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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Apremilast Accord

International non-proprietary name: apremilast

Procedure No. EMEA/H/C/006208/0000

Note

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



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List of abbreviations

ANOVA	Analysis of variance
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASMF	Active Substance Master File = Drug Master File
AUC	Area under the curve
BE	Bioequivalence
BD	Behçet's disease
cAMP	Cyclic adenosine monophosphate
CHMP	Committee for medicinal products for human use
CI	Confidence interval
C _{max}	Maximal plasma concentration
CoA	Certificate of Analysis
CV	Coefficient of variation
DMARD	Disease modifying antirheumatic drug
DQC	Dilution quality control
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
GC	Gas Chromatography
GCP	Good clinical practice
GLM	General linear model
GLP	Good laboratory practise
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices
HCL	Hydrochloric acid
HDPE	High-density polyethylene
HPLC	High Performance Liquid Chromatography
HQC	High quality control
ICH	International conference on harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IME	Important Medical Event
IMP	Investigational medicinal product
IR	Infrared
ISTD	Internal standard
K ₂ EDTA	Dipotassium ethylene diamine tetra acetate
LC-MS/MS	Liquid chromatography – tandem mass spectrometry
LDPE	Low-density polyethylene
LLOQ	Lower limit of quantification
LMQC	Low medium quality control
LQC	Low quality control
MACE	Major adverse cardiac event
MO	Major Objection
MQC	Medium quality control
NOEC	No observed effect concentration
NMR	Nuclear Magnetic Resonance
OECD	Organization for economic cooperation and development
PBT	Persistent, bioaccumulative and toxic
PDE	Phosphodiesterase
PDE	Permitted Daily Exposure
PE	Polyethylene

PEC	Predicted environmental concentration
Ph. Eur.	European Pharmacopoeia
PhV	Pharmacovigilance
PK	Pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	Psoriatic arthritis
PUVA	Psoralen and ultraviolet-A light
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QC	Quality control
RH	Relative Humidity
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
RP	Restricted Part (or Closed Part) of ASMF
RSD	Relative standard deviation
SOP	Standard operating procedure
$t_{1/2}$	Terminal half-life
TLC	Thin layer chromatography
T_{max}	Time to maximum plasma concentration
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 6 March 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Apremilast Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– ‘Generic of a Centrally authorised product’. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 October 2022.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

Psoriatic arthritis

Apremilast Accord, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy (see section 5.1).

Psoriasis

Apremilast Accord is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

Behçet's disease

Apremilast Accord is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is

composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Otezla instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Otezla, 10, 20 and 30mg, film coated tablets
- Marketing authorisation holder: Amgen Europe B.V., The Netherlands
- Date of authorisation: 15/01/2015
- Marketing authorisation granted by:
 - Union

- Union Marketing authorisation number: EU/1/14/981/001, EU/1/14/981/002, EU/1/14/981/003

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Otezla, 10, 20 and 30mg, film coated tablets
- Marketing authorisation holder: Amgen Europe B.V., The Netherlands
- Date of authorisation: 15/01/2015
- Marketing authorisation granted by:
 - Union
- Marketing authorisation number: EU/1/14/981/001, EU/1/14/981/002, EU/1/14/981/003

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Otezla 30mg, film coated tablets
- Marketing authorisation holder: Amgen Europe B.V., The Netherlands
- Date of authorisation: 15/01/2015
- Marketing authorisation granted by:
 - Union
- Marketing authorisation number(s): EU/1/14/981/001, EU/1/14/981/002, EU/1/14/981/003

1.3. Information on paediatric requirements

Not applicable

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.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Nadrah

The application was received by the EMA on	6 March 2023
The procedure started on	23 March 2023

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 June 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 June 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 July 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 October 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	20 November 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2023
The CHMP agreed on a list of outstanding to be sent to the applicant on	14 December 2023
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	23 January 2024
The CHMP Rapporteur 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	07 February 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Apremilast Accord on	22 February 2024

2. Scientific discussion

2.1. Introduction

This application concerns a generic version of apremilast 10 mg, 20 mg and 30 mg film-coated tablets under trade name Apremilast Accord film-coated tablets.

The chosen reference medicinal product with recognised efficacy and an acceptable level of safety is Otezla, which contains 10 mg, 20 mg and 30 mg of apremilast as film-coated tablets of Amgen Europe B.V. The Netherlands, and authorised in the community on 15th January 2015 (marketing authorisation numbers EU/1/14/981/001-003) via the centralised procedure (EMA/H/C/003746).

Both the test and reference product contain the same form of active substance - apremilast.

The reference product Otezla is indicated:

- Psoriatic arthritis: alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.
- Psoriasis: for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).
- Behçet's disease: for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

The applicant has applied for all the indications of the reference product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 10 mg, 20 mg, or 30 mg of apremilast as the active substance.

The other ingredients are cellulose microcrystalline (E460), lactose monohydrate, croscarmellose sodium (E468), magnesium stearate (E572) and silica colloidal anhydrous (E551).

For the tablet coating, hypromellose (E464), titanium dioxide (E171), di-acetylated monoglycerides (E472a), iron oxide red (E172). The 20 mg tablets also contain iron oxide yellow (E172). The 30 mg tablets contain iron oxide yellow (E172) and iron oxide black (E172).

