30 May 2024
EMA/341688/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pomalidomide Accord

International non-proprietary name: Pomalidomide

Procedure No. EMEA/H/C/006273/0000

Note

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

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Table of contents

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AR	Assessment report
ASMF	Active substance master file
AUC	Area under the curve
BE	Bioequivalence
BMI	Body mass index
CHMP	Committee for medicinal products for human use
CI	Confidence interval
C_{max}	Maximal plasma concentration
CQA	Critical quality attribute
CS	Clinical significant
CV	Coefficient of variation
DHPC	Direct healthcare professional communication
EC	European Commission
EPAR	European public assessment report
ERA	Environmental risk assessment
EU	European Union
EURD	European Union Reference Date
GC	Gas chromatography
GCP	Good clinical practise
GLM	General linear model
GLP	Good laboratory practise
HCP	Healthcare professional
HDPE	High-density polyethylene
HPLC	High performance liquid chromatography
ICF	Inform consent form
ICH	International council for harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IMP	Investigational medicinal product
IR	Infrared
ISR	Incurred sample reanalysis
K_2EDTA	Dipotassium ethylene diamine tetra acetate
KF	Karl Fischer titration
LDPE	Low-density polyethylene
LOQ	Limit of quantification
MAH	Marketing authorisation holder
MO	Major objection
MS/MS	Tandem mass spectrometry
NMR	Nuclear magnetic resonance
OECD	Organization for Economic Cooperation and Development
PDE	Permitted daily exposure
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PL	Package leaflet
PPP	Pregnancy prevention programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSD	Particle size distribution
PSUR	Periodic safety update report
PVC	Polyvinyl chloride
QA	Quality attribute
QC	Quality control
RP	Restricted part (or closed part) of ASMF

RSD	Relative standard deviation
SAE	Serious adverse event
SD	Standard deviation
SOP	Standard operating procedure
$t_{1/2}$	Terminal half-life
T_{max}	Time to maximum plasma concentration
UDU	Uniformity of dosage units
ULQ	Upper limit of quantification
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRPD	X-ray powder diffraction

Not all abbreviations will be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 11 September 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Pomalidomide Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'.

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 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:

> Pomalidomide Accord in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.
>
> Pomalidomide Accord in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last 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 Imnovid instead of non-clinical and clinical studies 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 10 years in the EEA:

- Product name, strength, pharmaceutical form: Imnovid, 1mg, 2mg, 3mg, 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:
- 1mg - EU/1/13/850/001; 005
- 2mg - EU/1/13/850/002; 006
- 3mg - EU/1/13/850/003; 007
- 4mg - EU/1/13/850/004; 008

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

- Product name, strength, pharmaceutical form: Imnovid, 1mg, 2mg, 3mg, 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:
- 1mg - EU/1/13/850/001; 005
- 2mg - EU/1/13/850/002; 006
- 3mg - EU/1/13/850/003; 007
- 4mg - EU/1/13/850/004; 008

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: Imnovid 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/13/850/004 and 008
- Bioavailability study number(s): CT.PLM.cap4.19.001(SHO-P4-644)

1.3. Information relating to orphan market exclusivity

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.5. 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	11 September 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 February 2024
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	3 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	1 May 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	15 May 2024
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 Pomalidomide Accord on	30 May 2024
The CHMP adopted a report on similarity of Pomalidomide Accord with Kyprolis (carfilzomib), Imnovid (pomalidomide), Ninlaro (ixazomib), Farydak (panobinostat), Darzalex (daratumumab), Blenrep (belantamab mafodotin), Abecma (idecabtagene vicleucel), Carvykti (Ciltacabtagene autoleucel) and Talvey (talquetamab)	30 May 2024

2. Scientific discussion

2.1. Introduction

This application concerns a generic application of a centrally authorised medicinal product according to Article 10(1) of Directive 2001/83/EC as amended.

The applicant has developed Pomalidomide Accord capsule, hard as a generic to the reference product Imnovid 1 mg, 2 mg, 3 mg, 4 mg hard capsule.

The indication as presented in the proposed SmPC is shown below.

Therapeutic indication

Pomalidomide Accord in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

Pomalidomide Accord in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

Posology and method of administration

The posology and method of administration are in line with the reference product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 1 mg, 2 mg, 3 mg, 4 mg of pomalidomide as active substance.

Other ingredients are:

Capsule contents : microcrystalline cellulose, maltodextrin, and sodium stearyl fumarate.

Capsule shell: gelatin, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172), indigo carmine aluminium lake (E132) (3 mg and 4 mg strength only), and erythrosine (E127) (4 mg strength only)

Printing ink (white ink): shellac, titanium dioxide (E171), and propylene glycol (E1520)

The product is available in OPA/Al/PVC/Al blister packs as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of active substance is 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione corresponding to the molecular formula C13H11N3O4. It has a relative molecular mass of 273.24 g/mol and the following structure:

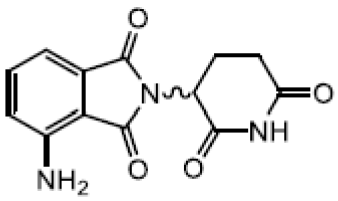

Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of elemental analysis, IR spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry (MS).

The active substance is a non-hygroscopic yellow powder, slightly soluble in acetone, acetonitrile, methylene chloride, methyl ethyl ketone, and tetrahydrofuran. Pomalidomide is very slightly soluble in ethanol, ethyl acetate, methanol, 2- propanol, and toluene and practically insoluble in water and aqueous media across the physiological pH range.

Pomalidomide is a chiral compound with one asymmetric carbon centre. The active substance is marketed as the racaemic mixture.

Polymorphism has not been observed in the active substance.

Manufacture, characterisation and process controls

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

The active substance is synthesised in 2 main steps using well defined starting materials with acceptable specifications. During evaluation, a major objection (MO) was raised by the CHMP in the restricted part of the ASMF requesting the re-definition of the proposed starting materials. Additional justification for the proposed starting material was provided by the applicant and the response was considered satisfactory.

Potential and actual impurities were well discussed with regards to their origin and characterised. Four solvents are used in the synthesis of pomalidomide. The solvents used in the last stage (1,4-dioxane and acetone) are routinely tested in the final active substance, the limits are those stated in ICH Q3C guideline. No class 1 solvents are employed in the synthesis. Since benzene is a potential contaminant in acetone, a test for benzene is included in the final active substance specification (conducted as skip test). The skip-testing strategy for benzene is acceptable.

