Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Enasidenib

Proprietary Product Name: Idhifa

Sponsor: Celgene Pty Ltd

April 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
2-HG	R(-)2-hydroxyglutarate
ACM	Advisory Committee on Medicines
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
AGI-16903	Enasidenib metabolite
AML	Acute myeloid leukaemia
AMLSG	Austrian Acute Myeloid Leukemia Study Group
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
AUC	Area under the plasma concentration time curve
$AUC_{0-\infty}$	Area under plasma concentration time curve from time zero extrapolated to infinity (∞)
AUC_{0-t}	Area under the plasma concentration time curve from time zero to the last measurable concentration (t)
BID	Twice daily (*Latin: bis in die*)
BMT	Bone marrow transplant
CD33	Cluster of differentiation 33
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
CR	Complete remission
CRi	Complete remission with incomplete haematologic recovery
CRp	Complete remission with incomplete platelet recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450

Abbreviation	Meaning
DLP	Data lock point
DLT	Dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukaemia Net
EMA	European Medicines Agency (European Union)
EU	European Union
EU-RMP	European Union-risk management plan
FDA	Food and Drug Administration (United States)
FLT3	Fms like tyrosine kinase 3
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
HSCT	Haematopoietic stem cell transplant
IDH	Isocitrate dehydrogenase
IDH1	Isocitrate dehydrogenase 1
IDH2	Isocitrate dehydrogenase 2
IRAC	Independent Response Adjudication Committee
IWG	International Working Group (for Diagnosis, Standardization of Response Criteria)
KM	Kaplan Meier
MDS	Myelodysplastic syndrome
mIDH2	Mutant isocitrate dehydrogenase 2
MLFS	Morphologic leukaemia-free state
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network (United States)
OAT1	Organic anion transporter 1
OATP1B1	Organic anion transporting polypeptide 1B1

Abbreviation	Meaning
ORR	Overall response rate
OS	Overall survival
PAR	Provisional Australian Register of Therapeutic Goods record
PD	Pharmacodynamic(s)
PETHEMA	Programa Español de Tratamientos en Hematología
PI	Product information
PK	Pharmacokinetic(s)
PS	Performance status
PSUR	Periodic safety update report
PT	Preferred Term
QD	Once daily (*Latin: quaque die*)
QTc	Corrected QT interval
R/R	Relapsed or refractory
RBC	Red blood cell
RMP	Risk management plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
T_{max}	Time of maximum plasma concentration
TNF	Tumour necrosis factor
UGT	Uridine 5'-diphospho-glucuronosyltransferase
US	United States
Vd	Volume of distribution

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved for provisional registration
Date of decision:	15 January 2020
Date of entry onto ARTG:	17 January 2020
ARTG numbers:	311541, 311542
, *Black Triangle Scheme*	Yes As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
Active ingredient:	Enasidenib
Product name:	Idhifa
Sponsor's name and address:	Celgene Pty Ltd Level 15, 60 City Road Southbank, VIC 3006
Dose form:	Film coated tablet
Strengths:	50 mg and 100 mg
Container:	Bottle
Pack size:	30
Approved therapeutic use:	*This medicine has Provisional Approval in Australia for the treatment of adult patients with relapsed or refractory acute myeloid leukaemia who are ineligible for haematopoietic stem cell transplant, and who have an isocitrate dehydrogenase-2 (IDH2) mutation confirmed by a validated diagnostic test.* *The decision to approve this indication has been made on the basis of preliminary clinical data from a Phase 1/2 clinical trial with a primary endpoint of overall response rate. An improvement in OS or PFS has not been established. The sponsor is required to submit further clinical data to confirm the efficacy and safety of the medicine.* The provisional registration period for the above medicine(s) is two years starting on the day specified in the ARTG certificate of registration.
Route of administration:	Oral

Dosage:	Treatment with Idhifa must be initiated and monitored under the supervision of a registered Specialist Physician experienced in the management of haematological and oncological malignancies. The recommended starting dose of Idhifa is 100 mg taken orally once daily. It is recommended to treat patients for a minimum of 6 months to allow time for clinical response and to continue treatment until disease progression or unacceptable toxicity. For further information refer to the Product Information.

Product background

This AusPAR describes the application by Celgene Pty Ltd (the sponsor) to provisionally register Idhifa (enasidenib) 50 mg and 100 mg film coated tablets for the following proposed indication:

> *Idhifa is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukaemia with an isocitrate dehydrogenase-2 (IDH2) mutation.*

Acute myeloid leukaemia (AML) is a heterogeneous condition affecting around 0.15 in 10,000 persons in Australia. It may arise *de novo*, be preceded by myelodysplastic syndrome (MDS), or be triggered by treatment with tumour necrosis factor (TNF)-alpha inhibitors. The treatment of AML has not substantially improved in the last 40 years, with 5 year survival of approximately 19% overall. The disease is characterised by various chromosomal abnormalities and genetic defects that are used to classify the disease and are also used to determine prognosis and determine likely response to therapy. The European Leukaemia Net (ELN) has a three tier risk stratification for such abnormalities, classifying the disease in to favourable, intermediate or adverse risk categories.[1]

About 10% of AML patients have an isocitrate dehydrogenase 2 (IDH2) mutation. Typically, this enzyme converts isocitrate to 2-ketoglutarate in the cellular mitochondria. However, IDH2 mutations confer a gain of function, whereby the aberrant enzyme catalyses the production of the oncometabolite R(-)2-hydroxyglutarate (2-HG). 2-HG competitively inhibits DNA and histone demethylases, which induces a block of haematopoietic cell differentiation. Hence, numbers of immature precursor cells are increased. While the mutant enzyme can contribute to malignant transformation, how they affect survival and the proliferation of established leukaemias is not well understood.

Relapse in AML can be expected in nearly all patients who initially achieve complete remission (CR), unless post-remission therapy is given. The therapy that provides the best chance to cure a patient with relapsed or refractory (R/R) AML is allogeneic haematopoietic stem cell transplantation (HSCT), and the best outcomes appear to be with myeloablative preparative regimens administered after attaining a CR. However, some patients may be cured with myeloablative HSCT despite residual disease at the time of HSCT. There is no consensus regarding the optimal regimen for achieving remission in patients with R/R AML. Some patients have AML with mutations (for example, isocitrate dehydrogenase 1 (IDH1), IDH2, fms like tyrosine kinase 3 (FLT3)) that are amenable to treatment with targeted agents, but no studies have directly compared targeted agents versus intensive chemotherapy as bridging therapies to transplantation in this setting. Chemotherapy for R/R AML is highly toxic, primarily to the haematopoietic system, and

[1] Döhner, H. et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017; 129(4): 424-447.

most patients will have a prolonged hospital stay and will require blood product support. There is a clear need for targeted, less toxic treatments in R/R AML.

Many of the newer agents recommended for specific mutations are not currently registered, at the time this submission was under consideration. These include gilteritinib for FLT3 mutation, ivosidenib for IDH1 mutation, and gemtuzumab ozogamicin for cluster of differentiation 33 (CD33) positive AML.

Enasidenib is a first-in-class small molecule selective inhibitor of a mutated form of IDH-2 (mIDH2). The proposed indication for enasidenib is for treatment of AML with a mutation in the gene that encodes IDH-2. Because enasidenib inhibits the mIDH2 protein, it reduces 2-HG production, which restores differentiation of leukemic cells into mature cells.