The product is available in PVC/PVDC-aluminium foil blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General information

The chemical name of apremilast is (S)-N-(2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-yl)acetamide corresponding to the molecular formula $C_{22}H_{24}N_2O_7S$. It has a relative molecular mass of 460.5 g/mol and the following structure:

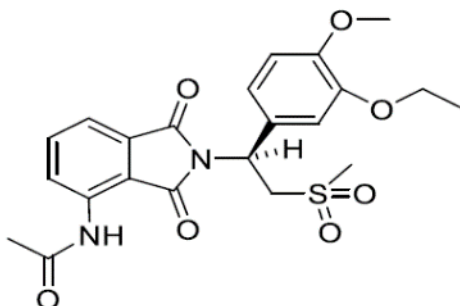


Figure 1. Active substance structure

The chemical structure of apremilast was elucidated by a combination of IR, UV, ¹H NMR, ¹³C NMR and mass spectroscopy. The solid state properties of the active substance were measured by XRPD.

The active substance is a white to pale yellow coloured non hygroscopic powder. It is practically insoluble in water and in ethanol.

Apremilast exhibits stereoisomerism due to the presence of one chiral centre. The stereocenter is formed during the manufacture of the active substance. Enantiomeric purity is controlled routinely by chiral HPLC in the active substance specification.

Polymorphism has been observed for apremilast, on the basis of literature searches seven potential polymorphic forms have been reported. The manufacturer of the active substance consistently produces polymorphic form B, and this is controlled in the active substance specification and measured by XRPD. The polymorphic form produced is thermodynamically stable.

2.2.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at one manufacturing site and sourced from one ASMF. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Apremilast is synthesised using well defined starting materials with acceptable specifications.

The initially proposed starting materials were not accepted and a Major Objection (MO) was raised requesting that the materials be redefined to earlier in the synthetic process as initially the number of steps performed under the GMP for active substances was limited. To resolve the MO the applicant redefined the starting materials as requested and provided justification and information relevant to the redefined starting materials.

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 new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised, including the potential for mutagenic impurities in line with ICH M7. Initially the information provided regarding potential mutagenic impurities was insufficient, and an MO was raised. To resolve this MO the applicant provided further information on the assessment of potential mutagenic impurities, including an updated evaluation covering the entire route of synthesis, details of in-silico evaluation methods, and information relevant to the control strategy such as spike and purge studies.

The active substance is packaged in a transparent polyethylene bag which complies with Ph. Eur. and Commission Regulation (EU) 10/2011, as amended. The polyethylene bag is placed in another polyethylene bag with two activated silica bags and then placed in triple laminated bag. This is finally packed into HDPE drum.

2.2.2.3. Specification(s)

The active substance specification includes tests for appearance, solubility, identity (IR, HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), assay (HPLC), impurities (HPLC), chiral related substances (HPLC), residual solvents (GC), Palladium content (ICP-OES), particle size (laser light diffraction), polymorphism (XRPD) and microbial quality (Ph. Eur.).

Impurity limits are set in line with ICH Q3A requirements and no impurities are present at greater than the qualification threshold.

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 data for three commercial size batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from three commercial batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions under acidic degradation, alkali degradation, oxidation degradation, thermal degradation, UV and fluorescent light degradation, increased humidity degradation were also provided on one batch.

The following parameters were tested: description, identification, loss on drying, related substances, chiral related substances, assay, XRPD. The analytical methods used were the same as for release and were stability indicating.

At long term and accelerated conditions, the active substance is stable and no out of specification results were observed. Under stress testing acidic, alkali, and oxidative stress testing conditions the active substance was not stable with decreasing assay results and increasing impurity levels detected. At other stress testing conditions, no significant degradation or instability was observed. No sensitivity to light was observed.

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 12 months and the applicant's selected storage condition of store at 25°C with excursions permitted to 15°C – 30°C in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is present in three strengths, 10 mg, 20 mg and 30 mg film-coated tablets. The appearance of the tablets is as follows:

Apremilast Accord 10 mg film-coated tablets are pink, diamond shaped, biconvex film-coated tablets debossed with "A1" on one side and plain on other side. The size of the tablet is approximately 8 x 5 mm.

Apremilast Accord 20 mg film-coated tablets are brown, diamond shaped, biconvex film-coated tablets debossed with "A2" on one side and plain on other side. The size of the tablet is approximately 10 x 6 mm.

Apremilast Accord 30 mg film-coated tablets are beige, diamond shaped, biconvex film-coated tablets debossed with "A3" on one side and plain on other side. The size of the tablet is approximately 12 x 6 mm.

The finished product has been developed to be a generic equivalent to the reference medicinal product Otezla 10 mg, 20 mg and 30 mg film-coated tablets. The objective was to prepare a film-coated tablet being essentially similar to the reference medicinal product.

Apremilast is poorly soluble and physical characteristics of the active substance could therefore impact clinical performance. The polymorphic form of the active substance is stable and controlled by XRPD in the active substance specification. The particle size distribution of the active substance has also been defined in line with the bioequivalent batch and is included in the active substance specification.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards or EU No. 231/2012. Functionality related characteristics were defined for relevant excipients and are reflected in the excipient specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The excipients selected are similar to those used in the reference product with the main difference coming from the different compositions of the (non-functional) film-coating. In addition to this, the cores of the proposed product contain the glidant colloidal anhydrous silica which is not present in the reference product. The composition of the proposed product strengths is acceptable and a bioequivalence study was performed.

A bioequivalence study was performed to compare the 30 mg proposed product strength to the 30 mg reference product strength. A biowaiver of strengths was sought for the 20 mg and 10 mg proposed strengths. These lower strengths are dose proportional to the 30 mg strength, manufactured by the same process, and fulfil the requirements outlined in the guideline on the investigation of bioequivalence. To support the request for the biowaiver of strengths, in-vitro dissolution testing was performed including comparisons at three pH conditions across the physiological pH range, 0.1N HCL, pH 4.5, pH 6.8, and additionally using the proposed method for QC dissolution testing. The in-vitro dissolution results were shown to be comparable across these conditions and supportive to the biowaiver request for the lower strengths. For further details of the bioequivalence study performed please refer to the clinical section.

