Acne conglobata	0	0	0	0	0	0	0	1 (0.5)
Dermatitis contact	0	0	1 (0.3)	0	0	1 (0.3)	0	0

Age Subgroup: 15-<18 Yrs

	Phase 1 & 2 PK/Safety [1]		Phase 2 & 3 Controlled [2]			Total [3]		Phase 3 LTE [4]
Body System Organ Class Preferred Term, n (%)	CB-03-01 (N=14)	Placebo (N=0)	CB-03-01 (N=289)	Placebo (N=228)	Retin-A® 0.05% (N=0)	CB-03-01 (N=303)	Placebo (N=228)	CB-03-01 (N=197)
Subjects with Any TEAEs Related to Study Medication	0	0	2 (0.7)	3 (1.3)	0	2 (0.7)	3 (1.3)	1 (0.5)
Skin and subcutaneous tissue disorders	0	0	1 (0.3)	2 (0.9)	0	1 (0.3)	2 (0.9)	1 (0.5)
Acne	0	0	1 (0.3)	1 (0.4)	0	1 (0.3)	1 (0.4)	0
Skin irritation	0	0	0	1 (0.4)	0	0	1 (0.4)	0
Acne cystic	0	0	0	0	0	0	0	1 (0.5)
General disorders and administration site conditions	0	0	1 (0.3)	1 (0.4)	0	1 (0.3)	1 (0.4)	1 (0.5)
Application site dryness	0	0	0	1 (0.4)	0	0	1 (0.4)	0
Application site acne	0	0	0	0	0	0	0	1 (0.5)
Application site hypersensitivity	0	0	1 (0.3)	0	0	1 (0.3)	0	0

Placebo = Vehicle cream. TEAE = Treatment-emergent adverse events.
[1] Phase 1 healthy subjects with planned treatment duration <=14 days: CB-03-01/02 (SAD), CB-03-01/04 (MAD), CB-03-01/33 (tQT).
Phase 1 healthy subjects with planned treatment duration 14-56 days: CB-03-01/05 (skin irritation intra-subject control) and CB-03-01/32 (skin irritation intra-subject control).
Phase 1 acne vulgaris subjects with planned treatment duration 14-56 days: 171-7151-203 (steady-state PK).
Phase 2 acne vulgaris subjects with planned treatment duration 14-56 days: 171-7151-202 (maximum use PK) and CB-03-01/28 (maximum use PK).
[2] Phase 2 acne vulgaris subjects vehicle-controlled: CB-03-01/03 and 171-7151-201.
Phase 3 acne vulgaris subjects vehicle-controlled: CB-03-01/25 and CB-03-01/26.
[3] Phase 3 LTE: CB-03-01/27 was not included in this column.
[4] Phase 3 acne vulgaris subjects LTE: CB-03-01/27 (subjects rolled over from CB-03-01/25 and CB-03-01/26).
Source Data: ADAE, ADSL Program: t-145.6.2.a-aerel-age.sas Version: 2025-06-06:13:06

Excluding the cases of nasopharyngitis and eye irritation (discussed above), and the two cases of HPA axis suppression (both cases in the subset 12-14 years, thoroughly discussed above), there were no differences between the groups in terms of adverse events related to study drug.

At termination of the initial assessment, the CHMP was of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety of clascoterone 1% cream was not properly or sufficiently demonstrated in the treatment of acne vulgaris in adolescents from 12 years to less than 18 years of age. Therefore, the CHMP recommended the refusal of the granting of the marketing authorisation for Winlevi in the sought indication "treatment of acne vulgaris in patients from 12 years of age and older.

For re-examination purpose, the Applicant presented the therapeutic context and unmet need for adolescents from 12 years of age and older with acne vulgaris, supported by the position papers of the experts. According to this, there is no approved treatment in the EU targeting sebum production at earlier stage of the disease for all genders. Male patients, including adolescents, are left without alternative treatment options to fixed combination products and oral antibiotics. The latter are often required far beyond recommended timeframes contributing to the global concerns of antimicrobial resistance.

Consistently with this clinical experience from expert's reports, published real-world case series data of clascoterone 1% cream in Canada (Lynde et al., 2025; Tay & Loo, 2025) including adolescents, showed that clascoterone either as monotherapy or in combination with systemic treatments, is effective and well tolerated regardless of acne severity, age, gender, and ethnicity, and led to clinical improvement. In addition, a positive post marketing experience has been reported in the US 4 years after approval as indicated by

prescribing trends, tolerability, and inclusion of clascoterone in the most recent acne treatment guidelines (Reynolds et al., 2024). This is supported by the approval of clascoterone for the topical treatment of acne vulgaris in patients ≥12 years or older in 9 countries (e.g USA (2020), Canada (2023), Australia (2024), UK (2025)).

5.1. Discussion and conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and took account of the views of the Ad-hoc Expert Group.

The Applicant responded to the CHMP **Ground 1** by clarifying that the risk of HPA axis suppression with clascoterone is minimal, supported by evidence and current clinical guidelines, and mainly relates to theoretical or high-dose situations rather than typical use. The following points have been addressed:

- Clascoterone's mechanism of action is exerted locally

- Clascoterone has a negligible systemic absorption following cutaneous application

- Clascoterone and its main metabolite cortexolone, has a weak glucocorticoid activity

- Nonclinical evidence of adrenal cortical atrophy is observed at exposures clinically nonrelevant in humans and not associated with effect on growth or sexual maturation

- Laboratory values indicative of HPA axis suppression were borderline, did not translate into clinical signs and symptoms and should be evaluated in light of the technical limitations of the ACTH test and the latest European Endocrinology guidelines

- There is no evidence of pathological adrenal insufficiency documented in the clinical programme and post marketing

- In its intended use, clascoterone has high safety margins.

Clascoterone exerts its action locally and has a negligible systemic absorption following topical application

The main issue of this point is the demonstration that clascoterone exerts its action locally with no systemic absorption when used as cream.

The Applicant reiterated that clascoterone activity is mediated by inhibiting the nuclear androgen receptor as substantiated by i*n vitro* evidence showing that it potently (50 nM) antagonizes the effects of androgens in primary human sebocytes to reduce sebum production and accumulation, and inflammatory mediators which are known drivers of the acne pathogenesis. In the in vivo hamster flank organ assay, topical application for 21 consecutive days to female Golden Syrian hamsters at doses up to 400 µg/day resulted in local reduction in the size of the flank organ produced by testosterone propionate; the contralateral (untreated) organ was not affected, thus accounting for the local effect.

The clinical evidence of the local effect of clascoterone is based on the efficacy results obtained in the 2 Phase 3 studies, in terms of (non)inflammatory lesion count.

The Applicant considered a number of PK studies to demonstrate the clinically irrelevant clascoterone systemic absorption following cutaneous administration and that clascoterone pharmacological action appears to be limited locally to the site of application. However, the only PK study assessing the systemic PK profile of clascoterone in adolescents, is study 171-7151-202: a Phase 2 Open Label Evaluation of the Adrenal

Suppression Potential and PK Properties of Cortexolone 17α-Propionate (CB-03-01, clascoterone) Cream Applied Every 12 Hours for Two Weeks in Subjects with Acne Vulgaris. Female and male subjects aged 12 and older with moderate to severe acne vulgaris on the face, chest and/or back, were treated with supratherapeutic doses of clascoterone 10 mg/g cream: adults were administered 6 g BID (12 g daily) and adolescents 4 g BID (8 g daily); drug quantities were ~6- and 5-fold higher than the amounts used in pivotal Phase 3 (studies CB-03-01/25 and CB-03-01/26) for adults and adolescents, respectively.

Results showed no difference in PK parameters between adults (n=20) and adolescents (n=22), and despite differences in dosing due to the body surface area of subjects, both groups demonstrated low levels of absorption and systemic exposure.

Data were affected by a high degree of variability although it was somehow less pronounced in adolescents than in adults.

PK analysis indicates that in both adolescents and adults clascoterone plasma concentrations were at a steady-state by Day 5 and during the assessment of adrenal suppression potential on Day 14, thus indicating no accumulation potential during treatment; at Day 14, accumulation ratio is approximately 2-fold than the first administration.

The systemic levels/exposure of clascoterone at steady state were still negligible. However, the study duration is too short to extrapolate any firm conclusion to clinical use foreseen by Phase 3 studies, for 3-month duration. However, no long-term adverse drug reactions were recorded in clinical studies and post-marketing use with clascoterone 10 mg/g.

Moreover, sampling after the first administration and at day 14 after the last administration, and only 2 trough levels at days 5 and 10, was not optimal to estimate the steady state, considering the mean half-life obtained in TQT study (CB-03-01/33) using 7.5% solution formulation of clascoterone (a different cutaneous formulation) which was 26.80 hours on day 4.

Overall, in adolescents at steady state, the mean highest observed exposure Cmax was 4.61 ng/mL, corresponding to 11.5 nM and the mean AUC_T was 30.97 ng·mL/h.

Although some study limitations (e.g., non-optimal sampling time, short duration) supratherapeutic doses of clascoterone in adolescent patients induced a Cmax at steady state still 20-fold lower the IC50 on human androgen receptor.

In another PK study in adult patients (171-7151-203) administered with clascoterone 10 mg/g 6 g daily for 6 weeks, no increase in the % of clascoterone and its main metabolites excreted in urine, was observed over 24 hr up to 42 days, thus indicating no variation in the amount of absorption.