Two potential genotoxic impurities have been identified. Both are controlled at in the active substance specification in accordance with ICH M7.

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.

The active substance is packaged in two low density polyethylene (LDPE) bags, then in a laminated aluminium (LDPE/Alu) bag and then in a high-density polyethylene (HDPE) container. The primary contact material complies with EC 10/2011 as amended.

Specification

The active substance specification by the manufacturer of finished product includes tests for appearance (visual), identification (IR, HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), residual solvents (GC), impurities (HPLC), assay (HPLC), optical rotation (Ph. Eur.), particle size distribution (Ph. Eur.), and microbial contamination (Ph. Eur.).

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 testing has been presented.

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the manufacturer stored in in a container closure system representative of that intended for the market for up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification, loss on drying, impurities and assay. No significant changes to any of the measured parameters were observed under long term and accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. No changes in physical properties (e.g., appearance, identification and loss on drying) or chemical characteristics (e.g., assay and impurities) were observed. All results remained within the specification limits. Pomalidomide is therefore considered to be photostable.

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 stored in the original packaging below 30ºC.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as follows:

1 mg strength: hard gelatin capsule, with a yellow body and red cap, with "PLM 1" printed in white ink on the capsule body. Capsule size 4 (approximately 14.3 mm in length).

2 mg strength: hard gelatin capsule, with an orange body and red cap, with "PLM 2" printed in white ink on the capsule body. Capsule size 2 (approximately 18 mm in length).

3 mg strength: hard gelatin capsule, with a turquoise body and red cap, with "PLM 3" printed in white ink on the capsule body. Capsule size 2 (approximately 18 mm in length).

4 mg strength: Hard gelatin capsule, with a dark blue body and red cap, with "PLM 4" printed in white ink on the capsule body. Capsule size 2 (approximately 18 mm in length).

The finished product has been developed to be a generic equivalent to the reference medicinal product Imnovid. Consequently, the objective was to prepare a hard capsule being essentially similar to the reference medicinal product.

As the active substance exhibits very low solubility in aqueous media across the physiological pH range. Therefore, particle size distribution (PSD) of the active substance may impact the performance of the finished product. Therefore, the active substance is micronised to reduce particle size.

No incompatibilities between the active substance and the excipients have been found in literature, nor have been observed during the stability studies.

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 in paragraph 2.1.1 of this report.

The objective of the formulation development was to develop hard gelatin capsules containing 1, 2, 3 and 4 mg of pomalidomide with a dissolution and stability profile comparable to reference medicinal product. Quality by design was applied to develop the generic medicinal product, however, no design space was claimed for the finished product.

Based on the clinical and pharmacokinetic (PK) characteristics as well as the *in vitro* dissolution, physicochemical characteristics of the reference product and intellectual property restrictions, a quality target product profile (QTPP) was defined for the finished product.

A list of quality attributes (QA) was identified and it was discussed why some were identified as critical. Appearance, assay, uniformity of dosage units (UDU), impurities, disintegration, dissolution and water content, and microbial limits were identified as the subset of critical quality attributes (CQAs) with potential to be affected by the formulation and/or process variables; therefore, they were investigated in more detail during development.

During formulation optimisation, different types of fillers, addition of a disintegrant and stability of the proposed formulation were investigated.

A dissolution method was established for the finished product. The effect of different paddle speed was evaluated. The selected stirring speed has been sufficiently justified to avoid a coning effect observed at lower paddle speeds.

The dissolution method was found to be discriminatory (for the proposed dissolution limit) with respect to i particle size and stressed capsules (2 weeks storage at 60°C/75 % RH).

In vivo bioequivalence has been evaluated and demonstrated between the 4 mg capsules of the test formulation and the reference product. To support the results obtained in the bioequivalence study, the test of one batch of the bio-batch of the proposed 4 mg product and the reference medicinal product Imnovid 4 mg were tested across the physiological pH range (0.1 N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8) with paddle apparatus.

Dissolution of <85% within 15 minutes was observed across the physiological pH range (pH 1 – 6.8). Therefore, f_2 values were calculated. The *in vitro* dissolution of test and reference products can be considered similar only at the pH 6.8. However, the in *vivo* results show they are equivalent.

Comparative dissolution profiles were provided for one batch of the 1 mg, 2 mg and 3 mg strengths versus the 4 mg biobatch. Dissolution of <85% within 15 minutes was observed across the

physiological pH range (pH 1 – 6.8), the f2-values >50 were calculated for each strength in all three media.

Biowaiver of strengths 1 mg, 2 mg and 3 mg was applied. However, the biowaiver of lower strengths could not be accepted during the evaluation (MO), as not all conditions for the biowaiver were met. The comparative dissolution tests in support of the requested biowaiver of strengths were conducted at 100 rpm and RSD was too high at the first time point (over 20%) for 2 mg strength.

On the basis of the MO, comparative *in vitro* dissolution testing was performed with the 1 mg, 2 mg and 3 mg strength and the biobatch of 4 mg strength at 50 rpm in three pH media (pH 1.0, pH 4.5 and pH 6.8). As variability was too high, similarity factors were calculated using the bootstrapping method. All similarity factors are >50, except for the 1 mg strength at pH 4.5. Incomplete dissolution and high variability (expressed in terms of relative standard deviation, RSD) may be caused due to coning effect, which was supported by photographs. According to the pictures, residue of the finished product was observed in each medium at 50 rpm. This supports the fact that the use of dissolution data at 50 rpm would not be fully representative of the product's performance.

Moreover, f_2 values at pH 4.5 and 6.8 were recalculated using the bootstrapping method to support the biowaiver of 2 mg strength, since relatively high variability was observed, even at 100 rpm. The recalculated f_2 values were 51 in pH 4.5 and 45 in pH 6.8 (< 50). The applicant attributed this dissimilarity to the high RSD seen at 5 minutes caused by the capsule shell. This is further supported with calculated f_2 value without capsule shell or without first 5 min time point (with capsule shell). Although the dissolution studies for the biowaiver cannot conducted without capsule shell, the results nonetheless indicate that the capsule shell is a significant contributor to the observed variability at the 5-minute timepoint.