Regulatory status

Idhifa (enasidenib) is considered a new chemical entity for Australian regulatory purposes.

Enasidenib was approved by the United States (US) Food and Drug Administration (FDA) on 1 August 2017 for the following indication:

> *Idhifa is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA approved test.*

At the time the TGA considered this application, applications were under review in Canada and Switzerland. An application in the European Union (EU) was withdrawn, following the provisional opinion of the European Medicines Agency (EMA) that the results of the study did not allow the conclusion that Idhifa was sufficiently effective in the treatment of R/R AML with an IDH2 mutation.[2]

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-04819-1-6

Description	Date
Positive Designation	Orphan: 30 April 2018; extension: 8 October 2018 Provisional: 27 September 2018
Submission dossier accepted and first round evaluation commenced	2 January 2019

[2] European Medicines Agency (EMA), Withdrawal of application for the marketing authorisation of Idhifa (enasidenib), 31 January 2020, EMA/47029/2020, accessed from the EMA website.

Description	Date
First round evaluation completed	6 September 2019
Sponsor provides responses on questions raised in first round evaluation	30 October 2019
Second round evaluation completed	13 January 2020
Delegate's Overall benefit-risk assessment	10 January 2020
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	15 January 2020
Completion of administrative activities and registration on the ARTG	17 January 2020
Number of working days from submission dossier acceptance to registration decision*	220

*Statutory timeframe for standard applications is 255 working days

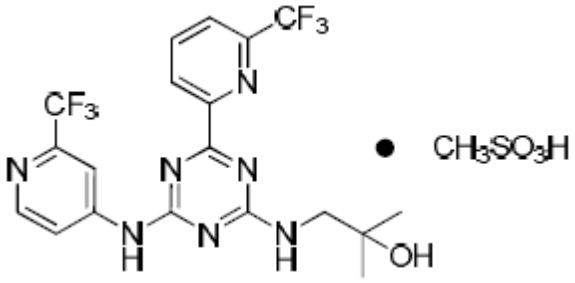
III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Enasidenib (structure shown in Figure 1, below), is a first in class small molecule oral inhibitor of mutant IDH2 variants. This compound belongs to the class of organic compounds known as 1,3,5-triazine-2,4-diamines. It is presented as a mesylate salt (the 50 mg product contains 60 mg enasidenib mesylate, and the 100 mg product contains 120 mg enasidenib mesylate).

Figure 1: Structure of enasidenib mesylate



The chemistry evaluator raised no outstanding issues to prevent approval.

The following is a summary from the quality evaluation:

- The proposed trade name is acceptable from a quality and clinical perspective.
- The provisional Australian Register of Therapeutic Goods records (PARs) for the proposed product have been reviewed and are acceptable from a quality perspective.
- The proposed specification for enasidenib imposed by the finished product manufacturer is acceptable.
- The finished product specifications for the product are acceptable.
- A shelf life of 2 years when stored below 25°C is recommended for the proposed products when stored in 90 mL square white opaque high-density polyethylene bottles with white polypropylene child resistant closures with Safe-Gard induction seal liner (tamper evident) and 2 g silica gel desiccant canister containing 30 tablets (all strengths).
- The manufacturing sites have current Good Manufacturing Practice (GMP) clearance.
- The proposed PI is acceptable from a quality perspective.
- Final mock-ups labels have been provided. The labels are acceptable from a quality perspective.

There are no outstanding issues with the chemistry and quality control aspects of the product.

Nonclinical

The non-clinical evaluator raised no objections to approval beyond finalisation of recommended PI changes.

The following points were summarised in the nonclinical evaluation:

- Enasidenib was shown to inhibit R140Q, R172S and R172K IDH2 mutants *in vitro*, acting with 44 to 220 times greater potency than against wild type IDH2. Cell-based assays showed marked reductions in cellular 2-HG, reversal of histone hypermethylation, and induction of cellular differentiation with enasidenib treatment. *In vivo* in mice bearing human R140Q IDH2 tumour xenografts, oral administration of enasidenib decreased serum and tumour 2-HG levels, increased blast cell differentiation in the bone marrow, and prolonged survival of the animals. These data offer support for utility in the proposed indication.
- The major circulating metabolite of enasidenib, AGI-16903, is also pharmacologically active. Its contribution to efficacy *in vivo* is seen to be low, however.
- Secondary pharmacodynamic (PD) studies revealed that enasidenib and AGI-16903 also possess potent antagonist activity at the adenosine A_3 receptor. Tachycardia and alterations in blood pressure were observed in enasidenib-treated dogs; no effects on cardiovascular function were apparent in monkeys though, despite higher exposure than in dogs.
- Pharmacokinetic (PK) studies showed good oral bioavailability of enasidenib in laboratory animal species, like humans. The speed of oral absorption was variable across species, with prolonged absorption seen in rats, but similarly fast absorption in monkeys and humans. The plasma half-life of enasidenib was much shorter in all of the laboratory animal species examined compared with humans. Appropriately to compensate, most of the toxicity studies employed twice daily dosing.

- Plasma protein binding by enasidenib and AGI-16903 was high in humans and animals. Wide tissue distribution of ^{14}C-enasidenib-derived radioactivity was seen following oral dosing in rats, with penetration of the blood-brain barrier and some melanin binding apparent.
- AGI-16903, formed by *N*-dealkylation, was the sole major circulating metabolite of enasidenib in humans. While rats formed only very low levels of this metabolite, it was readily formed in monkeys. Multiple cytochrome P450 (CYPs) enzymes and uridine 5'-diphospho-glucuronosyltransferases (UGTs) were shown to be involved in the metabolism of enasidenib *in vitro*. Excretion was mainly via the faeces in rats, as in humans, with biliary excretion demonstrated.
- Enasidenib inhibited CYP2C8, 2C9, 2C19 and 2D6, UGT1A1, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter 1 (OAT1), organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3, and AGI-16903 inhibited CYP1A2, BCRP and OATP1B1, at clinically relevant concentrations *in vitro*, indicating significant potential for Idhifa to affect the PK of co-administered drugs. Experiments with cultured human hepatocytes additionally showed induction of CYP3A4 by both compounds.
- Enasidenib showed a low to moderate order of acute toxicity by the oral route in animals.
- Repeat-dose toxicity studies were performed with enasidenib in rats and cynomolgus monkeys; the pivotal studies were of 3 months duration. A 1 week study conducted with an ester pro-drug form of enasidenib in dogs was also submitted. The key findings concerned elevated serum bilirubin (consistent with inhibition of UGT1A1), gastrointestinal toxicity, pancreatic acinar cells (atrophy and vacuolation), reproductive tissues (histopathological changes suggesting impairment of male and female fertility), and the cardiovascular system. With these occurring at exposure levels below or comparable to that of patients, all findings are considered potentially clinically relevant.
- Enasidenib was negative in the standard battery of tests for genotoxicity. No carcinogenicity studies have been conducted; this is acceptable for a medicine indicated for the treatment of advanced cancer.
- Embryofetal lethality was observed with enasidenib in rats at a low margin of the human exposure, justifying assignment to Pregnancy Category D;[3] (as the sponsor proposes).