The initially proposed QC dissolution method was not accepted and an MO was raised as insufficient justification has been presented concerning the selected level of surfactant present, the selected RPM of the method, and the discriminatory power. To resolve this MO the applicant justified the selected parameters for the QC dissolution method and demonstrated the discriminatory nature of the method. The method was shown to be discriminatory with respect to qualitative changes in the composition through increases in the lubricant amount and reduction in the amount of disintegrant present.

A direct compression manufacturing process was selected using a standard manufacturing process. Lubrication and blending times were selected following development studies to identify optimal uniformity parameters. No impact on dissolution was seen with over lubricated compositions or tablets compressed to various hardness ranges.

The primary packaging is PVC/PVDC-aluminium foil blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. *Manufacture of the product and process controls*

The manufacturing process is conducted at one finished product manufacturing site. The manufacturing process consists of four main steps: raw material sifting, blending and lubrication, compression and film coating of tablets. The process is considered to be a standard manufacturing process.

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

2.2.3.3. Product specification(s)

The finished product release specifications include appropriate tests for this kind of dosage form appearance, average tablet weight, identification (HPLC, IR), loss on drying (in-house), dissolution (HPLC), content uniformity (Ph. Eur.), assay (HPLC), related substances (HPLC), microbiological quality (Ph. Eur.).

The limits for related substances are appropriately set in line with ICH Q3B requirements, and the relevant qualification threshold is not exceeded.

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. Based on the risk assessment 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 proposed limit for QC dissolution was initially not set in line with the biobatch and the requirements of the reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action. An MO was raised concerning this aspect as differences in in-vitro dissolution profiles could lead to differences with respect to in-vivo behaviour. This MO was resolved by the tightening of the limit as requested in line with the biobatch dissolution performance as requested.

The analytical methods used have been adequately described and 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 three commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from three commercial batches of each strength of finished product stored for up to 12 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% 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.

Samples were tested for appearance, loss on drying (in-house), dissolution (HPLC), assay (HPLC), related substances (HPLC), and microbiological quality (Ph. Eur.). The analytical procedures used are stability indicating. At both long term and accelerated conditions no trends or out of specification results are observed. The product remains stable under all tested conditions.

With respect to ongoing stability programs: In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicate that product is photostable.

Based on available stability data, the proposed shelf-life of 24 months and with no special storage conditions as stated in the SmPC are acceptable.

2.2.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. 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. The results of tests carried out indicate 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.

During the assessment four MOs concerning Quality aspects were raised, for the active substance these concerned the initially proposed starting materials and the assessment of potential mutagenic impurities related to the active substance synthesis. In the finished product MOs were raised on the proposed method for QC dissolution and the discriminatory potential of this method, a separate MO was raised on the need to set the regular QC limit for dissolution in line with the performance of the biobatch.

The MO on the starting materials was resolved by redefining the starting materials as requested and providing sufficient justification and information related to the redefined materials. The MO on potential mutagenic impurities was resolved by the provision of further information on this aspect showing that such impurities are suitably assessed and controlled.

In the finished product the MO concerning the dissolution method was resolved by justification of the selected parameters for the method and demonstration of the discriminatory potential of the method. The MO concerning the limit proposed for dissolution in the specifications was resolved by tightening of the limit in line with the biobatch dissolution performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

The Applicant has provided consumption data for apremilast active-product-ingredient (API) between years 2019-2022. The presented data, which does not indicate a significant increase of API consumption during last four years for the combined sales volume, has been used for calculation of factor of penetration of apremilast film-coated tablets.

Table 1. Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD107 or ...	Log K_{ow} = 1.77	No Potential PBT
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)	0.0117	µg/L	> 0.01 threshold Y
Other concerns (e.g. chemical class)			N

Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106 or ...	Sludge: K_d : 28.7-40 L/kg ($n=2$) K_{oc} : 70- 91 L/kg ($n=2$) Soil: K_{oc} : 263-457 L/kg ($n=3$)			List all values
Ready Biodegradability Test	OECD 301	0-2% biodegradable			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT _{50, water} =1.5 days (SL), 0.6 days (SW) DT _{50, whole system} =1.9 days (SL), 0.7 days (SW) Apremilast: ≤ 3% AR in sediment at or after 14 days of incubation; one transformation product at max 17% AR in sediment on day 28			Shifting to sediment 10%, adsorption occurs
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>Species</i>	OECD 201	NOEC	3500	µg/L	Brachydanio rerio
<i>Daphnia</i> sp. Reproduction Test	OECD 211	NOEC	6300	µg/L	Daphnia magna
Fish, Early Life Stage Toxicity Test/ <i>Species</i>	OECD 210	NOEC	7200	µg/L	/
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	1x10 ⁶	µg/L	/

Since the PEC surface water for apremilast, determined in Phase I assessment, was greater than 0.01 $\mu\text{g/L}$, a Phase II environmental fate and effect analysis have been performed. No further testing in the aquatic compartment was carried out since the ratio $\text{PEC}_{\text{SURFACEWATER}}:\text{PNEC}_{\text{SURFACEWATER}}$ for the drug substance apremilast was below 1, which is in line with EMEA/CHMP/SWP/4447/00 Corr 2. It was therefore concluded that the apremilast and/or its metabolites are unlikely to represent a risk to the aquatic environment.

The partition coefficient for Apremilast was experimentally determined by the shake flask method (comparable to OECD Test Method 107). The resulting log Kow value of Apremilast was below 4.5 (PAR, Otezla, 2014). Thus, it is considered that apremilast is not a persistent, bioaccumulative and toxic (PBT) substance, and is unlikely to represent a risk to the aquatic environment, groundwater compartment, or micro-organisms in the STP. Furthermore, apremilast metabolites are also not expected to represent a risk to the aquatic environment, groundwater compartment, or the STP.