The biowaiver claim for the lower strengths (1 mg, 2 mg and 3 mg) at 100 rpm is considered acceptable as the coning effect is observed at lower speed (50 rpm). The applicant has sufficiently justified that the 5-minute timepoint can be ignored as it is not considered clinically relevant, given the capsule formulation. In this specific case, there are still sufficient time points to allow comparison of dissolution profiles without the 5-minute timepoint.

The manufacturing process development studies were based on the initial risk assessment. Previous experience was used to determine the degree of risk associated with each process step and its impact on the CQAs of the finished product.

Based on the results of the development studies, the control strategy for pomalidomide lab scale batches was determined, which includes pomalidomide and excipient material attributes to be controlled, proposed in-process controls and proposed ranges for the high-risk process parameters based on the development results.

In the qualification phase, scale-up trials were performed. The purpose of these trials was to optimise the manufacturing process at the batch size as intended for validation and commercial purposes.

After the scale up trials, two confirmatory batches of pomalidomide 1 mg and 4 mg capsules were produced to test the validity of the conclusions drawn during the scale up trials. The batches were manufactured at target conditions.

Upon manufacturing the scale up trial and qualification batches, it can be concluded that all the manufacturing steps for pomalidomide capsules (e.g., sieving of materials, blending and encapsulation) are reproducible and suitable for manufacturing the validation batches.

The primary packaging is OPA/Al/PVC/Al blister packs. The materials comply 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.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of 5 main steps: blend preparation, lubrication, encapsulation and packaging. The manufacturing process is considered to be non-standard, as the content of the active substance is low.

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.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), water content (KF), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), identification (HPLC, UV), assay (HPLC), impurities (HPLC), and microbial contamination (Ph. Eur.).

The proposed specification for the finished product is in line with ICH Q6A and it is generally acceptable for this type of dosage form.

The limit for the largest unspecified impurity is in line with ICH Q3B and is acceptable. The shelf-life limit for total impurities is in line with stability data and is acceptable.

Initially, dissolution limit was not in accordance with the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action EMA/CHMP/CVMP/QWP/336031/2017. Therefore, tightening of the dissolution limit was requested as a MO by the CHMP. The dissolution limit was tightened for all strengths which was accepted.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach. The evaluation of daily contribution of each individual component (i.e. active substance and excipients) has been provided for worst-case approach (4 capsules of Pomalidomide 1 mg). None of the elemental impurities exceeded 30% PDE threshold as per ICH Q3D so it was concluded that no further control of potential elemental impurities is needful at release or during the manufacturing process. It is acceptable that no additional controls are adopted.

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 appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results were provided for 3 commercial scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial batches per strength of finished product stored for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, dissolution, assay, and microbial contamination. The analytical procedures used are stability indicating. All stability results under long term and accelerated conditions were within the proposed specification limits. There is an increase in water content, however the other product quality parameters are not affected.

A bulk stability study was performed in one batch per strength at 25°C / 60% RH. The capsules were packed in double LDPE bags in a HDPE container with a desiccant bag in between the two LDPE bags. No significant changes were observed compared with the initial data.

In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No trends or out-of-specification results were observed. The results indicate that the finished product is photostable.

Based on available stability data, the proposed shelf-life of 3 years without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEPs from the suppliers of the gelatine used in the manufacture are provided.

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.

During evaluation, 3 major objections were raised by the CHMP in relation to definition of starting materials, dissolution data in support of the biowaiver of strengths and QC dissolution testing limits. The responses from the applicant to the MOs were considered satisfactory and all the issues were considered to be resolved, as explained above.

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.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design space was claimed for the manufacturing process of the finished product.

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 viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

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

No Environmental risk assessment (ERA) studies were submitted. This was justified by the applicant as the introduction of Pomalidomide Accord manufactured by Synthon Hispania S.L. Spain is considered unlikely to result in any significant increase in the combined sales volumes for all pomalidomide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The non-clinical sections of the proposed SmPC are identical to the reference product Imnovid.

The submitted non-clinical overview on the pre-clinical pharmacology, pharmacokinetics, and toxicology of pomalidomide is adequate. Grounds for non-providing new clinical data are adequately justified. The impurity profile and the safety of the excipients are considered acceptable.

Since proposed product is a generic product which does not include the addition of a new indication, a new patient population, or an increase in the maximum recommended therapeutic dose, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Pomalidomide Accord from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for hard capsules containing pomalidomide. To support the marketing authorisation application the applicant conducted one bioequivalence study with a cross-over design under fasting conditions. This study was the pivotal study for this application.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09 are of particular relevance.

GCP aspect

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

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

Exemption

The applicant requested a biowaiver for the 1, 2 and 3 mg strengths of pomalidomide capsules.

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 – January. 2010) biowaiver is justified when following conditions are fulfilled:
a) All the strengths are manufactured by the same manufacturer at the same manufacturing site using same manufacturing process.
b) The qualitative composition of the different strengths is the same.
c) The composition of the strengths is quantitatively proportional, i.e., the ratio between the amount of each excipient to the amount of active substance is the same for all the strengths.
d) The active substance exhibits a linear pharmacokinetics.
e) Similar *in vitro* dissolution data confirm the adequacy of waiving additional strengths from *in vivo* bioequivalence testing.

For Pomalidomide Accord capsules of strengths 1 mg, 2 mg, 3 mg, and 4 mg the conditions from a) to d) were fulfilled.

f_2 values calculated based on the dissolution results at paddle speed 100 rpm and with deletion of the 5 minutes time point confirm similarity of dissolution profiles of biobatch (4 mg) with lower strength batches (1 mg, 2 mg and 3 mg) in all relevant media (0.1 N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8).

f_2 at:	**0.1 N HCl (pH 1.0)**	**pH 4.5**	**pH 6.8**
4 mg vs. 1 mg	58	55	66
4 mg vs. 2 mg	69	83	67
4 mg vs. 3 mg	71	89	71

Tabular overview of clinical studies

To support the application, the applicant has submitted one bioequivalence study (Study Report Number Altasciences: SHO-P4-644).