Relative glucocorticoid potency of clascoterone

The Applicant tested clascoterone 10 mg/g cream with a vasoconstrictor activity test comparing it versus three positive controls, and particularly versus hydrocortisone 1% (10 mg/g) cream. This assay is considered the gold standard to evaluate the potency of topical glucocorticoids in vivo. The study showed that clascoterone 10 mg/g cream had lower vasoconstrictive effects than the lowest steroid potency class (hydrocortisone) in the vasoconstrictor assay. It should be noted that clascoterone has not corticosteroid effect, while its metabolite cortexolone (i.e. 11-deoxycortisol) has a weak corticosteroid activity and can be converted into cortisol. However, as topical clascoterone is metabolized into the active compound locally in the skin, the metabolite's vasoconstrictor effect would be indirectly reflected in the blanching response;

therefore, the lower glucocorticoid potency of clascoterone in respect other common topical steroids, is acknowledged.

Nonclinical evidence of adrenal cortical atrophy is observed at exposures clinically nonrelevant in humans and is not associated with effect on growth or sexual maturation in animals

The non-clinical safety package of clascoterone included repeated-dose toxicity studies conducted in rats and minipigs, using both subcutaneous and dermal routes. These studies are now primarily analysed with the intent to evaluate potential systemic endocrine effects, notably adrenal cortex atrophy and suppression of the HPA axis.

Clascoterone showed a dose and duration-dependent glucocorticoid-type response and an adrenal gland weight reduction as marker of HPA axis suppression, in the animal species examined. This effect was only observed at high systemic exposures, which exceeded the AUC measured in adolescents administered supratherapeutic doses of Winlevi 10 mg/g (clinical study 171-7151-202).

In rats, studies were performed through subcutaneous route and dermal route. Resulting safety margin range is wide (from 1, 2 to 8) and thus, does not fully support the claim of a "negligible risk". What emerges is that NOAEL decreases with treatment duration, independently from the route of administration. However, it is noted that such margins are calculated based on a clinical AUC (30.97 ng.h/mL) derived from supratherapeutic doses in adolescents, at a dose 4-6 fold higher than that recommended in adolescents and on multiple body a*reas*. Moreover, as indicated by the Applicant, lowest NOAELs are considered the most conservative because they are established based on the complete absence of adrenal weight reduction in both sexes. In some cases, adrenal weight decrease was observed only in male animals at higher doses, which suggests that these NOAELs may be underestimated. Finally, it is important to consider that rat skin differs significantly from human skin in terms of structure and permeability. Therefore, the predictivity of rat dermal toxicity studies for human risk assessment is limited, and results must be corroborated with data from more representative species such as the minipig and clinical safety evaluation.

In minipigs two studies were performed: a 6–9 months dermal study using a topical solution (5% and 15%) and a 9-month dermal study using a topical cream (1%, 2%, and 5%). Safety margins derived from these studies are higher with respect to rats' studies. In both cases NOAEL was established at 5%. It should be highlighted that in the topical solution-based study, the NOAEL at interim analysis (26 weeks) was established at the lowest dose level tested, while at termination (39 weeks) the NOAEL was set at the highest 15% dose level: this effect appears to correlate with cumulative exposure during study duration.

Thus, safety margins are far exceeding systemic exposure expected to occur after topical administration of Winlevi 10 mg/g cream in clinical use.

The main (endogenous) metabolite cortexolone, was detected in rats dosed with clascoterone topically (1.5% and 5% cream) for 13 weeks while in minipigs, cortexolone was sparsely detected after topical administration for 36-weeks.

No juvenile nonclinical toxicology studies have been performed. According to ICH S11, the choice of animal models is considered appropriate to support the safety profile of a topically applied steroidal antiandrogen. In particular:

• Rats aged 7 weeks, commonly used in toxicological studies, are regarded as physiologically comparable to early-adolescent humans (approximately 12–14 years), especially with respect to HPA axis maturation and endocrine responsiveness.

• Minipigs aged 4.5 months are considered a well-established translational model for human skin, due to similarities in epidermal structure, stratum corneum composition, dermal vasculature, and percutaneous absorption. At this age, minipigs approximate preadolescent to adolescent human physiology, and are therefore relevant for assessing systemic exposure from topical application in adolescent patients.

These models provide a suitable framework for evaluating potential systemic risks, including endocrine-related findings, under conditions of prolonged dermal exposure.

In conclusion, non-clinical data indicate a potential risk of HPA axis suppression, supported by a reduction in adrenal weight in rats and minipigs following prolonged topical use at high doses. The calculated safety margins are considered reassuring based on the low systemic exposure expected in clinical use.

Biochemical findings of HPA axis suppression and their interpretation

Given the weak glucocorticoid activity of cortexolone (the main metabolite of clascoterone), following an FDA's recommendation, the Applicant performed two studies using ACTH stimulation test: the maximum-dose study 171-7151-202 in 42 adults/adolescents and the high-dose study CB-03-01/28 in 27 children <12 years of age (which are not part of the target population). As a result, a potential risk of HPA axis suppression was hypothesized based on laboratory data (30-minute cortisol levels post-ACTH stimulation) in 5 adult/adolescents (see details below).

In study 171-7151-202, clascoterone 1% cream administered at 6 g per application (12 g daily) or 4 g per application in adolescents with BSA<=1.6m^2 was tested (at a dosage 5.7- and 4.7-fold higher than the amounts used in pivotal Phase 3 studies for adults and adolescents, respectively). Laboratory evidence (post-stimulation serum cortisol levels by ACTH test) of HPA axis suppression was detected in one out of 20 adult subjects (5%) and two out of 22 adolescent subjects (9%). In all these subjects, the 30-minute post-stimulation serum cortisol levels were just below the 18.0 µg/dL cut-off value (14.9; 17.0 and 17.7 µg/dL) and coincided with clascoterone 1% cream usage of 167.9 g (one adult), 105.8 g and 158.6 g (two adolescents) over 14 days, respectively.

This observed changes in post-stimulation cortisol did not result in any clinically evident sign or symptom, or in significant adverse events or changes in other laboratory results in the three impacted patients.

In Study CB-03-01/28, clascoterone 1% cream was tested in 27 paediatric acne patients aged 9 to <12 years (which is not the intended target population for clascoterone 1% cream). Patients were instructed to apply to the face and trunk BID for 2 weeks a total of 4 grams daily (twice the therapeutic dose recommended in adolescents). Within the evaluable population, two out of 23 (8.7%) subjects, both 10 years old, demonstrated biochemical evidence of abnormal HPA axis response at Day 14 under maximum use conditions as documented by a 30-minute post-stimulation serum cortisol level of ⩽18 µg/dL. In both cases, the subjects had borderline post-stimulation levels of cortisol, i.e., very close to the lower limit (18.0 and 16.1 µg/dL, respectively), coinciding with clascoterone 1% cream usage of 50.7 g and 56.0 g over 14 days. Both subjects returned to normal HPA axis function approximately 4 weeks after Day 14/end of study.

In both studies, none of the subjects had any findings in vital signs or other laboratory results indicative of adrenal suppression, such as for example hypotension, hypoglycaemia or hyponatremia. Therefore, the results described by the ACTH test were biochemical findings with no observed clinical consequences.

Importantly, all abnormal biochemical values in both studies were transient, did not require any intervention and spontaneously resolved without sequalae returning to normal values within 4 weeks after treatment suspension. Of note, the European Society of Endocrinology (ESE) guidelines acknowledge that even in the presence of biochemical signs of HPA axis suppression, "the risk of clinically significant adrenal insufficiency

or adrenal crisis remains very low.”. In any case, individual susceptibility is acknowledged (e.g. due to higher sensitivity of glucocorticoid receptor).

The ACTH test is a confirmatory test, that AHEG recommends being used only for patients with clear symptoms of adrenal insufficiency. However, in the studies conducted by the Applicant, the ACTH test was used in absence of suspicious signs of adrenal insufficiency, i.e., it was used as a screening test. The interpretation of ACTH test in a screening setting cannot be the same as in a diagnostic setting and must take into account the importance of pre-test and post-test probability, clinical presentation, and rates of false-positive results.

For interpretation of borderline cortisol values in the ACTH stimulation test the analytical characteristics of the assay used, particularly in light of evolving assay technologies, should be considered. The same ESE guidelines recognize the necessity to take into account that the cut-off value of the ACTH test (i.e. 18 µg/dL) used to identify suboptimal cortisol response used historically for polyclonal-based immunological assays is less specific than that for modern monoclonal technologies (requiring a lower cut-off value) due to cross-reaction with other cortisol-like compounds. This limitation implies that the traditional cortisol threshold may have been set artificially high due to overestimation by older, non-specific assays. As a result, cortisol values in the so-called "borderline" range (e.g., 15–18 µg/dL) may actually indicate adequate adrenal function when measured with more accurate methods. Based on the dossier submitted it seems that cortisol levels in the two studies were measured with an outdated polyclonal antibody test. ESE guidelines emphasize that even in the presence of biochemical findings suggestive of adrenal insufficiency, borderline values (e.g., 14–17 µg/dL) obtained using modern, specific monoclonal assays, further evaluation should be guided by clinical context, ACTH levels, and possibly a 60-minute post-stimulation sample.

Indeed, in the aforementioned studies, during the ACTH test, cortisol levels were measured only after 30 minutes, while guidelines (and common clinical practice) advice on dosing also at 60 minutes in order to identify subjects with normal response at this later timepoint. Since the 60-minute cortisol level was not measured, and considering the observed borderline values, it is possible that the number of subjects with abnormal response found in the Phase 2 studies is overestimated (i.e. more false positive results).

