Amsterdam, 24 July 2025
EMA/CHMP/325059/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Azacitidine Accord

International non-proprietary name: Azacitidine

Procedure No. EMEA/H/C/005147/X/0021

Note

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

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List of abbreviations

API	Active Pharmaceutical Ingredient
Alu	Aluminium
alu/PVC/ PCTFE	aluminium/polyvinyl chloride/polychlorotrifluoroethylene
ASMF	Active Substance Master File
BCS	Biopharmaceutics Classification System
BDL	Below the limit of detection
DL	Detection Limit
EC	European Commission
EEA	European Economic Area
GC	Gas Chromatography
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
ICH	International conference on harmonisation
ICP-OES	Inductively coupled plasma optical emission spectrometry
IR	Infra-red
LDPE	Low density polyethylene
LOQ	Limit of Quantitation
MAH	Marketing Authorisation holder
MO	Major Objection
MS	Mass spectroscopy
NMR	Nuclear magnetic resonance
NMT	Not more than
NOR	Normal Operating Range
PAR	Proven Acceptable Range
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
QC	Quality Control
QTTP	Quality target product profile
QL	Quantitation limit
RH	Relative Humidity
RPM	Revolutions per minute
RSD	Relative standard deviation
SD	Standard deviation
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
UV	Ultraviolet
XRPD	X-Ray (Powder) Diffraction

Not all abbreviations may be used

1. Background information on the procedure

1.1. Submission of the dossier

Accord Healthcare S.L.U. submitted on 29 July 2024 extensions of the marketing authorisation.

Extension application to introduce a new pharmaceutical form (film-coated tablet) associated with new strengths (200 and 300 mg) and new route of administration (oral use).
The RMP (version 2.0) is updated in accordance.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (c) (d) (e)> - Extensions of marketing authorisations

1.2. Information on Paediatric requirements

Not applicable.

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 MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4. Scientific advice

The MAH did not seek scientific advice from the CHMP.

1.5. Steps taken for the assessment of the product

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

Rapporteur: Hrefna Gudmundsdottir ; Co-Rapporteur: N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Bianca Mulder

The application was received by the EMA on	29 July 2024
The procedure started on	15 August 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 November 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	12 November 2024

The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	12 December 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	12 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	16 April 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	22 May 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	24 June 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 July 2025
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 Azacitidine Accord on	24 July 2025
The CHMP adopted a report on similarity of Azacitidine Accord with Dacogen, Mylotarg, Xospata, Daurismo, Vyxeos liposomal, Rydapt, and Tibsovo on (see Appendix on similarity)	24 July 2025

2. Scientific discussion

2.1. Problem statement

The current line extension application is aimed on registering Azacitidine Accord 200 mg and 300 mg film-coated tablets, recommended to be used

- as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).

2.2. Quality aspects

2.2.1. Introduction

This line extension concerns the additional registration of film-coated tablet dosage forms to the already approved powder for suspension for injection dosage form. The finished products is presented as film-coated tablets containing 200 mg or 300 mg of azacitidine as active substance.

Other ingredients are:

Tablet core: Mannitol, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate.

Film-coating for 200 mg: Hypromellose (E464), lactose monohydrate, polyethylene glycol (E1521), triacetin (E1518), titanium dioxide (E171), iron oxide red (E172).

Film-coating for 300 mg: hypromellose (E464), lactose monohydrate, polyethylene glycol (E1521), triacetin (E1518), titanium dioxide (E171),iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172).

The product is available in alu-alu blisters or alu/PVC/PCTFE blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

2.2.2.1. General information

The chemical name of azacitidine is 4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1H)-one corresponding to the molecular formula $C_8H_{12}N_4O_5$. It has a relative molecular mass of 244.20 g/mol and the following structure:

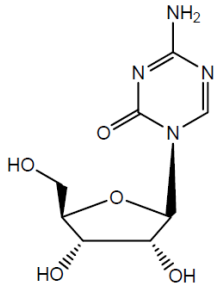

Figure 1: active substance structure

The chemical structure of azacitidine was elucidated by a combination of ^{1}H and ^{13}C NMR, MS, IR, UV and elemental analysis. The solid state properties of the active substance were measured by XRPD.