2.3.3. Discussion on non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of apremilast are well known and a literature-based non-clinical overview was considered appropriate by the CHMP. However, the discussion of the impurity profile was not included in the non-clinical overview provided at the time of submission. During the procedure, the applicant has updated the non-clinical overview to add a reference to Module 3, where impurity profiles and specifications are adequately discussed. All impurities are below specification levels for the reference (Otezla) and test (Apremilast Accord) products. Hence, the CHMP concluded that the impurity profiles are similar.

The presented environmental risk assessment for apremilast indicates there is no risk for the environment, given the prescribed usage, and this was agreed by the CHMP.

2.3.4. Conclusion on the non-clinical aspects

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film coated tableted containing apremilast. To support the marketing authorisation application, the applicant conducted one bioequivalence study (study No. 0374-22) with cross-over design under fasting.

No formal scientific advice by the CHMP was given for this medicinal product.

GCP aspect

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

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

Exemption

The bioequivalence study has been conducted using the highest strength (30 mg) of Apremilast Accord film-coated tablets. For lower strengths, 20 mg and 10 mg, the applicant has claimed biowaiver.

General biowaiver criteria specified were checked against the Guideline on the investigation of bioequivalence:

- According to Module 3, all strengths of Apremilast Accord are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths (coating components and colour agents are not required to follow this rule).

- According to SmPC of the reference product, apremilast pharmacokinetics are linear, with a dose-proportional increase in systemic exposure in the dose range of 10 to 100 mg daily.
- Drug products of all strengths have comparable *in vitro* dissolution profiles in all tested media.

All experimental conditions for *in vitro* dissolution experiments are in accordance with Guideline on the investigation of bioequivalence.

Tabular overview of clinical studies

To support the marketing authorisation application the applicant conducted one bioequivalence study (study No. 0374-22).

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
BE	0374-22	• m5-3-1-2-0374-22	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of apremilast tablets 30 mg in normal, healthy, adult human subjects under fasting condition.	Two-period, two-sequence, single oral dose, crossover bioequivalence study under fasting condition	Apremilast tablets 30 mg, single dose, oral	62	Healthy, adult human subjects	Single dose	Complete; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study No. 0374-22: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Apremilast Tablets 30 mg of Intas Pharmaceuticals Ltd., India with Otezla 30 mg film-coated tablets (Apremilast) of Amgen Europe B.V., Minervum 7061, 4817 ZK Breda, The Netherlands in normal, healthy, adult human subjects under fasting condition

Methods

- **Study design**

This study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study in normal, healthy, adult human subjects under fasting condition. The study was conducted under fasting conditions, which is acceptable as the drug product can be taken with or without food and the fasting condition is the most sensitive to identify differences between the formulations.

After an overnight fast of at least 10 hours, a single oral dose (30 mg) of either the test product or the reference product was administered with 240 ± 2 mL of drinking water at ambient temperature to the subjects in sitting posture. The IMP administration was as per the randomization schedule and under open label conditions.

Dosing dates were 25th January 2023 (Period I) and 29th January 2023 (Period II).

A washout period of 4 days was maintained between the successive dosing days. The washout period of 4 days is long enough in regard to the half-life of the studied active substance apremilast. It is longer than 5 times half-life of active substance (5 x 9 hours).

Subjects were checked-in clinical site at least 11 hours before drug administration and checked-out 48 hours after drug administration in both study period.

Parent compound (apremilast) was analysed in plasma samples.

The venous blood samples were withdrawn at pre-dose (0.000 hour) and 0.250, 0.500, 0.750, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.333, 3.667, 4.000, 4.500, 5.000, 5.500, 6.000, 8.000, 10.000, 12.000, 16.000, 24.000, 36.000 and 48.000 hours following IMP administration in each period. The sampling scheme to estimate pharmacokinetic parameters for conclusion regarding bioequivalence is adequate (frequent sampling around predicted T_{max} (according to reference SmPC T_{max} of apremilast is approximately 2.5 hours), at least 3-4 samples during the terminal log-linear phase for individual subject). Sampling period (48 hours) is long enough for concerned immediate-release drug product, since terminal elimination half-life of apremilast is approximately 9 hours according to SmPC of reference product Otezla. Furthermore, according the results extrapolated area was less than 20% for individual subject.

Fluid intake was standardized. Posture and physical activities after dosing were standardized. There were some restrictions (regarding taking some food and drinks, alcohol, tobacco, recreational drugs, unusual diet, concomitant medication) that subjects were to comply with prior to and during the course of this study.

During entire housing phase of study, standardised meals were provided to subjects as per meal menu designed by dietician and approved by Investigator. The date and time of meals were standardized and were the same for both periods. A composition of meals was the same for both periods.

- **Test and reference products**

Apremilast Accord 30 mg tablets manufactured by Intas Pharamceuticals Ltd., India has been compared to Otezla 30 mg film coated tablets (MAH: Amgen Europe B.V.).

- **Population(s) studied**

Only male subjects participated in the study, they met all the inclusion criteria and none of the exclusion criteria described in the study protocol.

A total of 66 subjects were checked in for Period-I of the study. 4 subjects of them were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I. As none of the subjects discontinued / were withdrawn from the study prior to dosing in Period-I, these 4 subjects were checked out of the facility. Hence, a total of 62 subjects were dosed in Period-I of the study.

Three (3) subjects discontinued from the study on their own accord in Period-II. Two (2) subjects were withdrawn from the study on medical grounds in Period-II. In Case report forms, it is confirmed that 3 subjects discontinued from the study on their own accord in Period-II (2 subjects reported to the facility for period-II check in but did not want to continue further participation in study due to personal reason, one subject did not report to the facility for period-II check in), 2 subjects were withdrawn from the study on medical grounds in Period-II.

