EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 January 2022
EMA/246681/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vildagliptin/Metformin hydrochloride Accord

International non-proprietary name: vildagliptin / metformin hydrochloride

Procedure No. EMEA/H/C/005738/0000

Note

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

Administrative information

Name of the medicinal product:	Vildagliptin/Metformin hydrochloride Accord
Applicant:	Accord Healthcare S.L.U. World Trade Center Moll de Barcelona S/N Edifici Est, 6a Planta 08039 Barcelona SPAIN
Active substance:	Vildagliptin/ Metformin hydrochloride
International Nonproprietary Name/Common Name:	vildagliptin / metformin hydrochloride
Pharmaco-therapeutic group (ATC Code):	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS, Combinations of oral blood glucose lowering drugs (A10BD08)
Therapeutic indication(s):	Vildagliptin/Metformin hydrochloride Accord is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus: - in patients who are inadequately controlled with metformin hydrochloride alone. - in patients who are already being treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets. - in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	50 mg / 850 mg and 50 mg / 1000 mg
Route(s) of administration:	Oral use

Packaging:	blister (Alu/Alu)
Package size(s):	30 tablets and 60 tablets

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List of abbreviations

AE	Adverse event
AR	assessment report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	Area under the plasma concentration versus time curve
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve from time
AUC_{0-t}	Area under the plasma concentration versus time curve from time
BE	Bioequivalence
BMI	Body mass index
CEP	Certificate of Suitability of the EP
CQA	Critical Quality Attribute
Cmax :	Maximum measured concentration of drug in plasma
DSC	Differential scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
ee	enantiomeric excess
EP	European Pharmacopoeia
ERA	Environmental Risk Assessment
FDA	US Food and Drug Administration
GC	Gas chromatography
GMP	good manufacturing practice
HDPE	high density polyethylene
HPLC	High performance liquid chromatography
HM-HDPE :	High Molecular High Density Polyethylene
ICH	International conference on harmonization
ICP	Inductively coupled plasma
IPA	isopropyl alcohol
IR	Infra-red
KF	Karl Fischer
LC	Liquid Chromatography
LDPE	Low Density Polyethylene

LLDPE Linear Low Density Polyethylene

MAA : Marketing Authorisation Application

MS Mass spectroscopy

MW Molecular Weight

NDMA N-Nitrosodimethylamine

NMR Nuclear magnetic resonance

PET : Polyethylene terephthalate

PSD Particle Size Distribution

Ph.Eur. European Pharmacopoeia

QTPP Quality Target Profile

RH Relative Humidity

SmPC : Summary of product characteristics

t1/2 : Elimination half-life

tmax : Time to reach the maximum concentration of drug in plasma

UDU Uniformity of Dosage Units

UV Ultra violet

XRD X-Ray Diffraction

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 23 October 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Vildagliptin/Metformin hydrochloride 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 17 September 2020.

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 indication:

Vildagliptin/Metformin hydrochloride Accord is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:

- in patients who are inadequately controlled with metformin hydrochloride alone.
- in patients who are already being treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.
- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

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 two bioequivalence studies with the reference medicinal product Eucreas 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 10 years in the EEA:

- Product name, strength, pharmaceutical form: Eucreas 50 mg/850 mg and 50 mg/1000 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 14-11-2007
- Marketing authorisation granted by:
  - Union

- Union Marketing authorisation number: EU/1/07/425/001-054

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

- Product name, strength, pharmaceutical form: Eucreas 50 mg/850 mg and 50 mg/1000 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 14-11-2007
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/07/425/001-054

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: Eucreas 50 mg/850 mg and 50 mg/1000 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 14-11-2007
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/07/425/001-054

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: Tomas Radimersky

The application was received by the EMA on	23 October 2020
The procedure started on	24 December 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 March 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	25 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 July 2021
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	23 August 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	16 November 2021
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	01 December 2021
The CHMP agreed on a second list of outstanding issues to be sent to the applicant on	16 December 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on	12 January 2022
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 Vildagliptin/Metformin hydrochloride Accord on	27 January 2022

2. Scientific discussion

2.1. Introduction

This centralised application for a marketing authorisation concerns a generic application according to article 10(1) of Directive 2001/83/EC for Vildagliptin/Metformin hydrochloride Accord (vildagliptin/metformin hydrochloride), film-coated tablets, 50 mg / 850 mg and 50 mg / 1000 mg. Application has been submitted by the applicant Accord Healthcare S.L.U., Spain.

The reference medicinal product is Eucreas available in the form of 50 mg / 850 mg and 50 mg / 1000 mg film-coated tablets (MAA No: EU/1/07/425, Novartis Europharm Limited, Ireland) authorised on 14 November 2007 in the EU.

Vildagliptin/Metformin hydrochloride Accord has the same quantity of the active substance, same pharmaceutical form, strengths and route of administration as the chosen reference medicinal product.

In addition, the proposed indication and posology are in line with the chosen reference medicinal product.

Two bioequivalence (BE) studies (one for the 50 mg/850 mg strength and one for the 50 mg/1000 mg strength) have been performed using the reference medicinal product, Eucreas.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 50 mg/850 mg or 50 mg/1000 mg of vildagliptin/metformin hydrochloride as active substances.

Other ingredients are hydroxypropylcellulose, low-substituted hydroxypropylcellullose, microcrystalline cellulose, magnesium stearate in the tablet core and hypromellose, titanium dioxide (E171), iron oxide yellow (E172), macrogol 6000 and talc in the film-coating.

The product is packed in aluminium-aluminium (Alu-Alu) blisters.

2.2.2. Active substance vildagliptin

2.2.2.1. General Information

The chemical name of vildagliptin is 2(S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl] pyrrolidine-2-carbonitrile corresponding to the molecular formula $C_{17}H_{25}N_3O_2$. It has a relative molecular mass of 303.39 g/mol and the following structure:

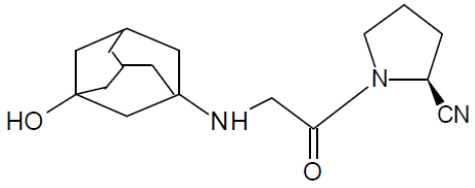

Figure 1: Vildagliptin active substance structure

The chemical structure of vildagliptin was elucidated by a combination of IR spectroscopy, mass spectrometry, ^{13}C-NMR spectroscopy, ^{1}H-NMR spectroscopy and elemental analysis.

The solid-state properties of the vildagliptin active substance were measured by differential scanning calorimetry (DSC) and X-Ray powder diffraction.

The vildagliptin active substance is a white to off white powder, freely soluble in water, in 0.1N HCl and in buffers with pH range from 4.1 to 9.0. The vildagliptin active substance is non-hygroscopic.

Vildagliptin exhibits stereoisomerism due to the presence of one chiral centre. The manufacturing process consistently manufactures the *S*-isomer. Enantiomeric purity is established by an isomeric purity specification in the advanced intermediate (2*S*)-1-(chloroacetyl)-2-cyanopyrrolidine and controlled routinely in the active substance specification by chiral HPLC.