The active substance is a non-hygroscopic white to off-white solid, sparingly soluble in water.

Azacitidine exhibits stereoisomerism due to the presence of four chiral centres. Three of the chiral centres originate in one of the starting materials while the fourth centre is generated during the synthesis of the active substance. Enantiomeric purity is controlled by a test for specific optical rotation in the specification of the active substance.

Polymorphism has been observed for the active substance and an overview of eight potential polymorphic forms was provided. The manufacturing process consistently results in polymorphic form I, and no conversion of the polymorphic form during the manufacturing process and stability studies was observed.

2.2.2.2. Manufacture, characterisation and process controls

This line extension included an additional source of the active substance which is intended for use with the tablet formulation and the ASMF procedure was used for this. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Satisfactory information concerning GMP standards was provided.

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

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in double transparent LDPE bags, placed inside a triple laminated bag with silica gel pouches and stored inside a HDPE drum. The container closure system complies with EC 10/2011 as amended.

2.2.2.3. Specification

The active substance specification**Error! Reference source not found.** includes tests for: description (visual), solubility (Ph. Eur.), identity (IR, HPLC), specific optical rotation (Ph. Eur.), sulphated ash (Ph. Eur.), water content (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), content of tin (ICP-OES), microbial quality (Ph. Eur.), and particle size distribution (laser light diffraction).

The active substance specification parameters and limits are in line with relevant guidelines and are acceptable.

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

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

2.2.2.4. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (5°C±3°C) and up to 6 months under accelerated (25°C±2°C / 60%±5% RH) conditions were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. The temperature conditions chosen for the studies are in line with those authorised for Vidaza, this is considered acceptable. Results on stress conditions in solution (acidic, basic and oxidising conditions), as well as solid state (heat and light) were also provided on one batch.

The following parameters were tested: identification, water content, related substances and assay, polymorphism. The analytical methods used were the same as for release and were stability indicating.

At the long term and accelerated conditions, all tested parameters were within the specifications and no changes were observed. The active substance is not considered sensitive to light. During the forced degradation studies decreases in assay values and corresponding increases in impurity values were seen, the highest degradation was observed under basic conditions,

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 12 months, with the storage condition of preserve in a tight container in light resistant packing and store at 2 to 8°C, as selected by the applicant.

2.2.3. Finished Medicinal Product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is presented as film-coated tablets of two strengths containing 200 mg or 300 mg of azacitidine. The appearances of the tablets are as follows:

200 mg: Pink colour, oval shaped, film coated tablet, debossed with "MA1" on one side and plain on other side (17.0 x 7.6 mm).

300 mg: Brown colour, oval shaped, film coated tablet, debossed with "MA2" on one side and plain on other side (19.0 x 9.0 mm).

The finished product was developed to be equivalent to Onureg 200 mg and 300 mg film-coated tablets. The development aimed to create a bioequivalent immediate release product with a comparable dissolution profile to the reference product and acceptable pharmaceutical stability. The quality target product profile QTTP was defined during pharmaceutical development.

The active substance azacitidine exhibits high solubility considering the intended dose and is regarded as a BCS Class III active substance. The physical characteristics of the active substance that could impact product performance have been discussed and suitably controlled where relevant. The polymorphic form is controlled in the specification of the active substance. The particle size distribution is also controlled in the active substance specification to enable suitable flow and blending properties during the manufacturing process of the finished product.

The formulation development strategy was to select common excipients similar to the reference product. Based on the excipient profile and the flow characteristics of the active substance, a direct compression strategy was followed. In addition to this, the dose proportional nature of the proposed formulations allowed for a common blend strategy which could be used for both proposed tablet strengths. The information gained during the development was used to inform the proposed commercial manufacturing process and control strategy.