57 subjects completed the clinical phase of the study successfully and were included in pharmacokinetic and statistical analysis.

62 subjects completed bioanalytical analysis (in which, 5 withdrawn subjects were also analysed as per protocol requirement).

The demographic data are presented and are appropriate.

Sample size calculation is presented and is appropriate. Sample size is adequate.

In Clinical study report only sampling deviations were reported as protocol deviations. Since the actual time is used for computation in pharmacokinetic and statistical analysis, the sampling time deviations are not expected to have any impact on the overall assessment of the study. List of sampling time point deviations used for pharmacokinetic evaluation has been presented.

- **Analytical methods**

Bioanalysis of study samples and within-study validation

Bioanalytical report titled Determination of Apremilast Concentrations in Study Samples Collected During Clinical Study No. 0374-22, dated 25th February 2023, has been provided.

The purpose of the study was to quantify apremilast in study subject samples. The concentrations of apremilast in plasma samples, with K₂EDTA as anticoagulant, were analysed using validated LC/MS-MS method over a concentration range of 1.502 to 904.177 ng/mL.

The sample analysis was performed at the bioanalytical facility. Bioanalytical phase has been performed from 30th January to 9th February 2023. The performance of the bioanalytical method was verified by bioanalytical laboratory.

Study sample information:

No. of subjects (as per protocol)	62
No. of sampling points (as per protocol)	27
Details of sampling time-points (as per protocol)	Pre-dose (0.000 hours), and at 0.250, 0.500, 0-750, 1.000, 1.250, 1.500, 1.750, 2.00, 2.250, 2.500, 2.750, 3.000, 3.333, 3.667, 4.000, 4.500, 5.000, 5.500, 6.000, 8.000, 10.000, 12.000, 16.000, 24.000, 36.000 and 48.000 hours post-dose
No. of periods (as per protocol)	2
Total No. of samples to be collected (as per protocol)	3348 (62 subjects x 27 time-points x 2 periods)
No. of subjects successfully completed clinical phase	57 (subject No. 1001-1011, 1013-1018, 1020-1037, 1039-1041, 1043-1052, 1054-1062)
No. of withdrawn/discontinued subjects	5 (subjects No. 1012, 1019, 1038, 1042, and 1053)
No. of samples not collected and not analysed	135 (period II of withdrawn/discontinued subjects)
No. samples analysed	3213

Maximal storage period of study samples (16 days at -55 °C) was within validated long-term stability of apremilast in K₂EDTA plasma (143 days at -65 ± 10°C & -22 ± 5°C).

Apremilast and Apremilast-d5 (ISTD) were extracted from plasma by Liquid-Liquid extraction method using extraction solvent. Information on HPLC System (model, manufacturer) used for analysis of study sample analysis has been provided. Analyst software Version 1.6.2 was used for data acquisition and evaluation of chromatographic data. BioLyte Software, Version 1.4 software was used to review the chromatographic data. All chromatograms were integrated automatically since manual integration was not allowed as per SOP.

The plasma concentrations of apremilast have been determined using LC-MS/MS method according to method SOP MS-1045-04 (dated 10th October 2022) and relevant system bioanalytical SOPs, which have been provided. Bioanalytical study plan has also been provided.

Certificates of analysis of reference standard apremilast and ISTD used in study sample analysis have been provided.

Calibration curve standard range was 1.505 to 903.795 ng/mL. Concentration levels of quality control samples were 1.530 ng/mL (LOQ QC (LLOQ)), 4.501 ng/mL (LQC), 101.372 ng/mL (LMQC), 286.902 ng/mL (MQC), 717.256 ng/mL (HQC) and 2702.267 ng/mL (DQC).

Structure of analytical run (8 calibration standards, quality control samples in duplicate, study samples, zero samples, and blank samples) was acceptable. Within an analytical run, study samples were bracketed by QC samples. All samples of one subject were analysed in one analytical run. All analytical runs (34 analytical runs) met analytical run acceptance criteria. The range of precision and accuracy of the back-calculated concentrations of the calibration curve standard points during the study were 1.3% to 3.9% and 96.5% to 104.5%, respectively. Mean precision and accuracy of quality

control samples were 4.0% to 4.4% and 96.5% to 102.9%, respectively. Coefficient of determination (r^2) was more than 0.99 for each accepted analytical run.

A total of 28 samples have been reinjected due to hardware error. Reinjected chromatographic data have been accepted, since the reinjected analytical runs were within the established Autosampler storage stability of 121.0 hrs (at 2 to 8°C).

A total of 39 samples (representing 1.2% of all analysed study samples) were reanalysed. Reasons for repeat sample analysis (Significant variations in response of internal standard – 30 samples, Laboratory Accident – 8 samples, Significant analyte concentration in pre dose sample of subject – 1 sample) are according to SOP Repeat analysis and acceptance of results AHM/BA/0059-2. Original and repeated concentrations have been presented. Repeated values have been reported for pharmacokinetic in statistical analysis.

For incurred sample reanalysis 218 samples were considered for ISR evaluation (10% of 1000 study samples + 5% of the 3213 study samples). This is appropriate for studies with more than 1000 study samples. All incurred samples were within the acceptance criteria as per SOP AHM/BA/0060-2. It is considered that results of the performed ISR reanalysis confirm the reproducibility of the analytical method.

100% of chromatograms were provided. SOP AHM/BA/0033-2 Chromatography acceptance criteria, re-injection, integration and reintegration on LC-MS/MS data systems has been provided. None of analytical runs were reintegrated. ISTD response plots have been provided for all analytical runs.

LLOQ (1.502 ng/mL) is less than 5% of min C_{max} .

There were no SOP nor protocol deviations during subject sample analysis.

