CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208623Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Epidemiology: ARIA Sufficiency Memo
Version: 2018-01-24

Date:	August 3, 2018
Reviewer/ Team Leader:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Deputy Division Director:	Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	Active Risk Identification and Assessment (ARIA) Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Migalastat (Galafold®)
Application Type/#:	NDA 208623
Applicant/Sponsor:	Amicus Therapeutics
OSE RCM #:	2017-2582

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION WHAT

1.1. Medical Product

NDA 208623 seeks U.S. approval for migalastat (Galafold®) as treatment for Fabry disease, an X-linked lysosomal storage disorder with birth prevalence estimated at ≈25 per 100,000. Migalastat received European approval in January 2016. Migalastat, a first-in-class small-molecule oral drug with FDA orphan designation, stabilizes certain mutated forms of α-galactosidase A (GLA).

Though highly variable, Fabry disease classically manifests as symptoms in childhood, proteinuria in early adulthood followed by slowly progressive renal failure, and death during the fourth decade of life from hypertrophic cardiomyopathy, myocardial infarction, cardiac arrhythmia, or stroke. Early manifestations of classic Fabry disease can include angiokeratoma (skin lesions), acroparesthesia (burning pain in hands or feet), hypohidrosis or anhidrosis (diminished sweating), and cornea verticillata (characteristic corneal opacity).[a] Depending on genotype and pattern of X-chromosome inactivation, women with mutated *GLA* can manifest Fabry disease as severe as men.

1.2. Describe the Safety Concern – Pregnancy Risk

A June 2018 review of NDA 208623 by the Division of Pediatric and Material Health (DPMH) contained the following details.[b]

- Migalastat is not genotoxic or mutagenic.
- Pregnant rabbits given high-dose migalastat consumed less food and gained less weight than normal, with toxic doses associated with post-implantation fetal loss, lower fetal weights, and delayed ossification of the fetal skeleton.
- Migalastat did not affect fertility in female rats.
- Migalastat reversibly reduced fertility in male rats.
- Three women with pregnancy exposure discontinued migalastat and delivered healthy infants.

With data "not sufficient to assess drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes," DPMH recommended a post-approval pregnancy surveillance program because of "the lack of data to inform the safety of migalastat in pregnancy."

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[a] Mehta A, Hughes DA. Fabry Disease. 2002 Aug 5 [Updated 2017 Jan 5]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1292/

[b] Mastroyannis C, Sahin L, Yao LP. June 8, 2018, Division of Pediatric and Maternal Health Memorandum: Galafold (migalastat HCl) for oral use. Filed under NDA 208623 on June 18, 2018.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☐ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: International single-arm prospective observational study

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population and Outcomes: ARIA is insufficient to identify the study population (babies that experienced *in utero* exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

We did not formally assess the other parameters given that the mother-infant linkage is not currently available in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

The following language (in draft form, as of August 2, 2018) has been proposed for PMRs related to pregnancy outcomes:

> *PMR 3412-4: Worldwide, prospective, single-arm, observational study in women exposed to Galafold (migalastat) during pregnancy and lactation to assess: risks of pregnancy complications, adverse effects on the developing fetus and neonate, and adverse effects on lactation and the breastfed infant. Pregnancy exposures and outcomes will be reported voluntarily by providers and patients (e.g. telephone contact number and/or website will be provided in the product's prescribing information). Complete data will be captured regarding pregnancy outcomes and any adverse effects in offspring. Results will be analyzed and reported descriptively. The study will collect information for a minimum of 10 years. Interim reports on the cumulative findings and analyses will be submitted annually. Data collected retrospectively from other sources will be analyzed separately and reported with the interim and final study reports.*

The finalized PMR language will be issued upon approval.

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/s/

JOEL L WEISSFELD
08/03/2018

SUKHMINDER K SANDHU
08/03/2018

JUDITH W ZANDER
08/03/2018

MICHAEL D NGUYEN
08/03/2018

ROBERT BALL
08/04/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 24, 2018
To:	Dragos Roman, MD Acting Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	GALAFOLD (migalastat)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 208623
Applicant:	Amicus Therapeutics U.S., Inc.

1 INTRODUCTION

On December 13, 2017, Amicus Therapeutics, U.S., Inc. submitted for the Agency's review a New Drug Application (NDA) 208623 for GALAFOLD (migalastat) capsules. GALAFOLD (migalastat) capsules is a New Molecular Entity (NME) with a proposed indication for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable alpha galactosidase A (GLA) gene variant based on in vitro assay data.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Error Products (DGIEP) on June 13, 2018 and February 8, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for GALAFOLD (migalastat) capsules.

2 MATERIAL REVIEWED

- Draft GALAFOLD (migalastat) capsules PPI and IFU received on July 6, 2018 and received by DMPP and OPDP on July 9, 2018.
- Draft GALAFOLD (migalastat) capsules Prescribing Information (PI) received on December 13, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 9, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10 and the IFU document using the Arial font, size 11.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
07/24/2018

MEETA N PATEL
07/24/2018

MARCIA B WILLIAMS
07/24/2018

LASHAWN M GRIFFITHS
07/24/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 19, 2018

To: Hong Vu, Regulatory Project Manager, (DGIEP)
Division of Gastroenterology and Inborn Errors Products (DGIEP)

Joette M Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for GALAFORD™ (migalastat) capsules, for oral use (Galaford)

NDA: 208623

In response to DGIEP's consult request dated February 8, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Galaford

PI and PPI/IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DGIEP on July 9, 2018, and are provided below. A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 21, 2018, and we have the following comments:

OPDP Internal Comment: We recommend including, "at the same time of day," to be consistent with the IFU.

OPDP Internal Comment: We recommend including language from the IFU, "Do not take Galafold two days in a row."

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
07/19/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From:	Amy M. Taylor, MD, MHS Medical Officer Division of Pediatric and Maternal Health
Through:	Hari Cheryl Sachs, MD, Team Leader Division of Pediatric and Maternal Health John J. Alexander, MD, MPH Deputy Director Division of Pediatric and Maternal Health
NDA Number:	208-623
Sponsor:	Amicus Therapeutics
Drug:	Galafold™ (migalastat)
Dosage Form and Route of Administration:	capsules, for oral use
Proposed Indication:	For the treatment of patients (b) (4) with Fabry disease and who have an amenable mutation
Consult request:	The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests DPMH's assistance with the review of the NDA and proposed pediatric labeling for Galafold™ (migalastat).

Background

The sponsor submitted an original NDA on December 13, 2017 for Galafold™ (migalastat) for the treatment of Fabry disease in patients who have an amenable mutation. (b) (4)

The sponsor received orphan designation for this product and indication on February 25, 2004. (b) (4)

(b) (4)

(b) (4)

(b) (4)

We have the following additional comments:

(b) (4)

Selected sponsor proposed pediatric labeling with DPMH suggested edits (strikethroughs represent deletions and underlining represents additions)

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. Important pediatric safety information should be placed in **4 Contraindications** or **5 Warnings and Precautions** as appropriate. For products without sufficient data to support pediatric indications, the pediatric information should

be limited to **8.4 Pediatric Use** as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use

(b) (4)

The safety and effectiveness of GALAFOLD have not been established in pediatric patients (b) (4)

Reviewer comment: (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) *the product will be indicated in adults only.* (b) (4)

Recommendations

(b) (4) (b) (4) safety and efficacy have not been established in pediatric patients.

DPMH participated in labeling meetings between April and June 2018 and these recommendations were communicated to DGIEP. Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations (see approval letter).

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/s/

HARI C SACHS
06/25/2018
I agree with these recommendations and am signing on behalf of Amy M. Taylor, MD, MHS

JOHN J ALEXANDER
06/26/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Memorandum

Date: June 8, 2018 **Date consulted:** February 21, 2018

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Leyla Sahin, M.D., Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Galafold (migalastat HCl) for oral use

Drug Class: Lysosomal Storage Diseases (LSD) or other Inborn Errors of Metabolism (IEM)

NDA: 208623

Applicant: Amicus Therapeutics

Subject: Pregnancy and Lactation Labeling as part of original NDA

Proposed Indication: For the treatment of patients (b) (4) with Fabry disease and who have an amenable mutation.

Materials Reviewed:

- DPMH consult request dated February 21, 2018 in DARRTS (Reference ID: 4224519)
- Applicant's submission for original NDA 208623, a 505(b)(1) application, dated December 13, 2017 and the Prescribing Information (PI) for Galafold
- Fabrazyme labeling (BLA 103979) approved on May 14, 2010

Consult Question:

DGIEP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation labeling subsections to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

INTRODUCTION

This is an original 505(b)(1) New Molecular Entity (NME) application for Galafold (migalastat HCl), submitted on December 13, 2017, with a proposed indication for the treatment of patients (b) (4) with Fabry disease and who have an amenable mutation. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on February 21, 2018, to provide input for appropriate labeling of the pregnancy and lactation subsections of Galafold (migalastat HCl) for oral use to comply with the PLLR.

Fabry disease is a rare, life-threatening genetic disorder. It is the most prevalent lysosomal storage disorder. It is an X-linked inborn error of the glycosphingolipid metabolic pathway. The disease is caused by the deficiency of the enzyme α-galactosidase A (α-Gal A). Deficiency in α-Gal A activity results from mutations in the *GLA* gene (the gene encoding α-Gal A). This results in accumulation of globotriaosylceramide (Gb3) and the deacylated derivative globotriaosylsphingosine (lysoGb3) within lysosomes in a wide variety of cells, thereby leading to the manifestations of the disease. Migalastat is a small molecule that stabilizes amenable mutant forms of the α-Gal A enzyme, resulting in the restoration of endogenous enzyme activity in the lysosome and thus catabolism of globotriaosylceramide (GL-3) and other disease substrates.[1]

BACKGROUND

Regulatory History

The current application is for a first-in-class orally administered treatment of Fabry disease. Orphan drug designation was granted for migalastat HCl on October 20, 2003

Fabrazyme for injection is the first approved drug for enzyme replacement therapy (ERT) for Fabry Disease. It was approved on April 24, 2003.

Drug Characteristics[2]

- Migalastat does not show detectable plasma protein binding
- The molecular weight of migalastat is 199.63 Daltons
- The mean plasma half-life is about 4 hours
- Migalastat is not (b) (4) mutagenic.

REVIEW

[1] Germain DP. Fabry Disease. Orphanet J Rare Dis: 2010;5:30

[2] Proposed Galafold labeling

PREGNANCY

Animal Data

During the drug development program, the effects of migalastat on embryonic and fetal development were evaluated in New Zealand White rabbits. Migalastat was administered from gestation day (GD) 6 to GD 19 twice daily by oral gavage. The higher doses resulted in moderate to marked reductions in food consumption and body weight/body weight gain in the treated females. In the presence of maternal toxicity (exposures greater than 30 times the recommended human dose based on AUC) there was an increase in post-implantation loss, reductions in mean fetal body weights, and increases in the incidences of delayed ossification compared to the vehicle control.[3] Please refer to the FDA toxicology review by Dr. Vinay Patil (review pending).

Review of Literature

Applicant's Review

No publications exist on migalastat use in pregnant women. During the drug development program, 3 pregnancies in total were reported. Administration of study drug was discontinued at the time the pregnancy was confirmed. All 3 newborns were healthy.[3]

Reviewer comment

These limited number of pregnancies are not sufficient to assess drug associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Pharmacovigilance Review

No additional pregnancies are reported.

DPMH Review

In addition, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for migalastat and use in pregnancy.

No publications were identified. Reprotox and Shepard's of Micromedex Solutions report no published human data on use of migalastat in pregnancy. GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation do not present any information.

