

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209606Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)**

Application Type	NDA
Application Number	209606
PDUFA Goal Date	August 30, 2017
OSE RCM #	2017-16; 2017-18
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
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Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 27, 2017
Subject	Review to determine if a REMS is necessary
Established Name	Enasidenib
Trade Name	Idhifa
Name of Applicant	Celgene
Therapeutic Class	Isocitrate dehydrogenase-2 inhibitor
Formulation(s)	50 mg and 100 mg tablets
Dosing Regimen	100 mg once daily until disease progression or unacceptable toxicity

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity enasidenib (Idhifa) is necessary to ensure the benefits outweigh its risks. Celgene submitted a New Drug Application Application (NDA) 209606 for enasidenib with the proposed indication as treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Boxed Warning, Warnings and Precautions and a Medication Guide as part of labeling to inform patients regarding the potential risks of differentiation syndrome.

DRISK and Division of Hematology Products (DHP) have determined that if approved, a REMS is not necessary to ensure the benefits of enasidenib outweigh its risks. The current standard treatment for AML is intensive chemotherapy potentially leading to an allogeneic stem cell transplant and is based mainly on the patient's ability to tolerate intensive treatment. There are no FDA-approved drugs specifically for relapsed or refractory AML, and there is no standard of care treatment regimen for these patients. Therefore, there remains a clear medical need for new treatments for these patients. In the clinical trial, enasidenib appeared efficacious in both its primary and secondary outcomes. The most concerning adverse reaction associated with the use of enasidenib is differentiation syndrome; this risk, and recommendations for its management, will be communicated in the Boxed Warning and Warnings and Precautions section of the product label.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) enasidenib (Idhifa) is necessary to ensure its benefits outweigh its risks. Celgene submitted a New Drug Application Application (NDA) 209606 for enasidenib with the proposed indication as treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation.¹ This application is under review in the Division of Hematology Products (DHP). The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Boxed Warning, Warnings and Precautions and a Medication Guide as part of labeling to inform patients regarding the potential risks of differentiation syndrome.

2 Background

2.1 PRODUCT INFORMATION

Enasidenib is a NME NDA type 505(b)(1) pathway application.^a It is an IDH2 inhibitor proposed for indication as treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation. Enasidenib inhibits certain mutant forms of IDH2 including R140Q, R172K, and R172S at approximately 40-fold lower concentrations than wild-type IDH2. The IDH enzymes catalyze the oxidative decarboxylation of isocitrate to alpha-ketoglutarate (α -KG), producing nicotinamide adenine dinucleotide phosphate (NADPH) in the process via the citric acid cycle. Enasidenib is prepared as 50 mg

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

and 100 mg tablets to be taken by the oral route.^{1,2} The proposed starting dose of enasidenib is 100 mg taken orally once daily until disease progression or unacceptable toxicity.^b Enasidenib was granted an Orphan drug designation on June 12, 2014, and a fast track designation on July 31, 2014. Enasidenib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for enasidenib (NDA 209606) relevant to this review:

- 07/18/2013: Investigation New Drug (IND) 117631 submission was received.
- 06/12/2014: Orphan Drug designation granted.
- 07/31/2014: Fast track designation granted.
- 07/26/2016: Applicant informed at pre-NDA meeting that FDA has preliminary concerns about the risk of differentiation syndrome and appropriate management guidelines may need to be communicated effectively to physicians in some manner. The need for a REMS for enasidenib will be made upon reviewing the NDA.
- 12/30/2016: NDA 209606 submission for enasidenib with the proposed indication for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation, received.
- 04/28/2017: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for enasidenib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Acute myelogenous leukemia (AML) is a form of cancer that is characterized by infiltration of the bone marrow, blood, and other tissues by proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated cells of the hematopoietic system.³ The pathophysiology in AML consists of a maturational arrest of bone marrow cells in the earliest stages of development. The mechanism of this arrest is under study, but in many cases, it involves the activation of abnormal genes through chromosomal translocations and other genetic abnormalities. This developmental arrest results in 2 disease processes. First, the production of normal blood cells markedly decreases, which results in varying degrees of anemia, thrombocytopenia, and neutropenia. Second, the rapid proliferation of these cells, along with a reduction in their ability to undergo programmed cell death, results in their accumulation in the bone marrow, the blood, the spleen, and the liver.⁴ The American Cancer Society estimates that approximately about 21,380 new cases of AML will be diagnosed in United States^c, and