Pre-study method validation

Bioanalytical method validation was performed at the bioanalytical facility.

The bioanalytical LC-MS/MS method for the quantification of apremilast in human plasma (containing K₂EDTA as an anticoagulant) was validated according to in-house SOP on Bioanalytical Method Validation LTR.BA-05-03 (25th April 2016), which was replaced by LTR.BA-05-04 on 17th November 2017. The initial bioanalytical method followed was as described in draft method SOP No. MS-1045-D-01.

Main bioanalytical method validation has been performed between 21st April 2017 and 2nd May 2017, and validation report dated 13th June 2017 has been provided. Five (5) partial validations have been performed: addendum I (9th October 2017), addendum II (22nd December 2017), addendum IV (1st August 2019) and addendum V (3rd November 2022). Addendum III was performed to reassess requisite stability in human plasma as to fulfil the requirement of Health Canada and has not been provided. This is acceptable since the partial validation was performed to fulfil regulatory requirements of Health Canada, which are not applicable in the EU.

Statement of compliance with principles of Good Laboratory Practice, Good Clinical Laboratory Practice and relevant SOPs of Lambda Therapeutic Research Ltd. and Quality assurance statement have been provided for main validation and all partial validations.

Certificates of analysis of reference standard apremilast and ISTD used in main validation and in partial validations have been provided. The applicant has provided certificates of analysis for all concomitant medications used in validation of method selectivity.

The bioanalytical method was validated, either pre-study and within study, according to Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 and ICH guideline M10, which came into force on 21st January 2023, respectively.

The following parameters have been pre-study validated: Selectivity, Short-term stock solution stability of analyte & ISTD, Short-term spiking solution stability of analyte at higher & lower level, Short-term stability of ISTD dilution, Precision and Accuracy, Selectivity in presence of co-administered drugs, Analyte stability in human whole blood, Reinjection Reproducibility, Matrix effect, Recovery, Matrix factor, Robustness & Ruggedness, Freeze & thaw stability, Bench top stability, Reagent stability, Mobile phase stability, Auto sampler carry-over, Interference potential by co-administered drugs, Wet extract bench top stability, Dry extract stability, Auto sampler stability, Limit of Detection, Long-term stock solution stability of analyte & ISTD, and Long-term spiking solution stability of analyte at higher & lower level. The method met the acceptance criteria for all the validation parameters evaluated, demonstrating acceptable performance.

The applicant has justified that the molecular weight of the metabolites is different from that of Apremilast and Apremilast-d5 (ISTD), and therefore due to a different mass/charge ratio they do not interfere with Apremilast quantitation. According to Guideline on bioanalytical method validation glucuronide metabolites are unstable and therefore subjected to back-conversion to parent molecule, either during the successive steps of the analysis (including extraction procedures) or storage. Therefore, the provided justification is not considered entirely appropriate. Nonetheless, The glucuronide conjugate of O-methylated apremilast would back-convert to O-methylated apremilast. Since O-methylated apremilast has a molecular weight different from that of Apremilast and Apremilast-d5 (ISTD), it is considered this metabolite would not affect analysis of Apremilast and Apremilast-d5 (ISTD) due to different mass/charge ratio. Consequently, the raised issue is considered resolved.

Although the method validation was carried out prior to ICM M10 coming into effect, the applicant has adequately demonstrated that the performed matrix effect experiment is meeting ICH M10 guideline requirements.

In partial validation (addendum I) long-term stability of analyte in human plasma using selective and reproducible LC-MS/MS method for the quantification of apremilast in human plasma was determined.

In partial validation (addendum II) selectivity in presence of co-administered drugs, matrix screening, and bench top stability have been evaluated in addition to verification of interfering potential by co-administered drugs.

Partial validation (addendum IV) provides results of calibration curve standard, quality control sample data, selectivity, sensitivity and all supporting documentation.

In partial validation (addendum V) standard calibration curve, quality control sample data, selectivity in presence of co-administered drugs, short term solution stability, long term spiking solution stability of drug at dilution QC level & long-term stability of intermediate ISTD dilution were determined.

No SOP deviation have been recorded during method validation and subsequent partial validations.

- **Pharmacokinetic variables**

The following pharmacokinetic parameters are derived individually for each analyzed subject from the plasma concentration vs. time profiles of Apremilast using non-compartmental model of Phoenix® WinNonlin® Version 8.3 (Certara L.P.): C_{max} and T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, terminal rate constant (λ_z), terminal Half-life ($t_{1/2}$) and $AUC_ \%Extrap_obs$ (%).

C_{max} , and AUC_{0-t} are considered primary pharmacokinetic parameters, others are considered secondary pharmacokinetic parameters.

Actual time-points of sample collection are used for the calculation of pharmacokinetic parameters.

All concentration values below the lower limit of quantification are set to zero for the pharmacokinetic and statistical calculations.

- **Statistical methods**

Descriptive statistics were to be calculated and reported for the pharmacokinetic parameters of apremilast.

The In-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were to be subjected to analysis of variance (ANOVA) for apremilast.

The ANOVA model was to be included sequence, subject (sequence), period and formulation as fixed effects.

Each analysis of variance was to be included calculation of least-squares means, the difference between adjusted formulation means and the standard error associated with this difference.

An F-test was to be performed to determine the statistical significance of the effects involved in the model at a significance level of 5% ($\alpha = 0.05$).

The power of the study was to be computed and reported for In-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for apremilast.

Ratio of geometric least squares means of test and reference formulations was to be computed and reported for In-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for apremilast.

Intra-subject variability was to be computed and reported for In-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for apremilast.

Any missing samples (M) or non-reportable (NR) concentration values were to be disregarded in pharmacokinetic and statistical analysis.

90% confidence intervals for the ratio of geometric least squares means between drug formulations were to be computed for In-transformed data of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for apremilast.