Polymorphism has been observed for vildagliptin. Form A, of which the X-Ray Diffraction (XRD) spectrum is matching with literature 'WO2006/078593 A2', is consistently manufactured by the proposed manufacturer. The polymorphic form is controlled via an identification test by XRD in the specification of the active substance (comparison of XRD pattern with reference standard). In the finished product, no polymorphic conversion was observed under the processing conditions or during storage (evaluation of the finished product after 6 months storage at 40 °C/75% RH).

2.2.2.2. Manufacture, characterisation and process controls

One manufacturer is proposed for vildagliptin. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Vildagliptin is synthesised in two main stages.

Adequate in-process controls are applied during the synthesis. Critical steps to be monitored during the manufacturing process of vildagliptin, as well as in-process specifications and corresponding test procedures were presented in the restricted part of the ASMF. The commercial manufacturing process for the active substance has been described in sufficient details.

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. In line with ICH M7, complementary evaluation with statistically-based (Q)SAR methodology were used for the evaluation of the potentially genotoxic impurities.

Residual solvents are controlled as per ICHQ3C, and relevant specifications have been established in the active substance.

The primary packaging material consists of a blend of HM-HDPE, LDPE and LLDPE and complies with Ph. Eur., the Guideline on plastic immediate packaging materials CPMP/QWP/4359/03 and EC 10/2011 as amended. This inner bag is placed in a triple laminated bag with desiccant, which are placed in a HDPE drum, sealed with plastic seal.

2.2.2.3. Specification(s)

The active substance specification includes tests for appearance, solubility (Ph. Eur.), identity (IR, HPLC, XRD), assay (HPLC), related substances (HPLC), enantiomeric purity (chiral HPLC), content of 3-amino-1-hydroxy adamantane (GC), residual solvents (GC), water content (Ph. Eur., KF), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), particle size (Malvern, laser diffraction), and microbial examination (Ph. Eur.).

The controls of impurities in active substance vildagliptin are adopted based on the ICH guidelines as well as on the developmental studies. Possible impurities of the final active substance are categorised as organic impurities, inorganic impurities, residual solvents, metal reagents / catalysts and genotoxic impurities. The information presented regarding potential impurities/degradation products is considered sufficient.

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, related substances, enantiomeric purity and 3-amino-1-hydroxy adamantane testing has been presented.

Batch analysis data of the active substance are provided. The results are within the specifications.

2.2.2.4. Stability

Stability data from three production-scale of vildagliptin from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 60 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 following parameters were tested: appearance, identification (XRD), water content (Ph. Eur., KF), loss on drying (Ph. Eur.), assay by HPLC, enantiomeric purity (HPLC), and related substances (HPLC). The analytical methods used were the same as for release and are stability indicating.

All tested parameters were within the specifications, without any significant trends.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable and does not require any special storage conditions. The stability results justify the proposed retest period of 3 years in the proposed container.

2.2.3. Active substance metformin hydrochloride

2.2.3.1. General Information

The chemical name of metformin hydrochloride is 1,1-dimethylbiguanide-hydrochloride corresponding to the molecular formula $C_4H_{12}ClN_5$. The salt form has a relative molecular mass of 165.6 g/mol and the following structure:

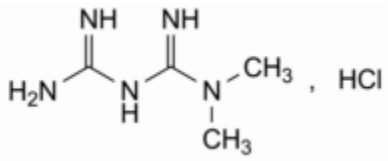

Figure 2: Metformin structure

The active substance is white or almost white crystals, freely soluble in water. Metformin hydrochloride is described in Ph. Eur. monograph no. 0931. As there is a monograph of metformin in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for metformin hydrochloride which has been provided within the current Marketing Authorisation Application. The active substance exhibits no stereoisomerism since there is no chiral centre.

2.2.3.2. Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

One manufacturer is proposed. The manufacturer produces the active substance in two different manufacturing sites located in India covered by the same CEP.

The primary packaging material consists of a double polyethylene bags placed either in a corrugated box or in a fibre drum, as described in the CEP. The double polyethylene bags are made of either LDPE or HM-HDPE.

2.2.3.3. Specification(s)

The active substance specification includes tests for: appearance, solubility (Ph. Eur.), identity (IR, chlorides, HPLC), appearance of solution (Ph. Eur.), assay (HPLC), related substances (HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), residual solvents (GC), bulk density/tapped bulk density (Ph. Eur.), particle size and nitrosamine impurities (NDMA, LC-MS).

The active substance specification applied by the finished product manufacturer is in accordance with the current Ph. Eur. monograph on metformin hydrochloride and the CEP, except for the assay specification. The test for residual solvents is proposed in addition to the Ph. Eur.

In addition to the Ph. Eur. monograph tests, the following tests are included in the applicant's active substance specification for metformin: bulk density (Ph. Eur. 2.9.34), particle size (sieve shaker) and NDMA (LC-MS) have been included in the specification. All additional methods have been adequately validated and described according to ICH Q2. Metformin hydrochloride is highly soluble, hence the particle size distribution (PSD) is not expected to impact the CQAs of the finished product.

Data from metformin hydrochloride batches have been provided demonstrating the consistency of the manufacturing process.

2.2.3.4. Stability

Stability data from both sites of the active substance manufacturers were provided on the active substance stored in both the proposed commercial containers.

The parameters tested are appearance, solubility, appearance of solution, assay, related substances, loss on drying. The analytical methods used were the same as for release and are stability indicating.

All tested parameters were within the specifications.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 3 years, and the proposed expiry period of 5 years without any special storage conditions in the proposed container.

2.2.4. Finished medicinal product

2.2.4.1. Description of the product and Pharmaceutical development

The finished product is presented as film-coated tablets containing 50 mg/850 mg or 50 mg/1000 mg of vildagliptin/metformin hydrochloride as active substances.

Vildagliptin/metformin hydrochloride 50 mg/850 mg film-coated tablets are yellow coloured, oval shaped, biconvex, film coated tablets, debossed with"GG2" on one side and plain on other side. Dimensions: 20.15 x 8.00 mm

Vildagliptin/metformin hydrochloride 50 mg/1000 mg film-coated tablets are dark yellow coloured, oval shaped, biconvex, film coated tablets, debossed with"GG3" on one side and plain on other side. Dimensions: 21.11 x 8.38 mm

The pharmaceutical development of the finished product contains quality by design (QbD) elements. The quality target product profile (QTPP) was defined as: similar qualitative composition and immediate release profile to the reference product Eucreas 50mg/850mg and 50mg/1000mg film-coated tablets, shelf life of at least 24 months at room temperature in its primary container closure system, ensuring tablet's integrity during shipping. The critical quality attributes (CQAs) identified were: dosage form, assay, uniformity of dosage units (UDU), organic purity, dissolution, loss on drying and elemental impurities.