Summary

Animal studies do not indicate any adverse effects apart from those that occurred with maternal toxicity. A review of the literature has failed to produce any human literature on migalastat use in pregnancy. Three migalastat exposed pregnancies that occurred during the clinical development program had normal outcomes; however, these data are not sufficient to assess drug -associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes.

Because of the lack of data to inform the safety of migalastat in pregnancy, a post-approval pregnancy surveillance program would help collect pregnancy outcome data in a systematic manner.

LACTATION

Animal Data

[3] NDA submission of December 13, 2017

During animal studies, migalastat was present in rat milk. Please refer to the FDA toxicology review by Dr. Vinay Patil (review pending).

Review of Literature
Applicant's Review
There are no human data available on the presence of migalastat in human milk, the effects on the breastfed infant, or the effects on milk production.

DPMH Review
In addition to the search by the applicant, DPMH also conducted a literature search in PubMed, Embase and the LactMed databases for migalastat and use in lactation as well as in GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation and Hale TW Medications and Mother's Milk[4].

No entries on migalastat were identified on maternal and infant levels of migalastat in association with breast feeding (presence of migalastat in breast milk) or the effects of migalastat on the breastfed infant or on milk production.

Summary
There are no human data available on whether migalastat HCl is present in human milk, or on the effects on breastfed infants, or on milk production. Migalastat was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Animal Data
As per the applicant, animal studies have shown that administration of migalastat to male rats showed transient and fully reversible infertility that was associated with migalastat treatment at all doses assessed. Complete reversibility was seen after 4 weeks off dose. Migalastat did not affect fertility in female rats. Please refer to the FDA toxicology review by Dr. Vinay Patil (review pending).

Summary
Migalastat is not genotoxic or mutagenic, and is not associated with major birth defects. Therefore, there is no need for pregnancy testing or contraception during treatment with Galafold.

CONCLUSIONS
Galafold (migalastat HCl) labeling has been edited to comply with the PLLR. DPMH revised subsections 8.1, 8.2, and 8.3 of labeling for compliance with the PLLR (see below).

DPMH refers to the final NDA action for final labeling.

The *Pregnancy*, *Lactation,* and *Females and Males of Reproductive Potential* subsections of Galafold labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Subsection 8.1**
  - The "Pregnancy" subsection of Galafold labeling was formatted in the PLLR format to

[4] Hale WT. Medications & Mothers' Milk. 2017, Seventh Edition. Springer Publishing Co., NY,NY

include: “Risk Summary” and “Data” headings.

- **Lactation, Subsection 8.2**
  - The “Lactation” subsection of Galafold labeling was formatted in the PLLR format to include the “Risk Summary” heading.

- **Females and Males of Reproductive Potential, Subsection 8.3**
  - The “Females and Males of Reproductive Potential” subsection of Galafold labeling was formatted in the PLLR format to include the “Infertility” subheading.

RECOMMENDATIONS

DPMH recommends a Pregnancy Surveillance Program as a post-marketing requirement to collect pregnancy outcome data following exposure to Galafold.

DPMH has the following recommendations for Galafold labeling.

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There were three pregnant women exposed to GALAFOLD in clinical trials and the data are not sufficient to assess drug associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, no adverse developmental effects were observed. *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the (b) (4) background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No adverse developmental effects were observed with oral administration of migalastat to pregnant rats and rabbits during organogenesis at doses up to 26 and 54 times, respectively, the recommended dose based on AUC. No effects on post-natal development were observed following oral administration of up to 500 mg/kg migalastat twice daily to pregnant rats (16 times the recommended dose based on AUC) during organogenesis through lactation.

8.2 Lactation

Risk Summary

There are no human data available on the presence of migalastat in human milk, the effects on the breastfed infant, or the effects on milk production. Migalastat is present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GALAFOLD and any potential adverse effects on the breastfed child from GALAFOLD or from the underlying maternal condition.

Animal Data

Migalastat concentrations in milk from rats following oral administration of up to 500 mg/kg twice daily (16 times the recommended human dose based on AUC) was approximately 2.5 times higher than levels in the rat maternal plasma at four hours post-dose. The concentration of migalastat in plasma from pups was approximately 11 times lower than the maternal plasma concentrations at 1 hour post-dose.

8.3 Females and Males of Reproductive Potential

Infertility

The effects of GALAFOLD on fertility in humans have not been studied. Transient and fully reversible infertility in male rats was associated with migalastat treatment at a systemic exposure (AUC) equivalent to the human exposure at the recommended dose. Complete reversibility was seen after 4 weeks after the termination of treatment. Migalastat did not affect fertility in female rats *[see Nonclinical Toxicology (13.1)]*.

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/s/

CHRISTOS MASTROYANNIS
06/15/2018

LEYLA SAHIN
06/15/2018

LYNNE P YAO
06/18/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 14, 2018
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 208623
Product Name and Strength:	Galafold (migalastat) capsule, 123 mg
Submission date:	June 11, 2018
Applicant/Sponsor Name:	Amicus Therapeutics
OSE RCM #:	(b) (4)
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMO

Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the revised carton labeling and container label (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review, OSE RCM #: (b) (4)[a].

2 CONCLUSION

We find the revised container label and carton labeling acceptable and have no further recommendations at this time.

[a]Abraham.S. Label and Labeling Review for Galafold (NDA 208623). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Oct 24. 32 p. OSE RCM No. (b) (4)

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/s/

SHERLY ABRAHAM
06/14/2018

SARAH K VEE
06/14/2018

Clinical Inspection Summary

Date	June 7, 2018
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Anita Zaidi, M.D., Medical Officer, DGIEP
NDA #	208623
Applicant	Amicus Therapeutics US Inc.
Drug	migalastat HCl
NME	Yes
Division Classification	Inborn Errors
Proposed Indication	Treatment of patients with Fabry disease with amenable mutations
Consultation Request Date	February 15, 2018
Summary Goal Date	June 8, 2018
Action Goal Date	August 13, 2018
PDUFA Date	August 13, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections for this NDA consisted of inspections of three clinical investigator (CI) sites and the sponsor Amicus Therapeutics US Inc. Inspections at one of the clinical sites and the sponsor have the preliminary classifications of No Action Indicated (NAI). Two clinical sites have the preliminary classifications of Voluntary Action Indicated (VAI). The data generated by these sites and the sponsor are acceptable in support of the application.

II. BACKGROUND

The sponsor submitted this NDA for Migalastat HCl for the indication of treatment of patients with Fabry disease, an X-linked lysosomal storage disorder, with mutations in the GLA gene that are responsive to AT1001 (aka AT1001-Responsive GLA mutation or "amenable mutations"). The iminosugar, migalastat hydrochloride, AT1001 (also referred to as 1-deoxygalactonojirimycin [DGJ] hydrochloride), is a competitive inhibitor of α-Gal A that has been shown to bind to the active site of the enzyme. In cultured cells from affected males with "amenable mutations," this binding results in improved folding, stability, and lysosomal trafficking of α-Gal A.

Fabry disease results from mutations in the gene that encodes the lysosomal hydrolase α-galactosidase A (α-Gal A), the enzyme responsible for catabolism of neutral glycosphingolipids with terminal α-galactosyl residues. The mutations in *GLA*, the gene encoding α-Gal A, lead to reduced cellular α-Gal A activity resulting in progressive accumulation and deposition of lysosomal glycosphingolipids, predominantly globotriaosylceramide (also known as GL-3, Gb3, and CTH) in cells throughout the body. For these studies, AT1001-Responsive (amendable) GLA mutations were determined by an *in vitro* assay using HEK 239 cells. This assay was validated during the time that the studies were ongoing.

Drug: Migalastat HCl

Study– Protocol number and title for all studies that were inspected

1. Protocol AT1001-011 entitled, "A Double-blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Pharmacodynamics of AT1001 in Patients with Fabry Disease and AT1001-Responsive GLA Mutations"

Number of subjects: 67 subjects
Number of sites: 36 sites
Number of countries where subjects were enrolled: 16
Dates that study was conducted: (b) (6)
Efficacy endpoints:

a. Primary: Percentage of subjects with a >50% reduction from baseline to Month 6 in kidney globotriaosylceramide (GL-3) inclusions per kidney interstitial capillary
b. Secondary: estimated glomerular filtration rate (eGFR)

2. Protocol AT1001-012 entitled, "A Randomized, Open-Label Study to Compare the Efficacy and Safety of AT1001 and Enzyme Replacement Therapy (ERT) in Patients with Fabry Disease and AT1001-Responsive GLA Mutations, Who Were Previously Treated with ERT"

Number of subjects: 60 subjects
Number of sites: 25 sites
Number of countries where subjects were enrolled: 10 countries
Dates that study was conducted: (b) (6)
Efficacy endpoints: Percent change from Baseline to 48 hours posttreatment

a. Annualized change in mGFR iohexol as assessed by plasma clearance of iohexol from Baseline through Month 18
b. Annualized change in estimated GFR (eGFR) assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (eGFR CKD-EPI) from Baseline through Month 18

Rationale for Site Selection: Sites were chosen based on enrollment and participation in each of the studies.

III. RESULTS (by site):

Name and Type of Inspected Entity/Address	Site #/Protocol # / # of Subjects	Inspection Dates	Classification
CI: Kathleen M. Nicholls, M.D. Department of Nephrology The Royal Melbourne Hospital Parkville, Victoria 3050, Australia	Site 4001 AT1001-011 Subjects: 10 AT1001-012 Subjects: 4	May 14 to 18, 2018	*NAI
CI: Raffaele Manna, M.D. Unità Operativa Complessa di Medicina Interna Istituto di Medicina Interna Rare diseases and Periodic Fevers Research Centre Università Cattolica del Sacro Cuore Largo F. Vito 1 - 00168 Roma, Italy	Site 1601 AT1001-011 Subjects: 5	May 7 to 11, 2018	*VAI
CI: Dominique Paul Germain, M.D. Division of Medical Genetics Unité Fonctionnelle de Génétique Médicale Hôpital Raymond Poincaré 104, Boulevard Raymond Poincaré 92380 Garches, France	Site 1101 AT1001-011 Subjects: :6 AT1001-012 Subjects :1	May 14 to 18, 2018	*VAI
Sponsor: Amicus Therapeutics US Inc. 1 Cedarbrook Dr, Cranbury, NJ 08512	AT1001-011 67 subjects AT1001-012 60 subjects	May 22 to 30, 2018	*NAI

Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data may be unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Kathleen M. Nicholls, M.D.
   Department of Nephrology, The Royal Melbourne Hospital, Parkville, Australia

Note: Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

For Protocol AT1001-011 at this site, 18 subjects were screened, 10 subjects (7 amendable and 3 non-amendable) were enrolled. Seven subjects (five amendable and two non-amendable) completed the study. Records for the seven amendable subjects were reviewed. One subject withdrew due to pregnancy and two other subjects who had been randomized to placebo withdrew consent. This information is contained in the study report and line listing in the NDA. For Protocol AT1001-012 at this site, six subjects were screened, and four subjects, all amendable, were enrolled and completed the study. Records for the four enrolled subjects were reviewed. For both studies, there was no evidence of under reporting of adverse events, and the efficacy endpoint data could be verified. No violations were noted and no Form FDA 483 was issued.

The studies appear to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

2. Raffaele Manna, M.D.
   Unità Operativa Complessa di Medicina Interna, Rare diseases and Periodic Fevers Research Centre, Università Cattolica del Sacro Cuore, Roma, Italy

Note: Observations below for this CI inspection are based on the Form FDA 483, communications with the FDA field investigator and the response to the Form FDA 483 submitted by the clinical investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

For Protocol AT1001-011 at this site, 11 subjects were screened, 5 subjects were enrolled and completed the study. Records for all five subjects were reviewed. There was no evidence of under reporting of adverse events and the efficacy endpoint data could be verified.