All statistical analyses for apremilast were to be performed using the PROC GLM of SAS® Version 9.4 (SAS Institute Inc, USA).

Criteria for conclusion of bioequivalence were as follows:

Bioequivalence of test product-T vs. reference product-R was to be concluded, if the 90% confidence interval fell within the acceptance range (80.00% - 125.00%) for In-transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) for apremilast.

- **Results**

The test to reference ratio of geometric least squares means with corresponding 90% CI for In-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} was within the acceptance range of 80.00-125.00% for apremilast. Therefore, the test product-T is considered to be bioequivalent to the reference product-R under fasting condition.

T_{max} values have been determined, which were comparable between test and reference products.

C_{max} of apremilast was not the first point of a concentration time curve in any subject.

Pre-dose plasma concentration of apremilast was below the limit of quantitation (1.505 ng/mL) for all subjects in both periods.

All subjects had apremilast plasma concentration curves where extrapolated area was <20%.

- **Safety data**

Clinical study was completed with two significant adverse events. There were no deaths or serious adverse events during the conduct of the study. The investigational products were well tolerated by healthy subjects, as a single dose administration.

There were no clinically significant findings in the vital sign assessments or the laboratory tests in any of the subjects in the study.

Volunteers who received concomitant medication due to adverse events were withdrawn from the study on medical grounds, therefore, concomitant medications do not have any impact on study results. Volunteers who experienced adverse events were treated appropriately and followed up until resolution of their adverse events.

- **Additional data**

The comparative in-vitro dissolution profile between test and reference product used in bioequivalence studies has been generated in Q.C. media, 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer.

Comparative dissolution profiles between bio-batches of test and reference product (30 mg strength) are considered similar in QC medium since more the 85% of apremilast is dissolved within 15 minutes. Dissolution profiles are considered similar without further mathematical evaluation.

In 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer dissolution profiles are considered similar based on f2 calculation ($f_2 > 50$), conditions for f2 calculation according to Guideline on the investigation of bioequivalence, Appendix I are fulfilled.

Experimental conditions for in vitro dissolution experiment are in accordance with Guideline on the investigation of bioequivalence, Appendix III and thus acceptable.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Discussion on clinical aspects

To support the application, the applicant submitted a review of clinical data as well as a randomised, two-period, two-sequence single dose crossover bioequivalence study under fasting conditions to demonstrate essential similarity with the reference product Otezla film-coated tablets.

The Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 was considered of particular relevance for the clinical assessment of this application.

The bioequivalence study No. 0374-22 was conducted with the highest strength, 30 mg.

For the lower strengths, 20 mg and 10 mg, biowaiver was claimed. General biowaiver criteria specified in the Guideline on the investigation of bioequivalence are met. During the procedure, the applicant clarified that f2 similarity factor calculation was considered as per Guideline on the investigation of bioequivalence, Appendix-1. RSD is less than 20% for the first point and less than 10% from second to

last time point, which is agreed by the CHMP. Furthermore, the applicant was requested to justify the use of multiple tablets (to obtain the same dose) in dissolution testing for biowaiver. In their response, the applicant explained that based on the dose dependent dissolution of different strengths and similar dissolution profiles in dose equivalent dissolution studies, the observed difference in dissolution profile of the biowaiver strengths (i.e. 10 mg and 20 mg) and the BE strength (i.e. 30 mg) is due to solubility of drug substance rather than characteristic of the drug product. This is agreed by the CHMP. In addition, apremilast is practically insoluble in water and in different buffer solutions (pH 1.2, pH 4.0 and pH 7.0), sink conditions in dissolution testing (900 mL, dissolution media 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer 6.8) cannot be achieved for all strengths. Therefore, in accordance with the guideline on the investigation of bioequivalence, it is acceptable to the CHMP to show similarity of dissolution profiles at the same dose. Overall, the CHMP concluded that biowaiver for lower strengths 10 mg and 20 mg is acceptable.

According to the SmPC of the reference product, apremilast can be taken with or without food. Therefore, the conduct of the single dose study under fasting condition to detect a potential difference between formulations is justified and in accordance with bioequivalence guidelines. The bioequivalence study was conducted under standardised conditions. During entire housing phase of study, standardised meals (in regard to composition and time of administration) were provided to subjects. The washout period of 4 days is long enough in regard to the half-life of the studied active substance apremilast. Sampling period was considered sufficient by the CHMP and sampling time schedule adequate.

Data regarding the test and reference product are provided. Reference product is purchased from Germany. Comparative dissolution profiles of test product biobatch and other production batches in QC medium are considered similar. Statement confirming that, the test product has the same quantitative composition and is manufactured by the same process as the one submitted for marketing authorization was provided.

The population chosen for Study No. 0374-22 is in accordance with the Guideline on the investigation of bioequivalence. A total of 66 subjects were checked in for Period-I of the study. All the checked in subjects satisfied all the inclusion and exclusion criteria. Four (4) subjects of them were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I. These subjects were checked out of the facility as none of the subjects discontinued / were withdrawn from the study prior to dosing in Period-I. Hence, a total of 62 subjects were dosed in Period-I of the study. 3 subjects discontinued from the study on their own accord in Period-II and 2 subjects were withdrawn from the study on medical grounds in Period-II. 57 subjects completed the clinical phase of the study successfully and were included in pharmacokinetic and statistical analysis. 62 subjects completed bioanalytical analysis (in which, 5 withdrawn subjects were also analysed as per protocol requirement). Case report forms confirm information on discontinued subjects.