The finished product is a fixed dose combination of vildagliptin (BCS Class I) and metformin hydrochloride (BCS Class III). The physicochemical properties of both substances have been discussed. Since both active substances are highly soluble, their PSD is not expected to impact the CQAs/QTPP of the finished product The effect of the PSD of active substance in relation to product behaviour and manufacturability have been evaluated and a limit has been set in the specification of metformin hydrochloride. X-Ray Powder Diffraction (XRPD) data on one batch of the finished product of each strength stored for up to six months under accelerated storage conditions has been provided confirming the physical stability of the desired polymorphic forms for both active substances. Vildagliptin (*R*)-isomer is controlled in the active substance specification.

The compatibility of a number of commonly used excipients, in proportions expected to be used during formulation, was evaluated for each active substance and for a combination of both active substances in a pre-formulation open-plate study under stressed conditions (50°C/ 75% RH, one month storage). Since no degradation of the active substances was observed, it was concluded that both active substances are compatible with the excipients at the studied levels. Critical functionality related characteristics of the excipients have been discussed. The choice of excipients used for the finished product have been justified. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with exception of iron oxide yellow (E171), which complies with EU No.231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the summary of product characteristics (SmPC).

The two proposed finished product strengths are not dose proportional and do not come from the same blend.

Process optimisation was carried out for kneading time, lubrication time, compression speed and compression force (with resulting tablet hardness).

The QC dissolution method was developed taking into account the solubility of vildagliptin and metformin hydrochloride at the different pH ranges of the gastrointestinal tract, and the feasibility to achieve sink conditions. The discriminatory power of the dissolution method was demonstrated by testing a batch with deviating composition (different amount of disintegrant quantity) versus a target batch, this for both strengths.

Bioequivalence studies in fed conditions were performed against the reference products. In both studies, the bioequivalence criteria with respect to Cmax, AUC 0-t and AUC 0-∞ for vildagliptin and metformin were met. The batch size of the tested products used in bioequivalence studies is representative as it corresponds to the production scale size.

The similarity of dissolution profiles of biobatches of the tested and reference products (both strengths) were demonstrated across the physiological pH range. Profiles were compared using f1/f2 testing, and statistical bootstrapping methodology as a supportive technique, as discussed in the clinical section of the report.

The primary packaging for the finished product is aluminium/aluminium blisters. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.4.2. Manufacture of the product and process controls

The manufacturing process consists of eight main steps: dry mixing/granulation, wet milling, drying, sizing, sifting of extra-granular components, lubrication, compression, film coating and packaging. It is adequately described. The process is considered to be a standard manufacturing process.

In-process controls for lubricated granules, uncoated tablets, coating stage and packaging steps have been described. The in-process controls are adequate for this type of manufacturing process. Successful process validation has been carried out on three consecutive commercial scale batches of each strength of finished product. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

The primary packaging materials for the intermediates are HDPE bags (for lubricated granules, uncoated tablets, and for film-coated tablets awaiting further processing), and triple laminated aluminium bags (PET/Al/LDPE) with silica gel bag (for the finished bulk tablets during transportation to the (re)packaging sites). These materials comply with Ph. Eur. and/or EC Requirements. The proposed holding time for lubricated granules, uncoated tablets and film-coated tablets are acceptable and supported by stability data.

2.2.4.3. Product specification(s)

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description (visual), average weight (in-house), identification (HPLC + UV), assay (HPLC), loss on drying (in-house), dissolution (HPLC for vildagliptin, UV for metformin hydrochloride), uniformity of dosage units (Ph. Eur., for vildagliptin by content uniformity, for metformin hydrochloride by mass variation), related substances (HPLC), residual solvents (GC), microbial examination (Ph. Eur.), *N*-nitrosodimethylamine (HPLC-MS).

A number of questions on tightening of limits were raised during the procedure. This resulted in the following changes: tightening of the dissolution limit (release and shelf life) according to the results obtained for biobatches; tightening of the release limits for loss on drying, total impurities of vildagliptin and total impurities of metformin hydrochloride based on batch results; tightening of the shelf life limit for total impurities of metformin hydrochloride based on stability results. Based on additional scientific rationale from the applicant (*in silico* report generated with Derek Nexus software), the vildagliptin impurities (related compounds 2 and 3) are considered as non-genotoxic, the shelf-life acceptance criteria of not more than 1% for concerned impurities were accepted, and omission of an *in vivo* study to qualify concerned impurities at the proposed limit was considered justified.

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 and ICP-MS test results presented for 3 batches of both active substances, it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

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 3 batches manufactured at the proposed commercial scale for each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.4.4. Stability of the product

Stability data from 3 production-scale batches of finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of vildagliptin/metformin hydrochloride film-coated tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the shelf-life specifications.

The analytical procedures used are stability indicating.

All tested parameters remained well within the applied acceptance criteria and no significant changes were observed after 18 months storage under long term conditions and 6 months storage under accelerated conditions. Only a slight increase in water content (accelerated conditions only) and vildagliptin impurities (accelerated and long-term conditions) was observed.

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. Based on the test results, it was concluded that the product is photostable in the proposed commercial packaging.

Based on available stability data, the proposed shelf-life of 2 years and without specific storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

2.2.4.5. Adventitious agents

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

2.2.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, three quality MOs, one related to the dissolution test limits, one to the nitrosamine impurities controls, and one related to GMP documentation deficiencies were resolved satisfactorily. 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.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.7. Recommendation(s) 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 Eucreas, film-coated tablets. The impurity profile has been only briefly discussed in Non-clinical Overview. However, more comprehensive data are provided in module 3, which is considered as sufficient.

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

2.3.2. Ecotoxicity/environmental risk assessment

The Applicant´s justification for omission of a full Environmental Risk Assessment (ERA) based on generic nature of the product was not sufficient and consumption data were required in line with Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010 Rev. 1, 2006). Following the provided clarification on some aspects of submitted consumption data, it is concluded that market authorization of the generic product in question is not expected to pose additional risks to the environment.

2.3.3. Discussion on non-clinical aspects

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product Eucreas, film-coated tablets. The applicant was requested to provide further in silico evidence as additional supporting evidence to qualify impurities (the reader is referred to quality part of the assessment). The issue has been solved.

No ERA studies were submitted. This was justified by the applicant as the introduction of Vildagliptin/Metformin hydrochloride Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all vildagliptin / metformin hydrochloride containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considers the justifications for absence of new non-clinical and ERA data as acceptable. From a non-clinical point of view, no conditions for marketing authorisation are anticipated.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing vildagliptin / metformin hydrochloride 50 mg / 850 mg and 50 mg / 1000 mg. To support the marketing authorisation application the applicant conducted two bioequivalence studies with cross-over design under fed conditions. These studies were the pivotal studies for

the vildagliptin / metformin hydrochloride 50 mg / 850 mg and 50 mg / 1000 mg film-coated tablets.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment, the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is 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.