A Form FDA 483 was issued because the investigator failed to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically:

1. For all subjects randomized, the Iohexol GFR Procedure Manual was not followed: For example, the Pre-Procedure Checklist was not found for any procedures for Subject (b) (6). The Sampling Times for Subject (b) (6) were not documented. The dose of Iohexol was not documented for any subjects.

Reviewer note: Violations were noted by the sponsor. The footnotes to Tables 11.24 and 11.29 in the clinical study report concerning the changes in GFR's state, "Based on the documented excessive iohexol dosing at study center 1601, during review of Stage 2 iohexol data, for 3 subjects at study center 1601, mGFRiohexol calculations were not performed. A fourth subject at study center 1601 discontinued the study prior to completion of Stage 2. For a fifth subject at study center 1601, mGFRiohexol was not performed due to subject's allergy to iohexol. All five subjects in study center 1601 were excluded in the analysis" for these tables.

2. For all subjects enrolled there is no documentation of the following inclusion criteria:
    a. Inclusion #5- Verification of stable dose of ACEIs or ARB for minimum of 4 weeks before baseline visit.
    b. Inclusion Criteria #6 - Subject agreement to use contraception during study. One Subject #(b) (6) became pregnant while on study.

Reviewer note: The CI responded in a letter of May 23, 2018 stating that the previous CI who enrolled the subjects was familiar with the histories. He stated that the subjects met the eligibility criteria and that there were available as documents external to the study.

3. Your site did not maintain original consent forms for all subjects enrolled and/or screened for this study.

Reviewer note: In his response of May 23, 2018, the CI stated that the site discovered during routine pre-inspection preparation that one of the three archive boxes could not be found. This box contained the informed consent documents. The site notified the local Ethics Committee and senior hospital administration. A broad search was conducted. The documents were not found, but corrective actions for archiving were instituted.

The clinical study report accurately reports the violations that occurred at this site concerning the misdosing of the iohexol that occurred at this site. The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

3. Dominique Paul Germain, M.D.
   Division of Medical Genetics, Unité Fonctionnelle de Génétique Médicale, Hôpital Raymond Poincaré, 92380 Garches, France

Note: Observations below for this CI inspection are based on the Form FDA 483 and communications with the FDA field investigator. The CI has not submitted a response to the Form FDA 483. An inspection summary addendum will be issued if conclusions change upon review of the final EIR and if the CI submits a response to the Form FDA 483.

For Protocol AT1001-011 at this site, 8 subjects were screened, 6 subjects were enrolled and completed the study. All enrolled subject records were reviewed. For Protocol AT1001-012 at this site, 1 subject who was amendable was screened, enrolled, and completed the study. This record was reviewed by the FDA field investigator. There was no evidence of under reporting of adverse events and the

efficacy endpoint data could be verified.

A Form FDA 483 was issued because the investigator failed to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically,

1. For Study AT1001-011 the adverse events observed and reported to the FDA for Subjects (b) (6) (placebo) and (b) (6) (active) do not have documentation of the CI's review or assessment for severity, relatedness and resolution.

Reviewer note: This appears to be an issue of documentation of review of the data concerning severity, relatedness and resolution by the CI prior to entering into the case report form (CRF) and does not impact the reporting of the adverse event itself. This appears to have occurred in these subjects because they were enrolled early in the study and the protocol specified documents did not contain space for these attributes. One subject was in the placebo arm and the other in the active treatment arm.

2. For Study AT1001-011 the Iohexol GFR studies for all subjects did not have documentation that the procedure was performed in accordance with the study protocol. For example, there was not documentation of the procedure used for the sampling, amount of contract material or the subject arm used for contract versus sampling as required in the procedure manual.

Reviewer note: The details of the lack of documentation are not available at the time of this review. These violations appear to be ones of documentation rather than clear procedural violations such as occurred at Site 1601 above. An addendum will be written when the final EIR is reviewed. If the Iohexol GFR will be an important value for regulatory decision making, the review division should conduct a sensitivity analysis removing the Iohexol GFR data from this site to determine if the result changes significantly.

Except for the conduct of the Iohexol GFR studies for Study AT1001-011, the studies appear to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

3. Amicus Therapeutics US Inc.
   1 Cedarbrook Dr, Cranbury, NJ 08512

Note: Observations below for this sponsor inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Protocols AT1001-011 and AT1001-012, including selection and oversight of contract research organizations (CROs), monitoring, financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data. The inspection included review of general correspondence and study master files, site monitoring for the clinical sites above, and handling of adverse events and other sponsor/monitor related activities. For Protocol AT1001-011 the procedures in

place for the firewall between the blinded and unblinded study personnel were reviewed and assessed. The sponsor submitted a response to an FDA information request of May 7, 2018. This concerned the timeline of the:

1. Validation of the GLP HEK assay,
2. Reassignment of the subjects from amenable to non-amenable,
3. Unblinding of Stage 1 (placebo controlled) data
4. Data analysis of primary efficacy by CT assay
5. Data analysis of post hoc primary efficacy using GLP-HEK assay

This timeline was reviewed with the sponsor and the data bases were examined to determine if the timelines were accurate. No violations were noted and no Form FDA 483 was issued.

The studies appear to have been conducted adequately and the data generated by this sponsor may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Covering for Kassa Ayalew, Branch Chief
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Office of Scientific Investigations

cc:
Central Doc. Rm.
Review Division /Division Director/Dragos Ramon
Review Division /Medical Team Leader/Patroula Smpokou
Review Division /Project Manager/Hong Vu
Review Division/Medical Officer/Anita Zaidi
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan D. Thompson
OSI/DCCE/GCP Reviewer/ Susan Leibenhaut
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

SUSAN LEIBENHAUT
06/07/2018

SUSAN D THOMPSON
06/07/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 21,2018

TO: Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Errors Products (DGIEP)
Office of Drug Evaluation III (ODEIII)
Office of New Drugs (OND)

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

Amanda E. Lewin, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection (b) (4) (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of study RR1001-26 (report #GLP-2012-003-FR; NDA 208623/S1) conducted (b) (4) (b) (4)

This was a data audit inspection for α-Galactosidase A enzyme activity in HEK-293 cells transiently transfected (b) (4) (b) (4) α-Galactosidase A mutants. No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, we conclude the data from the audited study are reliable. Thus, we recommend that the mutational analysis data from study RR1001-26 be accepted for further Agency review.

Inspected Study:

NDA 208623/S1

Study Number: **RR1001-26 (report #GLP-2012-003-FR)**
Study Title: "Quantification of α-Galactosidase A (α-Gal A) Activity in HEK-293 cells Transiently Transfected with Mutant or Wild-Type *GLA* cDNA and Incubated with AT1001-HCl"
Dates of conduct: [redacted]

Analytical site: [redacted]

OSIS scientists Kara A. Scheibner, Pharmacologist and Amanda E. Lewin, Pharmacologist audited the analytical portion of the above study [redacted].

[redacted]

[redacted]

(b) (4)

At the conclusion of the inspection, there were no significant inspectional findings and we did not issue Form FDA 483 to the analytical site.

Conclusion:

After reviewing the inspectional findings, we conclude the data from the audited study are reliable. Therefore, we recommend that the data from study RR1001-26 (report GLP-2012-003-FR; NDA 208623/S1) be accepted for further review.

Kara A. Scheibner, Ph.D.
Pharmacologist

Amanda E. Lewin, Ph.D.
Pharmacologist

Final Classification:

NAI - (b) (4)

FEI#: (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Kadavil/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin
OTS/OSIS/DGDBE/Cho/Jang/Choi/Skelly/Au/Scheibner

Draft: KAS 05/03/2018 AL 5/3/2018
Edit: GB 05/04/2018; 05/07/2018

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/Inspections/Analytical/ (b) (4)
(b) (4)

OSIS File #: BE 8008

FACTS: (b) (4)

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/s/

KARA A SCHEIBNER
05/21/2018

AMANDA E LEWIN
05/21/2018

GOPA BISWAS
05/21/2018

ARINDAM DASGUPTA
05/21/2018

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 15, 2018
Requesting Office or Division:	Division of Gastrointestinal and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 208623
Product Name and Strength:	Galafold (migalastat) capsule, 123 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Amicus Therapeutics
Submission Dates:	December 13, 2017 March 16, 2018
OSE RCM #:	(b) (4)
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 REASON FOR REVIEW

This review evaluates the labels and labeling for Galafold (NDA 208623), New Molecular Entity (NME) NDA, submitted on December 13, 2017. On March 16, 2018, revised prescribing information (PI) was submitted. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed PI, container label, and carton labeling for any areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Amicus Therapeutics submitted a NME NDA for Galafold for (b) (4) treatment of (b) (4) patients with a confirmed diagnosis of Fabry Disease and who have an amenable mutation. Migalastat is a first-in-class, orally administered, precision medicine proposed for treatment of patients with Fabry disease.

We identified areas in the PI, container label, and carton labeling that can be improved to increase the clarity of information to promote the safe use of the product. We

provide letter-ready recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, container label, and carton labeling can be improved to increase the clarity of information to promote the safe use of the product. We provide our recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. FULL PRESCRIBING INFORMATION: Section 16 how supplied/storage and handling

1. We recommend asking the Applicant to submit the actual NDC number. NDC number is currently denoted as XXXXX-YYYY-ZZ.

4.2 RECOMMENDATIONS FOR AMICUS THERAPEUTICS

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling Only (Outer sleeve):

1. Decrease the prominence and relocate the net quantity statement away from the product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.[a]

2. As currently displayed, NDC number is denoted by a placeholder (XXXXXXXXXXX), please submit the NDC number in the following format, XXXXX-XXXX-XX).[a]

3. Revise the sentence to read "Take on an empty stomach. Do not consume food at least 2 hours before and 2 hours after taking Galafold to give a minimum 4 hours fast." to be consistent with the Prescribing Information.

B. Container Label (Inner sleeve) Only:

4. Add a "Rx only" statement which is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.

5. Express the product strength as ‘123 mg per capsule’ to clarify that each individual capsule is 123 mg.[a]

[a]Draft Guidance for Industry: Safety Consideration for container labels and carton labeling design to minimize medication errors. 2013.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Galafold that Amicus Therapeutics submitted on December 13, 2017.

Table 2. Relevant Product Information for Galafold	
Initial Approval Date	N/A
Active Ingredient	migalastat
Indication	Indicated for (b) (4) treatment of (b) (4) (b) (4) patients with a confirmed diagnosis of Fabry Disease and who have an amenable mutation.
Route of Administration	oral
Dosage Form	capsule
Strength	123 mg
Dose and Frequency	1 capsule (123 mg) once every other day at the same time of day.
How Supplied	(b) (4) (b) (4) blister packs with aluminum foil lidding. Each pack size contains 14 capsules.
Storage	Store this medicinal product at USP Controlled Room Temperature of 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the Galafold labels and labeling submitted by Amicus Therapeutics on December 13, 2017.