The bioanalytical method (LC-MS/MS) for quantification of apremilast (parent drug) in human K₂EDTA plasma samples was pre-study validated according to Guideline on bioanalytical method validation and within study validated according to ICH guideline M10 on bioanalytical method validation and study sample analysis. Bioanalytical report and validation reports have been provided. Bioanalytical method is considered acceptable for study samples analysis. Handling of samples was considered adequate by the CHMP.

According to the Guideline in studies to determine bioequivalence after a single dose, AUC_{0-t} , $AUC_{0-\infty}$, residual area, C_{max} and T_{max} should be determined. Additionally, the Guideline lists the following parameters that may be included as PK variables: the terminal rate constant, λ_z , and $t_{1/2}$. The choice of pharmacokinetic variables is in accordance with Guideline on the investigation of bioequivalence and is thus acceptable to the CHMP. Pharmacokinetic parameters for apremilast were calculated using non-

compartmental methods. The software used for determination of pharmacokinetic parameters was Phoenix® WinNonlin® Version 8.3 (Certara L.P.). Actual time points of the sample collection are used for the calculation of pharmacokinetic parameters.

The statistical method used for the pharmacokinetic analyses is considered acceptable by the CHMP. Data transformations and statistical tests used are acceptable. The ln-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were to be subjected to analysis of variance (ANOVA) for apremilast. The ANOVA model included sequence, subject (sequence), period and formulation as fixed effects. All statistical analyses for apremilast were performed using the PROC GLM of SAS® Version 9.4 (SAS Institute Inc, USA).

The criteria for bioequivalence were predefined and are acceptable to the CHMP. The test to reference ratio of geometric least squares means with corresponding 90% CI for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} was within the acceptance range of 80.00-125.00% for apremilast. Therefore, the test product is considered to be bioequivalent to the reference product under fasting condition.

There were no deaths or serious adverse events during the conduct of the study. The investigational products (test and reference) were well tolerated by healthy subjects, as a single dose administration.

Appropriate statements on GCP were provided by the applicant. The applicant provided a list of inspections of clinical site and bioanalytical site where bioequivalence study was conducted. The outcomes of the most recent inspections performed by competent authorities/EU inspectors for clinical study site and bioanalytical study site were provided. The relevance of major and critical findings for concerned study 0374-22 has been addressed by the applicant and the CHMP concluded that critical and major findings do not have any impact on the concerned study 0374-22. Monitoring reports for study 0374-22 have been provided. According to monitoring reports there were no observations, that would have impact on the integrity of the study data. There are no other observations, which could raise concerns about the quality or validity of the sampling process or study sample analyses, the analytical method validation or the statistical analysis. Hence, the CHMP concluded that there is no concern with regard to the GCP compliance of the study.

The comparative dissolution profiles between biobatch of reference product Otezla 30 mg film-coated tablets and biobatch of test product Apremilast 30 mg film-coated tablets are considered as similar based on f_2 calculation for 0.1 N HCL, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer ($f_2 > 50$).

The application contained an adequate review of published literature data on clinical pharmacology, efficacy and safety of apremilast.

The clinical sections of the SmPC of the proposed product are in accordance with the reference product, Otezla 10 mg, 20 mg and 30 mg film-coated tablets.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study Apremilast Accord 30 mg tablets is considered bioequivalent with Otezla 30 mg film-coated tablets.

According to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6 the results of study No. 0374-22 with 30 mg formulation can be extrapolated to other strengths (10 mg and 20 mg).

Efficacy and safety of the proposed product is based on the efficacy and safety of the previously approved reference product Otezla.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns

Table 2. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Serious events of hypersensitivity • Suicidality • Serious events of depression
Important potential risks	• Vasculitis • Malignancies • Serious events of anxiety and nervousness • Serious infections including opportunistic infections and transmission of infections through live vaccines • Major adverse cardiac event (MACE) and tachyarrhythmia • Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast
Missing information	• Long-term safety

2.5.2. Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for following risks are presented in Annex 4 (not provided).

- Serious events of Hypersensitivity
- Vasculitis
- Suicidality
- Serious events of depression
- Malignancies
- Serious infections including opportunistic infections and transmission of infections through live vaccines
- MACE and tachyarrhythmia
- ✓ Myocardial infarction
- ✓ Cardiac arrhythmia & ECG changes
- ✓ Cerebrovascular accident (CVA)
- Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast.

Purpose: For collection and reporting of safety information while use of apremilast.

2.5.3. Risk minimisation measures

Routine risk minimisation activities are sufficient to manage the safety concerns of the reference medicinal product. Thus, no additional risk minimisation activities are considered warranted for this medicinal product.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the 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.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Otezla. The bridging report submitted by the applicant has been found acceptable.

2.7.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found unacceptable by the QRD Group for the following reasons: concerns were raised regarding the possibility to remove the blister from the wallet. The Group was not in a position to accept the request as more compelling proof was needed. This decision may be revisited in the future once samples demonstrating that it is not possible to tear apart the wallet are provided.

3. Benefit-risk balance

This application concerns a generic version of apremilast film-coated tablet. The reference product Otezla is indicated:

- Psoriatic arthritis: alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), for the treatment of active psoriatic arthritis (PsA) in adult patients who have had

an inadequate response or who have been intolerant to a prior DMARD therapy

- Psoriasis: for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).
- Behçet's disease: for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover design under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Fasting conditions are appropriate since SmPC of reference product Otezla recommends dosing 'with or without food' and fasting conditions are considered the most sensitive condition to detect potential differences between formulations. Concentration of parent drug apremilast were measured in plasma samples. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Apremilast Accord 30 mg tablets met the protocol-defined criteria for bioequivalence when compared with the Otezla 30 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Apremilast Accord is favourable in the following indications:

Psoriatic arthritis

Apremilast Accord, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy (see section 5.1).

Psoriasis

Apremilast Accord is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

Behçet's disease

Apremilast Accord is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

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.

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.

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

Not applicable.