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

about 10,590 deaths from AML in 2017.^d Acute myeloid leukemia is generally a disease of older people and is uncommon before the age of 45. The average age of a patient with AML is 67 years.⁵

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The general therapeutic strategy in patients with AML has not changed substantially in more than 30 years. The standard treatment is intensive chemotherapy potentially leading to an allogeneic stem cell transplant and is based mainly on the patient's ability to tolerate intensive treatment. Treatment of AML has been divided into induction chemotherapy and postremission (eg. consolidation) therapy.³ Although obtaining a remission is the first step in controlling the disease, it is also important for patients to emerge from the induction phase in a condition to tolerate subsequent more intensive treatments during consolidation to achieve durable disease control. Patients who do not receive postremission therapy may experience relapse, usually within 6 to 9 months.⁶ A complete response is achieved in 60 to 85% of adults who are 60 years of age or younger. In patients who are older than 60 years of age, complete response rates are inferior (40 to 60%).³ Although advances in the treatment of AML have led to significant improvements in outcomes for younger patients, prognosis in the elderly, who account for the majority of new cases, remains poor.⁷ Therefore, treatment results are generally analyzed separately for younger (18-60 years) patients and for older patients (>60 years). In patients who can tolerate intensive therapy, which may be limited by factors such as age and comorbid conditions, cytarabine and daunorubicin induction followed by high-dose cytarabine consolidation is frequently used. Intensifying induction therapy with a high daily dose of anthracycline plus intensive consolidation therapy resulted in a high complete-remission rate and prolonged overall survival in patients with AML. This regimen typically results in CR rates of 60-70% and 2-year OS of approximately 50% in patients < 60 years of age.⁸ Older patients fare less well, with CR rates of approximately 50% and 2-year overall survival of approximately 20%.⁹

There are no FDA-approved drugs specifically for relapsed or refractory AML, and there is no standard of care treatment regimen for these patients. Patients who are fit for intensive therapy should receive a salvage chemotherapy regimen followed by HSCT. About half will achieve a second complete remission, and 5-year survival of patients who achieve a second remission is about 40%.¹⁰ In large, phase 3 studies of high-dose cytarabine or investigator's choice (e.g., hypomethylating agents, multi-agent chemotherapy, cytarabine, hydroxyurea, or supportive care) in primary refractory AML or AML that has relapsed after 1 or more prior regimens, the rate of CR ranges from 12 to 16%, and median OS ranges from 3.3 to 6.3 months. There is a clear need for new treatments for patients with relapsed or refractory AML.¹¹

4 Benefit Assessment

The efficacy of enasidenib was evaluated in an open-label, single-arm, multi-center, two-cohort clinical trial (Study AG-221-C-001, NCT01915498). The study population included 207 patients with relapsed or refractory AML (103 in Cohort I and 104 in Cohort II) who were assigned to receive 100 mg of enasidenib daily and who had IDH2 mutations identified by the Abbott RealTime™ IDH2 assay, which is the FDA-approved test for selection of patients with AML for treatment with enasidenib. The rationale for pooling from different cohorts was based on consistency of demographic and baseline disease

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

characteristics of the trial populations, same dose regimen between the 2 cohorts, and consistent improvements in investigator assessed complete response (CR) and durability of the response across the two cohorts. The CR is an accepted clinical meaningful endpoint beneficial in patients with AML.^{11, e} Dose reductions were allowed for adverse events.

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for enasidenib. Efficacy was established on the basis of the rate of CR/complete response with partial hematologic recovery (CRh), the duration of CR/CRh, and the rate of conversion from transfusion dependence to transfusion independence. (b) (4)

^{11,1} The median follow-up was ^{(b) (4)} months (range 0.4 – 27.7 months).