Study Identifier	***Objective(s) of the Study***	***Study Design and Type of Control***	***Test Product(s); Dosage Regimen; Route of Administration***	***Number of Subjects***	***Healthy Subjects or Diagnosis of Patients***	***Duration of Treatment***	***Study Status; Type of Report***
SHO-P4-644	To determine the bioequivalence of two different formulations of pomalidomide after a single oral dose administration under fasting conditions.	Crossover, Fasting State	Test product: Pomalidomide 4 mg capsules Reference product: Imnovid 4 mg capsules (containing pomalidomide) ; 4 mg single dose; oral	Enrolled: 38; Withdrawn: 1; Completed: 37. Analyzed: 38; Pharmacokinetic and statistical analysis: 37 Safety analysis: 38	Healthy Subjects	Single dose	Complete; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study No: SHO-P4-644: Single dose, open label, randomized, two-treatment, two-sequence, two-period, crossover bioequivalence study comparing Pomalidomide 4 mg capsules with Imnovid 4 mg capsules (containing pomalidomide) in healthy adult male subjects under fasting conditions.

Methods

- **Study design**

This was a single oral dose, open labelled, randomised, two-period, two-treatment, two-sequence, cross over study conducted under fasting conditions. For the bioequivalence study the highest strength 4 mg of the pomalidomide immediate release formulation, test, and reference, was used. (For lower strengths- 1 mg, 2 mg, and 3 mg capsules- the biowaiver was claimed.) All is in line with the requirements of the "Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 01 – January 2010)" and the SmPC of the reference product, where is stated the formulation can be taken independent of meals and that pomalidomide exhibits a linear pharmacokinetics.

Subjects were randomly assigned to one of the two treatment sequences according to the randomisation schedule, which was created using software SAS.

As reported the blinding was conducted on the personnel of the bioanalytical facility and study participants who were only informed that they would receive Test or Reference product.

	Period 1	Period 2
Sequence AB	Test	Reference
Sequence BA	Reference	Test

Test = A; Reference = B

Subjects were admitted to the clinical research unit at least 10 hours prior to drug administration for each study period. For each study period, subjects received a single 4 mg oral dose of pomalidomide in the morning, after a supervised overnight fast. The chosen sampling schedule and period was sufficient to obtain a proper description of the plasma concentration over time to estimate PK parameters (T_{max} between 2-3 h), including extrapolated values. Considering the $t_{1/2}$ of pomalidomide (9,5h in healthy subjects) the 7 days washout period was considered sufficient (more than 5 half-lives).

Food and fluid intake was standardised, except for water which was provided ad libitum until 1-hour predose and 1 hour after the administration of the drug. Subjects fasted overnight for at least 10 hours prior to drug administration and until at least 4 hours after drug administration, when a standardised lunch was served.

In this study the plasma concentrations of pomalidomide were directly measured. In each study period, 21 blood samples were collected by direct venipuncture.

- **Test and reference products**

The information regarding test and reference product is summarised in the Tabular Overview presented below.

Product Characteristics	*Test Product*	*Reference Product*
Name:	Pomalidomide 4 mg capsules	Imnovid 4 mg hard capsules
Strength:	4 mg pomalidomide per capsule	4 mg pomalidomide per capsule
Dosage form:	Capsule	Capsule
Manufacturer:	Synthon Hispania S.L., Spain	Marketing Authorization Holder: Celgene Europe B.V., The Netherlands
Batch number:	190048	C2225AB
Batch size (biobatch):	11.0 kg (57,894 capsules)*	
Measured content(s): (% of label claim)	4.0 mg/capsule 100.9 %	4.1 mg/capsule 102.3 %
Commercial Batch Size:	11.0 kg (57,894 capsules)*	
Expiry date (Retest date):	December 2021	March 2022
Location of Certificate of Analysis:	Module 5.3.1.2 - Section 16.1.7.2	Module 5.3.1.2 - Section 16.1.7.2
Member State where the reference product is purchased from:		Denmark
This product was used in the following trials:	SHO-P4-644 (CT.PLM.cap4.19.001)	SHO-P4-644 (CT.PLM.cap4.19.001)

* Pomalidomide capsules is a generic of an orphan medicinal product (Imnovid) intended for the treatment of multiple myeloma. As volumes are expected to be low, a full commercial scale batch (less than 100,000 units) is used in the bioequivalence study.

The certificates of analysis for the test and the reference product bio-batch have been provided and the difference in content of active substance between reference and test product is less than 5.0%. The test product used in the bioequivalence study has the same qualitative and quantitative composition and is manufactured by the same manufacturing process as the medicinal product submitted for authorisation. The reference product is EU-registered and obtained in Denmark. The above-mentioned is in accordance with the Guideline on the Investigation of Bioequivalence.

- **Population studied**

A total of 38 healthy adult male subjects with mean age 40 years (±12, 20-59), weight 80.5 kg (±9.4, 59.4-107.3), height 177.8 cm (±6.5, 163.5 – 196.9), BMI 25.4 (±2.2, 19.8 – 29.3) and race: 28 white, 2 Asian, 8 black or African American; were included in this study. All the subjects meet all the inclusion and none of the exclusion criteria and were of normal health based on general physical examination and laboratory tests. None of the subjects had any relevant or significant previous medical history that could affect the study results.

The number of subjects was calculated based on the following estimates: T/R ratio of geometric LS means should fall within 95 and 105 %, maximum Intra-Subject CV up to 26.2% (C_{max}), power of at least 85%, level of significance 5%, bioequivalence limits = 80 – 125%. The assessment of 36 subjects was base for inclusion of 38 subjects in the study.

From the 38 subjects, who were included in the study, 37 subjects completed the study and were included in the PK and statistical evaluation. One subject (037) withdrew consent from the study for personal reasons on 14th February 2020 after dosing of period 1 and only received the Reference in period 1. Pomalidomide plasma concentrations of this subject were presented by applicant but were not included in pharmacokinetic and statistical analysis.

The study population was chosen according to the Guideline on the Investigation of Bioequivalence.

Protocol deviations

No major protocol deviations were reported.

- **Analytical methods**

Pre-study method validation

The bioanalytical HPLC-MS/MS method for the quantification of pomalidomide in human plasma (containing K_2EDTA as an anticoagulant) was validated according to SOP LAS-1742-01 for Determination of Pomalidomide in Human Plasma Using HPLC with MS/MS Detection (LOQ 0.500 ng/ml, ULQ 150.000 ng/ml).