At present, in the paediatric setting, there is no consensus among endocrinologists as to which type of stimulation test (either glucagon test, standard dose ACTH test or low-dose ACTH test) and what cortisol cut-off thresholds should be used to rule out HPA axis suppression. A lower cut-off for the low-dose ACTH stimulation test (≥15 µg/dL) has been suggested by some Authors and the AHEG as more appropriate since it might reduce false-positive results and still detects most cases of pituitary-adrenal axis dysfunction in children. In the opinion of the AHEG plasma cortisol sampling should be done around 8 am and the experts agreed with the threshold of less than 8-10 mcg/dL (220-275 nmol/L) indicating further evaluation by endocrinologist with a low-dose ACTH test.

Most importantly of all, however, is that in both Phase 2 studies conducted to assess possible HPA axis suppression, supratherapeutic doses (considerably higher than those currently recommended in the SmPC for adults and adolescents) were used. While this is reassuring, on the other hand, it is acknowledged that the IMP was used only for a limited amount of time (i.e., 2 weeks), and, thus, effects of prolonged treatment - an important factor for development of HPA axis suppression - could not adequately be addressed.

Further and strong reassurance comes from a Phase 3, open-label, long-term extension study (up to 52 weeks of treatment in total; study CB-03-01/27), focused on safety in subjects 9 years and older who already completed a previous study. A total of 609 subjects (including 302 adolescents) were enrolled and treated with clascoterone 1% cream twice daily for as long as required by their disease status, up to 52

weeks (i.e., the investigators could suspend the treatment and start it again based upon clinical evaluation). Although the Applicant did not specify the median follow-up, no local and systemic AEs clearly consistent with any clinical manifestations of HPA axis suppression were reported, indicating that even when used for a longer time (comparable to the duration of use expected in clinical practice) clascoterone 1% cream should not be able to induce clinically relevant HPA axis suppression.

Adrenal insufficiency in the clinical programme and post marketing setting

In the clinical development program of clascoterone no endocrine adverse events related to HPA axis suppression or adrenal insufficiency were reported.

Clascoterone for the topical treatment of acne vulgaris in patients ≥12 years or older is approved world-wide in 9 countries: US (2020), Canada (2023), Australia (2024), New Zealand (2024), Singapore (2024), UK (2025), Malaysia (2025), Jordan (2025), Mexico (2025).

Four cases reported as "serious HPA axis suppression/adrenal suppression" that mention Winlevi (clascoterone), have been submitted to FDA and are listed in the FDA Adverse Event Reporting System (FAERS). Of these, only one case, submitted by the marketing authorisation holder (MAH) of Winlevi in US was reported by a health care professional (HCP) and presents a potential causal relationship between the experienced event HPA axis suppression and the use of Winlevi; the case was deemed serious (medically significant) but no other clinical information is available. This case involved a 20-year-old female patient, who used Winlevi twice daily for three months on facial, chest, and back areas. No information is provided on medical history, how the diagnosis was made, and regarding event outcome.

It is noted that all reports were non-medically confirmed cases, and, thus, lack significant data, including time-to-onset, clinical signs and symptoms, diagnostic procedures. This, together with possibly confounding narratives, debates the reliability of HPA axis suppression diagnosis in patients treated with clascoterone at the recommended dosage. Moreover, none of the collected cases from the post-marketing surveillance include clinical signs or laboratory evidence consistent with HPA axis suppression, and none of these cases involved adolescent subjects (12-<18 years of age).

Conclusively, the assessment of the available post-marketing data is challenging and does not allow to draw any definitive conclusions on causal association between HPA axis suppression and the use of Winlevi.

When the very few cases of suspected HPA reported in the post-marketing setting (only US), even when considering some degree of under-reporting, are compared against the amount of tubes of clascoterone already sold in North America, it seems that, even in the remote hypothesis that all the reported cases were actual and clinically relevant HPA axis suppression events (a fact that is currently not supported by evidence), the probability of clinical HPA occurrence is indeed very low; this conclusion is shared.

The risk of impact on sexual or growth maturation of topic corticosteroid of mild potency is very low and some studies have explored this issue for children taking corticosteroid for skin conditions. Since there are no clear signs of HPA axis suppression, except for the reversible biochemical findings at the ACTH test, and since the glucocorticoid potency of clascoterone/metabolism is considered low/mild, it is deemed highly unlikely that clascoterone can exert any clinically relevant action on sexual or growth development, especially considering that the current proposed indication is from 12 years and above.

To corroborate further this argumentation, it can be useful to consider the narratives of the few events of alteration of sexual function described during the clinical trials; from these narratives no clear relationship emerges between clascoterone and alterations of sexual physiology. Besides the fact that, in most cases, the time of onset of the AE described is very close to the start of the treatment, it should be considered that

patients with acne often suffer from (systemic) hyperandrogenism: thus, it is expected that many female subjects with acne experience various degrees of sexual dysfunction (e.g. dysmenorrhea, amenorrhea, etc) as result of systemic hyperandrogenism. It is considered very likely that the explanation for the reported cases of sexual dysfunction in subjects with acne treated with clascoterone in the clinical trials and in the post-marketing setting is the underlying hyperandrogenism associated with the disease condition, and not treatment with clascoterone. Moreover, only on a theoretical ground, having clascoterone anti-androgenic effects, it *per se* should be beneficial, in a context of an underlying hyperandrogenism.

Importantly it should be noted that in clinical practice, also in patients treated with more potent systemic corticosteroids, there is no recommendation (see ESE guidelines) to perform ACTH test in absence of signs/symptoms to assess HPA axis function. Indeed, the common practice of tapering off the corticosteroid dosage is considered sufficient to restore the HPA axis to its full function from the suppression that inevitably occurs any time supraphysiologic dosages of corticosteroid are administered. Tapering is generally not required for short-term use of low-potency steroids on limited areas, and it should be noted that, in the previous CHMP assessment, it was not deemed necessary, in the adult population, to foresee any kind of biochemical test (let alone the ACTH test) nor any kind of tapering of the treatment.

In summary, the Applicant performed two Phase 2 studies to assess the possibility of HPA axis suppression, one study in adults and adolescents of 12 to <18 years of age and one study in paediatric patients 9 to 12 years of age, by measuring blood cortisol levels at 30 minutes after an ACTH test. Notably, supratherapeutic dosages of clascoterone 1% cream were used for a short duration of 2 weeks. The results showed, in a minority of patients (5% of adults, 9% of adolescents and 14.8% of children 9-12 years old), borderline biochemical evidence suggestive of some degree of HPA axis suppression. Importantly, none of the involved patients had any clinical sign/symptom or other laboratory finding consistent with clinically relevant HPA axis suppression. Moreover, no medical intervention was performed, and the biochemical findings spontaneously normalised after 4 weeks of treatment suspension (at a new ACTH test). Considering also methodological issues associated with ACTH assay used and that the Applicant did not perform a second cortisol dosage 60 minutes after the ACTH administration (as advised in the ESE guidelines and usually performed in clinical practice), the most likely interpretation is that the observed borderline biochemical changes are a transient asymptomatic finding of no clinical relevance. Even if the two dedicated studies were short-term, the long-term open label extension study (CB-03-01/27) did not identify any case of clinically relevant HPA axis suppression, thus reassuring also on the long-term treatment. The remaining uncertainties regarding long-term safety can adequately be addressed through the proposed conditions of use and risk minimisation measures.

Considering all the above together with Guidance on Risk Management Plan (RMP) in the EU (*EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.21),* evidence is currently considered insufficient to conclude that observed laboratory cortisol abnormality is consistent with clinically relevant HPA axis suppression, and that, consequently, this latter should be considered an important potential risk (and not identified) for clascoterone 1% cream (see response to Ground 3).

Consistently, in Winlevi's SmPC, at the section 4.8 ADR table, the preferred term "*ACTH stimulation test abnormal*" with frequency "Common" under SOC "*Investigations*" has been proposed by CHMP instead of "*HPA axis suppression*" with frequency "Unknown" under SOC "*Endocrine disorders*''. "*ACTH stimulation test abnormal*" indeed is the most appropriated since no clinical events have been observed compatible with the reported biochemical changes in study 171-7151-202 or in pivotal studies (see Ground 3).

In its intended use, clascoterone has high safety margins

The Applicant argues that the cumulative dataset supports the contention that the systemic absorption of clascoterone is negligible and that the true risk of HPA axis suppression is very low. This position was also unanimously agreed by the AHEG. However, any residual risk of HPA suppression should be assessed according to relative glucocorticoid potency of the medicinal product, especially when used extensively, for long durations, or in more vulnerable populations (see above response to Ground 2).

The Applicant proposes a revision of the SmPC to include two risk minimisation measures in adolescents that foresee: 1) a lower maximum daily dose (2 g = 4 fingertip units daily), which provides a safety margin of 4 to 6 fold as compared to the doses used in the maximum-dose HPA suppression studies where laboratory values indicative of HPA axis suppression were observed (studies CB-03-01/28 and 171-7151-201), and 2) the restriction of treatment to the face only.

Applying a principle of precaution, this can be endorsed, as higher daily dose and larger surface area of application - aside from duration of treatment - are both established risk factors for HPA axis suppression for topical glucocorticoids. In addition, other precautionary measures are considered necessary by the CHMP and the PRAC in the PI and RMP.

In relation to **Ground #2**, the Applicant presents wide-ranging arguments concerning the safety profile of clascoterone 1% cream when used in adolescents, particularly addressing the concerns raised by the CHMP related to HPA axis suppression and potential long-term developmental effects (growth, sexual maturation). The Applicant states that there is very low risk of HPA axis suppression and negligible chance of clinical adverse effects. Argumentations to support this include the product's minimal systemic absorption, clascoterone's inherently low glucocorticoid potency, and the strict limitations on both dosage and treatment area as specified in the product usage instructions. Together, these elements result in a risk of clinically relevant HPA axis suppression in adolescents treated with clascoterone that is at highest similar to the risk of patients treated with hydrocortisone, and considerably lower to the risk of clobetasol (both well-known topical corticosteroids).