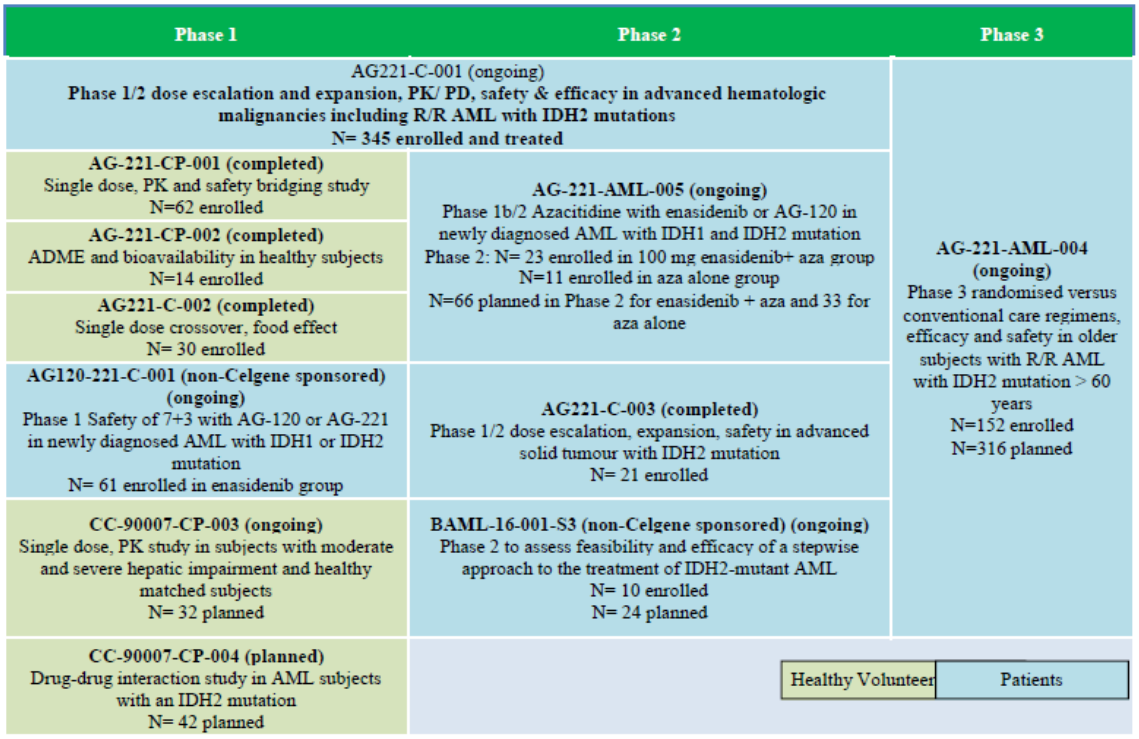
There are no nonclinical objections to the registration of Idhifa provided that the draft PI document is amended as directed.

Clinical

The dossier contains some, but not all, of the studies in the enasidenib clinical development program, in keeping with the provisional nature of this application. The clinical development programme is summarised as follows in Table 2.

[3] Australian Pregnancy Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Table 2: Clinical development programme for enasidenib



ADME = absorption distribution metabolism excretion; AML = acute myeloid leukemia; aza = azacytidine; IDH2 = isocitrate dehydrogenase isoform 2; PD = pharmacodynamics; PK = pharmacokinetics; R/R= relapsed/refractory

Note: The data cutoff date was 01 Sep 2017 for the ongoing studies. Clinical Pharmacology study CC-90007-CP-003 was initiated on 19 Sep 2017 so no subjects had been treated by the cut-off date.

Study AG221-C-003 was terminated early for business reasons, not related to patient safety concerns.

Results of the following studies, outlined in Table 3, were provided in the dossier.

Table 3: Studies provided in the clinical dossier

Phase	Study Name	Abbreviation used in this AusPAR	Description
I/II	AG221-C-001	-	A Phase I/II multicentre, open-label study conducted in 3 parts (001DE, 001Ex and 001P2), of PK/PD, safety and efficacy of enasidenib in advanced haematologic malignancies including R/R AML with IDH2 mutations. Two final clinical study reports (CSRs) have been provided: the Phase I CSR covers 001DE and 001Ex and the Phase II CSR covers 001P2. The sponsor has also conducted a combined analysis of all subjects with R/R AML in all three parts of the trial.
I	AG221-C-001 Phase I Dose Escalation	001DE	
	AG221-C-001 Phase I Expansion	001Ex	
II	AG221-C-001 Phase II	001P2	
I	AG-221-CP-001	Study PK	Single dose, open-label study to evaluate the PK and safety of enasidenib in healthy adult male Japanese subjects relative to healthy adult male Caucasian subjects.

Phase	Study Name	Abbreviation used in this AusPAR	Description
	AG-221-CP-002	Study ADME	Open-label 2-part study to evaluate the metabolism and excretion and determine absolute bioavailability of enasidenib in healthy male adult subjects.
	AG221-C-002	Study FE	Two way crossover study to assess PK and safety of a single dose of enasidenib in healthy male subjects when administered under fed and fasted conditions.

The ongoing Study AG221-C-001 had three parts or phases, namely a dose escalation phase (001DE), a Phase I expansion (001Ex) and a Phase II expansion (001P2). One CSR covered the first two phases and a second CSR covered the third phase. This single study gathered information on PK, PD, dose finding, safety and efficacy, and is the major data submitted for efficacy in the dossier. The three completed Phase I studies, namely Study AG-221-CP-001 (Study PK); Study AG-221-CP-002 (Study ADME) and Study AG221-C-002 (Study FE), studied PK, safety, absorption, distribution, metabolism and excretion (ADME) as well as bioavailability and food effect.

Multiple 'sub-studies' as a collective term, in PK and PD were conducted from those studies completed above, chiefly Study AG-221-C-001. They are described as follows in Table 4.

Table 4: Pharmacokinetic/pharmacodynamic studies using subjects from other studies

Study Name	Abbreviation used in this AusPAR	Subjects taken from study	Description
Study AG221-N-033-R1	Study R1	Not applicable	*In-vitro* study to determine plasma protein binding of enasidenib in human and animal plasma
Study AG221-C-001-QTCPK	Study QTC	Study AG221-C-001	This study assessed the relationship between enasidenib exposure (plasma concentration) and changes in QT/corrected QT interval (QTc)
Study AG-221-MPK-002	Study MPK	Study FE, Study PK, Study AG221-C-001	A PK comparison to assess the impact of different formulations on enasidenib PK exposure
Study AG-221-MPK-001	Study POP	Study AG221-C-001, Study PK, Study ADME	Population PK and exposure response of enasidenib

Study Name	Abbreviation used in this AusPAR	Subjects taken from study	Description
Study AG-221-C-001-PKPD	Study PKPD	Study AG221-C-001	PK/PD analysis of enasidenib in subjects with advanced haematologic malignancies with an IDH2 mutation
Study AG221-C-001-TD-2HG-002	Study 2HG	Study AG221-C-001	Analysis of 2-HG levels in patients treated with enasidenib
Study AG221-C-001-TD-IDH2VAF-002	Study IDH2	Study AG221-C-001	Analysis of mIDH2 variant allele frequency in patients treated with enasidenib
Study AG221-C-001-TD-CoMut-002	Study TD	Study AG221-C-001	Analysis of co-occurring mutations, impact on cohort risk and response to enasidenib

Additional data included:

- A statistical report for comparison of Study AG221-C-001 to historical data.
- Historical control analysis report for R/R AML historical data (University of Ulm 2018), this was supporting data to a published review paper.[4]
- Historical control analysis report for IDH2 R/R historical data (Programa Español de Tratamientos en Hematología (PETHEMA) registry).
- Retrospective chart review of hospitalisation of adult patients with AML with IDH2 mutation in France (interim report March 2018).
- Literature references were also included in the clinical dossier.