Bioanalytical method validation was performed at the bioanalytical facility

Bioanalytical method validation was evaluated according to the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) since analysis of study samples was performed before the ICH M10 Guideline (EMA/CHMP/ICH/660315/2022) has become effective (January 2023). The bioanalytical assay was sufficiently validated, validation was completed prior to the start of sample analysis. All parameters requested according to Guideline on the bioanalytical method validation were validated. Long-term stability was demonstrated for 41 days, which covers the maximum storage period of 32 days.

Study sample analysis and in-study validation

Bioanalytical report SHO-P4-644 Study for the determination of pomalidomide in human plasma using HPLC with MS/MS detection, dated 11th May 2020 was provided.

A validated HPLC method using MS/MS detection was employed in determining sample concentrations of Pomalidomide in human plasma. A Bioanalytical Plan containing information about the conduct of the bioanalytical portion of the study was completed and approved (18th February 2020) prior to sample analysis. The bioanalytical method SOP LAS-1742 details sample pre-treatment procedures,

chromatographic conditions, stock solution preparation procedures, and standard and QC sample preparation procedures. Other relevant bioanalytical SOPs have been provided.

The analytical method used for the study samples analysis is the same as the validated method (bioanalytical method SOP LAS-1742).

Subject samples details:

Expected as per protocol	1596 (38 subjects x 21 time points x 2 period)
Received samples	1575
Missing samples not received (e.g. dropouts, empty, missed blood draw, etc.)	21 (subject 37, all samples of period 2)
Received and not analyzed	1 (subject 5, period 1, 2h: sample was collected however, the volume of plasma obtained (less than 0.5 mL) was not sufficient for processing with acidification)
Received and analysis not required (e.g. placebos, alternates, dropouts, etc.)	N/AP
Number of samples analyzed	1574

Standard concentrations ranged from 0.500 ng/mL to 150.000 ng/mL (10 calibration standards). QC sample concentrations were 1.500 ng/mL, 6.000 ng/mL, 10.000 ng/mL, 20.000 ng/mL, 75.000 ng/mL and 112.500 ng/mL.

As potential significant carryover is expected with this bioanalytical method, samples were injected using ordered (i.e. non-randomised) sequences, where the order in which the samples are injected is chosen such that the impact can be minimised.

Quality assurance statement and Bioanalytical principal investigator's statement have been included in the bioanalytical report. Certificates of analysis of reference standard and internal standard used in study sample analysis have been provided.

Analytical method has been suitably within-study validated. Structure of analytical run (10 calibration standards, quality control samples in duplicate, study samples, zero samples, blank samples) was acceptable. All performed analytical runs met analytical run acceptance criteria. There were no rejected analytical runs. None of the analytical run was reinjected. There were no samples repeated for bioanalytical reasons.

134 study samples out of 1574 study samples were considered for ISR evaluation. It represents more than 10 % of the first 1000 samples and 5 % of the number of samples exceeding 1000 samples (574). Results of incurred sample reanalysis confirms the reproducibility of the analytical method.

The method was sensitive enough to quantify levels of 5% of the lowest C_{max} measured in the study.

There were no protocol, bioanalytical plan or SOP deviations.

In-study validation as well as ISR results demonstrated reliable performance of the method that was used during analyses of the samples from the study SHO-P4-644.

It is confirmed that the same type of bioanalytical devices was used during the validation and the bioanalysis (HPLC MS/MS API-5000). The analytical method used for the study samples analysis is the same as the validated method (bioanalytical method SOP LAS-1742).

- **Pharmacokinetic Variables**

The primary study endpoints were the pharmacokinetic (PK) parameters C_{max} and AUC_{0-t} of the pomalidomide. Also, secondary parameters T_{max}, $AUC_{0-\infty}$, Residual Area, λ_Z and $t_{1/2}$ were estimated. PK parameters were calculated by a non-compartmental approach using software Phoenix® WinNonlin® 8.0.

The area under the curve (AUC) was calculated by Linear Up Log Down trapezoidal rule. The terminal phase estimation was based on maximizing the coefficient of determination. Except for the subject (07) in first period (coefficient of determination for λ_Z was less than 80%), all the individual parameters of terminal phase (λ_Z, $AUC_{0-\infty}$, residual area, and $t_{1/2}$) were estimated.

The presentation of PK data and calculation of PK variables were in line with requirements of Guideline on the Investigation of Bioequivalence.

- **Statistical methods**

Descriptive statistics were calculated for plasma concentrations at each individual time point and for all PK parameters.

As certain PK parameters (λ_Z, $AUC_{0-\infty}$, residual area, and $t_{1/2}$) could not be determined for the first period in the subject (07), the corresponding subject was excluded from statistical comparison of that PK parameters. There was no influence on bioequivalence conclusion because it is based on C_{max} and AUC_{0-t} PK parameters.

The influence of the period, the sequence, and the treatment on the parameter T_{max} was determined using a non-parametric approach, that is the Wilcoxon's rank sum test or Mann-Whitney U-test. Natural logarithmic transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were statistically analysed using a parametric analysis of variance model (ANOVA). The fixed factors were the subject (nested within sequence), the treatment, the period, and the sequence effect at the 5% significance level. The conducted statistical analysis and explanations were appropriate.

Criteria for conclusion of bioequivalence: The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and the Reference for the ln-transformed parameters C_{max} and AUC_{0-t} should be within the 80.00 to 125.00% bioequivalence acceptance range.

Results

Table 1. Pharmacokinetic parameters for pomalidomide (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	SD	Arithmetic mean	SD
$AUC_{(0-t)}$ (ng.h/mL)	506.201	153.040	508.810	161.223
$AUC_{(0-\infty)}$ (ng.h/mL)	517.348	155.598	523.527	159.973
C_{max} (ng/mL)	53.402	11.038	59.400	12.525
T_{max}* (h)	3.00 (1.50 – 6.02)		2.00 (0.67 – 5.50)	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 2. Statistical analysis for pomalidomide (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	99.82	97.07 – 102.65	7.1
$AUC_{(0-\infty)}$	98.87	96.45 – 101.35	6.2
C_{max}	89.94	86.23 – 93.81	10.8
* estimated from the Residual Mean Squares			

The calculated 90% CI for C_{max} and AUC_{0-t} were within the 80.00-125.00% acceptance range. Therefore, based on this study, bioequivalence for the 4 mg strength under fasting conditions is considered demonstrated.