All excipients are well known pharmaceutical ingredients and their quality is compliant with relevant standards such as the Ph. Eur. One of the excipients, silicified microcrystalline cellulose, complies with the relevant USP monograph and relevant standards have also been described for the in-house film-coatings. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

A bioequivalence study was conducted to compare the 300 mg proposed tablet strength to the 300 mg Onureg reference product tablet. The results of this study were acceptable, for further details please refer to the clinical sections of this report. Comparative in-vitro dissolution studies were performed in addition to the bioequivalence study, the dissolution results at three pH conditions (pH 1.2, 4.5 and 6.8) showed that the in vitro dissolution profiles of the 300 mg test and reference product are similar. In support of the 200 mg proposed strength a biowaiver was requested considering the acceptable bioequivalence results of the 300 mg test product and dose proportionality of the formulations. The applicant provided comparative in-vitro dissolution data at three different pH values (pH 1.2, 4.5 and 6.8) between the proposed 300 mg and 200 mg strengths. The dissolution profiles were similar across the pH conditions and the request for the biowaiver was agreed as all relevant conditions for this were met.

The applicant performed considerable investigation into the discriminatory power of their chosen dissolution method. All investigations showed the active substance to be highly soluble with no

meaningful difference in dissolution evident despite the parameters varied. This was considered acceptable in light of the high solubility across the physiological pH range for the active substance.

The primary packaging is alu-alu blisters or alu-alu blisters or alu/PVC/PCTFE blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure systems has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site. During the procedure a major objection (MO) was raised by the CHMP as satisfactory evidence regarding GMP standards at the site was not available. To resolve this MO the applicant provided evidence that the site had been appropriately inspected by the relevant competent authorities.

The steps that can have a significant impact on the processability of the intermediates and on the resulting properties of the finished product have been identified as critical process steps. These steps are controlled by the respective normal operating range (NOR) and proven acceptable range (PAR) and adequate in-process controls. The applicant has provided sufficient data to justify the hold times proposed for the bulk product.

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

2.2.3.3. Product specification

The finished product release & shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), average weight, identification (HPLC & UV), water content (Ph. Eur.), dissolution (HPLC), assay (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC), microbiological quality (Ph. Eur.).

The specification for the control of the finished product contains the typical tests for this type of pharmaceutical form and the limits have been adequately 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 it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

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

The initially proposed limit for quality control (QC) dissolution could not be accepted as it had not been set in line with the dissolution performance of the batch used in the bioequivalence study. As this aspect could impact in-vivo performance an MO was raised by the CHMP, requesting the applicant to

tighten the limit for both tablet strengths in line with the bio-batch. To resolve this MO the applicant tightened the dissolution limit as requested.

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

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

2.2.3.4. Stability of the product

Stability data from three commercial scale batches of each strength of the finished product and in both packaging configurations stored for up to 36 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 are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, water content, dissolution, related substances, assay and microbial quality. The analytical procedures used are stability indicating. At long term and accelerated conditions no significant trends or out of specification results are observed. Increases in water content and hydrolysis products are seen for both packaging types, in particular during accelerated conditions. This trend is more pronounced in the alu/PVC/PCTFE presentation, however the results remain acceptable and within specification.

In addition, one batch of each strength were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No sensitivity to light was observed.

Based on available stability data, the proposed shelf-life of 36 months with no special storage condition as stated in the SmPC are acceptable.

2.2.3.5. Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure two MOs were raised on quality aspects these concerned evidence of appropriate GMP standards for the site conducting finished product manufacture and the need to tighten the specification limit for finished product dissolution in line with the batch used in the bioequivalence study. To resolve these aspects the applicant provided evidence that the site in question had been appropriately inspected for GMP standards, and tightened the specification limit for finished product dissolution as requested.

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.

2.2.5. 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. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of azacitidine are well known. As azacitidine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Submitted overview based on literature review is considered appropriate.

2.3.1. Ecotoxicity/environmental risk assessment

The MAH submitted an environmental risk assessment based on Phase I. The $PEC_{SURFACE\ WATER}$ (PEC_{SW}) for Azacitidine calculated according to the standard formula with a default value of Fpen (0.01) and the maximum daily dose of 300 mg resulted in value of 1,5 µg/L, which is above the action limit of 0.01 µg/L. The MAH then presented a refined F_{pen} calculations based on actual API consumption data of Azacitidine and epidemiological prevalence data.

The data of API consumption over last 4 years (2020-2023) is presented for several markets within EU along with population data and F_{pen} calculated accordingly. The highest value of refined F_{pen} (0.00016%) was used for the re-estimation of PEC_{SW} which resulted in a value of 0.00024 µg/L, which is below the action limit of 0.01 µg/L.