Pharmacology

Pharmacokinetics

Absorption is assumed to occur in the stomach and small intestine, based on the time of maximum plasma concentration (T_{max}) of 1 to 2 hours reported in Study ADME. In Study AG221-C-001, maximum plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC) were 1272 ng/mL and 58381 ng*h/mL, respectively, after a single 100 mg dose. In the PI, C_{max} is reported as 1.3 µg/mL after a single 100 mg dose of enasidenib, and 13 µg/mL at steady state for 100 mg daily. Allowing for the change in units, these figures match the data reported in Study AG221-C-001.

Bioavailability of a single 100 mg dose of oral enasidenib is 57.2%, as reported in the Study ADME.

[4] Dohner et al. Acute Myeloid Leukemia, *N Engl J Med*, 2015; 373: 1136-1152.

Dose proportionality was demonstrated for single dose enasidenib at 50 mg, 100 mg or 300 mg administration in healthy Japanese and Caucasian subjects. After single dose exposure of enasidenib at 50 mg, 100 mg or 300 mg, the point estimate of the ratios of area under the plasma concentration-time curve from time zero to the last measured concentration or time t (AUC_{0-t}), area under plasma concentration time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$) and C_{max} were comparable between healthy Japanese and Caucasian subjects. The point estimate of the ratios of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the metabolite AGI-16903 between Japanese and Caucasian subjects, following single-dose enasidenib at 50 mg, 100 mg or 300 mg, was inconsistent across dose exposures. However, at the proposed dose of 100 mg, the point estimate of the ratio of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} showed comparability between healthy Japanese and Caucasian subjects. The efficacy of the primary metabolite (AGI-16903) has not been reported from the clinical studies in healthy subjects or patients.

There was an observed increase in C_{max} and $AUC_{0-\infty}$ in the fed state: in fact, approximately 50% of AUC_{0-t} as one example, with C_{max} even higher. However, no specific recommendation in the PI was present that enasidenib should be taken with or without food. The sponsor was requested to justify the absence of such a recommendation and did so to the satisfaction of the clinical evaluator, noting statements regarding the effect of food on PK are present in the PI and the differences are not likely to be clinically relevant as it has no significant impact on steady-state.

Study POP estimated volume of distribution (V_d) at 192 L. From Study R1, protein binding was 98.5%.

Metabolism is by multiple CYP and UGT enzymes. The PK study that is ongoing will provide important missing data about potential drug interactions. Enasidenib and its metabolite AGI-16903 accounted for 89% and 10% respectively of circulating total radioactivity (TRA) exposure in *in-vitro* studies.

Study POP showed a terminal half-life of 190 hours, and mean total body clearance of 0.74 L/hr. Study ADME demonstrated that faecal elimination of enasidenib is predominant: 89% of enasidenib is eliminated in faeces and 11% in urine.

The ADME values provided in the PI match the PK data provided in the dossier.

Evaluation of mIDH2 variant allele frequency throughout treatment may supplement monitoring of clinically-derived response end-points. However, the full prognostic and predictive value of mIDH2 testing to direct enasidenib treatment is yet to be fully determined.

The lack of PK data, and therefore recommendations for dosing, in patients with degrees of hepatic impairment, renal impairment, and elderly populations is appropriately reported in the PI. The PI also contains a statement indicating that the safety and efficacy of enasidenib has not been established for a paediatric population.

Pharmacodynamics

Pharmacodynamic studies examined the following, as shown in Table 5.

Table 5: Overview of pharmacodynamic studies

PD Topic	Subtopic	Study ID
Primary pharmacology	Effect on PD QT/QTc interval	Study QTC
	Effect on 2-HG concentration	Study 2HG
Population PD and PK-PD analyses	Healthy subjects and those with haematological malignancies	Study POP
	Target population: effect on 2-HG	Study PKPD Study 2HG

Exposure to enasidenib did not result in QT/QTc interval prolongation.[5]

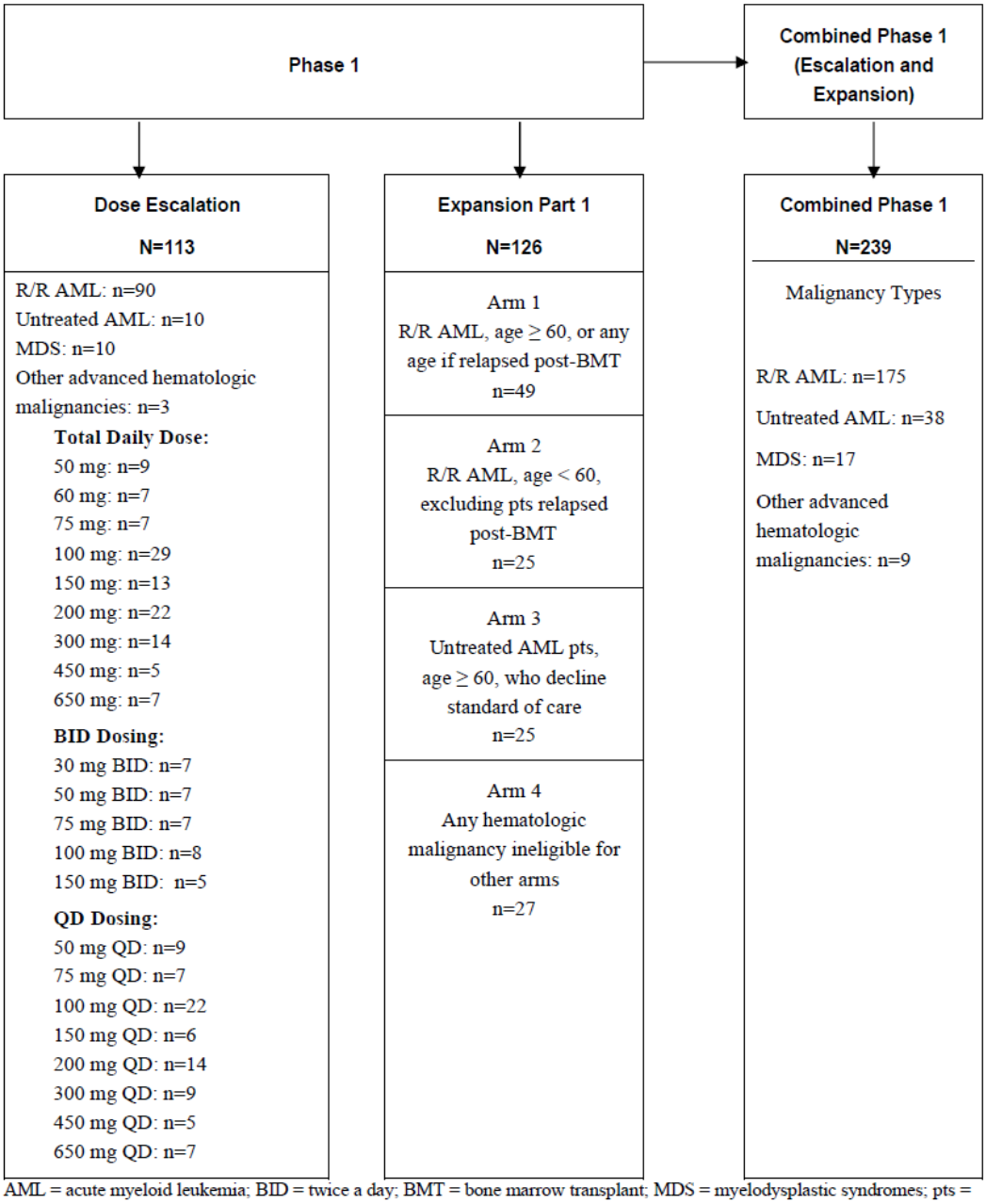
Study 2-HG was a sub-study of Study AG-221-C-001. Suppression of 2-HG production is variable according to mutant IDH2 status. As outlined in the clinical evaluation report, there appears to be two major mutations; R172 and R140. Baseline 2-HG concentrations were higher in patients with R172 mutation rather than R140 mutation, but this concentration did not appear to predict response to treatment in the Phase I patients. In the Phase I/II patients there was some correlation of clinical effect with baseline 2-HG measures. Essentially, the PD effect on the suppression of levels of 2-HG is variable with current data and not predictable, nor able to be accurately modulated by, dose amount or modification.