There were no pre-dose concentrations observed in any subject in any period.

C_{max} was not the first point in the concentration time curve in any of the subjects in both periods.

No dilution of study samples was needed for the current study.

Extrapolated area values were under 20% in all subjects, confirming that the sampling covered the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure.

As expected, the subject (nested in sequence) effect was found significant for ln-transformed C_{max}, AUC_{0-t} and AUC_{0-inf}. The observed statistically significant difference between treatments for ln transformed C_{max} based on ANOVA model, does not have an impact on the bioequivalence assessment, since the bioequivalence assessment is based on a CI approach that estimates similarity of the test and reference product.

- **Safety data**

Administration of the Test and Reference products to healthy subjects in this study was safe and well tolerated. No deaths or SAEs occurred in the study. Also, no subject was withdrawn by the investigator due to an AE (safety reasons).

A total of 18 AEs were experienced by 9 of the 38 subjects (24%) who participated in this study. Of these AEs, 10 occurred after administration of the Test product and 8 occurred after administration of the Reference product. Most of the AEs experienced during the study were considered drug-related (17/18; 94%). All AEs experienced during the study were resolved or were resolving at the end of the study. -The AE experienced most commonly in this study was headache, reported by 1 subject (3%) after administration of the Test product and 3 subjects (8%) after administration of the Reference product. Another AE experienced less frequently included fatigue, reported by 2 subjects (5%) after administration of the Test. The remaining AEs of dizziness, hypoaesthesia, vessel puncture site swelling, abdominal pain upper, dry mouth, increased appetite, muscular weakness, cough, erythema, and pruritus were experienced by no more than 1 subject (3%) per treatment group.

In general, there were no clinical laboratory results that were considered CS by the investigator. Furthermore, there were no out-of-range vital signs considered CS reported in this study.

No additional concern arises regarding the safety of the test product.

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 has submitted the results of a randomised, single dose, laboratory-blinded, 2-treatment, 2-period, 2-sequence, crossover bioequivalence study under fasting conditions to demonstrate essential similarity with the reference product Imnovid hard capsules.

The bioequivalence study SHO-P4-644 has been conducted with the highest strength, 4 mg. For the lower strengths, 1 mg, 2 mg and 3 mg, a biowaiver was requested. The comparative dissolution tests in support of the requested biowaiver of strengths were conducted at 100 rpm.

The applicant demonstrated that the coning effect occurred at 50 rpm. Therefore, the selected higher paddle speed of 100 rpm was justified. In addition, comparing dissolution profiles omitting the 5-minute time point was also considered acceptable, considering the high variability which was observed and that such an early time point is not clinically relevant and is also in accordance with Guideline on the investigation of bioequivalence. The request of the biowaiver of lower strengths was thus considered acceptable.

According to the SmPC of the reference product, pomalidomide 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. The washout period of 7 days is long enough regarding the half-life of the studied active substance pomalidomide. Sampling period was sufficient, sampling time schedule was adequate.

A total of 38 male subjects were included in this study. Population was chosen according to protocol of the study (inclusion and exclusion criteria). 37 subjects received the test and 38 subjects received the reference product. One subject discontinued the study for personal reasons. 37 subjects completed the study and were included in the PK evaluation. Case report form for subject 37 who discontinued from the study has been provided. It is confirmed that subject 37 withdrew consent from the study for personal reasons. Plasma samples for drop-out subject 37 were assayed and pomalidomide concentrations are provided.

The bioanalytical method for quantification of pomalidomide (parent drug) in human plasma samples was pre-study and in-study validated according to Guideline on bioanalytical method validation. The bioanalytical method is considered acceptable for study samples analysis. The applicant confirmed that the same type of bioanalytical devices was used during the validation and the bioanalysis.

Primary pharmacokinetic parameters were C_{max} and AUC_{0-t} of pomalidomide. Additional PK parameters estimated were AUC_{0-inf}, T_{max}, T_{LQC}, T_{LIN}, residual area, K_{el} and $t_{1/2}$. Evaluation of plasma PK parameters was based on actual PK sampling times. The main absorption and disposition parameters were calculated using a non-compartmental approach. The linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations was used to estimate the area under the curve.

Statistical methods described are in accordance with the Guideline on the Investigation of Bioequivalence. The natural logarithmic transformation of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were used for all statistical inference. Pharmacokinetic parameters were statistically analysed using an ANOVA model. The fixed factors included in this model at the 5% significance level were the subject (nested within sequence), the treatment, the period and the sequence effects. Handling of missing data was appropriate. Statistical analysis has been performed using SAS statistical software (version 9.4) using the GLM procedure.

The criteria for bioequivalence were predefined and are acceptable. The calculated 90% CI for C_{max} and AUC_{0-t} were within the 80.00-125.00% acceptance range. Therefore, based on this study, bioequivalence for the 4 mg strength under fasting conditions is considered demonstrated.

Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study. The products had similar safety profiles. No additional concern arises regarding the safety of the test product.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study Pomalidomide Accord is considered bioequivalent with Imnovid.

The results of study SHO-P4-644 with the 4mg formulation CAN be extrapolated to other strengths 1mg, 2mg, 3mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 3. Summary of safety concerns

Important identified risks	• Teratogenicity • Severe infection due to neutropenia and pancytopenia • Thrombocytopenia and bleeding • Cardiac failure • Non-melanoma skin cancer
Important potential risks	• Other second primary malignancies • Cardiac arrhythmia
Missing information	• None

2.5.2. Pharmacovigilance plan

Study; Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due dates**
Category 3: Monitoring of implementation of the PPP				
Short title: Pregnancy	To monitor the implementation	Teratogenicity	Data will be collected on a	Data will be reviewed on an on-going basis

Study; Status	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
prevention programme for Pomalidomide (Category 3 study) Status: Planned	of the PPP on a country-specific basis		regular basis after product launch and to report results in PSURs, in accordance with the PSUR schedule, in-line with DLP of latest EURD list	as a part of signal detection and reported within PSURs in-line with EURD list