Table 1: Efficacy results in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)^{11,1}

(b) (4)



In the population of relapsed or refractory (R/R) AML subjects who received 100 mg enasidenib daily and were IDH2 positive, there was a numerical difference for the sponsor assessed CR rates between Cohort I (16.5%) and Cohort II (12.5%). The median duration of CR for the combined Cohort I & Cohort II was 9.7 months with 95% CI of (5.5, NA) using Kaplan-Meier (KM) method. However, the estimated median durations of response were different between Cohort I (11.5 month) and Cohort II (6.5 month). The median follow-up times were different between Cohort I (8.3 month) study and Cohort II (5.5) study. The differences in response rates and durations of response indicate variations between the two trials. The statistical reviewer stated that caution should be exercised in the interpretation of the pooled results.¹¹

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

The secondary end points included overall survival (OS), the median time to first response, the median time to best response, and the rate of conversion from transfusion dependence to transfusion independence. The estimated median OS in the Cohort II population of 6.6 months was shorter in comparison with the Cohort I population of 9.1 month. However, time to event endpoints such as OS is not interpretable in single arm studies as it includes the natural history of the disease.^{11,1}

For patients who achieved a CR or CRh, the median time to first response was 1.9 months (range, 0.5 to 7.5 months) and the median time to best response of CR/CRh was 3.7 months (range, (b) (4) to 11.2 months). By the end of Month 6, (b) (4)% (39 of (b) (4) patients) of patients achieved a best response of CR/CRh. (b) (4)

11,1

5 Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for enasidenib. The safety analysis of enasidenib primarily focuses on 214 patients with relapsed or refractory AML treated in a phase 1/2 trial. The median duration of exposure to enasidenib at the time of data analysis was 4.3 months (range 0.3 to 23.6). The 30-day and 60-day mortality rates observed with enasidenib were 4.2% (9/214) and 11.7% (25/214), respectively.¹

The most common adverse reactions ($\geq 20\%$) of any grade were nausea, vomiting, diarrhea, bilirubin increased, and decreased appetite.

Deaths

There were a total of 127 (59%) on-treatment all cause deaths (i.e. death for any cause within 28 days of the last dose of AG-221). The cause of death in the majority of subjects was related to disease progression of AML or complications of their underlying AML disease, mainly within infection and respiratory failure, intracranial hemorrhage, and cardiac arrest. A total of 62 (29%) subjects had 1 or more treatment-emergent adverse events (TEAE) with an outcome of death (Grade 5 TEAE). There were 15 deaths in on Phase I of AG-221-C-001 considered by the FDA to be at least possibly related to enasidenib. Infection with or without neutropenia was clearly the root cause of death in 4 cases. In all cases, the subject had prior prolonged periods of neutropenia or lymphopenia that may have potentially contributed to the infection. There were 11 deaths on Phase I not definitively caused by infection, in which six of the cases include manifestations of respiratory distress, pulmonary edema, and/or multi-organ dysfunction consistent with differentiation syndrome. The rest five of the cases have other possible causes of death (e.g. infection, underlying malignancy). Due to the overlap in clinical manifestations, it is difficult to distinguish between differentiation syndrome and sepsis in the absence of cultures.¹¹ (See Section on differentiation on syndrome). While narratives are not available for patients enrolled on Phase II of the study, the all-cause mortality as calculated by the FDA for the 214 subjects in the Primary Safety Pool was 4% (95% CI, 2-8%) at day 30 and 24% (95% CI, 19-31%) at day 90. The clinical reviewers stated that the all-cause mortality observed in patients treated with enasidenib compares favorably to the 10-20% seen in patients treated with chemotherapy.¹¹

Serious Adverse Events (SAE)

Serious adverse reactions (\geq Grade 3) were reported in 77.1% of patients. The most frequent serious adverse reactions ($\geq 2\%$) were leukocytosis (10%), (b) (4)

Overall, 114 of 214 (61%) of treated subjects had a dose interruption (n=114; 53%), dose reduction (n=21; 10%), or permanent discontinuation/withdrawal (n=24; 11%) due to an adverse event. The most common adverse reactions leading to dose interruption were febrile neutropenia (n=12; 6%), sepsis (n=9; 4%), hyperbilirubinemia (n=8; 4%), pneumonia (n=8; 4%), differentiation syndrome (n=8; 4%), dyspnea (n=8; 4%), pyrexia (n=7; 3%), leukocytosis (n=6; 3%), and fatigue (n=6; 3%).¹¹

Differentiation Syndrome

In the clinical trial, 14% of patients treated with enasidenib experienced differentiation syndrome (DS), including 7% \geq Grade 3 events. DS is caused by rapid proliferation and differentiation of myeloid cells and can be fatal if untreated. While there is no diagnostic test for DS, symptoms in patients treated with enasidenib include acute respiratory distress represented by dyspnea and/or hypoxia (68%) and need for supplemental oxygen (76%); pulmonary infiltrates (73%) and pleural effusion (45%); renal impairment (70%); fever (36%); lymphadenopathy (33%); bone pain (27%); peripheral edema with rapid weight gain (21%); and pericardial effusion (18%). Hepatic, renal, and multi-organ dysfunction have also been observed. DS has been observed with and without concomitant hyperleukocytosis, and as early as 10 days and at up to 5 months after enasidenib initiation.