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container label (Inner sleeve)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SHERLY ABRAHAM
05/15/2018

SARAH K VEE
05/16/2018

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 208623
Brand Name	Galafold®
Generic Name	AT1001 (migalastat hydrochloride)
Sponsor	Amicus Therapeutic, Inc.
Indication	Use in patients with Fabry disease who have an amenable mutation in the GLA gene. Galafold reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types.
Dosage Form	Oral capsule containing 150 mg migalastat hydrochloride
Drug Class	A pharmacological chaperone that is designed to selectively and reversibly bind with high affinity to the active sites of certain mutant forms of α-Gal A
Therapeutic Dosing Regimen	150 mg once every other day (QOD)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Single dose: 2000 mg, Multiple dose: 250 mg BID
Submission Number and Date	13 Dec 2017; SDN 001
Review Division	DGIEP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of AT1001 (migalastat hydrochloride, 150 mg and 1250 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between AT1001 (150 mg and 1250 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, double-blind, four-period crossover study, 52 healthy subjects received a single oral dose of AT1001 150 mg, AT1001 1250 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for AT1001 (150 mg and 1250 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
AT1001 150 mg	1	-0.1	(-2.2, 1.9)
AT1001 1250 mg	8	-0.2	(-2.2, 1.8)
Moxifloxacin 400 mg*	2	10.9	(8.7, 13.0)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints was 7.9 ms.

The supratherapeutic dose (1250 mg) produces mean C_{max} and $AUC_{0\text{-}inf}$ values of 7.8-fold and 7.0-fold higher than those for the therapeutic dose (150 mg), respectively. These concentrations are above those for the predicted worst case scenario of severe renal impairment and results show that at these concentrations there are no detectable prolongations of the QT-interval. No drug-drug interaction studies were conducted. Migalastat is not a substrate for P-gP *in vitro* and it is considered unlikely that migalastat would be subject to drug-drug interactions with CYP450 enzymes. No studies have been carried out in subjects with impaired hepatic function. From the metabolism and excretion pathways, it is not expected that a decreased hepatic function would significantly affect the pharmacokinetics of migalastat. The concentration-QTc analysis for AT1001 (migalastat) did not reveal a positive slope for the relationship.

2 PROPOSED LABEL

The sponsor has not proposed any labeling language related to QT.

The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of GALAFOLD on the QTc interval was evaluated in a Phase 1 randomized, placebo and positive controlled, double-blind, single-dose, crossover thorough QTc study in 52 healthy adult subjects. At the single dose 8.3-fold of the single therapeutic dose, GALAFOLD did not prolong the QTc interval to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Migalastat is an analogue of the terminal galactose of GL-3 that acts as a pharmacological chaperone, selectively and reversibly binding with high affinity to the active site of wild-type α-Gal A and specific mutant forms of α-Gal A. Migalastat binding stabilizes these mutant forms of α-Gal A in the endoplasmic reticulum. Migalastat is being developed by Amicus Therapeutics for (b) (4) treatment of adult (b) (4) with a confirmed diagnosis of Fabry disease (α-Gal A deficiency) and who have an amenable mutation.

3.2 MARKET APPROVAL STATUS

Migalastat has not been approved for marketing in any country

3.3 PRECLINICAL INFORMATION

The effect of AT1001 (0.00475, 0.0475, 0.475, 4.75, and 47.5 μM) on the potassium selective Ikr (tail) current was investigated in vitro in a GLP study using Chinese hamster ovary cells (CHOK1 cells) stably transfected with hERG; the whole-cell patch-clamp technique was used. AT1001 had little or no effect on hERG potassium currents at any concentration tested. The IC_{50} value was determined to be greater than 47.5 μM.

3.4 PREVIOUS CLINICAL EXPERIENCE

Phase 2 studies of AT1001 were conducted in male and female patients with Fabry disease. Among the cardiac findings of Fabry disease are electrocardiographic abnormalities, including left ventricular hypertrophy, ST segment changes, and T-wave inversion, as well as arrhythmias, intermittent supra-ventricular tachycardia, and a short PR interval.

Five male subjects in Study FAB-CL-203 and 9 female subjects in Study FAB-CL-204 each received a single dose level on an every-other-day regimen for the entire duration of their participation. Of these, 9 received 150 mg once every other day (5 males, 4 females), two female subjects received 50 mg once every other day, and three female subjects received 250 mg once every other day.

Four subjects (one male, three females) had potentially clinically significant (PCS) post-baseline QTcB values (above 450 msec). None of the subjects with a post-baseline QTcB above 450 msec had an increase from baseline greater than 60 msec. All four of these subjects were on 150 mg AT1001 once every other day.

Of the three female subjects, two of these subjects had a QTcB above 450 msec at their screening visit (461 and 502 msec), although neither subject had a QTcB above 450 msec on the ECG recorded just before dosing on Day 1. Additionally, only one of these female subjects had a QTcB outside the range of 450 msec to 470 msec, which is within the normal range for females. The only longer QTcB (484 msec) occurred in the subject whose QTcB at screening was 502 msec.

The only male with a PCS post-baseline QTcB had a QTcB on Day 56 of treatment of 452 msec 3 hours after dosing . His QTc interval was in the normal range on all other ECG tracings.

None of the QTcB abnormalities were deemed to be clinically significant or reported as adverse events.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of migalastat's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 68456 on 06/09/2009. The planned QT/QTc analysis approach appeared acceptable to FDA in the protocol review. The sponsor submitted the study report AT1001-010 for migalastat hydrochloride (AT1001), including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Double-Blind, Randomized, Double- Dummy, Positive and Placebo Controlled, Four Arm Cross-Over Study of the Effects of a Single Dose of AT1001 (Migalastat Hydrochloride), at the Proposed Therapeutic and Supra-Therapeutic Dose, on the QT/QTc Intervals in Healthy Subjects

4.2.2 Protocol Number

AT1001-010 (b) (4)

4.2.3 Study Dates

02 Jun 2009 – 01 Jul 2009

4.2.4 Objectives

The primary objectives of this study were to:

- Evaluate the effect of a single oral dose of AT1001 on ventricular repolarization in healthy subjects compared to placebo at the proposed therapeutic dose of 150 mg
- Evaluate the effect of a single oral dose of AT1001 on ventricular repolarization in healthy subjects compared to placebo at the proposed supra-therapeutic dose of 1250 mg
- Evaluate the change from baseline of QTc interval corrected by QTcB, QTcF, and QTcI (subject-specific) at the Tmax using 12-lead electrocardiograms on the day of dosing

The secondary objectives were to:

- Determine if there was a pharmacodynamic relationship between the duration of the QTc intervals and the plasma concentration of AT1001
- Obtain additional pharmacokinetic information on AT1001 in healthy subjects when AT1001 was administered orally at the proposed therapeutic and supra-therapeutic dose
- Provide additional safety information

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 4-sequence, crossover design with four dosing occasions. Each dosing occasion was followed by washout period of 5 – 7 days.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were over-encapsulated.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 4 treatments:

- Dose Group A (Therapeutic)

  A single oral dose of AT1001 solution at a 150 mg dose and an oral moxifloxacin over- encapsulated placebo tablet administered as a single oral dose

- Dose Group B (Supra-Therapeutic)

  A single oral dose of AT1001 solution at a 1250 mg dose and an oral moxifloxacin over- encapsulated placebo tablet administered as a single oral dose

- Dose Group C (Placebo)

  A single oral dose of AT1001 placebo solution plus a moxifloxacin over-encapsulated placebo tablet administered as a single oral dose

- Dose Group D (Moxifloxacin)

  A single oral dose of AT1001 placebo solution plus a moxifloxacin over-encapsulated 400 mg tablet administered as a single oral dose

4.2.6.2 Sponsor's Justification for Doses

Based on the results of clinical studies to date, 150 mg once every other day was chosen as the therapeutic dose. The supra-therapeutic dose of 1250 mg selected for this study was chosen as in past studies it appeared to represent the maximum exposure attainable with a single dose of AT1001 and resulted in plasma concentrations approximately 8-fold higher than the therapeutic dose in Study FAB-CL-104.

Single doses of AT1001, 150 mg (therapeutic dose) or 1250 mg (supra-therapeutic dose), were used in this thorough QTc study as accumulation was not demonstrated at steady

state in a previous pharmacokinetic study of 150 mg AT1001 administered once every other day.

Reviewer's Comment: Acceptable. The major elimination pathway is renal. As per the information in the protocol review, "urinary elimination data in healthy volunteers and the results of preclinical studies to assess metabolism and protein binding suggest that a more than 3-fold increase in exposure would be an unlikely worst case clinical scenario". The reviewer's comment in the protocol review states, "Dose justification is reasonable based on the information presented in appendix 5.1. A single dose study is reasonable because AT1001 has short $T_{1/2}$, does not accumulate with repeat dosing, and is not extensively metabolized". In this study, the selected supra-therapeutic dose provided adequate exposure coverage over expected worst case scenario of exposure in patients with severe renal impairment.

4.2.6.3 Instructions with Regard to Meals

Subjects fasted overnight and were dosed at the 0 hour on Day +1 of each study period (Period 1,2, 3 and 4). After administration of the AT1001 solution or placebo for AT1001 solution, 25 mL of room temperature rinse water was added to the container, the water in the container was gently swirled and the 25 mL of rinse was ingested.

Reviewer's Comment: Acceptable. According to Study FAB-CL-103, food decreased the rate and extent of AT1001 bioavailability (C_{max} and $AUC_{0-\infty}$) by approximately 40% and 38%, respectively. T_{max} was delayed by approximately 28% (from 3.1 to 3.9 hrs) when AT1001 capsules were administered with food in healthy male volunteers. Based on these results, it is reasonable that AT1001 capsules are taken on an empty stomach.

4.2.6.4 ECG and PK Assessments

ECG Assessments: A 12-lead Holter recorder was placed on each subject for 24 hours. This was placed 1.5 hours prior to the assigned subject specific dosing time. Three ECGs were extracted in triplicate from the 12-lead Holter recorder within a 10 minute window beginning at -60 min, -30 min and -15 min before the subject's specific dosing time. These electrocardiograms were used to determine the primary ECG baseline.

The post-dose ECG time points were extracted in triplicate from the 12-lead Holter recorder within a 10 minute window beginning at +30 min, +1 hour, +2 hours, +2.5 hours, +3 hours, +3.5 hours, +4 hours, +6 hours, +8 hours, + 10 hours, +12 hours, and +22 hours 30 min. The allowable time deviation was ±5 minutes. These ECGs were not visible to the staff at the clinical site during the study.

PK Assessments: On Study Day +1 of each Cross-over Arm, blood samples were drawn for the determination of AT1001 and moxifloxacin plasma levels at the following sampling time points: pre-dose (0 hour), 0.5, 1, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 22.5 hours after the initiation of dose administration. Plasma samples that were drawn for the determination of the concentrations for moxifloxacin were not to be analyzed unless the QT response observed following moxifloxacin administration was different than the expected response.

Reviewer's Comment: Acceptable. The ECG/PK sampling schedule was adequate to cover effects near T_{max} (~3 h postdose) and any potential delayed effects up to 22.5 h postdose.

4.2.6.5 Baseline

The average of pre-dose QT/QTc values on Day 1 of each period was used as baseline for that period.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 52 healthy adult subjects (26 females and 26 males) were randomized to the study. One subject withdrew consent before period 2 and the remaining 51 subjects completed the study. All 52 subjects were included in the safety, PK, and PD populations.

The average age (SD) of the 52 subjects was 29.2 (11.3) years, ranging from 21 years to 54 years. Most subjects (41/52, 78.8%) were White, 5 subjects (5/52, 9.6%) were Black or African American, and 4 subjects (4/52, 7.7%) were Asian. Four subjects (4/52, 7.7%) were of ethnicity Hispanic or Latino, with the remaining 48 subjects (48/52, 92.3%) being Not Hispanic or Latino.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsor used mean change in QTcI as the primary endpoint; it was analyzed by a repeated measures mixed effects linear model that included the effects of subject, study drug, ECG time point, and study drug-by-ECG time point interaction. The sponsor's results for mean placebo-corrected change from baseline in QTcI (ΔΔQTcI) are displayed in the following Table 2.

The sponsor also analyzed mean change in QTcF using the same statistical model. The findings from this alternative analysis were consistent with that of QTcI.