Tabular overview of clinical studies

To support the application, the applicant has submitted two bioequivalence studies, Project no. 0622-19 (for vildagliptin / metformin hydrochloride 50 mg / 850 mg) and Project no. 0623-19 (for vildagliptin / metformin hydrochloride 50 mg / 1000 mg).

Protocol No.	Study Title
0622-19	An open label, balanced, randomized, two-treatment, two period, two-sequence, crossover, single oral dose, bioequivalence study of two formulations of Vildagliptin 50 mg and Metformin Hydrochloride 850 mg Tablets in healthy, adult, human subjects under fed condition
0623-19	An open label, balanced, randomized, two-treatment, two period, two-sequence, crossover, single oral dose, bioequivalence study of two formulations of Vildagliptin 50 mg and Metformin Hydrochloride 1000 mg Tablets in healthy, adult, human subjects under fed condition

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Project no. 0622-19 An open label, balanced, randomized, two-treatment, two-period, two-sequence, crossover, single oral dose, bioequivalence study of two formulations of Vildagliptin 50 mg and Metformin Hydrochloride 850 mg Tablets in healthy, adult, human subjects under fed condition.

Methods

- **Study design**

This study is designed as an open label, balanced, randomized, two-treatment, two-period, two-sequence, crossover, bioequivalence study of Vildagliptin 50 mg and Metformin Hydrochloride 850 mg tablets (Intas Pharmaceuticals Limited, India) and Eucreas 50 mg/850 mg film-coated tablets (Novartis Pharma GmbH, Roonstraße 25, D-90429 Nuremberg, Germany) in normal, healthy, adult, human subjects under fed condition.

After an overnight fast of at least 10 hours, the subjects were served a standardized high fat high calorie vegetarian breakfast, which they consumed within 30 minutes. A single oral dose (Vildagliptin 50 mg/ Metformin Hydrochloride 850 mg) of either the test product or the reference product was administered to the subjects at

30 minutes after serving the breakfast. The IMP was administered in sitting posture with 240 ± 02 mL of drinking water containing 20% glucose solution at ambient temperature. The IMP administration was as per the randomization schedule and under open label conditions.

As per the protocol, a total of twenty-seven (27) blood samples were to be collected from each subject in each period.

Randomization

This was a randomised study design. The order of receiving Test Product-T and Reference Product-R for each subject in each period of the study was determined according to the randomisation schedule. Equal allocation of subjects to each sequence was ensured.

Blinding

This was an open label study hence blinding was not done. However, the analysts performing the assay of the drug in plasma were unaware of the sequence of administration of the Reference Product-R and Test Product-T to the individual subjects.

- **Test and reference products**

Vildagliptin 50 mg and Metformin Hydrochloride 850 mg Tablets manufactured by Intas Pharmaceuticals Limited (batch Y14800, exp. Date: 30 September 2021) has been compared to Eucreas 50 mg/850 mg film-coated tablets manufactured by Novartis Pharma GmbH (Batch No: WFU02 (lot) , exp. Date: 30 June 2020).

- **Population(s) studied**

Based on the estimates provided by the sponsor, the maximum intra subject variability observed for primary pharmacokinetic parameter was found to be ~23%; the sample size computation was determined using SAS by considering the following assumptions:

a. T/R ratio = 90.0-110.0%,

b. intra-subject C.V. (%) ~ 23%,

c. significance level = 5%,

d. power ≥ 80%,

e. bioequivalence limits = 80.00-125.00%.

Based on the above estimates, a sample size of 48 subjects were required to establish bioequivalence between formulations with adequate power. Considering approximately 15% dropouts and/or withdrawals, a sample size of 56 subjects were sufficient to establish bioequivalence between formulations with adequate power for this pivotal study.

A total of 58 subjects (X-1 and X-2) were checked in for Period-I of the study. Subject Nos. X-1 and X-2 were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I.

Both the extra subjects were checked out of the facility as none of the subjects discontinued / were withdrawn from the study prior to dosing in Period-I.

No female volunteers were checked in for the study. Hence, as per the protocol, a total of 56 subjects were dosed in Period-I of the study.

The mean ± SD of age, height, weight and BMI of 56 subjects, who were dosed in the study and 54 subjects who were included in the BE evaluation is as follows:

Table 1 – Demographic and other baseline characteristics

Parameter (Units)	Mean ± SD	
	N = 56 (Dosed Subjects)	N=54 (Subjects included in BE evaluation)
Age (years)	32.4 ± 6.50	32.3 ± 6.42
Height (cm)	166.90 ± 4.595	166.86 ± 4.672
Weight (kg)	66.527 ± 9.0395	66.596 ± 9.0955
BMI (kg / m^2)	23.876 ± 3.0510	23.912 ± 3.0706

One subject was withdrawn from the study on the grounds of emesis in Period-I.

One subject was withdrawn from the study on medical grounds in Period-I.

In all, 54 subjects completed the study successfully.

Pharmacokinetic and statistical population:

The study was planned so as to obtain the data from 56 evaluable subjects. Out of the dosed 56 subjects, 54 subjects completed clinical phase of the study successfully.

Table 2 – Subjects excluded from the PK analysis

Subject No	Sequence	Period	Date of Discontinuation/ Withdrawal	Reason for Discontinuation/Withdrawal
xxxx	TR	1	13 June 2020	The subject had complaint of single episode of vomiting at 13:42 hours on 13 June 2020. Hence, he was withdrawn from the study on the grounds of emesis.
xxxx	RT	1	14 June 2020	The subject's axillary temperature recording done at 09:21 hours on 14 June 2020 was 100.0°F. Hence, he was withdrawn from the study on medical grounds.

Plasma samples of all 56 subjects (including the 2 withdrawn subjects) were analysed.

A total of 54 subjects were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

The plasma concentrations of vildagliptin and metformin in the study samples were determined by two separate validated LC-MS/MS methods at Lambda Therapeutic Research Ltd., India. Vildagliptin was analysed between

19 June 2020 and 28 June 2020 and metformin between 18 June 2020 and 29 June 2020. Vildagliptin and its internal standard, vildagliptin-d7, were extracted from heparinized plasma using liquid-liquid extraction method into ethyl acetate. Metformin and its internal standard, metformin-d6, were extracted from heparinized human plasma using solid-phase extraction method.

In the study, fifty-six (56) subjects were dosed. A total of fifty-four (54) subjects completed the trial successfully, were analysed and included in the final statistical analysis. In each period, a total of twenty-four (24) vildagliptin and twenty-six (26) metformin blood samples were collected from each subject.

Theoretical number of samples of vildagliptin expected as per protocol was 2688 (56 subjects x 2 periods x 24 blood collections per period). There were 55 samples not received (samples from withdrawn subjects). Total number of samples collected and analysed was 2633.

Theoretical number of samples of metformin expected as per protocol was 2912 (56 subjects x 2 periods x 26 blood collections per period). There were 62 samples not received (samples from withdrawn subjects). Total number of samples collected and analysed was 2850.