2.5.3. Risk minimisation measures

Safety concern	Risk minimisation measures
Teratogenicity	Routine risk minimisation measures: • SmPC sections 4.3, 4.4, 4.6, 4.8 and 5.3 • PIL section 02 • The prescription only status of the product Additional risk minimisation measures: • Pregnancy Prevention Programme (PPP)
Severe infection due to neutropenia and pancytopenia	Routine risk minimisation measures: • SmPC sections 4.2, 4.4 and 4.8 • PIL sections 02 and 04 • The prescription only status of the product Additional risk minimisation measures: None
Thrombocytopenia and bleeding	Routine risk communication: • SmPC section 4.2, 4.4 and 4.8 • PIL sections 02 and 04

Safety concern	Risk minimisation measures
	• The prescription only status of the product. Additional risk minimisation measures: • Additional HCP Educational Materials • Additional Patient Educational Material
Cardiac failure	Routine risk communication: • SmPC section 4.4 and 4.8. • PIL sections 02 and 04 • The prescription only status of the product Additional risk minimisation measures: • Additional HCP Educational Materials
Non-Melanoma Skin Cancer	Routine risk communication: • SmPC section 4.4 and 4.8 • PIL sections 02 and 04 • The prescription only status of the product Additional risk minimisation measures: None
Other second Primary Malignancies	Routine risk communication: • SmPC section 4.4 • PIL sections 02 • The prescription only status of the product Additional risk minimisation measures: None
Cardiac Arrhythmia	Routine risk communication: • SmPC section 4.4 and 4.8 • PIL section 04

Safety concern	Risk minimisation measures
	• The prescription only status of the product Additional risk minimisation measures: None

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 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 Imnovid 1/2/3/4 mg hard capsules and Solifenacin succinate 5/10 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of pomalidomide hard capsules. The reference product Imnovid is indicated for:

- in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

- in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical 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 is considered sufficient.

The bioequivalence study forms the pivotal basis with a single centre, randomised, single dose, laboratory-blinded, 2-treatment, 2-period, 2-sequence, crossover design under fasting conditions. The study design is 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 Imnovid 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 pomalidomide 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 are adequate.

The test formulation of Pomalidomide Accord 4 mg hard capsules met the protocol-defined criteria for bioequivalence when compared with the reference product Imnovid 4 mg capsules hard. 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 is thus considered to be demonstrated.

The results of study SHO-P4-644 with the 4 mg formulation can be extrapolated to other strengths 3 mg, 2 mg and 1 mg, according to conditions in the Guideline on the Investigation of Bioequivalence.

A benefit/risk ratio comparable to the reference product can be concluded.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Pomalidomide Accord is not similar to Abecma (Idecabtagene vicleucel), Blenrep (Belantamab mafodotin), Carvykti (Ciltacabtagene autoleucel), Darzalex (Daratumumab), Farydak (Panobinostat), Kyprolis (Carfilzomib), Ninlaro (Ixazomib), and Talvey (talquetamab) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

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

Pomalidomide Accord in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

Pomalidomide Accord in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last 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.

- **Additional risk minimisation measures**

1. The MAH shall agree the details of a controlled access programme with the National Competent Authorities and must implement such programme nationally to ensure that:
   - Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) pomalidomide are provided with an Educational Healthcare Professional's Kit containing the following:
     - Educational Healthcare Professional brochure
     - Educational brochures for patients
     - Patient card
     - Risk awareness forms
     - Information on where to find latest Summary of Product Characteristics (SmPC)
2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the launch of the medicinal product.
3. The MAH should agree on the implementation of the controlled access programme in each Member State.
4. The MAH should agree the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.

Key elements to be included

Educational Healthcare Professional's Kit

The Educational Healthcare Professional's Kit shall contain the following elements:

Educational Healthcare Professional brochure

- Brief background on pomalidomide
- Maximum duration of treatment prescribed
    - 4 weeks for women with childbearing potential
    - 12 weeks for men and women without childbearing potential
- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Guidance on handling the blister or capsule of Pomalidomide for healthcare professionals and caregivers
- Obligations of the healthcare professionals who intend to prescribe or dispense pomalidomide
    - Need to provide comprehensive advice and counselling to patients
    - That patients should be capable of complying with the requirements for the safe use of pomalidomide
    - Need to provide patients with appropriate patient educational brochure, patient card and/or equivalent tool
- Safety advice relevant to all patients
    - Description and management of thrombocytopenia including incidence rates from clinical studies
    - Description and management of cardiac failure
    - Local country specific arrangements for a prescription for pomalidomide to be dispensed
    - That any unused capsules should be returned to the pharmacist at the end of the treatment
    - That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide
- Description of the PPP and categorisation of patients based on sex and childbearing potential
    - Algorithm for implementation of PPP
    - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if unsure
- Safety advice for women of childbearing potential
    - The need to avoid foetal exposure
    - Description of the PPP
    - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
    - That if she needs to change or stop using her method of contraception she should inform
        - The physician prescribing her contraception that she is on pomalidomide
        - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
    - Pregnancy test regime
        - Advice on suitable tests
        - Before commencing treatment
        - During treatment based on method of contraception
        - After finishing treatment
    - Need to stop pomalidomide immediately upon suspicion of pregnancy

    - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
    - The need to avoid foetal exposure
    - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had a vasectomy)
        - During pomalidomide treatment
        - For at least 7 days following final dose
    - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide treatment
    - That if his partner becomes pregnant whilst he is taking pomalidomide or shortly after he has stopped taking pomalidomide he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop pomalidomide immediately upon suspicion of pregnancy, if female patient
    - Need to refer patient to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy immediately
    - Pregnancy reporting form
- Local contact details for reporting adverse reactions

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

- Brochure for women patients of childbearing potential and their partner
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All educational brochures for patients should contain the following elements:

- That pomalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That pomalidomide may cause thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Guidance on handling pomalidomide for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for pomalidomide to be dispensed
- That the patient must not give pomalidomide to any other person
- That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days after discontinuation of pomalidomide treatment
- That the patient should tell their doctor about any adverse events
- That any unused capsules should be returned to the pharmacist at the end of the treatment

The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential

- The need to avoid foetal exposure
- Description of the PPP
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:

    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
- Pregnancy test regime
    - Before commencing treatment
    - During treatment (including dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop pomalidomide immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP and not using effective contraception (even if the man has had vasectomy)
    - During pomalidomide treatment (including dose interruptions)
    - For at least 7 days following final dose
- That if his partner becomes pregnant, he should inform his treating doctor immediately
- That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide treatment

Patient Card or equivalent tool

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Check box (or similar) which physician ticks to confirm that patient is using effective contraception (if woman of childbearing potential)
- Pregnancy test dates and results

Risk Awareness Forms

There should be 3 types of risk awareness forms:

- Women of childbearing potential
- Women of non-childbearing potential
- Male patient

All risk awareness forms should contain the following elements:

- teratogenicity warning
- patients receive the appropriate counselling prior to treatment initiation
- affirmation of patient understanding regarding the risk of pomalidomide and the PPP measures
- date of counselling
- patient details, signature and date
- prescriber name, signature and date
- aim of this document i.e. as stated in the PPP: "The aim of the risk awareness form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of pomalidomide. It is not a contract and does not absolve anybody from his/her responsibilities with regard to the safe use of the

product and prevention of foetal exposure."