Expanding on its position, the Applicant asserts that the theoretical risks of growth impairment and gonadal axis disruption are not substantiated by the available body of scientific literature, clinical trial data, and post-approval surveillance. Clinical studies, including long-term use, have not shown any cases of impaired sexual maturation or growth in adolescents treated with clascoterone. Menstrual disorders reported during studies and after marketing were rare, non-serious, and not clearly linked to the drug. As the frequency of these AEs were lower than what is typically seen in females with acne, the underlying hormonal imbalances commonly associated with acne are likely responsible for these issues.

Therefore, the Applicant maintains that the safety profile observed in studies strongly supports the conclusion that such effects are highly improbable, if not virtually impossible, under recommended conditions of use. Furthermore, they emphasize that concerns about these potential outcomes are speculative in nature rather than being anchored in empirical observations or scientific consensus.

It is agreed with the Applicant that clascoterone's reduced potency, combined with the need for metabolic conversion, underpin the low risk of significant systemic glucocorticoid effects, when the medicinal product is used as according to conditions for use. Indeed, clascoterone's glucocorticoid effect is mediated through its metabolite, cortexolone (11-deoxycorticosterone). For cortexolone to fully manifest glucocorticoid activity, it must be enzymatically converted in the adrenal cortex by 11β-hydroxylase into cortisol (hydrocortisone). Pharmacological in vitro data showed that the glucocorticoid receptor was activated with 4 to 100 times lower potency by cortexolone compared to cortisol (Engels M, 2019).

Nevertheless, the use of glucocorticoids, whether systemic or topical, particularly when applied to large body areas, for prolonged periods, at high doses, or with high glucocorticoid activity, can lead to iatrogenic endocrine disorders, such as suppression of the HPA axis and of the hypothalamic-pituitary-gonadal axis. It is known that the risk of HPA axis suppression is higher in children, and although systemic absorption of cutaneous clascoterone and its main metabolite cortexolone, is negligible, there could be individual factors (e.g. use over large surfaces, prolonged use, occlusive applications, genetic predisposition) that may contribute to an increased systemic exposure. However, indication for Winlevi in children aged under 12 years is not sought, and for adolescents treatment is limited to the face with the SmPC advising against misuse.

To frame the risk of endocrine adverse events within the well-known treatment scenario of topical glucocorticoids, information available for nationally authorised creams, such as hydrocortisone, the reference standard for comparing the potency of other glucocorticoids, and clobetasol can be used. Hydrocortisone 1% cream, a low-potency corticosteroid but considered more potent than clascoterone (by in vitro and in vivo comparative data), when used at a small amount of 20 mg/day (140 mg/week) for mild, localized inflammatory skin conditions is associated with a very low risk of HPA axis suppression events. In the SmPC of hydrocortisone 1% cream the frequency of HPA axis suppression risk is classified as Very rare (<1/10,000). Clobetasol propionate 0.05% cream, instead, a very potent topical corticosteroid is used in adolescents ⩾12 years old with severe, localized, steroid-responsive dermatoses that have failed lower-potency treatments, but only short-term (maximum 2 weeks), on thick skin, and under close supervision as at high risk of clinically relevant adrenal suppression. The risk of HPA suppression is increased with use of >50 g/week of clobetasol (equivalent to 30 g/week of hydrocortisone). In the nationally authorised SmPC of products containing clobetasol for topical use (cream, shampoo) the adverse event is grouped as Uncommon (⩾1/1,000 to <1/100) or Very rare (<1/10,000). Based on the above, it is concluded that the risk of HPA suppression associated with use of topical glucocorticoids is strictly related to the potency of the substance and to the product's instructions for use. Winlevi has a low-potency corticosteroid activity that for use in adolescents can adequately be managed with posology recommendations (Winlevi 1% cream 2 g/day corresponding to 20 mg/day of clascoterone), indications for use (treatment of facial acne vulgaris only), and clinical monitoring.

In general, chronic suppression of gonadal hormone production through disruption of the HPG axis could lead to hypogonadism, menstrual irregularities, reduced libido, and infertility. When evaluating clinical evidence on adverse events related to growth and sexual maturation, it is noted that during clinical development of clascoterone and Winlevi's post-approval surveillance no growth-related AEs were reported, and only non-serious sexual and menstrual disorders have been submitted. However, current clinical and pharmacological evidence does not establish a causal relationship, as the available data indicate that reported menstrual disorders in Winlevi users are within or below expected background rates for women with acne, a group already at increased risk due to higher frequency of underlying systemic hyperandrogenism. Published literature supports the notion that menstrual irregularities and acne frequently co-occur, often because of underlying hyperandrogenism and Polycystic Ovary Syndrome. While there is no evidence of a causal relationship between clascoterone and menstrual disorders in female adolescents with acne, this patient population—particularly those with menstrual irregularities related to androgen excess—might otherwise benefit from anti-androgenic therapy. However, clascoterone has negligible systemic absorption, making such systemic hormonal effects unlikely.

Non-clinical data are aligned with clinical findings showing that clascoterone does not significatively bind GnRH receptors and lacks estrogenic or off-target receptors activity, with minimal risk of direct interference with hypothalamic–pituitary axis. The repeat dose toxicology studies in adolescent-equivalent animal models,

did not demonstrate growth impairment or delayed sexual impairment at clinically relevant exposures. However, as expected, at supratherapeutic doses adrenal cortical atrophy is observed suggesting the potential for systemic endocrine effects at high doses or prolonged use (See response to Ground 1).

In summary, current evidence indicates that clascoterone 1% cream poses minimal risk of significant endocrine effects in adolescents when used as directed, with safety precautions and clinical guidance adequately addressing any potential concerns. Long-term clinical consequences of hormone imbalance, such as growth and sexual maturation impairment, are highly unlikely and should not represent a concern in clascoterone 1% cream use in adolescents.

With regards to **Ground #3**, it is acknowledged that pre-clinical and clinical data do not provide sufficient evidence about the risk of HPA axis suppression, and no clinical events have been observed compatible with the reported biochemical changes in study 171-7151-202 or in pivotal studies. Further, the very limited number of post-marketing cases reported does not add any conclusive information.

As robust evidence on clinical relevance of the observed laboratory changes is lacking and in accordance with the GVP V on RMP, the risk of HPA axis suppression should be considered as an important potential risk. This is agreed by the PRAC and CHMP. It should be noted that the potential risk of HPA axis suppression with Winlevi was considered low by the experts of AHEG.

Considered the limited evidence supporting a risk of a clinically relevant HPA axis suppression resulting from responses to Grounds #1 and #2, the conduction of a clinical trial on adolescents with acne prior to authorising clascoterone in this population is deemed not necessary by the CHMP as clinical data on this age group have already been collected in pivotal and long-term extension studies.

Besides the routine risk minimisation measures proposed by the Applicant to address the potential risk of HPA axis suppression particularly in adolescents (e.g. treatment of the face only, max two fingertip units of cream twice a day every almost 8 hours, Winlevi's presentation in tubes containing 10 g, 30 g or 60 g cream which enables effective oversight of its proper application of 2 g/day in adolescents allowing a maximum treatment duration of 1 month, avoidance of occlusive dressing – all measures aimed at minimising the risk of systemic exposure in a population more susceptible to clinically relevant HPA-axis suppression), the CHMP and PRAC considered necessary the implementation of additional RMMs. Dose adjustment according to age is part of standard clinical practice for the majority of medicinal products indicated in both paediatric and adult populations and is considered appropriate in the context of risk minimisation of potential risk.

Further, both PRAC and CHMP Rapporteurs are of the opinion that restricted medical prescription should be implemented, and that treatment should be initiated and supervised by a physician with experience in diagnosis and treatment of acne vulgaris. This approach can allow for flexibility in line with the variations across national healthcare systems.

The AHEG agreed that a first follow-up after 3 months and regular assessments every 3 months are needed for both adults and adolescents; in adolescents the first evaluation visit after 1 month can be optional depending on the patient's adherence to treatment and/or safety considerations. Accordingly, a wording has been added in section 4.2 of the SmPC. This recommendation is consistent with existing European and US clinical guidelines for the treatment of acne vulgaris, which suggest quarterly monitoring of both systemic and topical treatments for the entire treatment duration.

However, since it cannot be excluded that adolescent patients will apply an amount of cream higher than 2 g/day considering the social impact of the disease, additional risk minimisation measures are proposed by

PRAC. Relying solely on tube size does not sufficiently address the concern, as it does not prevent intentional or accidental overuse.

Further, to ensure a timely, accurate diagnosis and optimal management of adrenal insufficiency, and to improve patient outcomes and prevent potentially life-threatening events, it is considered necessary to introduce the following warning in section 4.4 of the SmPC; if adrenal insufficiency is suspected, morning serum cortisol levels could be measured and patient may be referred for endocrinological evaluation; treatment should be interrupted if HPA axis suppression is confirmed.

At this stage, educational materials for HCPs are deemed necessary to improve awareness about the risk of HPA axis suppression and treatment compliance recommendations. The provision about educational material for prescribers also finds support in the European Society of Endocrinologists guidelines which highlight the importance of providing appropriate information, especially to the patient, to understand the actual risk of HPA axis suppression and how to manage it. As this is a first-in-class medicine, the PRAC agreed on the need for an HCP checklist to support HCPs in delivering key instructions on the correct use of the product and raise awareness on the potential risk of HPA axis suppression. The PRAC also agreed that the HCP checklist should highlight the need to actively inform patients of the contraindication during pregnancy, to ensure that pregnancy status is verified before starting treatment and on the recommendation to use appropriate contraception method(s). Key elements for the HCP checklist are indicated in Annex II.