The majority of the changes from baseline were decreases. The maximum increase of the QTcI response occurred at 12 hours postdose for the 150 mg and 1250 mg doses of AT1001, 0.06 msec and 0.08 msec respectively. These values are not clinically significant. In both of AT1001 groups, the largest of the upper bounds of placebo-subtracted change of QTcI were 2.06 msec at 12 hours.

Table 2: Placebo-subtracted Change from Baseline and Upper Bound of the One-sided 95% CI – QTcI (msec) (Sponsor's Results)

Hours post-dose	AT1001 150 mg	UB	AT1001 1250 mg	UB
0.5	0.03	2.02	-1.11	0.88
1	-0.01	1.99	-1.56	0.43
2	-0.64	1.36	-2.14	-0.15
2.5	-0.84	1.15	-2.67	-0.69
3	-1.96	0.04	-2.83	-0.84
3.5	-1.90	0.09	-3.36	-1.37
4	-0.29	1.70	-1.60	0.39
6	-1.29	0.71	-1.28	0.71
8	-0.80	1.20	-0.17	1.82
10	-1.87	0.13	-1.63	0.37
12	0.06	2.06	0.08	2.06
22.5	-2.32	-0.31	-0.88	1.12

(Source: the sponsor's clinical study report, Table 11.5.4-2, page 62)

Reviewer's Comments: We agree with the sponsor's conclusions. We chose mean change from baseline in QTcF as the primary endpoint and conducted our independent analysis using repeated measures mixed effects model with a different covariate set. Our findings have the same conclusions as those specified by the sponsor. Please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

The sponsor assessed assay sensitivity using the same statistical model shown for the primary endpoint but with covariates sequence and period added; it was done for QTcI only at 2, 2.5, 3, and 3.5 hours postdose.

Placebo-subtracted changes of QTcI from baseline were calculated from the primary statistical model. The moxifloxacin treatment results in Table 3 show the mean changes from baseline of QTcI subtracted by the corresponding placebo mean of QTcI as estimated from the repeated measures statistical model and the associated lower bounds (LB) of the one-sided 95% CIs. The times for comparison of lower one-sided confidence bounds with 5 msec were 2.0 through 3.5 hours. Each of these lower bounds exceeded 5 msec and the overall time course of the moxifloxacin response was as expected. The highest mean was 10.85 msec at 2.0 hours postdose and was associated with the highest of the lower bounds, 9.26 msec. Thus, QTcI sensitivity to positive control was confirmed.

Table 3: Placebo-subtracted Change from Baseline – QTcI (msec) and Lower One-sided 95% CIs for Moxifloxacin (Sponsor's Results)

Hours post-dose	Moxifloxacin 400 mg	LB
0.5	4.66	NA
1	8.02	NA
2	10.85	9.26
2.5	10.18	8.92
3	9.01	7.76
3.5	9.53	7.74
4	10.69	NA
6	7.22	NA
8	9.05	NA
10	4.57	NA
12	6.54	NA
22.5	3.54	NA

(Source: the sponsor's clinical study report, Table 11.5.9-1, page 67)

Reviewer's Comments: We agree with the sponsor's conclusions. Please see the reviewer's independent analysis for assay sensitivity in section 5.2.

4.2.8.2.3 Categorical Analysis

Outlier values of QTcI greater than 450 msec were noted in 3 subjects (5.9%) in the AT1001 150 mg group, in 4 subjects (7.7%) in the AT1001 1250 group, and in 2 subjects (3.9%) in the placebo group. Outlier values of QTcF greater than 450 msec were noted in 2 subjects (3.9%) in each of the AT1001 groups and in 2 subjects (3.9%) in the placebo group.

Analysis of changes from the time-matched baseline revealed that no subject had an increase from baseline in QTcI or QTcF interval greater than 30 msec.

While there were more outliers of QTcI on AT1001 than on placebo, the overall number of findings is very small and no inference of repolarization effects can be made.

4.2.8.3 Safety Analysis

No deaths, serious adverse events (SAEs), or other significant adverse events (AEs) occurred during the study. No subject discontinued the study due to an AE. Of the 52 enrolled subjects, only 1 subject withdrew consent due to a schedule conflict before period 2.

There were no episodes of ventricular tachycardia or fibrillation, syncope, or seizures.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for migalastat are presented in Table 4 and the mean drug concentration-time profile is illustrated in Figure 1. The mean C_{max} was 13197 ng/mL following a 1250 mg dose and 1700 ng/mL following a 150 mg dose. C_{max} and $AUC_{0\text{-}inf}$ values in the thorough QT study were 7.8- and 7.0-fold higher, respectively, following administration of 1250 mg migalastat super dose compared with 150 mg drug, the intended clinical dose.

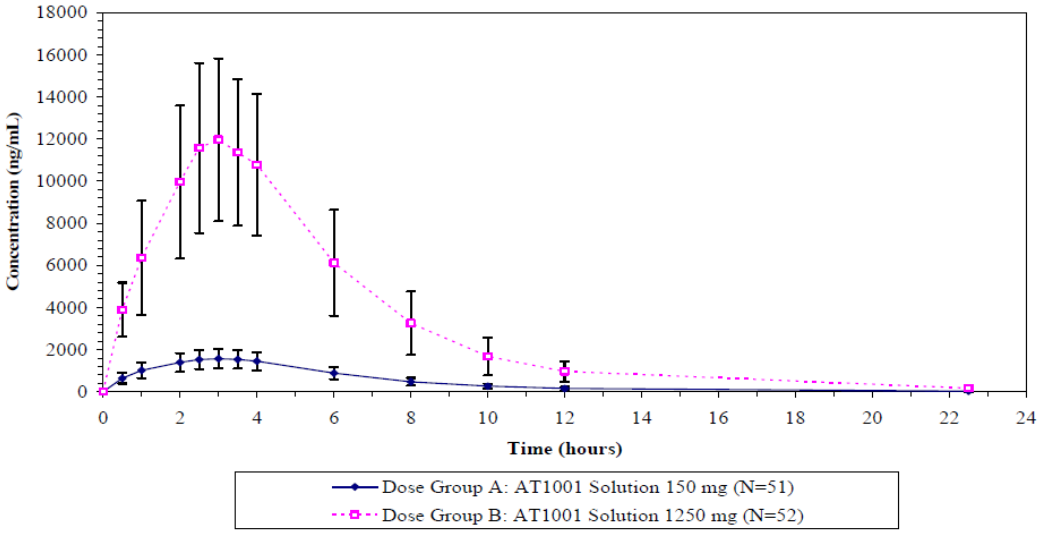
Table 4: Arithmetic Mean (±SD) Pharmacokinetic Parameters of Migalastat

PK Parameter	Dose Group A (AT1001 Solution 150 mg) (Therapeutic) (N=51)	Dose Group B (AT1001 Solution 1250 mg) (Supra-Therapeutic) (N=52)
AUC_{0-t} (ng·hr/mL)	10654.26 (± 2612.25)	74189.57 (± 20096.95)
$AUC_{0-\infty}$ (ng·hr/mL)	10806.17 (± 2666.15)	75183.89 (± 20350.42)
C_{max} (ng/mL)	1700.22 (± 464.62)	13197.12 (± 3906.50)
T_{max}^{*} (hr)	3.00 (1.00 - 6.00)	3.00 (2.00 – 4.00)
λ_z (K_{el}) (1/hr)	0.1824 (± 0.0174)	0.1756 (± 0.0195)
$T_{½}$ (hr)	3.84 (± 0.39)	4.00 (± 0.46)

Median and range are reported for T_{max}.

(Source: Table 11.4.7-1 on page 56 of Applicant's Clinical Study Report AT1001-010)

Figure 1: Mean (±SD) Migalastat Concentration-time Profile for 1250 mg and 150 mg Migalastat

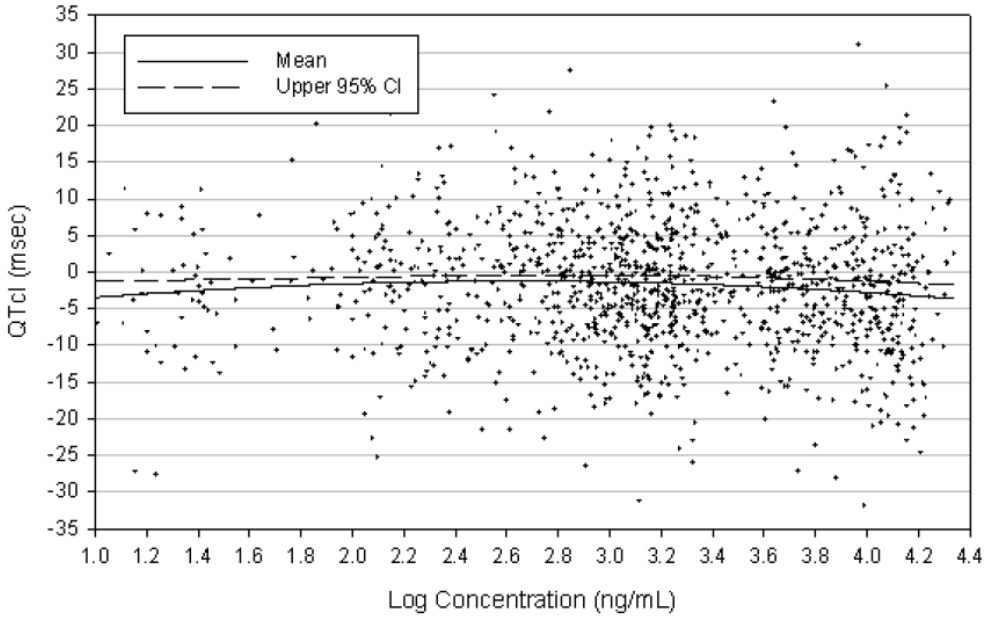


(Source: Figure 11.4.7-1 on page 55 of Applicant's Clinical Study Report AT1001-010)

4.2.8.4.2 Exposure-Response Analysis

The relationship between placebo-subtracted differences in changes from baseline in QTcI intervals and log AT1001 plasma concentration was assessed. A scatter plot of these data is shown in Figure 2. A repeated measures regression was run on these data, with an estimated linear slope of -0.521 (p=0.168).

Figure 2: Placebo-subtracted Changes in QTCI vs. Log AT1001 Concentration



(Source: Figure 11.5.8-1 on page 66 of Applicant's Clinical Study Report AT1001-010)

Reviewer's Analysis: The reviewer's analysis confirmed that there was no statistically significant positive slope for the concentration-QTc relationship (see Section 5.3).

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

5.2 STATISTICAL ASSESSMENTS

Since no large changes in heart rate were observed, i.e., mean changes ≤10 bpm (section 5.2.2), QTcF was used for primary analysis. We also used QTcI as supportive analysis.

No assessment of the QT/RR correction methodology is necessary.

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for AT1001

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment, sequence, period, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in Table 5 and Table 6.