Furthermore, the MAH considered the maximum prevalence data for of Acute myeloid leukaemia (AML) at 0.0043% (obtained from literature) for refined F_{pen}. The estimated PEC_{SW} based on that was 0.0064 µg/L, less than the action limit of 0.01 µg/L.

A Phase II assessment is thus not deemed necessary as the Phase I assessment has concluded that Azacitidine tablets are unlikely to represent a risk for the environment following its recommended usage in patients and no further risk assessment is required. Furthermore, the submitted product is intended for generic substitution. Hence no increase in environmental load is to be expected. The ERA is therefore expected to be similar and not increased.

2.3.2. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology in the application contains an adequate review of published non-clinical data.

2.3.3. Conclusion on the non-clinical aspects

There are no objections to the approval of Azacitidine Accord film-coated tables from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspects

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

The MAH 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.

2.4.2. Clinical pharmacology

Study 033-22: A Randomized, Open-Label, Three-Treatment, Three-Arm, Three-Period, Single-Dose, Multi-Center, Cross-over Study to Assess Bioequivalence of Azacitidine Tablets of Intas Pharmaceuticals Ltd., India compared with ONUREG™ under Fasting Condition in Patients with Acute Myeloid Leukaemia in Remission Phase.

Methods

- **Study design**

The study was an open label, randomised, three-treatment, three-arm, three-period, single-dose, multi-centre, crossover bioequivalence study in 60 patients with acute myeloid leukaemia in remission phase, under fasting conditions.

- **Test and reference products**

Treatment	
Test product	Azacitidine tablet 300 mg, manufactured by Intas Pharmaceuticals Ltd., India.
Reference-R1 (US)	ONUREG (azacitidine) tablet 300 mg, manufactured by Celgene Corporation, Summit, NJ 07901.
Reference-R2 (EU)	ONUREG (azacitidine) tablet 300 mg manufactured by Celgene Distribution B.V. Orteliuslaan 1000 3528 BD, Utrecht, Netherlands.

- **Population(s) studied**

A total of 60 patients of Asian race were enrolled in the study (30 females and 30 males; 19 -69 years) and dosed in period 1. All 60 patients completed the study but 59 were included in the EU and US pharmacokinetic and statistical analysis, respectively.

Reasons for the dropouts/withdrawals:

One patient had no reported concentration values following dosing in any period and was therefore excluded from the PK set.

- **Analytical methods**

The study samples were analysed by a validated LC-MS/MS method after solid phase extraction method. The method validation was completed on 08-Oct-2023, before onset of the initial bioanalytical phase of the study in line with bioanalytical method SOP no. MS-1817-00. Initial bioanalytical phase of the study started on 11-Oct-2023.

Amendment I (dated 13-Feb-2024) to the method validation report was initiated to update the method and to perform requisite experiments to validate a change in column, run time, chromatographic condition (mobile phase composition) and injection volume following an investigation into a consistent poor chromatography in several consecutive runs which led to the rejection of the entire data of all samples analyzed up to that point (total of 36 patients) with the Method SOP MS-1817-00.

Analysis in line with method SOP no. MS-1817-01 (dated 22-Jan-2024) was initiated on 23-Jan-2024.

Amendment II (dated 18-Mar-2023) included the results of long-term stability of analyte in human plasma and analyte stability in human whole blood in ice cold water batch maintained at or below 4°C (established for 42.0 minutes).

The method was fully and partially validated in human plasma and can be summarized as follows:

Calibration range: 3.006 ng/mL to 500.136 ng/mL

QC concentrations (ng/mL): 3.059 (LLOQ), 8.998 (LQC), 59.194 (LMQC), 159.984 (MQC), 399.961 (HQC) and 1496.800 (DQC)

Sample analysis (according to method SOP no. MS-1817-01) took place on 23-Jan-2024 to 14-Feb-2024.

The accuracy and precision of the QC samples at 8.998, 29.597, 59.194, 159.984 and 399.961 ng/ml during analysis of patient samples were as follows:

Inter-run accuracy: 99.2% to 100.3%,

Inter-run precision: 3.0% - 6.6%.

Duration of sample storage until completion of analysis was 169 days from the first sample collection (26-Aug-2023) to the last sample analysis.