Risk awareness forms for women of childbearing potential should also include:

- Confirmation that the physician has discussed the following:
    - the need to avoid foetal exposure
    - that if she is pregnant or plans to be, she must not take pomalidomide
    - that she understands the need to avoid pomalidomide during pregnancy and to apply effective contraceptive measures without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
    - that if she needs to change or stop using her method of contraception she should inform:
        - the physician prescribing her contraception that she is taking Pomalidomide
        - the physician prescribing pomalidomide that she has stopped or changed her method of contraception
    - of the need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and after treatment
    - of the need to stop pomalidomide immediately upon suspicion of pregnancy
    - of the need to contact their doctor immediately upon suspicion of pregnancy
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide
    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for women with no childbearing potential should also include:

- Confirmation that the physician has discussed the following:
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide
    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for male patients should also include:

- Confirmation that the physician has discussed the following:
    - the need to avoid foetal exposure
    - that pomalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a WCBP not on effective contraception (even if the man has had a vasectomy)
    - that if his partner becomes pregnant, he should inform his treating doctor immediately and always use a condom
    - that he should not share the medicinal product with any other person
    - that he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide
    - that he should return the unused capsules to the pharmacist at the end of treatment

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

1. The MAH shall agree the details of a controlled access programme with the National

Competent Authorities and must implement such programme nationally to ensure that:

- Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) pomalidomide are provided with an Educational Healthcare Professional's Kit containing the following:
    - Educational Healthcare Professional brochure
    - Educational brochures for patients
    - Patient card
    - Risk awareness forms
    - Information on where to find latest Summary of Product Characteristics (SmPC)

2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the launch of the medicinal product.
3. The MAH should agree on the implementation of the controlled access programme in each Member State.
4. The MAH should agree the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.

Key elements to be included

Educational Healthcare Professional's Kit

The Educational Healthcare Professional's Kit shall contain the following elements:

Educational Healthcare Professional brochure

- Brief background on pomalidomide
- Maximum duration of treatment prescribed
    - 4 weeks for women with childbearing potential
    - 12 weeks for men and women without childbearing potential
- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Guidance on handling the blister or capsule of Pomalidomide for healthcare professionals and caregivers
- Obligations of the healthcare professionals who intend to prescribe or dispense pomalidomide
    - Need to provide comprehensive advice and counselling to patients
    - That patients should be capable of complying with the requirements for the safe use of pomalidomide
    - Need to provide patients with appropriate patient educational brochure, patient card and/or equivalent tool
- Safety advice relevant to all patients
    - Description and management of thrombocytopenia including incidence rates from clinical studies
    - Description and management of cardiac failure
    - Local country specific arrangements for a prescription for pomalidomide to be dispensed
    - That any unused capsules should be returned to the pharmacist at the end of the treatment

    - That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide
- Description of the PPP and categorisation of patients based on sex and childbearing potential
    - Algorithm for implementation of PPP
    - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if unsure
- Safety advice for women of childbearing potential
    - The need to avoid foetal exposure
    - Description of the PPP
    - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
    - That if she needs to change or stop using her method of contraception she should inform
        - The physician prescribing her contraception that she is on pomalidomide
        - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
    - Pregnancy test regime
        - Advice on suitable tests
        - Before commencing treatment
        - During treatment based on method of contraception
        - After finishing treatment
    - Need to stop pomalidomide immediately upon suspicion of pregnancy
    - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
    - The need to avoid foetal exposure
    - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had a vasectomy)
        - During pomalidomide treatment
        - For at least 7 days following final dose
    - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide treatment
    - That if his partner becomes pregnant whilst he is taking pomalidomide or shortly after he has stopped taking pomalidomide he should inform his treating doctor immediately
- Requirements in the event of pregnancy
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- That the patient should tell their doctor about any adverse events
- That any unused capsules should be returned to the pharmacist at the end of the treatment

The following information should also be provided in the appropriate brochure:

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    - After finishing treatment
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- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP and not using effective contraception (even if the man has had vasectomy)
    - During pomalidomide treatment (including dose interruptions)
    - For at least 7 days following final dose
- That if his partner becomes pregnant, he should inform his treating doctor immediately
- That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide treatment

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Risk awareness forms for women of childbearing potential should also include:

- Confirmation that the physician has discussed the following:
    - the need to avoid foetal exposure
    - that if she is pregnant or plans to be, she must not take pomalidomide
    - that she understands the need to avoid pomalidomide during pregnancy and to apply effective contraceptive measures without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
    - that if she needs to change or stop using her method of contraception she should inform:
        - the physician prescribing her contraception that she is taking Pomalidomide
        - the physician prescribing pomalidomide that she has stopped or changed her method of contraception
    - of the need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and after treatment
    - of the need to stop pomalidomide immediately upon suspicion of pregnancy
    - of the need to contact their doctor immediately upon suspicion of pregnancy
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide
    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for women with no childbearing potential should also include:

- Confirmation that the physician has discussed the following:
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide
    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for male patients should also include:

- Confirmation that the physician has discussed the following:
    - the need to avoid foetal exposure
    - that pomalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a WCBP not on effective contraception (even if the man has had a vasectomy)
    - that if his partner becomes pregnant, he should inform his treating doctor immediately and always use a condom
    - that he should not share the medicinal product with any other person
    - that he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide
    - that he should return the unused capsules to the pharmacist at the end of treatment

These conditions fully reflect the advice received from the PRAC.