Table 5: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = A: AT1001 150 mg

	ΔQTcF (ms) AT1001 150 mg (N=51)	ΔQTcF (ms) Placebo (N=51)	ΔΔQTcF (ms) AT1001 150 mg	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
0.5	-3.8	-3.0	-0.7	(-2.7, 1.3)
1	-1.6	-1.5	-0.1	(-2.2, 1.9)
2	-3.6	-2.8	-0.9	(-3.0, 1.3)
2.5	-2.4	-0.7	-1.7	(-4.1, 0.7)
3	-2.5	-0.4	-2.1	(-4.4, 0.2)
3.5	-2.3	-0.4	-1.9	(-4.0, 0.2)
4	-2.3	-1.9	-0.4	(-2.5, 1.7)
6	-8.0	-6.3	-1.7	(-4.0, 0.6)
8	-10.5	-9.5	-1.0	(-3.0, 1.0)
10	-6.4	-4.8	-1.6	(-3.9, 0.6)
12	-5.9	-5.5	-0.5	(-2.6, 1.7)
22.5	-4.6	-1.9	-2.7	(-4.8, -0.6)

Table 6: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = B: AT1001 1250 mg

	ΔQTcF (ms) AT1001 1250 mg (N=52)	ΔQTcF (ms) Placebo (N=51)	ΔΔQTcF (ms) AT1001 1250 mg	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
0.5	-4.2	-3.0	-1.2	(-3.2, 0.8)
1	-2.8	-1.5	-1.3	(-3.4, 0.7)
2	-5.0	-2.8	-2.2	(-4.4, -0.1)
2.5	-3.6	-0.7	-2.9	(-5.3, -0.5)
3	-3.0	-0.4	-2.6	(-4.9, -0.4)

	ΔQTcF (ms) AT1001 1250 mg (N=52)	ΔQTcF (ms) Placebo (N=51)	ΔΔQTcF (ms) AT1001 1250 mg	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
3.5	-3.2	-0.4	-2.8	(-4.9, -0.7)
4	-3.0	-1.9	-1.1	(-3.2, 1.0)
6	-7.8	-6.3	-1.5	(-3.8, 0.8)
8	-9.7	-9.5	-0.2	(-2.2, 1.8)
10	-6.6	-4.8	-1.8	(-4.1, 0.4)
12	-6.2	-5.5	-0.7	(-2.9, 1.4)
22.5	-3.1	-1.9	-1.2	(-3.3, 0.9)

The largest upper bounds of the 2-sided 90% CI for the mean differences between AT1001 150 mg and placebo, and between AT1001 1250 mg and placebo were 1.9 ms and 1.8 ms, respectively.

We used QTcI, the sponsor's primary analysis, as our alternative analysis parameter. The results for QTcI analysis are displayed in Table 7. The interpretation of study results from QTcI analysis is consistent with that from QTcF analysis.

Table 7: Analysis Results of ΔQTcI and ΔΔQTcI

	AT1001 150 mg (N=51)			AT1001 1250 mg (N=52)		
	ΔQTcI (ms)		ΔΔQTcI (ms)	ΔQTcI (ms)		ΔΔQTcI (ms)
Time (hour)	**LSmean**	**LSmean Placebo**	**LSmean (90% CI)**	**LSmean**	**LSmean Placebo**	**LSmean (90% CI)**
0.5	-3.5	-3.2	-0.4 (-2.4, 1.6)	-4.4	-3.2	-1.3 (-3.3, 0.7)
1	-1.8	-1.4	-0.4 (-2.5, 1.6)	-3.1	-1.4	-1.7 (-3.8, 0.3)
2	-3.9	-2.8	-1.1 (-3.2, 1.1)	-5.2	-2.8	-2.4 (-4.5, -0.2)
2.5	-2.3	-1.1	-1.2 (-3.7, 1.2)	-4.0	-1.1	-2.9 (-5.3, -0.5)
3	-2.7	-0.3	-2.4 (-4.8, -0.1)	-3.4	-0.3	-3.1 (-5.4, -0.7)
3.5	-2.4	-0.0	-2.3 (-4.6, -0.1)	-3.6	-0.0	-3.6 (-5.8, -1.4)
4	-2.0	-1.3	-0.8 (-3.0, 1.5)	-3.1	-1.3	-1.8 (-4.0, 0.4)
6	-7.5	-5.8	-1.7 (-4.1, 0.7)	-7.3	-5.8	-1.5 (-3.8, 0.9)
8	-10.2	-9.0	-1.2 (-3.3, 0.8)	-9.4	-9.0	-0.4 (-2.5, 1.6)

	AT1001 150 mg (N=51)			AT1001 1250 mg (N=52)		
	ΔQTcI (ms)		ΔΔQTcI (ms)	ΔQTcI (ms)		ΔΔQTcI (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
10	-6.5	-4.1	-2.4 (-4.6, -0.1)	-6.0	-4.1	-1.9 (-4.1, 0.3)
12	-5.3	-4.9	-0.4 (-2.6, 1.8)	-5.1	-4.9	-0.1 (-2.4, 2.1)
22.5	-4.4	-1.7	-2.8 (-4.9, -0.7)	-2.8	-1.7	-1.1 (-3.2, 1.0)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval was 8.7 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 7.9 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin could be detected from the study.

Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

	ΔQTcF (ms) Moxifloxacin 400 mg (N=51)	ΔQTcF (ms) Placebo (N=51)	ΔΔQTcF (ms) Moxifloxacin 400 mg		
Time (hour)	LSmean	LSmean	LSmean	90% CI	Adjust 90% CI*
0.5	1.7	-3.0	4.7	(2.7, 6.7)	(2.0, 7.5)
1	6.5	-1.5	8.0	(5.9, 10.0)	(5.1, 10.8)
2	8.1	-2.8	10.9	(8.7, 13.0)	(7.9, 13.8)
2.5	9.4	-0.7	10.2	(7.8, 12.5)	(6.9, 13.4)
3	8.7	-0.4	9.1	(6.8, 11.3)	(6.0, 12.2)
3.5	9.2	-0.4	9.5	(7.4, 11.7)	(6.7, 12.4)
4	8.9	-1.9	10.8	(8.7, 12.9)	(7.9, 13.6)
6	0.9	-6.3	7.2	(4.9, 9.5)	(4.1, 10.3)
8	-0.5	-9.5	9.0	(7.0, 11.0)	(6.3, 11.8)
10	-0.2	-4.8	4.6	(2.4, 6.8)	(1.5, 7.7)

	ΔQTcF (ms) Moxifloxacin 400 mg (N=51)	ΔQTcF (ms) Placebo (N=51)	ΔΔQTcF (ms) Moxifloxacin 400 mg		
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**	**Adjust 90% CI***
12	1.0	-5.5	6.5	(4.4, 8.6)	(3.6, 9.4)
22.5	1.7	-1.9	3.6	(1.6, 5.7)	(0.8, 6.5)

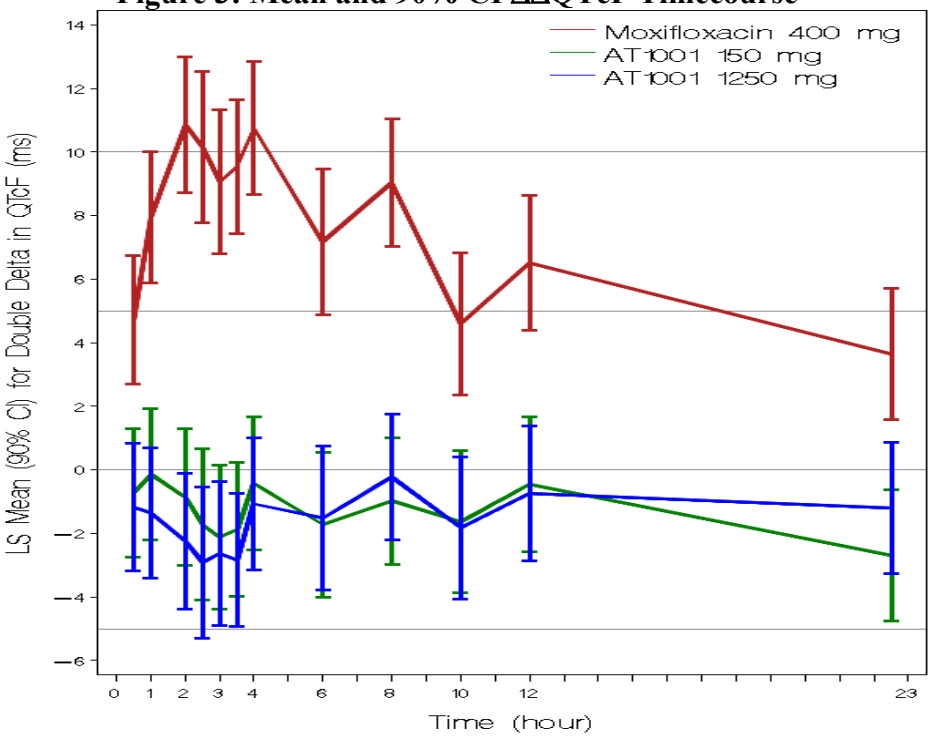
* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 4 time points around moxifloxacin C_{max}.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

(Note: CIs are all unadjusted including moxifloxacin)

Figure 3: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 9: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<=480 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	52	613	50 (96.2%)	598 (97.6%)	2 (3.8%)	15 (2.4%)
Placebo	51	611	49 (96.1%)	600 (98.2%)	2 (3.9%)	11 (1.8%)
Moxifloxacin 400 mg	51	612	47 (92.2%)	582 (95.1%)	4 (7.8%)	30 (4.9%)
AT1001 150 mg	51	612	49 (96.1%)	601 (98.2%)	2 (3.9%)	11 (1.8%)
AT1001 1250 mg	52	623	50 (96.2%)	616 (98.9%)	2 (3.8%)	7 (1.1%)

Table 10 lists the categorical analysis results for ΔQTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 10: Categorical Analysis of ΔQTcF

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Placebo	51	611	51 (100%)	611 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	51	612	50 (98.0%)	609 (99.5%)	1 (2.0%)	3 (0.5%)
AT1001 150 mg	51	612	51 (100%)	612 (100%)	0 (0.0%)	0 (0.0%)
AT1001 1250 mg	52	623	52 (100%)	623 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 11. The largest upper limits of 90% CI for the HR mean differences between AT1001 150 mg and placebo and AT1001 1250 mg and placebo were 3.1 bpm and 3.8 bpm, respectively.

The outlier analysis results for HR are presented in Table 12.

Table 11: Analysis Results of ΔHR and ΔΔHR

	AT1001 150 mg (N=51)			AT1001 1250 mg (N=52)		
	ΔHR (bpm)		ΔΔHR (bpm)	ΔHR (bpm)		ΔΔHR (bpm)
Time (hour)	**LSmean**	**LSmean Placebo**	**LSmean (90% CI)**	**LSmean**	**LSmean Placebo**	**LSmean (90% CI)**
0.5	-0.9	0.1	-1.0 (-2.3, 0.3)	-0.4	0.1	-0.5 (-1.8, 0.7)
1	-1.5	0.1	-1.6 (-3.0, -0.1)	0.1	0.1	-0.0 (-1.5, 1.4)
2	-2.3	-1.1	-1.3 (-2.6, 0.1)	-2.0	-1.1	-1.0 (-2.3, 0.4)
2.5	-1.2	0.3	-1.5 (-2.8, -0.1)	-0.6	0.3	-0.9 (-2.2, 0.5)
3	-0.9	0.3	-1.2 (-2.5, 0.2)	-0.6	0.3	-0.9 (-2.2, 0.5)
3.5	-0.1	-0.7	0.5 (-0.9, 1.9)	-0.3	-0.7	0.4 (-1.0, 1.8)
4	0.5	1.8	-1.3 (-2.9, 0.3)	0.9	1.8	-0.9 (-2.5, 0.7)
6	8.4	9.4	-1.0 (-3.0, 0.9)	10.1	9.4	0.7 (-1.3, 2.6)
8	5.1	3.8	1.2 (-0.6, 3.1)	5.8	3.8	1.9 (0.1, 3.8)
10	9.3	9.1	0.3 (-1.4, 1.9)	10.3	9.1	1.3 (-0.4, 2.9)

	AT1001 150 mg (N=51)			AT1001 1250 mg (N=52)		
	ΔHR (bpm)		ΔΔHR (bpm)	ΔHR (bpm)		ΔΔHR (bpm)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
12	6.7	6.6	0.1 (-1.7, 1.9)	7.3	6.6	0.7 (-1.1, 2.4)
22.5	2.7	3.1	-0.4 (-2.1, 1.2)	3.1	3.1	-0.0 (-1.7, 1.7)

Table 12: Categorical Analysis for HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline	52	52 (100%)	0 (0.0%)	44 (84.6%)	8 (15.4%)
Placebo	51	51 (100%)	0 (0.0%)	46 (90.2%)	5 (9.8%)
Moxifloxacin 400 mg	51	50 (98.0%)	1 (2.0%)	47 (92.2%)	4 (7.8%)
AT1001 150 mg	51	51 (100%)	0 (0.0%)	43 (84.3%)	8 (15.7%)
AT1001 1250 mg	52	52 (100%)	0 (0.0%)	45 (86.5%)	7 (13.5%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 13. The largest upper limits of 90% CI for the PR mean differences between AT1001 150 mg and placebo and AT1001 1250 mg and placebo were 3.2 ms and 4.7 ms, respectively.