In conclusion, the following set of routine RMMs has been agreed by the CHMP in the product information to mitigate the important potential risk of HPA-axis suppression.

For adolescents and adults:

- Medicinal product subject to restricted medical prescription to medical doctors with experience in the diagnosis and treatment of acne vulgaris
- Clinical evaluation to assess safety and compliance (every 3 months of treatment)
- Avoidance of occlusive dressing
- If adrenal insufficiency is suspected, morning serum cortisol levels could be measured and patient maybe referred for endocrinological evaluation, and treatment should be interrupted in case HPA axis suppression is confirmed
- "Instruction for use" in the PL with clear instructions supported by images and illustrations, to guide correct dosing and application, particularly for adolescents (fingertip unit and face only)

Further minimisation measures for adolescents only:

- Restriction of therapeutic indication (limited to the face)
- posology (max two fingertip units of cream twice a day corresponding to 2 g daily vs 5 g in adults)
- No more than 60 grams a month should be used (corresponding to one 60-gram tube or two 30-gram tubes)
- physician may decide to conduct the first evaluation visit earlier than 3 months, depending on the patient's adherence to treatment and/or safety considerations)

Finally, the risk of HPA axis suppression with long-term use of Winlevi in adolescents should, if feasible, be further characterised through a post-marketing safety study (PASS) whose main objective is to evaluate the potential risk of HPA axis suppression with long-term use of Winlevi in adolescents, including incidence,

impact on growth and sexual maturation, and identification of risk factors. This is agreed by the CHMP. The Applicant should submit a feasibility assessment within 3 months of EC decision accordingly.

In order to identify any differences in terms of development, sexual maturation and growth, as well as different sensitivity to iatrogenic effect of glucocorticoids relating to the risk of HPA axis suppression which would impact the benefit/risk profile, adolescent subgroup analyses were provided: 12 to 14 years of age (puberty) and 15 to <18 years of age (post-puberty). The only relevant difference observed was the two cases of ACTH stimulation test abnormal in two female patients in the 12-14 year cohort vs none in the older age cohort (study 171-7151-202). It should be noted that the two female patients were 14.7 and 14.8 year-old, thus borderline between the two age subgroups. This finding together with the fact that the incidence of ACTH stimulation test with clascoterone was even higher in children <12 years of age (Study CB-03-01/28), may support the hypothesis that susceptibility to HPA axis suppression might be more frequent in younger subjects due to a thinner skin barrier, higher surface area-to-body weight ratio, and immature HPA axis, all of which may increase systemic absorption. Thus, the addition of the sentence in SmPC section 4.4 that "the paediatric population may be at increased risk of HPA axis suppression'' is warranted.

5.2. Risk Management Plan

5.2.1. Safety concerns

Important identified risks	• None
Important potential risks	• Hypothalamic-pituitary-adrenal (HPA) axis suppression • Reproductive toxicity
Missing information	• None

5.2.2. Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Study ID: CB-03-01/43 **Title:** Post-marketing safety study to characterise the potential risk of HPA axis suppression with long-term use of Winlevi in adolescents. (Planned)	**Part A:** To assess the feasibility of relevant data sources suitable for evaluation of the potential risk of HPA axis suppression with the use of clascoterone for facial acne vulgaris in adolescents. **Part B:** Execution of the chosen study design following the feasibility assessment.	Potential risk of HPA axis suppression in adolescents	Submission of feasibility assessment Protocol to be completed Interim reports Final study report	3 months after EC Decision on Winlevi Subject to feasibility Defined within the specific post-marketing procedure Within one year of the end of data collection

5.2.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypothalamic-pituitary-adrenal (HPA) axis suppression	**Routine risk minimization measures:** SmPC Section 4.1 and 4.2 recommend that, in adolescents, the use of clascoterone cream must be limited to the face. SmPC Section 4.2 states that in adolescents, the total daily dose should not exceed four (4) fingertip units (corresponding to approximately 2 g of 10mg/g clascoterone cream). A warning that the application must be done without using occlusive dressings is included in Section 4.2 of the SmPC. Sections 4.4 and 4.8 of the SmPC include a warning of HPA axis suppression with potential risk factors and symptoms and recommendation to consider measuring morning serum cortisol levels if HPA axis suppression is suspected and referring the patient for endocrinological evaluation. Treatment should be interrupted if HPA axis suppression is confirmed. A recommendation to patients is included in Section 2 of the PL, not to use Winlevi over large areas of skin for a long time or cover the area with a bandage or dressing, as this can increase the risk of developing adrenal suppression and to stop treatment if feeling unusually tired or unwell when using and to discuss with doctor. The doctor could consider to test the patient's blood cortisol levels and to refer them to an endocrinologist. Pack size is limited to 60 grams maximum, corresponding to approximately one month of treatment for adolescents. **Additional risk minimisation measures:** Healthcare professional checklist	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CB-03-01/43 Post-marketing safety study to characterise the potential risk of HPA axis suppression with long-term use of Winlevi in adolescents. (Planned) Final study report: Within one year of the end of data collection.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Reproductive toxicity	**Routine risk minimisation measures** SmPC section 4.3 includes a contraindication during pregnancy and Section 4.6 states that women of childbearing potential have to therefore use an effective contraceptive method during treatment with Winlevi and for at least 10 days after the last dose. Additionally, in section 4.4 it is specified the warning on the pregnancy status of women of childbearing potential that should be verified prior to initiating treatment with clascoterone. A recommendation to patients in Section 2 of the PL to ask their doctor for advice if pregnant or planning a pregnancy and to use birth control while using Winlevi and for at least 10 days after stopping treatment. **Additional risk minimisation measures:** Healthcare professional checklist Patient card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

5.2.4. Conclusion

The CHMP considered that the risk management plan version 0.11 is acceptable.

5.3. Pharmacovigilance

5.3.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

5.3.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 26.08.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

5.4. Product information

5.4.1. User consultation

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

5.4.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Winlevi (Clascoterone) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

5.5. Other considerations

The timelines for the ERA studies have been revised by the Applicant during the re-examination. Given the current lead times of 8–12 months for initiating the Fish Life Cycle Toxicity Test (FLCTT) and an additional 14 months estimated from test initiation to draft report, the full completion of the ERA testing is now estimated for 2028 which is agreed by the CHMP.

The timelines for the DDI study with oral contraceptives have been revised by the Applicant during the re-examination. No drug-drug interaction studies have been conducted with clascoterone cream. Risk of cumulative adverse reactions with other topical or systemic acne treatments, in particular anti-androgen treatment (off-label spironolactone or combined oral contraceptive) cannot be ruled out and can induce several side-effects, such as loss of libido, impairment of spermatogenesis, feminizing effects, and impairment of liver function. The following revised study timelines are agreed by the CHMP.

- Study design and protocol finalization: within end of April 2026
- Submission of the Clinical Trial Application to Competent Authority: within end of June 2026
- Study conduct (FPI – LPO): October 2026 to January 2027
- Final CSR: within June 2027.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

Acne vulgaris is a chronic inflammatory skin condition of pilosebaceous glands that typically begins at puberty and may continue through adulthood with flares often coinciding with increasing serum androgens (Arora, 2011; Taylor, 2011). It is one of the most common dermatological disorders worldwide (AAD, 2019) with its incidence and severity influenced by genetics and environment (Arora, 2011).

The condition commonly manifests with papules, pustules, or nodules primarily on the face, although it can also affect the upper arms, trunk, and back. Its primary lesion is known as "comedo". The severity of this condition can vary, ranging from a mild presentation with only a few comedones to more severe forms characterized by disfiguring inflammatory manifestations, which can lead to hyperpigmentation, scarring, and adverse psychological effects (Sutaria, 2023).

Acne vulgaris affects approximately 9% of the population worldwide and approximately 85% of those aged 12 to 24 years (Eichenfield, 2021). Acne is often the first sign of puberty in boys and girls, and this onset is thought to be secondary to hormonal surges leading to increased sebum production (Goldberg, 2011). Although the prevalence of acne is highest in adolescents and young adults, it can also occur in younger children. However preadolescent acne is a rare disease, affecting only 3.5% of patients (Frénard, 2021).

6.1.2. Available therapies and unmet medical need

The treatment armamentarium for acne vulgaris includes both topical and systemic products. Treatments target one or more of the primary pathogenic factors: sebaceous gland hypersecretion stimulated by androgen production, bacterial proliferation, and abnormal keratinization with resultant follicular obstruction and inflammation.

Numerous formulations of topical preparations include creams, gels, lotions, solutions, and washes. Skin irritation is a common side effect of topically administered anti-acne medications. Topical treatment may last 6–8 weeks or continue for many years. For the management of severe acne, the European guidelines recommend combining a topical therapy with a systemic therapy (M. Vasam et al, 2023).