The 6 deaths in the Phase 1 of the study showed manifestations of respiratory distress, pulmonary edema, and/or multi-organ dysfunction consistent with differentiation syndrome. Death occurred in one patient, which was suspected as a treatment-related TEAE (cardiac tamponade). The subject experienced pericardial effusion, which was complicated by the cardiac tamponade leading to death. Retrospective analysis of this case suggests that pericardial effusion was a likely sign of differentiation syndrome. This patient was changed to “do-not-resuscitate”, and did not receive any treatment or intervention. Two of other deaths which represent DC as a possible alternative cause of death by FDA analysis have not appeared to have received steroids during the course of treatment. The fourth patient who showed multi-focal infection and mild pulmonary edema has received steroids, but subsequently died from respiratory failure. The fifth patient revealed pleural effusions in addition to the pneumonia. The patient was empirically treated with dexamethasone for differentiation syndrome, with no improvement in symptoms, and developed multi-organ failure and died. The sixth patient had developed pharyngeal mucositis and acute respiratory distress syndrome (ARDS). The subject later diagnosed with differentiation syndrome, although the basis of this is not reported. The patient was treated with dexamethasone, antibiotics and mechanical ventilation. The subject developed severe capillary leak syndrome, renal failure, bilateral pleural effusions and fever, and died with investigator-determined cause of death as sepsis. The FDA considers that differentiation syndrome remains a possible cause of this death.¹¹

Study treatment was temporarily interrupted during treatment for DS in 8 (4%) subjects. As per protocol guidelines for its management, subjects with diagnosed or suspected DS of any grade were treated with high doses of intravenous or oral steroids..

The risk of DS will be included in the label as a Boxed Warning. Management of DS, including recommendations for initiating oral or intravenous steroids and hemodynamic monitoring, will be included in the Warnings and Precautions section of the label to increase the prominence of this information and promote mitigation of DS. Monitoring and dosage modifications for toxicities to address the safety issues with enasidenib will be included in the Dosage and Administration section of the label. Additionally, the applicant will be required to conduct a post-marketing required (PMR) study to characterize enasidenib-related DS, looking at incidence, diagnostic criteria, and effective treatment based on data and pooled analysis from their trial in AML.¹²

Embryo-Fetal Toxicity

Based on animal embryo-fetal toxicity studies, enasidenib can cause embryo-fetal harm when administered to a pregnant woman. In animal embryo-fetal toxicity studies, enasidenib caused embryo-fetal toxicities starting at 0.1 times the steady state clinical exposure based on the area under the concentration-time curve (AUC) at the recommended human dose. The risk of embryo-fetal toxicity will be communicated in the Warnings and Precautions section of the label.

Leukocytosis

Enasidenib can induce myeloid proliferation resulting in a rapid increase in white blood cell (WBC) count. Leukocytosis was the most frequently reported adverse reaction in the clinical trial with an overall incidence of all grades of 12% (26 patients). In the clinical trial, leukocytosis without evidence of infection or disease progression occurred in 12% of patients. Grade ≥ 3 leukocytosis occurred in 6% (12 patients) of enasidenib -treated patients. The risk of leukocytosis will likely be communicated in the Adverse Reactions section of the label.

Tumor Lysis Syndrome

In the clinical trial, tumor lysis syndrome (TLS) was reported in 6% (13) of patients treated with enasidenib. Grade ≥ 3 TLS occurred in 6% (12 patients) of enasidenib -treated patients. No events were considered as either life-threatening or fatal, and no patients required dose reduction or discontinuation. The risk of TLS will be communicated will likely be communicated in the Adverse Events section of the label.

Elevated Bilirubin

Enasidenib may interfere with bilirubin metabolism through inhibition of UGT1A1. Direct bilirubin elevations $\geq 2x$ ULN were observed in 38% of patients. Thirty three percent of patients with total bilirubin elevations ($\geq 2x$ ULN) had no concomitant elevation of transaminases or other Grade ≥ 3 adverse events related to liver disorders. Grade ≥ 3 were reported for 15% patients. Twenty-eight percent of Grade ≥ 2 bilirubin elevations were evident in the first month of treatment. No patients required a dose reduction for hyperbilirubinemia; treatment was interrupted in 3.7% of patients, for a median of 6 days. Three patients (1.4%) discontinued enasidenib permanently due to hyperbilirubinemia. The risk of hyperbilirubinemia will likely be communicated in the Adverse Reactions section of the label.