Dose selection

The main study, Study AG-221-C-001, had as a first part of the study; Part 001DE (dose escalation). The full Phase I layout of Study AG-221-C-001 is shown in Figure 2.

[5] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation. The QTc is the QT interval corrected for heart rate.

Figure 2: Overview of Study AG-221-C-001 Phase I



AML = acute myeloid leukemia; BID = twice a day; BMT = bone marrow transplant; MDS = myelodysplastic syndromes; pts = patients; QD = once a day; R/R AML = relapsed/refractory acute myeloid leukemia.
Data as of the 01 Sep 2017 cutoff.

One can see that those with R/R AML in this dose escalation part of the study numbered n = 90. The study is ongoing, and at data cut off for this submission, all subjects had completed at least six 28 day cycles of treatment. The study examined subjects with advanced haematologic malignancies with an IDH2 mutation. It is unclear from the clinical evaluation report what portion of those in the Phase I arms transferred to Phase II. However, when data were collectively analysed, a figure of 214 subjects with R/R AML treated with enasidenib is given.

Dose escalation used a standard 3+3 design, each cohort was to enrol a minimum of 3 subjects. Daily doses ranging from 50 mg to 650 mg were assessed. The dose was doubled from one cohort to the next until Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or greater drug-related toxicity was observed in any subject in each cohort. Following assessment of the event(s), increases in dose were 50% or less until a maximum tolerated dose (MTD) was then determined. MTD was defined as the highest dose that causes dose limiting toxicity (DLT) in < 2 of 6 subjects. DLTs were specifically defined for both haematologic and non-haematologic events. The evaluator was satisfied with these definitions.

The MTD was in fact not reached, but an increasing proportion of subjects required dose modification or reduction to remain on treatment doses above 300 mg, with 60.0% and 85.7% of those receiving 450 mg and 650 mg daily doses, respectively, requiring such dose reduction for treatment emergent adverse events (TEAEs) that did not qualify as DLTs.

The selection of the 100 mg daily dose was in fact based upon PK/PD and efficacy data rather than this dose escalation study, as a result. It appears the 100 mg daily was sizably below the dose level whereupon drug-induced toxicities became an issue.

Efficacy

As previously described, the key Study AG-221-C-001 had a 001Ex part and a 001P2 part, both of which were used primarily for efficacy data in this dossier.

The 001Ex component had 4 arms:

- Arm 1: mIDH2 R/R AML and aged ≥ 60 years, or any subject with AML regardless of age who has relapsed following a bone marrow transplant (BMT).
- Arm 2: mIDH2 R/R AML and aged < 60 years, excluding subjects with AML who have relapsed following a BMT.
- Arm 3: Untreated mIDH2 AML and aged ≥ 60 years that declined standard of care chemotherapy.
- Arm 4: IDH2-mutated advanced haematologic malignancies not eligible for Arms 1 to 3.

Hence, Arms 1 and 2 are of key interest. Relapsed AML was defined per International Working Group (IWG) criteria,[6] as bone marrow blasts ≥ 5%, or reappearance of blasts in the blood, or development of extramedullary disease. Resistant AML was defined per IWG criteria as failure to achieve CR or complete remission with incomplete haematologic recovery (CRi) following completion of initial treatment, with evidence of persistent leukaemia by blood and/or bone marrow examination.

Part 001P2 enrolled 105 subjects, all with R/R AML.

Eligibility criteria were considered satisfactory by the clinical evaluator. Subjects were given 100 mg once daily, which could be escalated to 200 mg once daily if response was not optimal or evidence of relapse had occurred after a response, either in the peripheral blood or bone marrow. Subject demographics were consistent with the AML disease population in Study AG-221-C-001 as a whole.

Subjects in Part 001P2 had relapsed after allogeneic transplantation, were in second or later relapse, were refractory to initial or re-induction treatment, or had relapsed within

[6] Cheson, B.D. et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia, *J Clin Oncol*. 2003; 21(24): 4642-4649.

1 year of treatment and were not in the National Comprehensive Cancer Network (NCCN) guideline 'favourable risk' category.[7]

Dosing occurred continuously with 100 mg daily on 28 day cycles. The dose could be increased to 200 mg daily based upon a reduced neutrophil count without any TEAEs of Grade 3 or higher, *or* no partial response being observed for at least 2 cycles of treatment and again, no suspected TEAEs of Grade 3 or higher, or there was evidence of relapse or progressive disease.

The primary efficacy endpoint used was overall response rate (ORR), not a typical measure for a primary endpoint. It was also more liberal in that it included those with partial response as well as morphologic leukaemia-free state (MLFS). However, data clearly show the breakdown of each response category. For ease of comprehension of data, presented here are the collective data, not separate sets from Part 001P2 and 001Ex.

Some points from Study AG-221-C-001 Part 001P2 specifically are worthwhile based on the statistical planning of at least a 33.6% response in subjects. The lower bound of 95% confidence interval (CI) is stated by the evaluator as being met, with ORR of 33 out of 105 or 31.4% (95% CI 22.7, 41.2). Median overall survival (OS) in the R/R AML group of n = 105 was 7.0 months. Median duration of ORR was 5.6 months, stated as based on best-response data from 39 subjects. Median duration of CR (n = 21) was 6.7 months. It is also noted some subjects were dosed with 200 mg daily to achieve these results, but the evaluator notes such numbers were few.

One point to note here is that, for the 105 R/R AML subjects in the Phase II 001P2, by data cut off 99 had ceased treatment, with the chief reasons being disease progression, an adverse event (AE) or death. It is unclear from the evaluation what median treatment duration this represents.

The evaluator considered OS as the most meaningful efficacy variable, given that enasidenib is not curative. The 7.0 months median value for Part 001P2 was considered clinically significant.

Combined data

Subject disposition for the combined data was as follows in Table 6.

Table 6: Subject disposition for combined efficacy data

	Combined Phase I/II 100 mg (N = 214) n (%)	Combined Phase I 100 mg (N = 109) n (%)	Phase II 100 mg (N = 105) n (%)
Treatment status			
Ongoing	11 (5.1)	5 (4.6)	6 (5.7)
Discontinued	203 (94.9)	104 (95.4)	99 (94.3)
Study status			
Ongoing	32 (15.0)	14 (12.8)	18 (17.1)
Discontinued	182 (85.0)	95 (87.2)	87 (82.9)

[7] National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology, Acute Myeloid Leukemia, 2015.