For mild to moderate acne, both AAD (American Academy of Dermatology) and European Dermatology Forum (EDF) guidelines recommend topical monotherapy or combination treatments (e.g., benzoyl peroxide, retinoids, or topical antibiotics), favouring multi-mechanism approaches and limiting systemic antibiotic use. Both the AAD and the EDF recommend oral isotretinoin as first-line treatment for severe acne due to its ability to target all major pathogenic factors. When isotretinoin is not suitable, both guidelines support combination therapy with oral antibiotics, benzoyl peroxide, and topical retinoids. The European guidelines additionally recommend hormonal therapies (e.g., oral contraceptives) for female patients with signs of androgen excess. The 2024 AAD Acne Guidelines offer a conditional recommendation for the use of topical clascoterone cream 1% in patients aged 12 and older with acne vulgaris, as part of a multimodal topical regimen that addresses multiple pathogenic pathways while considering its cost and accessibility. The use of topical and systemic antibiotics in acne treatment contributes to the development of antimicrobial resistance

(AMR), particularly involving *Cutibacterium acnes* and other skin flora. Prolonged or inappropriate antibiotic use can lead to reduced treatment efficacy and cross-resistance to other bacterial pathogens

Available pharmacological treatments include oral administered contraceptives, spironolactone (with antiandrogen properties) and isotretinoin. Spironolactone does not currently have a formal indication for acne treatment in most countries, both hormonal therapy and spironolactone are not indicated for male patients, and not all men are candidates for isotretinoin. Isotretinoin should be used with caution in patients with history of depression, anxiety, or mood disorders, more prevalent or unrecognized in adolescents, and requires frequent monitoring (liver function, lipids, pregnancy test). As for clascoterone, isotretinoin is teratogenic and requires strict pregnancy prevention programs, which can be challenging in adolescents.

In this scenario, topical androgen-targeted treatments may be appropriate for both male and female patients with acne who prefer to avoid systemic therapy or require localized treatment, such as adolescents.

In summary, while the therapeutic arsenal for acne vulgaris includes both topical and systemic options, many of the currently available treatments present limitations related to contraindications, adverse effects, the need for close monitoring, or limited patient acceptability. These constraints contribute to an unmet medical need, particularly in specific patient populations such as males and adolescents or individuals requiring androgen-targeted therapy but for whom systemic exposure is not desirable.

Clascoterone, a First-in-Class medicine, may help address this gap by offering a topical alternative that is mechanistically aligned with systemic hormonal therapies—acting as an androgen receptor inhibitor—while providing localized action without systemic hormonal side effects. It may also be suited for use as part of a multimodal therapeutic approach.

6.1.3. Main clinical studies

Clinical evidence was based on two Pivotal Phase 3 studies CB-03-01/25 and CB-03-01/26, multicentre, randomized, double-blind, vehicle-controlled, parallel-group comparison studies of the safety and efficacy of CB-03-01 cream, 10 mg/g applied twice daily for 12 weeks in male and female subjects, 9 years of age or older with moderate to severe acne vulgaris on the face.

Eligible subjects must have acne vulgaris of the face (which can include the nose) with an Investigator's Global Assessment (IGA) score of 3 or 4, at least 30 to a maximum of 75 inflammatory lesions (papules, pustules, and nodules), and at least 30 to a maximum of 100 non-inflammatory lesions (open and closed comedones).

The 3 co-primary Efficacy endpoints were (hierarchical) at week 12:

- P1: Proportion of subjects in each group achieving "success" defined as an IGA score of "clear (score=0)" or "almost clear (score=1)" AND at least a two-point reduction in IGA compared to Baseline.
- P2: Absolute change from Baseline in Non-inflammatory Lesions Count (NILC) in each group
- P3: Absolute change from Baseline in Inflammatory Lesions Count (ILC) in each group.

The secondary efficacy endpoints were (hierarchical) at week 12:

- S1: Absolute change from Baseline in total lesion count (TLC) in each group
- S2: Percent change from Baseline in TLC in each group
- S3: Percent change from Baseline in NILC in each group
- S4: Percent change from Baseline in ILC in each group

6.2. Favourable effects

The efficacy endpoints used in pivotal Phase 3 studies conducted in adult, adolescent and paediatric patients showed the superiority of clascoterone cream applied twice daily on the face versus vehicle after a 3-month period of treatment:

- "success" (Proportion of subjects with a ≥ 2-point reduction in IGA and IGA score of 0 or 1) was 19.5% for clascoterone group compared to 7.7% for vehicle group (p<0.0001)
- absolute change from baseline of non-inflammatory lesions count was -19.3 vs -11.8 (p<0.0001)
- absolute change from baseline of inflammatory lesions count was -19.8 vs -13.9 (p<0.0001)
- in moderate acne, the repeated analysis of the IGA success with logistic regression showing an efficacy for clascoterone of 21.3% vs vehicle 8.9% as pooled data, i.e. 12.4% of absolute difference;
- a new analysis of IGA responders (patients achieving an IGA score of 0 or 1 and at least 2-point reduction in IGA) among the European patients with moderate acne (IGA=3 at baseline), with results of 26.2% for clascoterone vs 8.5% for the vehicle, i.e. 17.7% of absolute difference.

Open-label long-term follow-up study shows an increased effect over time, that however seems not to differ from vehicle.

Adolescents (12-<18 years) are part of the applied indication and represented 44.5% (n=641) of the total study population in pivotal studies (n=1440). Analyses of IGA score with at least 2-point reduction and a score of 0 or 1 at 12 weeks showed a marginal effect of clascoterone in adolescents (14.9%). The beneficial effect of clascoterone over placebo was confirmed for both the adolescent age subsets (12-14y and 15-18y, pooled from two studies).

In the re-examination, the Applicant has proposed to restrict the indication in adolescents to the face.

6.3. Uncertainties and limitations about favourable effects

The claimed new mechanism of action could not be fully elucidated to ensure that clascoterone has a peripheral anti-androgenic effect only.

The effect of clascoterone cream on acne vulgaris is considered modest (19.5% from pooled data) in both pivotal studies. The absolute changes in NILC and ILC are also considered limited. However, it is recognised that the effect has been satisfactorily demonstrated compared to vehicle based on the primary endpoint (IGA score 0 or 1).

The follow-up study including subjects from the 3-month pivotal studies and treated for an additional 9-month period aimed giving safety data. Thus, efficacy beyond 3 months is poorly documented and makes difficult interpretation of results concerning the long-term effect.

Evaluation of clascoterone on the trunk is also poorly documented. Only percentage of patients with IGA score 0 or 1 issued from the open-label study were provided: 40.2% (Investigator's last assessment) and 59.2% (at 9 months).

A potential rebound effect has not been evaluated during the clinical studies. As clascoterone has glucocorticoid properties, an exacerbation could be expected at the time of treatment discontinuation with a reactivation of lesions with greater intensity than their pre-treatment state. A warning advising on caution and seeking medical advice in these cases or considering other treatment options was recommended.

6.4. Unfavourable effects

The main unfavourable effect of clascoterone when given at supratherapeutic doses is "ACTH-stimulation test abnormal", suggesting potential HPA axis suppression.

Clascoterone is supposed to be hydrolysed into the skin to cortexolone, a physiological component of the pool of endogenous corticosteroids, an intermediate in the synthesis of glucocorticoid steroids. HPA axis suppression was studied in two Phase 2 studies at doses that were ~5-6-fold higher than the dose used in pivotal Phase 3 studies. Perturbations were observed in some patients with clascoterone at supratherapeutic doses for 2 weeks. Seven subjects (7/69, 10%) had abnormal cosyntropin stimulation tests at D14. Although abnormal ACTH test results were just below the lower limit, the frequency of abnormal results seems inversely correlated to age (5% of adult subjects, 9.1% of adolescent subjects, and 14.8% of paediatric subjects 9-11 years). ACTH test results normalised in all subjects 4 weeks after stopping the clascoterone cream. In both studies, the apparently blunted HPA axis response was not associated with clinical signs or symptoms.

A few cases (n=4, 2 adults and 2 of unknown age) of serious 'Adrenal suppression' and 'Hypothalamic pituitary adrenal axis suppression' were reported post marketing in USA, where clascoterone cream is marketed since 2020, however causal relationship could not be established.

No growth-related AEs were reported, and only non-serious sexual and menstrual disorders have been submitted during clinical development or post-marketing of clascoterone. A causal relationship could not be established, as the available data indicate that reported menstrual disorders in Winlevi users are within or below expected background rates for women with acne.

The level of evidence is currently considered insufficient to conclude that observed laboratory cortisol abnormality is consistent with clinically relevant HPA axis suppression. This is corroborated by the AHEG's view. In accordance with the definitions of the GVP, the risk of HPA axis suppression has been re-classified as potential risk during the re-examination.

Given that only post-stimulation serum cortisol test results were reported close under the lower limit (18 µg/dL) with no signs and symptoms compatible with adrenal insufficiency, the preferred term "*ACTH stimulation test abnormal*" with frequency "Common" under SOC "*Investigations*" has been implemented instead of "*HPA axis suppression*" with frequency "Unknown" under SOC "*Endocrine disorders*'' in the ADR table in section 4.8 of the SmPC.

Local skin reactions (LSRs) are also observed: oedema, erythema/redness, pruritus, scaling/dryness, skin atrophy, stinging/burning, striae rubrae, telangiectasia. The excipients cetyl alcohol and propylene glycol may also cause local skin reactions. The proportion of subjects in clinical trials experiencing these local skin reactions was similar between the treatment groups. The intensity of each LSR during the studies was no or trace/mild for most subjects. The most common treatment-emergent LSRs were erythema, scaling/dryness, and pruritus. New or worsening LSRs after day 1 that were more reported in clascoterone group than in vehicle group, in Pool A, were Striae Rubrae (2.4% vs 1.4%), Oedema (3.5% vs 3.2%), and Scaling/Dryness (10% vs 9.5%). Three clascoterone-treated subjects reported hypersensitivity of mild or moderate intensity. One of these subjects was discontinued from the study due to this event. These events all resolved without intervention.