Certificates of analysis of vildagliptin, vildagliptin-d7 and metformin-d6 hydrochloride as well as USP certificates of metformin hydrochloride were attached to the Bioanalytical Report.

Separately weighed stocks were used for the preparation of calibration curve standards and quality control samples. Calibration curve standards and quality control samples were stored in the freezer maintained at -65 ± 10°C.

Summary of accuracy and precision for back-calculated concentrations of vildagliptin and metformin in calibration standards:

Vildagliptin			
Accuracy	97.1 % to 101.4 %	Precision	1.5 % to 3.7 %
Metformin			
Accuracy	97.8 % to 101.4 %	Precision	1.3 % to 4.4 %

Summary of accuracy and precision for QC samples of vildagliptin and metformin:

Vildagliptin			
Accuracy	99.5 % to 101.6 %	Precision	1.5 % to 3.9 %
Metformin			
Accuracy	101.4 % to 107.5 %	Precision	2.3 % to 3.9 %

All analytical runs passed the acceptance criteria. A total of eleven (11) and one (1) individual samples were re-assayed as per SOP for vildagliptin (0.4%) and metformin (0.03%), respectively.

In order to assess the reproducibility of bioanalytical results, incurred samples were selected to cover the entire concentration range. A total of 185 vildagliptin and 196 metformin study samples were re-analysed for the incurred sample reproducibility test. A total of 98.4 % and 100 % of the re-analysed samples met the criteria of assay reproducibility for vildagliptin and metformin respectively.

There was no SOP or Study Protocol/Plan deviation.

Bioanalytical methods validation

A LC-MS/MS method for the estimation of vildagliptin in sodium heparin human plasma was developed and validated at Lambda Therapeutic Research in 2019. Validation results are presented in the Method Validation Report MV(I)-462-19 and in Addendum I - V. The method was partially validated to extend long-term stability of analyte in human plasma (Addendum I, II), to validate the stability in presence of combination drug (Add I, IV, V), to perform selectivity in presence of metabolite vildagliptin carboxylic acid (Add III).

Summary of the vildagliptin validation results:

Linearity (weighted $1/c^2$)	$r^2 \geq 0.99$
Calibration curve range	2.023 ng/mL to 1003.957 ng/mL
Within-run precision	0.6% to 2.6%
Within-run accuracy	99.9% to 113.7%
Between-run precision	2.9% to 8.0%
Between-run accuracy	99.1 to 105.5%
IS-normalized MF	LQC: 1.0021 (2.1 %CV)
	HQC: 0.9938 (0.8 %CV)
	No significant ion suppression or enhancement.
Dilution integrity (1/5)	The % CV and accuracy within the acceptance limit.
Mean recovery of analyte	58.2 % (14.3 %CV)
Mean recovery of IS	68.6 % (6.5 %CV)

In addition, selectivity using normal, haemolysed and lipemic plasma, selectivity in presence of co-administered drugs, sensitivity, matrix effect, reinjection reproducibility, batch size, carry-over, and stability of vildagliptin in solutions, in biological matrix and extract were investigated.

Summary of vildagliptin stability results:

Stability in whole blood	2.0 hours at room temperature in presence of metformin
Short-term stability in matrix	10 hours in ice cold water bath in presence of metformin
Wet extract bench top stability	2 hours at room temperature
Autosampler stability	97 hours at 2.0°C to 8.0°C
Dry extract stability	121.0 hours at -22 ± 5°C
Freeze-thaw stability	Five (5) cycles at -65 ± 10°C in presence of metformin
Long-term stability in matrix	246 days at -65 ± 10°C & 185 days at -22 ± 5°C in presence of metformin

A LC-MS/MS method for the estimation of metformin in human plasma was developed and validated at Lambda Therapeutic Research Limited in 2011. Validation results are presented in the Method Validation Report MV-415-11 and Addendum I to XX for 0622-19 and up to Addendum XXII for 0623-19 study. The method was

partially validated to change the calibration range for higher strength products assessment (Addendum III), to extent the long-term stability data, to generate the long-term stability data in presence of other drugs, to requisite experiments as per new SOP, to perform selectivity and sensitivity experiments, to update the method and to validate a few changes in instrument (from Quattro Premier XE to Thermo Quantum Ultra) and mobile phase composition (Addendum XVIII and XX)

Summary of the metformin validation results substantial for 0622-19 and 0623-19 studies:

	Addendum XVIII
Linearity (weighted $1/c^2$)	$r^2 \geq 0.99$
Calibration curve range (ng/mL)	5.091 to 3499.289
Within-run precision	1.0% to 3.9%
Within-run accuracy	97.9% to 101.5%
Between-run precision	1.8% to 5.2%
Between-run accuracy	98.9% to 102.1%
IS-normalised matrix factor	LQC: 1.0053, 1.5%CV
	HQC: 1.0261, 0.6%CV
Dilution integrity (5x)	The % CV and accuracy within the acceptance limit.
Recovery of analyte	88.2 %,90.4 % and 91.7 % (≤ 2.9 % CV)
Recovery of IS	99.8 %

In addition, selectivity using normal, haemolysed and lipemic plasma, selectivity in presence of co-administered drugs, haemolysis effect, sensitivity, robustness in case of different column and analyst, reinjection reproducibility, carry-over, batch size and stability of metformin in solutions, matrix and extracts were investigated.

Summary of metformin stability results:

Stability in whole blood	2 hours on bench at room temperature in presence of vildagliptin
Short-term stability in matrix	10 hours at room temperature (Add III)
	12 and 15 hours at room temperature in presence of vildagliptin (Add XII and Add XI, respectively)
Autosampler stability	49 hours at 2 to 8°C (Add XX - TSQ Quantum Ultra)
	100 hours at 2 to 8°C (Add III - Quattro Premier XE)
Post-preparative stability (wet extract bench top stability)	2 hours at room temperature
Freeze-thaw stability	Five (5) cycles at -65 ± 10°C in presence of vildagliptin (Add XII)

Long-term stability in matrix	140 days at -65 ± 10°C and at -22 ± 5°C 105 days at -65 ± 10°C & at -22 ± 5°C in presence of vildagliptin Add XXII: 141 days at -65 ± 10°C

- **Pharmacokinetic variables**

These pharmacokinetic parameters were derived individually for each analysed subject from the concentration vs. time profiles of Vildagliptin and Metformin in plasma using noncompartmental model of Phoenix® WinNonlin® Version 8.1 (Certara L.P.).

Primary pharmacokinetic parameters were C_{max} and AUC_{0-t}.

Secondary pharmacokinetic parameters were $AUC_{0-\infty}$, T_{max}, λ_z, $t_{1/2}$ and AUC_%Extrap_obs.

Actual time-points of the sample collection were used for the calculation of pharmacokinetic parameters. All concentration values below the lower limit of quantification were set to zero for the pharmacokinetic and statistical calculations.