The outlier analysis results for PR are presented in Table 14.

Table 13: Analysis Results of ΔPR and ΔΔPR

	AT1001 150 mg (N=51)			AT1001 1250 mg (N=52)		
	ΔPR (ms)		ΔΔPR (ms)	ΔPR (ms)		ΔΔPR (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.5	-0.5	0.3	-0.7 (-2.4, 0.9)	0.3	0.3	0.1 (-1.6, 1.7)
1	-1.5	-1.8	0.3 (-1.7, 2.3)	0.9	-1.8	2.7 (0.7, 4.7)
2	-0.8	-0.3	-0.6 (-2.4, 1.3)	-0.1	-0.3	0.1 (-1.7, 2.0)
2.5	-1.5	-0.7	-0.7 (-2.5, 1.0)	-0.6	-0.7	0.1 (-1.6, 1.8)

	AT1001 150 mg (N=51)			AT1001 1250 mg (N=52)		
	ΔPR (ms)		ΔΔPR (ms)	ΔPR (ms)		ΔΔPR (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
3	-1.2	-1.5	0.2 (-1.7, 2.2)	-0.6	-1.5	0.9 (-1.0, 2.8)
3.5	-1.5	-1.9	0.4 (-1.5, 2.3)	-0.6	-1.9	1.3 (-0.6, 3.2)
4	-2.8	-0.9	-1.9 (-4.1, 0.3)	-0.8	-0.9	0.1 (-2.1, 2.3)
6	-6.1	-4.6	-1.5 (-4.2, 1.2)	-4.6	-4.6	-0.1 (-2.7, 2.6)
8	-4.3	-5.3	1.0 (-1.2, 3.2)	-4.8	-5.3	0.5 (-1.7, 2.7)
10	-4.5	-4.2	-0.4 (-2.7, 1.9)	-5.3	-4.2	-1.1 (-3.4, 1.2)
12	-3.1	-3.0	-0.0 (-2.2, 2.2)	-2.8	-3.0	0.3 (-1.9, 2.5)
22.5	-3.1	-0.6	-2.5 (-4.8, -0.2)	-0.6	-0.6	-0.1 (-2.4, 2.2)

Table 14: Categorical Analysis for PR

	Total N		PR<=200 ms		200<PR<=220 ms		PR>220 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	52	613	50 (96.2%)	600 (97.9%)	2 (3.8%)	13 (2.1%)	0 (0.0%)	0 (0.0%)
Placebo	51	611	50 (98.0%)	607 (99.3%)	1 (2.0%)	4 (0.7%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	51	612	49 (96.1%)	601 (98.2%)	1 (2.0%)	10 (1.6%)	1 (2.0%)	1 (0.2%)
AT1001 150 mg	51	612	50 (98.0%)	603 (98.5%)	1 (2.0%)	9 (1.5%)	0 (0.0%)	0 (0.0%)
AT1001 1250 mg	52	623	50 (96.2%)	612 (98.2%)	2 (3.8%)	11 (1.8%)	0 (0.0%)	0 (0.0%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 15. The largest upper limits of 90% CI for the QRS mean differences between AT1001 150 mg and placebo and AT1001 1250 mg and placebo were 0.6 ms and 0.2 ms, respectively.

The outlier analysis results for QRS are presented in Table 16.

Table 15: Analysis Results of ΔQRS and ΔΔQRS

	AT1001 150 mg (N=51)			AT1001 1250 mg (N=52)		
	ΔQRS (ms)		ΔΔQRS (ms)	ΔQRS (ms)		ΔΔQRS (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.5	0.1	0.1	0.0 (-0.4, 0.5)	-0.1	0.1	-0.2 (-0.7, 0.2)
1	-0.1	0.3	-0.4 (-0.9, 0.1)	-0.4	0.3	-0.7 (-1.2, -0.2)
2	0.3	0.3	0.0 (-0.5, 0.6)	-0.5	0.3	-0.8 (-1.3, -0.2)
2.5	0.0	0.2	-0.2 (-0.7, 0.4)	-0.6	0.2	-0.9 (-1.4, -0.3)
3	-0.4	0.1	-0.5 (-1.0, 0.1)	-0.2	0.1	-0.4 (-0.9, 0.2)
3.5	-0.3	0.3	-0.6 (-1.1, -0.0)	-0.8	0.3	-1.1 (-1.6, -0.5)
4	-0.4	-0.0	-0.4 (-1.0, 0.2)	-0.8	-0.0	-0.8 (-1.4, -0.2)
6	-0.0	0.7	-0.7 (-1.5, 0.0)	-0.5	0.7	-1.2 (-1.9, -0.4)
8	-0.9	0.0	-1.0 (-1.6, -0.3)	-0.7	0.0	-0.7 (-1.4, -0.0)
10	-0.7	-0.2	-0.5 (-1.3, 0.3)	-1.0	-0.2	-0.8 (-1.6, 0.0)
12	-0.4	-0.1	-0.3 (-1.0, 0.5)	-0.7	-0.1	-0.6 (-1.4, 0.2)
22.5	0.1	0.6	-0.5 (-1.3, 0.2)	0.1	0.6	-0.6 (-1.3, 0.2)

Table 16: Categorical Analysis for QRS

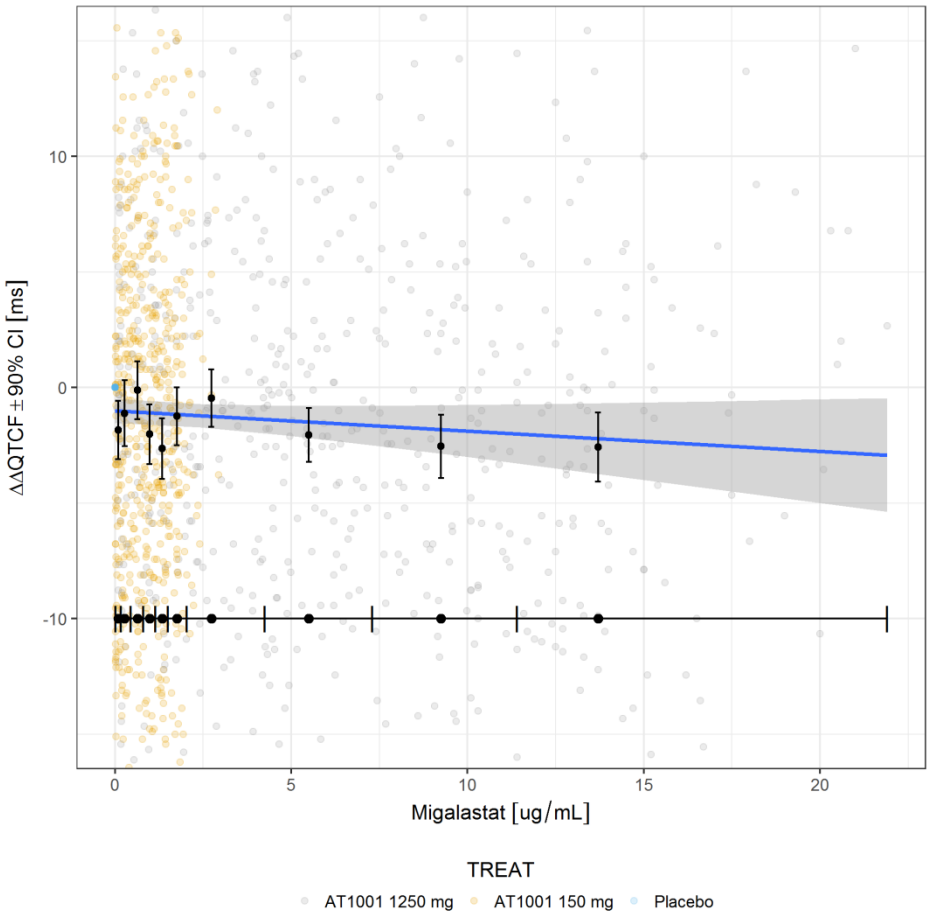
	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	52	613	52 (100%)	613 (100%)	0 (0.0%)	0 (0.0%)
Placebo	51	611	51 (100%)	611 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	51	612	51 (100%)	612 (100%)	0 (0.0%)	0 (0.0%)
AT1001 150 mg	51	612	51 (100%)	612 (100%)	0 (0.0%)	0 (0.0%)
AT1001 1250 mg	52	623	51 (98.1%)	622 (99.8%)	1 (1.9%)	1 (0.2%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

Exposure-response Relationship

The concentration-QTc relationship was investigated using the recommended prespecified linear mixed-effects model. The slope estimate from the model was -0.088 ms per µg/mL (p=0.2). The relationship is visualized in Figure 4 with no statistically significant positive slope for exposure-response relationship. Mean predicted ΔΔQTcF at the geometric mean C_{max} (12651 ng/mL) of migalastat for the supratherapeutic dose (1250 mg) is -2.1 ms with upper bound of 90% CI of -0.7 ms. The upper bound is well below the 10 ms regulatory threshold.