Reproductive toxicity has been observed in animal studies administered subcutaneously. Based on these findings and the drug's mechanism of action as an androgen receptor inhibitor, clascoterone may pose a risk of fetal harm. Clascoterone is therefore contraindicated during pregnancy and pregnancy status of women of

childbearing potential should be verified prior to initiating treatment with clascoterone. The exclusion of a potential pregnancy prior to initiating treatment with Winlevi is considered an essential measure, particularly in adolescents. In this population, the physiological menstrual irregularity typical of puberty necessitates an objective confirmation of non-pregnancy before starting therapy.

Clastogenic effect (aneugenic with a threshold of 50 µg/mL) has also been identified in in vivo male rat micronucleus test following subcutaneous administration. Considering the >100-fold margin identified at the NOEL with a threshold genotoxicity mechanism, in accordance with «SWP/NcWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug (EMA/CHMP/SWP/74077/2020 rev. 1*), clascoterone could be considered as an active substance «whose mechanism of genotoxicity is known to have a threshold which is not expected to be attained in patients ». Consequently, contraception during the treatment period and continued for up to 5 elimination half-lives, or 10 days is required for women of childbearing potential to prevent exposure during pregnancy. Reproductive toxicity is listed in the RMP as important potential risk.

6.5. Uncertainties and limitations about unfavourable effects

Regarding the risk of HPA axis suppression, uncertainties on unfavourable effects are grounded on limited data on the clascoterone systemic absorption/accumulation potential in adolescent patients where data are available only at 2 weeks of treatment. Nonetheless, supratherapeutic doses of clascoterone in adolescent patients induced a Cmax at steady state still 20-fold lower the IC50 on human androgen receptor.

A few cases of suspected endocrine adverse events were reported within post-marketing surveillance in the US, where clascoterone cream is marketed since 2020. However, causal relationship between the medicinal product and the adverse event could not be established. Moreover, many female subjects with acne also have systemic hyperandrogenism, explaining a higher background rate of menstrual disorders.

Taking into account the effects of anti-androgenic drug on mood disorders, the risk of depression, which is not considered important at this stage, cannot be ruled out during long term treatment. However, current clinical data do not support a causal relationship with clascoterone and this risk is considered as theoretical at this stage. This will be followed up via routine PV.

There are no adequate data on the use of clascoterone in pregnant and breastfeeding women. Clascoterone induced fetal malformations at all subcutaneous dose levels tested in rats and postimplantation loss and embryotoxicity at non-maternotoxic doses in rabbits. Although systemic absorption of cutaneous clascoterone and its main metabolite cortexolone, is negligible, there could be individual factors (e.g. use over large surfaces, prolonged use) that may contribute to an increased systemic exposure. Moreover, based on its mechanism of action (androgen receptor inhibition), WINLEVI can cause foetal harm. Considering all the above and the genotoxicity potential of clascoterone, the medicine is contraindicated during pregnancy. Women patients of childbearing potential should use an effective contraceptive method during treatment and for 10 days after the last dose (see SmPC).

There is no data on exposure during breastfeeding.

Although clascoterone up to 5 mg/mL cream (50 mg/g) was not carcinogenic after daily topical administration in a 2-year rat carcinogenicity study, benign sebaceous cell adenomas in male rats occurred at 50 mg/g and were considered test article related.

6.6. Effects Table

Table 32: Effects Table for Winlevi for the treatment of acne vulgaris in adults and adolescents (face only)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Refs
Favourable Effects						
Lesion clearance at week 12	Proportion of subjects with a ≥ 2-point reduction in IGA and IGA score of 0 or 1	N (%) Adjusted proportion Point estimate	N=126 (17.5%) 19.5% 2.9	N=42 (5.8%) 7.7%	p<0.0001 in both pivotal studies, sensitivity analyses showed similar results. Clinically relevant outcome.	Pooled data from Phase 3 Studies CB-03-01:25 and /26
	Absolute change from baseline in NILC	LS mean Point estimate	-19.3 -7.5	-11.8		
	Absolute change from baseline in ILC	LS mean Point estimate	-19.3 -5.9	-13.9		
Unfavourable Effects						
LSR	Treatment-Emergent (New or Worsening) Local Skin Reactions After Day 1)	N	687	662	LSRs were observed during the 12-week treatment and occurred in a similar percentage of subjects treated with vehicle. The excipients cetyl alcohol and propylene glycol may also cause LSRs.	Pool A
	- erythema	N (%)	84/687 (12.2%)	101/662 (15.3%)		Pool A
	- scaling and dryness	N (%)	72/687 (10.5%)	68/662 (10.3%)		Pool A
	- pruritus	N (%)	52/687 (7.6%)	55/662 (8.3%)		Pool A

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Refs
Post-ACTH cortisol abnormal			7/69 (10.1%): 5% (1/20) in adults, 9.1% (2/22) in adolescent, 14.8% (4/27) in paediatric subjects aged 9-11 years	N/A	Post-stimulation serum cortisol test results were close under the lower limit (18 µg/dL). No signs and symptoms compatible with adrenal insufficiency were reported.	Two Phase 2 studies 171-7151-202 and CB-03-01/28 using clascoterone at supratherapeutic dosages

Abbreviations: LSR=local skin reaction; N/A= not applicable

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Favourable effect

Many of the currently available treatments present limitations related to contraindications, adverse effects, the need for close monitoring, or limited patient acceptability. These constraints contribute to an unmet medical need, particularly in specific patient populations such as males and adolescents or individuals requiring androgen-targeted therapy but for whom systemic exposure is not desirable.

Clascoterone is a first-in-class topical anti-androgen that may help fill a current therapeutic gap in acne treatment and offers the potential to be integrated into multimodal treatment regimens alongside agents such as retinoids and benzoyl peroxide to target the multifactorial nature of acne.

In both pivotal studies the co-primary endpoints were statistically met after a 3-month period of treatment. The proportion of responders (defined as the proportion of subjects with a ≥ 2-point reduction in IGA and IGA score of 0 or 1 on a 4-point scale) was 19.5% compared to 7.7% in the vehicle group. In the subgroup of baseline IGA=3, the success rate was 18.9% and 10.4% in IGA=4.

In adolescents, a success rate of 14.9% was found, and efficacy confirmed in subgroups according to age ranges (12-14y and 15-<18y).

The efficacy of clascoterone for the treatment of acne in the claimed indication is considered demonstrated in adults and adolescents from 12 years of age and older.

Unfavourable effect

The unfavourable effect of "ACTH-stimulation test abnormal" associated with clascoterone 1% cream has been observed in dedicated studies conducted with supratherapeutic dosage to evaluate serum cortisol levels

after ACTH stimulation. Overall, <10% of subjects showed borderline cortisol levels when using the cut-off of 18 µg/dL (5% of adult subjects, 9.1% of adolescent subjects): these were interpreted as biochemical signs suggestive of HPA axis suppression. However, clinical data for longer treatment (up to 1 year) are available for a relevant number of adolescents and did not show related endocrine disorder adverse events. Moreover, the few cases of 'Adrenal suppression' and 'Hypothalamic pituitary adrenal axis suppression' reported in the post-marketing period in the US (where clascoterone 1% cream is marketed since 2020) could not establish a causal relationship between the medicinal product and the undesirable effect. Notably, neither in clinical development nor in the post-marketing setting adverse events related to growth or sexual maturation were reported.

The opinion of the expert panel of dermatologists in acne vulgaris and paediatrician endocrinologists during the AHEG meeting significantly contributed to the interpretation of these clinical data. All experts agreed that the risk of HPA axis suppression is low even though certain individuals, for instance, those with a sensitive glucocorticoid receptor can be more susceptible. The group made a clear distinction between adrenal disturbance of the HPA axis due to the treatment and the clinical syndrome of adrenal insufficiency implying that biochemical data abnormal in patients with no clinical signs of adrenal insufficiency should not be regarded in the same way as in patients presenting clinical evidence or symptoms of adrenal insufficiency.

On this point, the European Society of Endocrinology (ESE) guidelines acknowledge that even in the presence of biochemical signs of HPA axis suppression, *"the risk of clinically significant adrenal insufficiency or adrenal crisis remains very low."*

Further, it is not known how well the ACTH test preforms in adolescents with acne being treated with a medicine such as Winlevi. They cannot draw very strong conclusions based on the time-point that the test was done in the Winlevi studies. But overall, the actual results found did not cause alarm. However, the group's opinion was that the ACTH test should be used only for patients with clear clinical symptoms of adrenal insufficiency or for those having evidence of low morning baseline plasma cortisol. The ACTH-stimulation test is not a screening test but a confirmatory test. They clarified that the cortisol thresholds of the ACTH test are usually local as they are dependent of the cortisol assay used, but a stimulated value ≥ 15 mcg/dL or 450 nmol/L indicates a normally functioning HPA axis.

In patients with evident risk factors (such as reduced longitudinal growth during treatment) or mild symptoms of potential adrenal insufficiency (such as nausea early in the morning), morning baseline cortisol should be measured first (in accordance with the joined Endocrine Society and European Society of Endocrinology practice guideline). Plasma cortisol sampling should be done around 8 am and the experts agreed with the threshold of less than 8-10 mcg/dL (220-275 nmol/L) indicating thus the need for further evaluation by endocrinologist with a low-dose ACTH test.

It is therefore considered that the level of clinical evidence is not sufficiently robust to draw firm conclusions on the risk of HPA axis suppression, but it is acknowledged that the risk cannot be ruled out, especially in individuals with a sensitive glucocorticoid receptor.

During the re-examination, a set of routine and additional risks minimisation measures in ensuring the proper use of Winlevi and mitigation of the risk of HPA axis suppression particularly in adolescents were proposed and supported by the AHEG. These were subsequently endorsed by the CHMP as follows.