6 Expected Postmarket Use

The proposed indication is for the treatment of patients with relapsed or refractory AML with an IDH2 mutation. It is expected that oncologists/hematologists, who are familiar with the management of chemotherapeutic toxicities such as DS, embryo-fetal toxicity, leukocytosis and tumor lysis syndrome, will be the primary health care providers to prescribe enasidenib and the use will be in both inpatient and outpatient setting.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for enasidenib beyond routine pharmacovigilance and labeling. The applicant proposes a Boxed Warning in the labeling and a Medication Guide as part of labeling to inform patients regarding the potential risks of differentiation syndrome.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for enasidenib, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Enasidenib is an IDH2 inhibitor proposed for the treatment of patients with relapsed or refractory AML with an IDH2 mutation. Based on the efficacy and safety information currently available, the clinical reviewers stated that enasidenib shows clinical meaningful benefit to patients with AML, and recommends approval of enasidenib for the treatment of patients with relapsed or refractory AML with an IDH2 mutation.

DRISK and DHP have determined that if approved, a REMS is not necessary to ensure the benefits of enasidenib outweigh its risks. Labeling, including a Boxed Warning, and Warnings and Precautions will be used to communicate the safety issues and management of toxicities associated with enasidenib. The most concerning adverse reactions observed with the use of enasidenib are DS, leukocytosis, tumor lysis syndrome and hyperbilirubinemia. The most commonly reported TEAEs were disorders characteristic for subjects with AML and other hematologic malignancies, such as anemia, febrile neutropenia and thrombocytopenia, pneumonia with dyspnea and cough, and general disorders, including fatigue and pyrexia. Enasidenib appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling. The current standard treatment for AML is intensive chemotherapy potentially leading to an allogeneic stem cell transplant; treatment is based mainly on the patient's ability to tolerate the intensive regimen. There are no FDA-approved drugs specifically for relapsed or refractory AML, and there is no standard of care treatment regimen for these patients. Therefore, there remains a clear medical need for new treatments for the patients with relapsed or refractory AML. The risk of DS will be included in the label as a Boxed Warning; recommendations for the management of DS will be included in the Warnings and Precautions section of the label to increase the prominence of this information and promote its mitigation. The adverse reactions of TLS, leukocytosis, and hyperbilirubinemia will likely be communicated in the Adverse Reactions section of the label. Monitoring and dosage modifications for toxicities will be included in the Dosage and Administration section of the label. To better characterize safety the Agency has issued five PMRs and one PMC.¹²

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of enasidenib. The management of the risks associated with enasidenib treatment can be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated specifically REMS.

10 References

- ¹ Proposed Prescribing Information for enasidenib as currently edited by the FDA, last updated June 23, 2017.
- ² Celgene. Clinical Overview for Enasidenib, dated December 30, 2016.
- ³ Doehner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. *N Engl J Med*. 2015 Sep 17;373(12):1136-52.
- ⁴ Acute myelogenous leukemia (AML): Pathophysiology. Medscape. <http://emedicine.medscape.com/article/197802-overview#a3>. Accessed May 5, 2017.
- ⁵ What are the key statistics about acute myeloid leukemia? American Cancer Society. <https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html>. Accessed May 5, 2017.
- ⁶ Kumar CC. Genetic Abnormalities and Challenges in the Treatment of Acute Myeloid Leukemia. *Genes & Cancer*. 2011;2(2):95-107.
- ⁷ De Kouchkovsky I, Abdul-Hay M. 'Acute myeloid leukemia: a comprehensive review and 2016 update'. *Blood Cancer J*. 2016;6(7):e441.
- ⁸ Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1249-1259.
- ⁹ Estey E, Dohner H. Acute myeloid leukaemia. *Lancet*. 2006;368(9550):1894-1907.
- ¹⁰ Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
- ¹¹ Ward, A. DHP Multidisciplinary Clinical Review (draft) for NDA 209606 enasidenib, dated June 27, 2017.
- ¹² Late-Cycle Meeting Background Package, dated June 14, 2016

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/s/

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