Of the 214 subjects in this combined analysis, median age was 68.0 years (range 19 to 100) with 63 (29.4%) aged < 60 years and 51 (23.8%) aged ≥ 75 years. 109 (50.9%) were male, and 76.6% were white. 49 (22.9%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 and 132 (61.7%) had an ECOG PS of 1. Baseline transfusion history was collected retrospectively and calculated using the period of the 4 weeks prior to and 4 weeks after the first dose of enasidenib for Parts 001DE and 001Ex, and 8 weeks prior to the first dose for 001P2. Overall, in the combined 001DE/Ex/P2 population, 71.5% of the R/R AML subjects were red blood cell (RBC) transfusion dependent with a median of 3 transfusions (range 1 to 23). 61.7% were platelet transfusion dependent at Baseline with a median of 4.5 (range 1 to 32). Note that transfusion status is of interest, mainly as it is used as an argument for benefit of the drug in the results, that is, a reduction in the number of subjects who were transfusion-dependent. The median number of prior anticancer therapies received by the combined Phase I/II R/R AML population was 2.0 (range: 1.0 to 5.0). Most subjects received 1 (47.2%) or 2 (30.4%) prior regimens.

The most common systemic therapies for AML received by subjects prior to entering this study were antimetabolites (98.6%), specifically, cytarabine (73.8%), azacitidine (29.0%) and decitabine (27.1%), and cytotoxic antibiotics and related substances (68.7%), specifically, idarubicin (36.4%) and daunorubicin (31.3%).The key efficacy results in terms of ORR and both the ORR definition of this trial and the more typical definition of CR+CRi/complete remission with incomplete platelet recovery (CRp), are given as follows in Table 7.

Table 7: Key efficacy results for the combined Study AG-221-C-001 (Parts 001DE, Ex, and P2) by total daily dose of 100 mg

Efficacy parameters	Combined Phase I/II 100 mg (N = 214)	
	Investigator assessment	IRAC assessment
Response		
Overall Response Rate (CR + CRi + CRp + PR + MLFS)[a] (n [%])	83 (38.8)	76 (35.5)
(95% CI)[b]	(32.2, 45.7)	(29.1, 42.3)
KM Median Duration of ORR (months)[c]	5.6	5.6
(95% CI)	(3.8, 7.4)	(3.7, .5)
Complete Remission Rate (n [%])	42 (19.6)	41 (19.2)
(95% CI)[b]	(14.5, 25.6)	(14.1, 25.1)
KM Median Duration of CR (months)[c]	7.4	7.4
(95% CI)	(6.5, 16.3)	(5.6, 11.5)
CR+ CRi / CRp Rate (n [%])	62 (29.0)	59 (27.6)
(95% CI)[b]	(23.0, 35.5)	(21.7, 34,1)
KM Median Duration of CR+CRi/CRp (months)[d]	6.7	6.5
(95% CI)	(5.3, 9.7)	(5.1, 7.4)
Non- CR Responses		
CRi/CRp	20 (9.3)	
PR	9 (4.2)	
MLFS	12 (5.6)	
SD	98 (45.8)	
PD	19 (8.9)	
Overall Survival		
Number (%) of Events	157 (73.4)	
Number (%) Censored [d]	57 (26.6)	
Duration of Overall Survival (months) [e]		
Median (95% CI)	8.8 (7.7, 9.6)	

IRAC = Independent Response Adjudication Committee. KM = Kaplan Meier. Response was evaluated by the Investigator according to the 2003 revised IWG criteria for AML.[6] a Percentages are based on the number of subjects in each group. b 2-sided Exact Binomial 95% CI. c Duration of response is calculated as the date of the first documented response to the date of the first documented disease relapse, progression or death due to any cause, whichever occurs first. Percentile was estimated using Kaplan-Meier method. d Subjects alive were censored at the last date known to be alive or a pre-specified data cut off date. Subjects who only had a baseline record were censored at the first dose date. e Overall survival was calculated as the time from the first dose to the date of death due to any cause. Percentile was estimated using Kaplan-Meier method. Data cut off date: 1 September 2017.

Hence, the ORR, as defined, was in the high 30%. In the case of investigator assessed, it was 38.8% (83 out of 214). A CR occurred in around 1 in 5 subjects. Overall, survival is given as a median of 8.8 months (95% CI 7.7., 9.6).

Treatment was a median of 4.6 months, that is, just under 5 cycles (range 1.0 to 38.0). Interestingly, time to first response was a median of 1.9 months and time to best response a median of 3.7 months, suggesting 2 cycles of treatment are needed prior to knowing whether or not the patient will respond.

Of 153 patients who were transfusion dependent at Baseline, 66 (43.1%) became transfusion independent with treatment, and 65.5% of those transfusion independent at baseline maintained this status during any 56 day post-baseline period.

It appears that those with the R140 mutation showed some correlation with decreased 2-HG concentration levels on treatment, but those with the R172 mutation were equivocal. As the evaluator concluded, nothing can be specifically claimed with regard to disease response and correlation with concentrations of 2-HG which is surprising given the described mechanism of action. Perhaps other paths are at play as well.

Historical data

A report derived from European registries provided some historical data on those in comparable groups of patients who were not treated with enasidenib. Compared information was:

- IDH2 mutation status of R/R AML patients,
- Patient characteristics aligned as much as possible with Study AG-221-C-001 inclusion criteria,
- Prognostic factors known to have an impact on overall survival, for example, age, number of prior AML therapies et cetera,
- Other baseline characteristics that may help to describe the considered populations (sex and cytogenetic characteristics).

The baseline for historical data was considered to be the date of last relapse or refractory disease.

Data for the Austrian AML Study Group (AMLSG) cohort was as follows in Table 8.

Table 8: Overall survival Kaplan Meier analyses of the Austrian Acute Myeloid Leukaemia Study Group cohort and Study AG-221-C-001

Parameter	AMLSG (N = 207)	Unadjusted Study AG-221-C-001 (N = 214)	Adjusted Study AG-221-C-001 (N = 214)
Number of deaths	159	157	134
Median OS (months)	6.4	8.8	11.4
95% CI	(5.7, 8.3)	(7.7, 9.6)	(9.3, 14.2)
3 month survival rate (%)	70.9	79.6	82.8
95% CI	(64.7, 77.1)	(74.2, 85.1)	(77.6, 87.9)

Parameter	AMLSG (N = 207)	Unadjusted Study AG-221-C-001 (N = 214)	Adjusted Study AG-221-C-001 (N = 214)
12-month survival rate (%)	36.1	33.7	45.7
95% CI	(29.4, 42.8)	(26.9, 40.4)	(38.5, 53.0)

The data suggests an OS benefit to enasidenib.

A further database (PETHEMA) used similar key prognostic factors and the population seemed closely aligned with the Study AG-221-C-001 population. Not surprisingly then, the median OS was 8.8 months (95% CI 7.8, 9.5).

There were other analyses and literature, but it is not intended they be individually presented in this document. In summary, the historical comparison data mainly considers OS, not ORR. These historical data, with potential confounders one must admit, suggest an OS benefit over conventional treatments. Differences between patients and disease characteristics limit the robustness of such a comparison and thus the subsequent conclusions.

There did seem to be a fairly consistent higher rate of CR with enasidenib use rather than that of conventional treatments with the datasets that were compared.