- Restriction of indication to treatment of facial acne vulgaris;

- Restriction of prescription by a physician experienced in the diagnosis and treatment of acne vulgaris;

- Introduction of a maximum daily dose of 2 g/day (2 Finger Tip Units per application);

- No more than 60 grams a month (corresponding to one 60-gram tube or two 30-gram tubes)

- Cream application without using occlusive dressing;

- Clinical evaluation after the first 3 months of treatment or earlier depending on the patient's adherence to treatment and/or safety considerations, and re-assessment every 3 months of treatment;

- Warning on HPA axis suppression with recommendation to measure morning serum cortisol levels and to refer patients for endocrinological evaluation if adrenal insufficiency is suspected;

- Treatment interruption in case HPA axis suppression is confirmed;

- "Instruction for use" in the PL with clear instructions supported by images and illustrations, to guide correct dosing and application, particularly for adolescents (fingertip unit and face only);

- Implementation of an educational material through HCP checklist to deliver key instructions on the correct use of the product and raise patients' awareness of the potential risk of HPA axis suppression.

Although the experts agreed that the risk of HPA axis suppression is low, they recognised that it is difficult to quantify it, given the wide variability in baseline cortisol levels in adolescents in general and the lack of data on long-term use. A post-marketing safety study (PASS) to further characterised the potential risk of HPA axis suppression with long-term use of Winlevi in adolescents, including incidence, impact on growth and sexual maturation, and identification of risk factors, was recommended by PRAC and agreed by the CHMP. The Applicant should submit a feasibility assessment within 3 months of EC decision accordingly.

Finally, clascoterone at the recommended dosage shows high safety margins which is reassuring in case of potential misuse/overdose. No clinically relevant effects associated with HPA axis suppression are anticipated in this context.

Reproductive toxicity has been observed in animal studies administered subcutaneously. Based on these findings and the drug's mechanism of action, clascoterone may pose a risk of fetal harm. Therefore, clascoterone is contraindicated during pregnancy and pregnancy status of women of childbearing potential should be verified prior to initiating treatment with clascoterone. To further minimise this potential risk, it is agreed that the checklist should be implemented to assist HCP in ensuring that patients are actively informed of the contraindication during pregnancy, that pregnancy status is verified before starting treatment, and that recommendation is given to use an effective contraception method. Moreover, it is also agreed that a patient card should be implemented to ensure that women of childbearing potential are aware of the necessity for contraception during and up to 10 days following treatment discontinuation.

Overall, the revised set of risk minimisation measures and the pharmacovigilance activities are considered appropriate and sufficient to address the risks of HPA axis suppression and reproductive toxicity in light of all available safety data for clascoterone.

6.7.2. Balance of benefits and risks

Acne vulgaris is a benign chronic inflammatory skin condition of pilosebaceous glands that typically begins at puberty and may continue through adulthood. Acne is highly prevalent during adolescence, affecting up to 85% of teenagers, and can significantly impact self-esteem, social interactions, and overall quality of life.

An unmet medical need is recognised, particularly in specific patient populations such as males and adolescents or individuals requiring androgen-targeted therapy but for whom systemic exposure is not desirable. Clascoterone, a first-in-class topical anti-androgen, may help address this gap.

Benefit of clascoterone 1% cream can be concluded from pivotal Phase 3 studies that showed evidence of efficacy of clascoterone compared to a vehicle at 3-month to treat acne vulgaris on the face. Although considered modest (i.e. proportion of subjects achieving treatment success at week 12: 19.5% for clascoterone vs 7.7% for the vehicle), the effect is statistically significant and clinically relevant. Efficacy results were confirmed in adolescent patients aged 12 years and older. Data from an open-label long-term follow-up study data have shown a similar effect.

The potential HPA axis suppression of Winlevi is related to the weak glucocorticoid activity of clascoterone mediated by its main metabolite cortexolone and represent an established glucocorticoid class-specific risk. Clascoterone 1% cream may be associated with HPA axis suppression according to the finding of borderline lower serum cortisol levels after ACTH stimulation in no more than 10% of patients receiving a supratherapeutic dosage in dedicated studies (5% adults; 9% adolescents). However, this concern is considered not fully applicable to Winlevi when used at the recommended dose, also taking into account methodological limitations of the test. Moreover, it does not appear to be indicative of clinically relevant adverse endocrine outcomes. Neither in clinical development nor in the post-marketing data in the US adverse events related to growth or sexual maturation were reported.

Under the proposed conditions of use including the revised indication and the agreed set of risks minimisation measures, the systemic bioavailability of clascoterone provides high safety margins for a potential glucocorticoid effect which make unlikely a negative gonadotropin effect on growth and sexual maturation in adolescents. It is therefore concluded, considering the implementation of the agreed risk minimisation measures and pharmacovigilance activities, that clascoterone in the treatment of facial acne vulgaris in adolescent has a therapeutic benefit and favourable safety profile. The favourable efficacy and safety profile in adults were already demonstrated in the initial assessment.

6.8. Conclusions

The overall benefit/risk balance of Winlevi is positive subject to the conditions stated in section 7 'Recommendations following re-examination'.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded, by majority decision, that the benefit/risk profile of Winlevi is positive in the following indications:

Adults

Winlevi is indicated for the treatment of acne vulgaris.

Adolescents (from 12 to <18 years of age)

Winlevi is indicated for the treatment of facial acne vulgaris.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Prior to launch of Winlevi in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Winlevi is marketed, all healthcare professionals, patients/carers who are expected to prescribe or use Winlevi, have access to/are provided with the following educational package.

<u>Checklist for healthcare professionals</u>

The Checklist for healthcare professionals should contain the following key elements:

- HPA-axis suppression
  - Provide clear instruction on correct use of Winlevi (dose, administration schedule and site of application for adult and adolescent, respectively)
  - Inform patients about the risk of HPA-axis suppression and advice on signs and symptoms suggestive of this condition
  - Monitor patient's adherence to the recommendation on correct use at follow-up visits

- Consider measuring morning serum cortisol levels if HPA axis suppression is suspected and referring the patient for endocrinological evaluation. Treatment should be interrupted if HPA axis suppression is confirmed

- Reproductive toxicity
  - Inform patient about the contraindication during pregnancy due to the risk of potential fetal harm and congenital malformations
  - Verify pregnancy status prior to initiating treatment
  - Counsel on contraception during treatment with Winlevi, recommending use of an effective method of contraception
  - Advise on continued use of contraception for at least 10 days after last administration

Patient card (provided with each medicine pack)

The Patient Card should contain the following key elements:

- Inform patient about the contraindication during pregnancy due to the risk of potential fetal harm and congenital malformations
- Verify pregnancy status prior to initiating treatment
- Counsel on contraception during treatment with Winlevi, recommending use of an effective method of contraception
- Advise on continued use of contraception for at least 10 days after last administration

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

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that clascoterone is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0076/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, in the Package Leaflet.

Divergent position

A divergent position to the majority recommendation is appended to this report.

APPENDIX

DIVERGENT POSITION DATED 25 August 2025

DIVERGENT POSITION DATED 25 August 2025

Winlevi - EMEA/H/C/006138/0000

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Winlevi (clascoterone) in the treatment of facial acne vulgaris in adolescent.

Clascoterone is a new chemical entity with claimed local anti-androgenic activity, acting as an androgen receptor inhibitor. Although studies in humans have shown that clascoterone is poorly absorbed, data suggests a systemic effect:

- HPA axis suppression was studied in two Phase 2 studies and perturbations were observed in some patients who received clascoterone at 4 g and 6 g during 2 weeks. Seven subjects (7/67, 10%) had abnormal ACTH stimulation tests at D14, which returned to normal 4 weeks after stopping the clascoterone cream;
- Although information was limited, 2 serious cases reported HPA axis suppression and one serious case reported adrenal suppression were reported post marketing in the USA.

The opinion of the *Ad Hoc* Expert Group is that HPA axis suppression is low but cannot be ruled out, and that it should be clearly mentioned for the attention of physicians and patients. In patients with evident symptoms (such as abnormal growth during treatment) or mild symptoms (such as mild occasional fatigue or nausea), cortisol should be measured followed if abnormal by a low-dose ACTH test.

During the procedure, the Applicant did not rule out the risk of HPA axis suppression. Initially HPA axis suppression was mentioned in section 4.8 of the SmPC under the heading Endocrine disorders, but it was subsequently reclassified under the heading Investigations as "Adrenocorticotropic hormone (ACTH) stimulation test abnormal". This is not considered acceptable.

In addition, the Applicant proposed a set of measures to address this concern, including limitation of the daily dose in adolescents to 2 g/day, which is reflected by limiting the application of the cream to the face. This position is not considered appropriate, as it casts doubt on a risk that could be clearly investigated prior to marketing authorisation.

To conclude:

- In both pivotal studies, Winlevi applied 1 g twice daily for 12 weeks, showed a modest effect in acne vulgaris: IGA success was 17.5% in the clascoterone group versus 5.8% in the vehicle group;
- Uncertainties pertain concerning the consequences of the HPA axis suppression such as retardation of growth and/or an impact on sexual maturation, when Winlevi will be used for long-term treatment of adolescents (i.e., from 12 years to less than 18 years of age)

It is also considered that routine pharmacovigilance will not detect symptoms of HPA axis suppression (low, rare and/or unspecific). Thus in order to definitely address this potential risk, the applicant should have adequately assessed the effect of clascoterone on the HPA axis in adolescents aged 12-18 years at the dose intended for the treatment of acne before granting the MA in this population.

Therefore, it is the opinion of the divergent CHMP members that the benefit-risk balance of Winlevi is positive in the treatment of acne vulgaris in adults but negative in the treatment of facial acne vulgaris in adolescent.

Alexandre Moreau

Bruno Delafont