Figure 4: ΔΔQTcF vs. Migalastat concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There are no clinically relevant effects on PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen: 150 mg QOD Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose: Cmax 1700 (27.4) ng/mL and AUC 10,806 (24.7) ng*h/mL Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen: Cmax 1180 (32.9) ng/mL and AUC 9033 (35.1) ng*h/mL	
Maximum tolerated dose	Include if studied or NOAEL dose: 1500 mg/kg/day	
Principal adverse events	Include most common adverse events; dose limiting adverse events: Most Common AEs (≥ 10%) at 150 mg QOD: Headache (35.1%), Nasopharyngitis (31.3%), Diarrhea (23.1%), Abdominal Pain (22.4%), Nausea (19.4%), Urinary Tract Infection (17.9%), Back Pain (16.4%), Cough (14.9%), Vomiting (14.2%), Pyrexia (12.7%). Dose limiting adverse events are Headache and dizziness were the most common adverse reactions reported at doses of migalastat of up to 1250 mg and 2000 mg, respectively.	
Maximum dose tested	Single Dose	Specify dose: 2000 mg
	Multiple Dose	Specify dosing interval and duration: 250 mg BID
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC: Cmax 13844 (42.0) ng/mL and AUC 73838 (27.0)
	Multiple Dose	Mean (%CV) Cmax and AUC: Cmax 2185 (33.6) and AUC 12244 (26.0)
Range of linear PK	Specify dosing regimen: 50 mg to 1250 mg	
Accumulation at steady state	Mean (%CV); specify dosing regimen: no significant accumulation at 150 mg BID	
Metabolites	Include listing of all metabolites and activity: 3 O-glucuronides, M1, M2, and M3, comprising 5%, 2%, and 6% of sample radioactivity. Activity unknown	
Absorption	Absolute/Relative Bioavailability	Mean (%CV): Absolute BA = 74.6%; Relative BA = 99%
	Tmax	• Median (range) for parent: 3h (1h – 6h) • Median (range) for metabolites: N/A
Distribution	Vd/F or Vd	Mean (%CV): 70.2 (32.7) L
	% bound	Mean (%CV): none detectable

Elimination	Route	• Primary route; percent dose eliminated: renal; 77% • Other routes: Feces: 20%
	Terminal t½	• Mean (%CV) for parent: 3.8h • Mean (%CV) for metabolites: N/A
	CL/F or CL	Mean (%CV): 12.5 (26.8) L/h
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC: No clinically relevant difference between young and elderly
	Sex	Specify mean changes in Cmax and AUC: No clinically relevant difference between genders
	Race	Specify mean changes in Cmax and AUC: No clinically relevant difference between Caucasian and Japanese
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC: Renal impairment: no change in Cmax from normal renal function; 1.2-, 1.8-, and 4.5-fold increases in AUC for mild, moderate, and severe renal impairment groups; hepatic impairment study not performed
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC: No DDI studies performed
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat): Cmax decreased by 15% and 39% for high-fat and low-fat meals, respectively; AUC decreased by 37% and 40% for high-fat and low-fat meals, respectively
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose: The worst case scenario in exposure to the supra-therapeutic dose is Cmax 12579 (29.6) ng/mL and AUC 72165 (27.1) ng*h/mL for supra-therapeutic dose of 1250 mg; this represents a 7.4 fold increase and 6.7 fold increase, respectively to the therapeutic dose of 150mg.	
Preclinical Cardiac Safety	Summarize *in vitro* and *in vivo* results per S7B guidance: No QT-interval or cardiac events reported for preclinical safety	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures,	

	ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths): The comprehensive clinical development program for migalastat for the treatment of Fabry disease was comprised of 20 studies: ten Phase 1 studies, one Phase 2a drug-drug interaction (DDI) study, five Phase 2 studies, two Phase 3 studies, and two Phase 3 open-label, long-term extension studies. As of the safety data cut-off date of 10 February 2017, 386 subjects have been exposed to any dose of migalastat (including 194 healthy subjects and 24 subjects with renal impairment in Phase 1 studies and 168 subjects with Fabry disease in Phase 2 and Phase 3 studies). A total of 160 subjects received migalastat monotherapy in Phase 2 and Phase 3 studies (ISS Table 4.2.1, ISS TLF Part 1 in Module 5.3.5.3). A total of 123 clinical trial subjects with Fabry disease have been exposed to migalastat hydrochloride (HCl) 150 mg *quaque altera die* (QOD; once every other day) for at least one year (ISS Table 3.2.1, ISS TLF Part 1 in Module 5.3.5.3.). For information on the doses used in each study, and the number of patients who received each dose, please see module 2.7.4 Table 1 and Table 2. The TQT study AT1001-010 (designed in compliance with ICH E14) demonstrated that migalastat was negative for effects on cardiac repolarization at clinical and supra-therapeutic doses. In the AT1001-010, fifty-two subjects, 26 males and 26 females, were randomly assigned to receive four dose groups in one of four treatment sequences; fifty-one subjects completed (25 males and 26 females). More details can be found in the AT1001-010 CSR (Module 5.3.4.1). As the TQT study showed no effect on QT/QTc prolongation, no separate tabular summaries of cardiac AEs were prepared. All cardiac AEs are presented by SOC and PT in the Integrated Safety tables (please see the last column of ISS Table 4.3.2 (Module 5.3.5.3) for migalastat only and for a comparison to placebo ISS Table 1.3.2 (Module 5.3.5.3). For phase 1 studies please refer to the corresponding outputs in the individual CSRs.

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/s/

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03/19/2018

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03/20/2018

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February13, 2018

To: Donna Griebel, M.D., Director
Division of Gastroenterology and Inborn Errors Products (DGEIP)

Through: Dominic Chiapperino, Acting Director
Martin Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Silvia N. Calderon Ph.D., Senior Pharmacologist
Controlled Substance Staff

Subject: NDA 208623, Galafold (migalastat Hydrochloride) oral capsules
Indication: For the treatment of patients with Fabry disease with amenable mutations.
Dosages: 150 mg oral capsules (123 mg as a free base), one capsule every other day at the same time of the day.
Sponsor: Amicus Therapeutics

Materials reviewed: NDA 208623 for filing purposes.
IND 68456, Nonclinical review (DARRTS, IND 68456, Yao, Da Lin, 7/27/2004).

I. Background

This memorandum is in response to a consult request dated December 23, 2017, from the Division of Gastroenterology and Inborn Errors Products (DGEIP) pertaining the fileability of NDA 208623, Galafold oral capsules, and in lieu of a filing checklist.

Chemically, migalastat is the nonproprietary name given to the drug substance, (+)-(2R,3S,4R,5S)-2-(hydroxymethyl)piperidine-3,4,5-triol. Migalastat is formulated in the proposed drug product as the hydrochloride salt, and the salt is also known by the code name of AT1001 and by the more general name of 1-deoxygalactonojirimycin (DGJ) hydrochloride.

A drug may have abuse potential if the drug has central nervous system (CNS) activity, if it is chemically or pharmacologically similar to other known drugs of abuse, or if the drug produces psychoactive effects that may be indicative of a potential for abuse such as mood or cognitive changes (e.g., euphoria, hallucinations).

II. Conclusions

1. There is no need to further evaluate the potential for abuse of migalastat, based on the following:
   a. In the Irwin test, oral doses of 3 mg/kg, 30 mg/kg, and 100mg/kg in rats did not produce changes in CNS functions such as spontaneous activity, excitability, and sensory motor functions (DARRTS, IND 68456, Yao, Da Lin, 7/27/2004, non-clinical review).
   b. Migalastat is not chemically or pharmacologically related to other drugs of abuse.
   c. Based on the Sponsor's proposed label, the most common adverse drug reactions of migalastat are headache, nasopharyngitis, (b) (4), (b) (4), nausea, urinary tract infection, (b) (4) (b) (4) (b) (4) and pyrexia.

III. Recommendations to the Division

Based on the properties of migalastat described above, we believe that CSS need not be involved in the review of this NDA. Consequently, CSS will not submit a filing checklist for NDA 208263.

CSS requests that the Division consult CSS if the DGIEP review team identifies any abuse-related concerns associated with the drug through the course of their review of this NDA.

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/s/

SILVIA N CALDERON
02/13/2018

MARTIN S RUSINOWITZ
02/13/2018

DOMINIC CHIAPPERINO
02/13/2018

REVIEW MEMORANDUM

Date:	January 30, 2018
Received:	January 22, 2018
To:	Hong Vu, Pharm. D., M.S., CDER/OND/ODEIII/DGIEP
From:	Jessica Chu, Ph.D., CDRH/OIR/DCTD
Through:	Paula Caposino, Ph.D., CDRH/OIR/DCTD
Subject:	CDER consult request ICCR2018-02200 for NDA 208623
CDRH Tracking #:	ICC1800083
Drug Sponsor:	Amicus Therapeutics
Drug Name:	Galafold (Migalastat Hydrochloride)

A. Consult request

The following request was made by CDER/OND/ODEIII/DGIEP:

"On 12/13/2017, the Division of Gastroenterology and Inborn Errors Products (DGIEP) within CDER received an original NDA submission for Galafold (migalastat HCl) for the treatment of Fabry disease with amenable mutations.

DGIEP is seeking input from OIR on the GLA genotyping tests that are commercially available (e.g., Sanger sequencing and Next-generation sequencing) and its use in clinical trial.

In the NDA submission, the sponsor referenced a meeting held with OIR on 4/19/2013 in which they sought clarification that a GLA genotyping assay is not needed as a companion diagnostic for use with migalastat capsules. The sponsor also referenced their written correspondence to OIR dated 7/1/2015 providing follow up information on the GLA genotyping assay.

Therefore, DGIEP is consulting OIR on whether the sponsor's additional information/data submitted in 2015, as well as any other information, are satisfactory and that the sponsor does not need approval for a companion diagnostic for the marketing of migalastat (primarily focusing on the GLA genotyping assays used commercially to identify Fabry patient mutations). If it is not satisfactory, please advise on what additional information OIR would need from the sponsor in order to make a determination. To clarify, we are referring to the genotyping assay used in the clinical trials and the GLA genotyping assays available commercially in labs in the U.S. that identify the patients' mutations."

B. Background

- April 19, 2013: OIR, CDER and Amicus Therapeutics met for an OIR-led pre-submission meeting (b) (4) regarding the development of a companion diagnostic for use with Migalastat HCl. During the discussion, OIR indicated that if the majority of Fabry patients have GLA genotyping performed as part of the standard of care and practice guidelines, then a GLA genotyping companion diagnostic may not be necessary. OIR indicated that the sponsor would have to document the overall genotyping rate in Fabry patients as part of the diagnostic workup for newly diagnosed patients and patients diagnosed a long time ago. Additionally, the information regarding the frequency of genotyping and current clinical practice should be from the U.S. and from all clinical settings that may manage Fabry patients (i.e., not just expert centers).

- July 1, 2015: OIR received a follow up letter to Q130196 from Amicus Therapeutics. In the letter and supporting information, Amicus Therapeutics asserted that GLA genotyping is routinely performed in the majority of patients with Fabry disease. This was based on a prospective U.S. survey study assessing rates of GLA molecular testing as recommended by expert diagnostic guidelines conducted by (b) (4) (b) (4). The survey results for 12 U.S. centers and 670 total patients indicated that > 90% of patients are routinely genotyped in the U.S. Additionally, the sponsor indicated a change of Fabry disease diagnostic clinical practice with the increased ease of performing GLA molecular testing for Fabry disease. A copy of this information was also submitted separately to IND 68456.

- September 4, 2015: OIR provided a consulting review to CDER for IND 68456 regarding a question asked as part of a sponsor pre-NDA meeting request. The sponsor specifically asked in Question 2: "Does the Division agree that the current standard of care in the U.S. includes reliable determination of GLA genotype in Fabry patients, and that PMA approval of a new companion diagnostic genotyping assay is not required?" OIR provided the following comments to CDER regarding this question: "Sequencing of the GLA gene is routine as part of the diagnostic workup for Fabry. In this scenario, CDRH is not in a strong position to require a companion diagnostic submission for the selection of patients with specific GLA-mutations. We defer to CDER on this question and CDRH does not object if CDER determines that a companion diagnostic is not required."

- September 9, 2015: CDER, OIR and Amicus Therapeutics met for a CDER-led pre-NDA meeting to discuss and agree on the format of the nonclinical and clinical sections of the NDA for Galafold. FDA had sent preliminary comments to Amicus Therapeutics on September 8, 2015. As captured in CDER's memorandum of meeting minutes, page 5, FDA stated that "FDA agrees that sequencing of the GLA gene is part of the diagnostic workup for Fabry disease, and that a companion diagnostic may not be required."

C. Comments to CDER

Based on the above discussions with the sponsor and feedback provided by OIR to CDER in September 2015, OIR understands that sequencing of the GLA gene is part of the standard diagnostic workup for Fabry disease. Therefore, a companion diagnostic GLA genotyping assay to identify Fabry patients' "amenable" mutations may not be required for the marketing of migalastat.

Jessica Chu -S
2018.01.30
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Jessica Chu, Ph.D.
Scientific Reviewer
CDRH/OIR/DCTD

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/s/

HONG VU
02/08/2018
I am signing this review memo from CDRH on behalf of Jessica Chu.