Overall, considering pooled trial data and historical data, the evaluator was of the view that there was likely a few months' advantage in OS with enasidenib use over conventional treatments, this is apart from considering the different safety profile of using conventional treatments or enasidenib.

Safety

Regarding exposure to enasidenib in the clinical trial programme, essentially 688 patients represent the cohort receiving any dose of drug. Of these, those with R/R AML numbered 396 across trials and compassionate use programmes.

The evaluator concludes that single dose studies up to 300 mg daily of enasidenib did not reveal safety concerns.

Only pivotal study data are presented here unless other data have specific concerns, in which case they will be cited along with their source.

Treatment related TEAEs in 3% or greater of subjects in Study AG-221-C-001, by System Organ Class (SOC) and Preferred Term (PT), are shown as follows in Table 9.

Table 9: Study AG-221-C-001 treatment related treatment emergent adverse events in 3% or greater of subjects by System Organ Class and Preferred Term

System Organ Class / Preferred Term	R/R AML 100 mg dose (n = 214)	All R/R AML (n = 280)	All subjects (n = 345)
Subject With at Least 1 TEAE reported as treatment-related	178 (83.2)	227 (81.1)	284 (82.3)
Blood and lymphatic system disorders	47 (22.0)	57 (20.4)	70 (20.3)

System Organ Class / Preferred Term	R/R AML 100 mg dose (n = 214)	All R/R AML (n = 280)	All subjects (n = 345)
Anaemia	14 (6.5)	18 (6.4)	25 (7.2)
Leukocytosis	16 (7.5)	22 (7.9)	25 (7.2)
Thrombocytopenia	7 (3.3)	11 (3.9)	15 (4.3)
Gastrointestinal disorders	96 (44.9)	121 (43.2)	151 (43.8)
Constipation	7 (3.3)	10 (3.6)	12 (3.5)
Diarrhoea	33 (15.4)	45 (16.1)	52 (15.1)
Nausea	59 (27.6)	76 (27.1)	95 (27.5)
Vomiting	37 (17.3)	46 (16.4)	52 (15.1)
General disorders and administration site conditions	57 (26.6)	73 (26.1)	90 (26.1)
Asthenia	10 (4.7)	14 (5.0)	16 (4.6)
Fatigue	31 (14.5)	41 (14.6)	51 (14.8)
Oedema Peripheral	9 (4.2)	13 (4.6)	17 (4.9)
Pyrexia	13 (6.1)	14 (5.0)	15 (4.3)
Hepatobiliary Disorders	22 (10.3)	29 (10.4)	33 (9.6)
Hyperbilirubinaemia	16 (7.5)	21 (7.5)	24 (7.0)
Investigations	95 (44.4)	127 (45.4)	157 (45.5)

MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, SOC = System Organ Class. Data represent number (%) of subjects. SOC and PT were coded using the MedDRA dictionary version 20.0. SOC and PT are sorted by alphabetic order. If a subject experienced multiple AEs under the same PT (SOC), then the subject was counted only once for that PT. TEAEs were defined as any AEs that began or worsened on or after the start of study drug through 28 days after the last dose of study drug. Related = suspected (possibly or probably) by the investigator to be related. Data as of the 1 September 2017 cut off.

There were 121 (35.1%) on treatment, all cause deaths. Those causes reported in 1% or more of subjects were disease progression, AML and underlying complications of the malignancy, such as infection, multiple organ dysfunction syndrome, and sepsis, as well as respiratory failure. One hundred and twenty-six (36.5%) post-treatment deaths were recorded, with those causes greater than 1% being disease progression, death not otherwise specified, AML and pneumonia and respiratory failure. These types of events are mirrored in other trial and compassionate use data.

Sixty-five subjects (18.8%) had at least one TEAE that led to permanent discontinuation. Most frequent were sepsis, leucocytosis and respiratory failure. Infection and sepsis were primarily those TEAEs leading to permanent discontinuation in other studies.

A total of 65 (18.8%) subjects had at least 1 TEAE that led to permanent study drug discontinuation. The SOCs for which most subjects experienced an event were Infections and Infestations (4.3%), Respiratory, Thoracic and Mediastinal Disorders (3.8%), and Blood and Lymphatic System Disorders (3.5%). The most frequently reported TEAEs that led to discontinuation (occurring in ≥ 1.0% of subjects overall) were sepsis (2.6%), leukocytosis (2.0%), and respiratory failure (1.7%).

Sixteen (4.6%) subjects had at least 1 treatment-related TEAE that led to permanent study drug discontinuation, and no specific event occurred in more than 2 subjects.

A number of possible specific issues were examined with respect to regulatory impact. However, few of these were identified as relevant. Prolonged QT/QTc was not an issue with this drug. *In vitro* studies showed enasidenib inhibits uridine 5'-diphospho glucuronosyltransferase family 1 member A1 (UGT1A1), the enzyme that metabolises bilirubin, thus adverse events with associated bilirubin rise were common. The relationship was essentially dose dependent. Major TEAEs associated with the drug are bilirubinaemia and differentiation syndrome. Significant treatment disruption was not caused by either, although early recognition and treatment of differentiation syndrome was required.

Overall, the evaluator did not raise any significant safety issues with the drug and the safety profile is consistent with the drug's mechanism of action. Safety was not an aspect of the drug that worked to deteriorate its risk/benefit profile.

Risk management plan

- The sponsor has submitted European Union-risk management plan (EU-RMP) version 0.1 (4 May 2018; data lock point (DLP) 1 September 2017) and Australian specific Annex (ASA) version 1.1 (30 November 2018) in support of this application. In response to TGA questions, the sponsor has submitted updated EU-RMP version 0.2 (8 January 2019; DLP 1 September 2017) and ASA version 1.2 (8 January 2019).
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 10.[8]

Table 10: Summary of safety concerns for enasidenib

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Differentiation syndrome	ü*	ü†	ü‡	ü‖
	Tumour lysis syndrome	ü*	–	ü	–
Important	Fetal toxicity	ü*	–	ü	–

[8] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
potential risks	QT interval prolongation	ü	–	ü	–
Missing information	Safety in patients with moderate to severe hepatic impairment	ü	ü§	ü	–
	Safety in elderly patients (≥ 85 years of age)	ü	ü§	ü	–
	Long term safety	ü	ü§	ü	–

* Specific adverse drug reaction follow-up form. † Meta-analysis study. ‡ Boxed warning in PI and Consumer Medicines Information (CMI). ‖ Patient alert card in product package. § Clinical studies

The RMP was considered satisfactory by the RMP evaluator. There are no outstanding recommendations for the sponsor.

The recommendations to the Delegate were made as follows.

There were two recommendations addressed to the Delegate for consideration at the second round evaluation:

- Recommendation 14: Given the addition of 'long-term safety' as missing information, it is recommended that the Delegate consider including a statement in the PI that data on long-term follow-up of up to 3 years is limited, along the lines of the following information provided in the RMP:
  - 'In Study AG221-C-001, 46% of patients received 6 or more, and 19% received 12 or more 28-day cycles of treatment. Long-term follow-up of up to 3 years in the clinical development programme is limited; however, follow-up of 3 years is being conducted in Study AG221-C-001 and long-term safety is also being assessed in Study AG-221-AML-004'.
- Recommendation 15: Given the addition of 'safety in elderly patients (≥ 85 years of age)' as missing information, it is recommended that the Delegate consider including a statement in the PI that data on safety in elderly patients (≥ 85 years of age) is limited.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> The Idhifa EU-Risk Management Plan (RMP) (version 0.2, dated 8 January 2019, data lock point 1 September 2017), with Australian Specific Annex (version 1.2, dated 8 January 2019), included with submission PM-2018-04819-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the periodic safety update report (PSUR) requirement:

> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

As Idhifa is being considered for a provisional registration it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> Idhifa (enasidenib) is to be included in the Black Triangle Scheme. The PI and CMI for Idhifa must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.