A total of 3420 samples were analysed. A total of 140 individual samples were reanalysed, due to significant variation in internal standard response (104), elimination of low calibration curve standard (24), concentration above highest standard (06), poor chromatography (05) and no internal standard response (01).

Incurred sample reanalysis (ISR) was performed on 221 samples out of 3420 samples for Azacitidine in order to evaluate the incurred sample reproducibility; 215 (97.3%) samples were within acceptance criteria.

All the selected ISR samples from one patient, demonstrated more than 20% difference from original results. Thus, in line with SOP on Incurred sample reproducibility (AHM/BA/0069-2) an investigation was conducted into why that occurred. The investigation concluded a considerable difference between the patient´s samples from Lot-1 (from original analysis) and Lot-2 samples (used for repeat analysis and ISR analysis). Hence selected samples from Lot-1 and Lot-2 were re-processed and re-analysed, upon

which a considerable difference in the concentration values between the samples lots was confirmed, with a concentration data reported for samples of Lot-1, but below LOOQ for the samples of Lot-2. No bioanalytical anomaly could be identified which explained this difference, and furthermore an investigation at the clinical site identified no reasons for this discrepancy. Based on this the patient´s data was considered unreliable and all samples of this patient were identified as Not Reportable (NR).

- **Pharmacokinetic Variables**

The primary pharmacokinetic parameters for this study were as follows for **EU analysis:**

Primary Pharmacokinetic Parameters: C_{max} and AUC_{0-t}.

Secondary Pharmacokinetic Parameters: $AUC_{0-\infty}$, T_{max}, AUC_%Extrap_obs, R^2 adjusted, λz, and $t_{1/2}$.

- **Statistical methods**

Descriptive statistics were to be computed and reported for plasma concentration data and pharmacokinetic parameters of azacitidine.

For continuous variables the summary statistics presented were to be the number of observations, mean, standard deviation, median, minimum and maximum values. Categorical values were to be summarized using frequencies and percentages.

All statistical analyses were to be conducted using the SAS version 9.4. Pharmacokinetic analyses were to be performed using Phoenix WinNonlin version 8.3. The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were to be subjected to Analysis of Variance (ANOVA) for Azacitidine.

The ANOVA model included terms for Center, Sequence, Sequence*Center, Patient (Sequence*Center), Formulation, Formulation*Center and Period (Center) effects. The Sequence, Center and Sequence*Center effect were to be tested using the Patient (Sequence*Center) as an error term.
Each analysis of variance included calculation of least-squares means, the difference between adjusted formulation means and the standard error associated with this difference.

The above statistical analyses were to be done using PROC MIXED SAS® Procedure (for US analysis) and PROC GLM SAS® procedure (for EU analysis). Additionally, the applicant was requested to submit an ANOVA analysis with all fixed effects for *sequence, subject within sequence, period and formulation.*

Where the number of participants for BE evaluation was < 5 participants in any Center, then that Center was to be combined to another Center.

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

The 90% confidence interval for the ratio of geometric least squares means between drug formulations were to be calculated and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Azacitidine.

Criteria for conclusion of bioequivalence – EU analysis:
Based on the statistical results of 90% confidence interval for the ratio of the geometric least squares means for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t}, conclusion would be drawn for Test Formulation-T vs. Reference Formulation-R2.

Bioequivalence was concluded if the 90% confidence interval for the ratio of geometric least squares means between test and reference formulations fell within the acceptance range of 80.00 - 125.00% for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Azacitidine.
The data of $AUC_{0-\infty}$ was provided as supportive information only.

Results

Table 1. Pharmacokinetic parameters for Azacitidine (non-transformed values)**-** Study 033-22

Pharmacokinetic parameter	Test (N=59)	Reference-R1 (US) (N=59)	Reference-R2 (EU) (N=59)
	arithmetic mean ± SD	arithmetic mean ± SD	arithmetic mean ± SD
C_{max} (ng/mL)	157.03 ± 97.61	155.84 ± 107.45	160.22 ± 96.65
$AUC_{(0-t)}$ (h*ng/mL)	257.13 ± 176.24	256.87 ± 156.13	264.01 ± 153.09
$AUC_{(0-\infty)}$ (h*ng/mL)	261.87 ± 177.96	262.02 ± 156.82	268.37 ± 153.06
Tmax (h)*	0.83 (0.33 - 2.67)	1.00 (0.17 - 2.33)	1.00 (0.33 - 2.67)