- **Statistical methods**

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

The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were subjected to analyses of variance (ANOVA) for Vildagliptin and Metformin. ANOVA model included Sequence, Subject (Sequence), Formulation and Period as fixed effects. Each analysis of variance included calculation of least squares means, the difference between adjusted formulation means and the standard error associated with the differences. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha = 0.05).

Using two one-sided tests for bioequivalence, 90% confidence intervals for the ratio of geometric least squares means between drug formulations were calculated for ln-transformed data of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Vildagliptin and Metformin.

Bioequivalence of Test Product-T vs. Reference Product-R was concluded, if the 90% confidence interval fell within the acceptance range (80.00%, 125.00%) for ln-transformed pharmacokinetic parameters for Vildagliptin and Metformin.

Results

The study was planned so as to obtain the data from 56 evaluable subjects. Out of the dosed 56 subjects, 54 subjects completed clinical phase of the study successfully.

Plasma samples of all 56 subjects were analysed. In which, the two withdrawn subjects were also analysed as per protocol requirement.

A total 54 subjects were included in the pharmacokinetic and statistical analysis.

Table 3 Pharmacokinetic parameters for vildagliptin (non-transformed values)

Pharmacokinetic parameter	Test (N=54)		Reference (N=54)	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	1143.90	209.32	1113.54	244.37
$AUC_{(0-\infty)}$	1199.40	223.63	1162.21	259.95
C_{max}	179.68	52.46	183.08	64.68
T_{max}*	5.00 (0.68 – 8.02)		4.33 (0.67 – 8.00)	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t = 16 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 4 Statistical analysis for vildagliptin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-t)}$	104.0%	(99.14%, 109.16%)	15.0%
C_{max}	100.0%	(93.12%, 107.48%)	22.5%
* estimated from the Residual Mean Squares			

Formulation and Period effects were found to be statistically insignificant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Vildagliptin.

Sequence effect was found to be statistically insignificant for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} but it was found to be statistically significant for ln-transformed pharmacokinetic parameter $AUC_{0-\infty}$ for Vildagliptin.

Table 5 Pharmacokinetic parameters for metformin (non-transformed values)

Pharmacokinetic parameter	Test (N=54)		Reference (N=54)	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	16377.12	3308.24	15807.02	3435.14
$AUC_{(0-\infty)}$	16478.95	3335.15	15900.27	3456.40
C_{max}	1622.04	414.63	1617.92	399.64
T_{max}*	4.69 (1.33 – 10.00)		4.00 (1.33 – 8.00)	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t = 36 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 6 Statistical analysis for metformin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-t)}$	104.1%	(100.37%, 108.05%)	11.5%
C_{max}	100.3%	(95.53%, 105.24%)	15.1%
* estimated from the Residual Mean Squares			

Formulation and Period effects were found to be statistically insignificant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Metformin.

Sequence effect was found to be statistically insignificant for ln-transformed pharmacokinetic parameter C_{max} but it was found to be statistically significant for ln-transformed pharmacokinetic parameters AUC_{0-t} and $AUC_{0-\infty}$ for Metformin.

Conclusion regarding statistically significant effects:

The cause for significant sequence effect may not be found with certainty. Therefore, under special circumstances the significant sequence effect can be ignored. The study [1] was a single dose study [2] was in healthy volunteers, [3] was not comparing an endogenous substance, [4] had an adequate washout and [5] used appropriate design and analysis. Hence, this sequence effect is just statistically significant for AUC0-t and AUC0-∞ and can be ignored.

Subject (Sequence) effect was found to be statistically significant for ln-transformed pharmacokinetic parameters C_{max}, AUC0-t and AUC0-∞ both for Vildagliptin and Metformin.

Since each subject is assigned only one sequence, subjects are said to be nested within sequence. This Subject (Sequence) effect is tested by the Residual and should be highly significant. This significance is an indication that the purpose of using the crossover design has been realized in that the between-subject variance is significantly larger than the residual.

Conclusion regarding bioequivalence:

The test to reference ratio of geometric least square means with corresponding 90% CI for ln-transformed pharmacokinetic parameters C_{max} and AUC0-t were within the acceptance range of 80.00-125.00%. Therefore, the Test Product-T is considered to be bioequivalent to the Reference Product-R under fed condition.

- **Safety data**

Two (02) adverse events (AEs) were reported by two (02) subjects during the conduct of the study. Both the AEs were reported in Period-I of the study. One (01) AE was reported in subject after administration of Test Product-T and one (01) AE was reported in subject after administration of Reference Product-R.

Both the AEs were mild in nature and the subjects were followed up until resolution of their AEs.

The causality assessment was judged as unlikely for one (01) AE and as possible for the other AE.

There were no deaths or serious AEs reported during the conduct of the study.

However, out of the total reported two (02) AEs, one (01) AE was significant. The subject was withdrawn from the study on medical grounds. He was treated appropriately and followed up until resolution of AE. The causality assessment was judged as unlikely for the AE.

Project no. 0623-19 An open label, balanced, randomized, two-treatment, two-period, two-sequence, crossover, single oral dose, bioequivalence study of two formulations of Vildagliptin 50 mg and Metformin Hydrochloride 1000 mg Tablets in healthy, adult, human subjects under fed condition

Methods

- **Study design**

This study is designed as an open label, balanced, randomized, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study of Vildagliptin 50 mg and Metformin Hydrochloride 1000 mg tablets (Intas Pharmaceuticals Limited, India) and Eucreas 50 mg/1000 mg film-coated tablets (Novartis Pharma GmbH, Roonstraße 25, D-90429 Nuremberg, Germany) in normal, healthy, adult, human subjects under fed condition.

After an overnight fast of at least 10 hours, the subjects were served high fat high calorie vegetarian breakfast, which they consumed within 30 minutes.

A single oral dose (Vildagliptin 50 mg/ Metformin Hydrochloride 1000 mg) of either the test product or the reference product was administered to the subjects at 30 minutes after serving the breakfast. The IMP was administered in sitting posture with 240 ± 02 mL of drinking water containing 20% glucose solution at ambient temperature. The IMP administration was as per the randomization schedule and under open label conditions.

As per the protocol, a total of twenty-seven (27) blood samples were to be collected from each subject in each period.

Randomization

This was a randomised study design. The order of receiving Test Product-T and Reference Product-R for each subject in each period of the study was determined according to the randomisation schedule. Equal allocation of subjects to each sequence was ensured.

Blinding

This was an open label study hence blinding was not done. However, the analysts performing the assay of the drug in plasma were unaware of the sequence of administration of the Reference Product-R and Test Product-T to the individual subjects.

- **Test and reference products**

Vildagliptin 50 mg and Metformin Hydrochloride 1000 mg Tablets, manufactured by Intas Pharmaceuticals Limited (batch Y14805, exp. Date: 30 September 2021) has been compared to Eucreas 50 mg/850 mg film-coated tablets manufactured by Novartis Pharma GmbH (Batch No: WFU02 (lot), exp. Date: 30 June 2020).