As Idhifa is being considered for a provisional registration the following wording regarding confirmatory trial data is recommended for the condition of registration subject to the Delegate's review of the Clinical Study Plan:

> Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.
>
> Specifically the sponsor must conduct studies as described in the clinical study plan in version 0.2 (date 8 January 2019) of the Australia-Specific Annex. The following study report should be submitted to TGA:
>
> - Study AG-221-AML-004, by the second quarter of 2021.

It is recommended that inclusion of the Patient Alert Card in the product package be considered by the Delegate as a condition of registration. This has already been agreed by the sponsor.

Risk-benefit analysis

Delegate's considerations

The drug has been given both orphan status and provisional designation in Australia. It was therefore considered by a Delegate to be a potentially major therapeutic advance. It was approved for use by the FDA on 1 August 2017 for an essentially similar indication. There are multiple requirements of the company related to the approval in the USA, including several post-market studies looking into enasidenib differentiation syndrome, long-term safety, efficacy in comparison to conventional treatment regimens, effects of multiple dosing on PK and metabolic enzyme systems and potential adjustment of dosing in hepatic impairment. Of particular note, is data versus conventional treatments, as this was absent in the dossier apart from an attempt to compare to historical control data cropped from registries and literature.

The drug has a specific mechanism of action, which in theory provides a more targeted therapy to help a specific group of AML patients without the toxicity profile of other chemotherapeutic agents. It has been found to be appropriate for both orphan designation and provisional designation by a TGA Delegate.

The US FDA has approved the drug for this indication essentially, with requirements for considerable post-marketing trials and data to be generated.

It was withdrawn in the EU, because the EU evaluators required head-to-head efficacy outcomes against conventional treatments and these data have yet to exist.[2]

Clearly, the drug is for a subset of the adult AML population with the specific mutation described and laboratory testing is required to establish this.

The 'Phase II Part' (001P2) of Study AG-221-C-001 was the primary data to support efficacy, and was pooled with Part 001Ex also for greater subject numbers to be examined.

The ORR parameter, not a typical primary endpoint in such a trial, demonstrates what appears to be a few months' advantage over conventional treatments, although this is based upon comparison with historical controls and the inherent shortcomings of those data, not a head-to-head randomised controlled trial.

OS also appears to have a favourable couple of months' advantage when examining the data in comparison to that achieved by other treatments in the view of the clinical evaluator.

There is a characteristic set of adverse events for enasidenib, however, the drug appears to be reasonably well tolerated, with many adverse effects able to be dealt with by careful monitoring. High grade adverse effects were rare, but the PI specifically addresses some specific adverse reactions. The adverse reactions are not such that they result in a negative risk/benefit profile in the opinion of the clinical evaluator or the Delegate.

Objections were not raised by the quality or nonclinical evaluators, once desired PI charges had been agreed to. The clinical evaluator's final PI edits were addressed in correspondence from the sponsor dated 16 September 2019.

The RMP evaluator is in favour of approval, with some conditions of registration cited.

The clinical evaluator also has listed the conditions that should be imposed with approval:

- The sponsor will provide the full clinical study report of the AG-221-AML-004 study as soon as it becomes available in 2020.
- The sponsor will provide the full clinical study reports of the following post-market studies required by the FDA, as soon as available:
  - Meta-analysis to characterise enasidenib related differentiation syndrome (PMR 3240-1).
  - To characterise the long-term safety of enasidenib in R/R AML, submit the final study report with 3 years of follow-up data of the AG221-C-001 trial. Include data from approximately 280 patients with R/R AML (PMR 3240-2).
  - A study sufficient to characterise the long-term safety of enasidenib compared to conventional care regimens in patients with AML (PMR 3240-3).
  - Pharmacokinetic trials to evaluate the effect of multiple doses of enasidenib on the single dose pharmacokinetics of sensitive substrates of CYP3A4, CYP2D6, CYP2C19, CYP2C9, UGTs, P-gp and BCRP to address the potential for excessive drug toxicity (PMR3240-4).
  - A clinical pharmacokinetic trial to determine the appropriate dose of enasidenib in patients with hepatic impairment.

The above conditions are in addition to those provided by the RMP evaluator, as outlined in the Section '*Proposed wording for conditions of registration*', above.

Proposed action

Based on the limited data set available for this product, given its provisional status and the reasonable currently known safety profile, it is considered acceptable to provisionally register this product for the indication described until supplementary clinical data outlined in the conditions of registration are provided.

Advisory Committee Considerations[9]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the provisional registration of Idhifa (enasidenib) 50 mg and 100 mg film coated tablets, indicated for:

> *This medicine has Provisional Approval in Australia for the treatment of adult patients with relapsed or refractory acute myeloid leukaemia who are ineligible for haematopoietic stem cell transplant, and who have an isocitrate dehydrogenase-2 (IDH2) mutation confirmed by a validated diagnostic test.*
>
> *The decision to approve this indication has been made on the basis of preliminary clinical data from a Phase 1/2 clinical trial with a primary endpoint of overall response rate. An improvement in OS or PFS has not been established. The sponsor is required to submit further clinical data to confirm the efficacy and safety of the medicine.*

The provisional registration period for the above medicine(s) is two years starting on the day specified in the ARTG certificate of registration.

Specific conditions of registration applying to these goods

- Idhifa (enasidenib) is to be included in the Black Triangle Scheme. The PI and CMI for Idhifa must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.
- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

  Specifically the sponsor must conduct studies as described in the clinical study plan in version 0.2 (date 8 January 2019) of the Australia-specific Annex. The following study report(s) should be submitted to TGA.

[9] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- AG-221-AML-004 study as soon as it becomes available in 2020.

The sponsor will provide the full clinical study reports of the following post-market studies required by the FDA, as soon as available:

- Meta-analysis to characterise enasidenib related differentiation syndrome (PMR 3240-1).
- To characterise the long-term safety of enasidenib in R/R AML, submit the final study report with 3 years of follow-up data of the AG221-C-001 trial. Include data from approximately 280 patients with R/R AML (PMR 3240-2).
- A study sufficient to characterise the long-term safety of enasidenib compared to conventional care regimens in patients with AML (PMR 3240-3).
- Pharmacokinetic trials to evaluate the effect of multiple doses of enasidenib on the single dose pharmacokinetics of sensitive substrates of CYP3A4, CYP2D6, CYP2C19, CYP2C9, UGTs, P-pg and BCRP to address the potential for excessive drug toxicity (PMR3240-4).
- A clinical pharmacokinetic trial to determine the appropriate dose of enasidenib in patients with hepatic impairment.

Further guidance for sponsors is available on the TGA website.

- The Idhifa EU-RMP (version 0.2, dated 8 January 2019, DLP 1 September 2017), with ASA (version 1.2, dated 8 January 2019), included with submission PM-2018-04819-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on GVP Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Idhifa approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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