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 Azacitidine (ln-transformed values), US analysis (N=59), Study 033-22

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference-R1 (US)	90% Confidence Intervals	Intra patient CV%
C_{max}	100.8	93.92-108.09	21.4
$AUC_{(0-t)}$	100.7	92.72-109.31	25.2
$AUC_{(0-\infty)}$	100.4	92.65-108.75	24.5

Table 3. Statistical analysis for Azacitidine (ln-transformed values), EU analysis (N=59), Study 033-22

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference-R2 (EU)	90% Confidence Intervals	Intra patient CV%
C_{max}	100.2	93.10- 107.92	24.2
$AUC_{(0-t)}$	96.3	88.12- 105.32	29.4
$AUC_{(0-\infty)}$	96.3	88.37- 105.01	28.4

- ***Exemption***

The Applicant is seeking marketing authorisation for Azacitidine Accord film-coated tablets with 2 strengths, namely 300 mg, and 200 mg.

A strength based biowaiver was applied for the additional strength of 200 mg based on the *in vivo* data (bioequivalence study) of the 300 mg strength. The justification for the strength based biowaiver is as follows:

a) Azacitidine 200 mg and 300 mg Tablets are manufactured at the same manufacturing site i.e. Intas Pharmaceutical Limited using a similar manufacturing process.

b) Azacitidine demonstrates linear pharmacokinetics over the therapeutic dose range.

c) The qualitative compositions of Azacitidine 200 mg tablets are the same as that of Azacitidine 300 mg Tablets.

d) The formulations of both the strengths are dose proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance(s) are the same for both strengths.

e) In-vitro dissolution profile is similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Table 4. Dissolution conditions for biowaiver request

Dissolution testing Site		Study Report Location: Please refer "Module 3.2.P.2.2"
Dissolution Conditions	Apparatus	Type II PADDLE
	RPM	50 RPM
	Medium	0.1 N HCl , pH 4.5 Acetate buffer pH 6.8 Phosphate buffer
	Volume	500 ml
	Temperature	37 ± 0.5°C
	Surfactant	-

Table 5. *In vitro* dissolution data for biowaiver request for Azacitidine Accord film-coated tablets 300 mg and 200 mg

Dissolution Medium		**Collection Time (minutes or hours)**					**f2***
		5	**10**	**15**	**20**	**30**	
Azacitidine 200 mg tablets B. No. M2102391 (Biowaiver batch)	0.1 N HCl	76	88	90	92	93	
	pH 4.5 Acetate buffer	64	69	69	69	66	
	pH 6.8 Phosphate buffer	62	71	75	75	75	
Azacitidine 300 mg tablets B. No. M2210502 (BE test batch)	0.1 N HCl	85	87	94	96	94	*
	pH 4.5 Acetate buffer	65	69	69	68	65	94.89
	pH 6.8 Phosphate buffer	69	74	77	77	77	71

* Both formulations show more than 85% of drug release within 15 minutes. Hence, Dissolution profiles are considered similar without any mathematical calculation for similarity

2.4.2.1. Pharmacodynamics

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

2.4.3. Discussion on clinical pharmacology

To support this application, the MAH submitted one study, no. 033-22. The study was an open-label, randomised, three-treatment (test product, US reference product and EU reference product), three-arm, three-period, single-dose, multi-center, cross-over bioequivalence study of Azacitidine 300 mg tablet and ONUREG 300 mg tablets (US reference and EU reference) under fasting condition in patients with acute myeloid leukaemia in remission phase. A total of sixty patients (60) were enrolled and dosed in Period 1, in line with the protocol. Sixty (60) patients completed the study, but 59 patients were included in the PK and statistical analysis, since no concentration data were available for one patient in any of the periods.

The pivotal bioequivalence study was conducted in line with the general bioequivalence guidance in terms of design, analyte, and parameters for bioequivalence assessment.

The results of study no. 033-22 indicate that the test product is bioequivalent with the EU reference product under fasting conditions as the 90% CI of the ratio for geometric least square means of ln-transformed data of AUC_{0-t} and C_{max} for Azacitidine of the test and reference product falls within the conventional acceptance criterion of 80.00-125.00%.