- **Population(s) studied**

Based on the estimates provided by the sponsor, the maximum intra subject variability observed for primary pharmacokinetic parameter was found to be ~23%; the sample size computation was determined using SAS by considering the following assumptions:

a. T/R ratio = 90.0-110.0%,
b. intra-subject C.V (%) ~ 23%,
c. significance level = 5%,
d. power ≥ 80%,
e. bioequivalence limits = 80.00-125.00%.

Based on the above estimates, a sample size of 48 subjects were required to establish bioequivalence between formulations with adequate power. Considering approximately 15% dropouts and/or withdrawals, a sample size of 56 subjects were sufficient to establish bioequivalence between formulations with adequate power for this pivotal study.

A total of 58 subjects (X-1 and X-2) were checked in for Period-I of the study. Subject Nos. X-1 and X-2 were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I.

Both the extra subjects were checked out of the facility as none of the subjects discontinued / were withdrawn from the study prior to dosing in Period-I.

No female volunteers were checked in for the study. Hence, as per the protocol, a total of 56 subjects were dosed in Period-I of the study.

The mean ± SD of age, height, weight and BMI of 56 subjects, who were dosed in the study and 54 subjects who were included in the BE evaluation is as follows:

Table 7 – Demographic and other baseline characteristics

Parameter (Units)	Mean ± SD	
	N = 56 (Dosed Subjects)	N=54 (Subjects included in BE evaluation)
Age (years)	34.5 ± 5.58	34.6 ± 5.64
Height (cm)	167.14 ± 4.811	167.05 ± 4.854
Weight (kg)	63.834 ± 9.1049	64.048 ± 9.1851
BMI (kg / m^2)	22.833 ± 2.9227	22.931 ± 2.9145

One subject discontinued from the study on his own accord in Period-II.

One subject was withdrawn from the study on the grounds of protocol non-compliance in Period-II.

In all, 54 subjects completed the clinical phase of the study successfully.

Pharmacokinetic and statistical population:

The study was planned so as to obtain the data from 56 evaluable subjects. Out of the dosed 56 subjects, 54 subjects completed the clinical phase of the study successfully.

Table 8 – Subjects excluded from the PK analysis

Subject No	Sequence	Period	Sex	Age (Years)	Reason
xxxx	RT	II	Male	31	The subject discontinued from the study on his own accord.
xxxx	RT	II	Male	31	The subject was withdrawn from the study on the grounds of protocol non-compliance.

Plasma samples of all 56 subjects (including the two withdrawn subjects) were analysed.

A total of 54 subjects were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

The plasma concentrations of vildagliptin and metformin in the study samples were determined by two separate validated LC-MS/MS methods at Lambda Therapeutic Research Ltd., India. Vildagliptin was analysed between

17 July 2020 and 28 July 2020 and metformin between 23 July 2020 and 01 August 2020. Vildagliptin and its internal standard, vildagliptin-d7, were extracted from heparinized plasma using liquid-liquid extraction method into ethyl acetate (Method SOP No. MS-1408-00). Metformin and its internal standard, metformin-d6, were extracted from heparinized human plasma using solid-phase extraction method (Method SOP No. MS-1402-00).

In the study, fifty-six (56) subjects were dosed. A total of fifty-four (54) subjects completed the trial successfully, were analysed and included in the final statistical analysis. In each period, a total of twenty-four (24) vildagliptin and twenty-six (26) metformin blood samples were collected from each subject.

Theoretical number of samples of vildagliptin expected as per protocol was 2688 (56 subjects x 2 periods x 24 blood collections per period). There were 48 samples not received (samples from withdrawn and discontinued subjects). Total number of samples collected and analysed was 2640.

Theoretical number of samples of metformin expected as per protocol was 2912 (56 subjects x 2 periods x 26 blood collections per period). There were 52 samples not received (samples from withdrawn and discontinued subjects). Total number of samples collected and analysed was 2860.

Certificates of analysis of vildagliptin, vildagliptin-d7 and metformin-d6 hydrochloride as well as USP certificates of metformin hydrochloride were attached to the Bioanalytical Report.

Separately weighed stocks were used for the preparation of calibration curve standards and quality control samples. Calibration curve standards and quality control samples were stored in the freezer maintained at -65 ± 10°C.

Summary of accuracy and precision for back-calculated concentrations of vildagliptin and metformin in calibration standards:

Vildagliptin			
Accuracy	97.6 % to 101.2 %	Precision	1.1 % to 2.8 %
Metformin			
Accuracy	98.7 % to 101.5 %	Precision	1.3 % to 4.1 %

Summary of accuracy and precision for QC samples of vildagliptin and metformin:

Vildagliptin			
Accuracy	99.3 % to 101.5 %	Precision	2.4 % to 3.6 %
Metformin			
Accuracy	101.1 % to 109.7 %	Precision	1.8 % to 3.3 %

All analytical runs of vildagliptin passed the acceptance criteria. One analytical run of metformin failed acceptance criteria and was re-assayed. A total of two (2) and four (4) individual samples were re-assayed as per SOP for vildagliptin (0.1%) and metformin (5.6% including repeated run), respectively.

In order to assess the reproducibility of bioanalytical results, incurred samples were selected to cover the entire concentration range. A total of 185 vildagliptin and 196 metformin study samples were re-analysed for the incurred sample reproducibility test. A total of 97.8% and 100 % of the re-analysed samples met the criteria of assay reproducibility for vildagliptin and metformin, respectively.

There was no Study Protocol deviation and one minor SOP deviation without impact on study data.

Bioanalytical methods validation

For bioanalytical methods validation, please see description for Project no. 0622-19.

- **Pharmacokinetic variables**

These pharmacokinetic parameters were derived individually for each analysed subject from the concentration vs. time profiles of Vildagliptin and Metformin in plasma using non-compartmental model of Phoenix® WinNonlin® Version 8.1 (Certara L.P.):

Primary pharmacokinetic parameters were C_{max} and AUC_{0-t}.

Secondary pharmacokinetic parameters were $AUC_{0-\infty}$, T_{max}, λz, $t_{1/2}$ and AUC_%Extrap_obs.

Actual time-points of the sample collection were used for the calculation of pharmacokinetic parameters. All concentration values below the lower limit of quantification were set to zero for the pharmacokinetic and statistical calculations.

- **Statistical methods**

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

The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were subjected to analyses of variance (ANOVA) for Vildagliptin and Metformin. ANOVA model included Sequence, Subject (Sequence), Formulation and Period as fixed effects. Each analysis of variance included calculation of least squares means, the difference between adjusted formulation means and the standard error associated with the differences. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha = 0.05).

Using two one-sided tests for bioequivalence, 90% confidence intervals for the ratio of geometric least squares means between drug formulations were calculated for ln-transformed data of C_{max}, AUC0-t and AUC0-∞ for Vildagliptin and Metformin.