The concentration data of the subject that was excluded from the analysis was not presented with the clinical study report. A sensitivity analysis with the original concentration data of this subject included was however provided which confirmed the bioequivalence between the test product and the EU reference product.

The biowaiver request for the lower strength is considered acceptable since Azacitidine demonstrates linear pharmacokinetics over the therapeutic dose range. Furthermore, the requirements of the general biowaiver criteria of the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr** are considered fulfilled and the biowaiver therefore considered justified for the 200 mg strength. Tabular *in vitro* dissolution data of 12 units including individual values, mean values and RSD (%) of the investigated products have been provided. The data provided was generated under three different testing conditions (0.1M HCl, pH 4.5 and pH 6.8) with paddle apparatus at 50 rpm in 500 ml.

The applicant concludes similarity is demonstrated between the two strengths of the test products since more than 85% release was observed at pH 0.1M HCl (the profiles can therefore be concluded to be similar without further mathematical evaluation) and at pH 4.5 and 6.8 similarity was demonstrated with F2 >50.
This is agreed and the biowaiver is therefore justified for the 200 mg strength.

2.4.4. Conclusions on clinical pharmacology

Bioequivalence has been appropriately shown between the test product and reference product in patients under fasting conditions in line with the EU guideline on the investigation of bioequivalence.

There are no objections to the approval of Azacitidine Accord film-coated tablets from a clinical pharmacology point of view.

2.4.5. Clinical safety

A total of 18 adverse events were reported by nine (09) of 60 patients during the study. Four (04) adverse events were reported by four patients (04) following administration of the test product. Seven (07) adverse events were reported by three (03) patients following the administration of Reference-R1 (US) product. Seven (07) adverse events were reported by five (05) patients following the administration of Reference-R2 (EU) product.

Out of these 18 adverse events, 15 were mild and 03 were moderate in nature. The causality assessment was judged as certain for 3 adverse events, probable/likely for 7, possible for 2 and as unlikely for 6 adverse events. The outcome of all (18) the adverse events was Recovered/Resolved.

No serious adverse event occurred, and no death occurred during the conduct of the study.

2.4.6. Discussion on clinical safety

The adverse advents have been adequately analysed including incidence by treatment, relation with investigational medicinal product, intensity and time of onset and resolution.

There were no serious adverse events during the conduct of this study. Overall, the drugs tested were generally safe and well tolerated by the patients included in this study.

2.4.7. Conclusions on the clinical safety

There are no objections to the approval of Azacitidine Accord film-coated tables from a clinical safety point of view.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	Haemorrhagic events* Infections
Important potential risks	None
Missing information	None

** for injection formulation only*

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP considered that the risk management plan version 2.0 is acceptable.

2.5.5. Pharmacovigilance system

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

2.5.6. 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.

2.6. Product information

2.6.1. 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 Onureg 200 mg and 300mg film-coated tablets and Solifenacin succinate 5/10mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

This application is aimed at registering Azacitidine Accord 200 mg and 300 mg film-coated tablets.

The application is based upon Article 10(1) (a) (iii) (essentially similar products i.e. generics) of Directive 2001/83/EC. The reference product Onureg (Azacitidine) film-coated tablets 200 mg and 300 mg is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).

From a clinical perspective, this application does not contain new data 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 an open label, randomized, three-treatment (test product, US reference product, EU reference product), three-arm, three-period, single-dose, multi-centre, crossover bioequivalence study in patients. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The study was conducted under fasting conditions, which is considered appropriate. 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 Azacitidine Accord 300 mg film-coated tablet met the protocol-defined criteria for bioequivalence when compared with the EU reference product, Onureg 300 mg tablet. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, and C_{max} were all contained

within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations has been demonstrated.

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.

3.1. Conclusions

The overall benefit/risk balance of Azacitidine Accord is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Azacitidine Accord is not similar to Dacogen, Mylotarg, Xospata, Daurismo, Vyxeos liposomal, Rydapt, and Tibsovo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Azacitidine Accord 200 and 300 mg film-coated tablets is favourable in the following indication(s):

Azacitidine Accord is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Azacitidine Accord 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).

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.