Bioequivalence of Test Product-T vs. Reference Product-R was concluded, if the 90% confidence interval fell within the acceptance range (80.00%, 125.00%) for ln-transformed pharmacokinetic parameters for Vildagliptin and Metformin.

Results

The study was planned so as to obtain the data from 56 evaluable subjects. Out of the dosed 56 subjects, 54 subjects completed the clinical phase of the study successfully. Plasma samples of all 56 subjects were analysed. In which, the two withdrawn subjects were also analysed as per protocol requirement.

A total 54 subjects were included in the pharmacokinetic and statistical analysis.

Table 9 Pharmacokinetic parameters for vildagliptin (non-transformed values)

Pharmacokinetic parameter	Test (N=54)		Reference (N=54)	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	1030.10	233.31	1016.28	224.81

Pharmacokinetic parameter	Test (N=54)		Reference (N=54)	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-\infty)}$	1069.39^	232.99^	1063.95^	218.19^
C_{max}	153.75	45.03	147.10	41.68
T_{max}*	5.75 (1.33 – 10.00)		5.00 (1.00 – 10.02)	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t = 16 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)			

^N=52 observations were used for calculation.
Note: Terminal rate constant (lambda_z) cannot be estimated based on obtained concentration data for subject nos. xxxx (Period-I, T) and xxxx (Period-I, R). Hence, AUC0-inf and other elimination phase dependent parameters cannot be calculated. Hence, same was also excluded from the other treatment arm.

Table 10 Statistical analysis for vildagliptin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-t)}$	101.6%	(98.59%, 104.73%)	9.4%
C_{max}	105.3%	(98.62%, 112.47%)	20.6%
* estimated from the Residual Mean Squares			

Formulation effect was found to be statistically insignificant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Vildagliptin.

Sequence effect was found to be statistically insignificant for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} but it was found to be statistically significant for ln-transformed pharmacokinetic parameter AUC0-∞ for Vildagliptin.

Period and Subject (Sequence) effects were found to be statistically significant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Vildagliptin.

Table 11 Pharmacokinetic parameters for metformin (non-transformed values)

Pharmacokinetic parameter	Test (N=54)		Reference (N=54)	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	17229.63	3504.69	17504.11	3897.48
$AUC_{(0-\infty)}$	17338.65	3538.31	17615.19	3928.10
C_{max}	1586.60	445.03	1694.66	582.27
T_{max}*	6.04 (2.00 – 10.00)		5.51 (1.00 – 10.02)	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t = 36 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 12 Statistical analysis for metformin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-t)}$	98.9%	(95.83%, 102.06%)	9.8%
C_{max}	95.8%	(90.83%, 100.95%)	16.5%

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
* estimated from the Residual Mean Squares			

Formulation effect was found to be statistically insignificant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Metformin.

Sequence, Period and Subject (Sequence) effects were found to be statistically significant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC0-∞ for Metformin.

Reasoning for statistically significant effects both for vildagliptin and metformin:

The cause for significant sequence effect may not be found with certainty. Therefore, under special circumstances the significant sequence effect can be ignored. The study [1] was a single dose study [2] was in healthy volunteers, [3] was not comparing an endogenous substance, [4] had an adequate washout and [5] used appropriate design and analysis. Hence, this sequence effect is just statistically significant for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and can be ignored.

In the study, clinical conditions were kept identical in both the period of the study, and there were no pre-dose concentrations observed. The decision of bioequivalence is based on the 90% confidence interval by Schuirmann two one sided 't-test' which is within the acceptance criteria 80.00-125.00%. This significant period effect for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ is just statistically significant and can be ignored.

Since each subject is assigned only one sequence, subjects are said to be nested within sequence. This Subject (Sequence) effect is tested by the Residual and should be highly significant. This significance is an indication that the purpose of using the crossover design has been realized in that the between-subject variance is significantly larger than the residual.

Conclusion:

The results of this study demonstrate that, the criteria used to assess bioequivalence between the test and reference formulations were fulfilled for Vildagliptin and Metformin.

The test to reference ratio of geometric least square means with corresponding 90% CI for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} were within the acceptance range of 80.00-125.00%. Therefore, the Test Product-T is considered to be bioequivalent to the Reference Product-R under fed condition.

- **Safety data**

There were no adverse events during the conduct of the study.

Upon conclusion of the clinical portion of the study, the results from all subjects who completed post-study procedures including laboratory tests and vital signs measurements confirmed the absence of significant changes in the subjects' state of health.

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 company has submitted two bioequivalence studies. The applicant has conducted an open labelled randomised, two-period, two-sequence, cross-over, single dose, comparative bioequivalence study of Vildagliptin/Metformin 50 mg/850 mg tablets Accord and Vildagliptin/Metformin 50 mg/1000 mg tablets Accord and Eucreas 50 mg/850 mg film-coated tablets and Eucreas 50 mg/1000 mg film-coated tablets of Novartis Europharm Limited, Germany in healthy adult subjects under fed conditions.

Overall, the CHMP concluded that bioequivalence has been demonstrated. 90% CIs fell into the predefined limit 80-125%, for both AUC_{0-t} and C_{max}.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence studies Vildagliptin/Metformin hydrochloride Accord 50 mg / 850 mg and 50 mg / 1000 mg, film-coated tablets, is considered bioequivalent with Eucreas 50 mg / 850 mg and 50 mg / 1000 mg, film-coated tablets.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	Drug induced liver injury (DILI) Acute pancreatitis Lactic acidosis
Important potential risks	Muscle events/myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded)
Missing information	None

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities. This is endorsed.

Routine pharmacovigilance activities

The MAH has proposed specific adverse reaction targeted follow-up questionnaires for follow up of events of lactic acidosis, DILI, acute pancreatitis, and muscle events, respectively. This is overall accepted.

2.5.3. Risk minimisation measures

No additional risk minimisation measures have been proposed. This is endorsed by the CHMP and PRAC.

The safety information in the proposed product information is aligned to the reference medicinal product.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 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 Eucreas film-coated tablets and Solifenacin succinate 5/10mg 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 Vildagliptin/metformin film-coated tablets (50 mg/850 mg and 50 mg/1000 mg). The reference products Eucreas 50 mg/850 mg film-coated tablets and Eucreas 50 mg/1000 mg film-coated tablets are indicated for type 2 diabetes mellitus.

No non-clinical 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 was considered sufficient.

To support this application, the Applicant has submitted two bioequivalence studies. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. 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.

In Project no. 0622-19, the test formulation of Vildagliptin/metformin hydrochloride 50 mg/850 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the Eucreas 50

mg/850 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

In Project no. 0623-19, the test formulation of Vildagliptin/metformin hydrochloride 50 mg/1000 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the Eucreas 50 mg/1000 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

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 Vildagliptin/Metformin hydrochloride Accord is favourable in the following indication:

Vildagliptin/Metformin hydrochloride Accord is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:

- in patients who are inadequately controlled with metformin hydrochloride alone.
- in patients who are already being treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.
- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

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 medical prescription.

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.