CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210656Orig1s000

OTHER REVIEW(S)

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:	November 19, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 210656
Product Name and Strength:	Daurismo (glasdegib) tablets, 25 mg, 100 mg
Applicant/Sponsor Name:	Pfizer, Inc.
FDA Received Date:	November 13, 2018
OSE RCM #:	2018-890-2
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised container label for Daurismo (Appendix A) to determine if it is acceptable from a medication error perspective. The revised container label was submitted to the NDA because there was a revision to the National Drug Code (NDC) number for the 100 mg strength by the Applicant. We note, that there was no change to NDC number of the 25 mg strength, and therefore the container label remains unchanged since our last review.[a]

2 CONCLUSION

The revised container label for the 100 mg strength of Daurismo is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Garrison N. Label and Labeling Review for DAURISMO (NDA 210656). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 10. RCM No.: 2018-890-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 13, 2018

Container label

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/s/

NICOLE B GARRISON
11/19/2018

HINA S MEHTA
11/19/2018

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:	October 10, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 210656
Product Name and Strength:	Daurismo (glasdegib) tablets, 25 mg, 100 mg
Applicant/Sponsor Name:	Pfizer, Inc.
FDA Received Date:	August 31, 2018 and September 10, 2018
OSE RCM #:	2018-890-1
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised container labels for Daurismo (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.[a] We note the Applicant requested to maintain the proposed language for the Dosage and Use statement as the 21 CFR 201.55 does not mandate specific language on container label when referencing the package insert for dosage.

2 CONCLUSION

We find the revised container labels for Daurismo are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Garrison N. Label and Labeling Review for DAURISMO (NDA 210656). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 20. RCM No.: 2018-890.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 10, 2018

Container labels

(b) (4)

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/s/

NICOLE B GARRISON
10/10/2018

HINA S MEHTA
10/10/2018

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:	September 17, 2018
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Lidoshore, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	DAURISMO (glasdegib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 210656
Applicant:	Pfizer, Inc.

1 INTRODUCTION

On April 27, 2018, Pfizer, Inc. submitted for the Agency's review an original New Drug Application (NDA) 210656 for DAURISMO (glasdegib) tablets. DAURISMO (glasdegib) is a New Molecular Entity (NME) with a proposed indication (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on June 14, 2018 and June 13, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for DAURISMO (glasdegib) tablets.

2 MATERIAL REVIEWED

- Draft DAURISMO (glasdegib) tablets MG received on April 27, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 4, 2018.
- Draft DAURISMO (glasdegib) tablets Prescribing Information (PI) received on April 27, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 4, 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.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is 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 MG 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 MG.

Please let us know if you have any questions.

5 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

RUTH I LIDOSHORE
09/17/2018

RACHAEL E CONKLIN
09/17/2018

BARBARA A FULLER
09/17/2018

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

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

Memorandum

Date: 09/14/18

To: Thomas Iype, Regulatory Project Manager, DHP

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, Team Leader, OPDP

Subject: OPDP Labeling Comments for DAURISMO (glasdegib) tablets, for oral use

NDA: 210656

In response to DHP's consult request dated June 13, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for DAURISMO (glasdegib) tablets, for oral use.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on August 31, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.

Section	Statement from Draft (if applicable)	OPDP Comment
14 Clinical Studies	"Improvement in OS was consistent across prespecified subgroups by cytogenetic risk."	Is this claim of consistency of effect supported by quantitative means? If not, OPDP recommends deleting this statement as it has implications for promotion of the drug.

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/s/

RACHAEL E CONKLIN
09/14/2018

Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	NDA 210656
Supporting Document Number	0
Proprietary Name **(nonproprietary name)**	DAURISMO (glasdegib)
Receipt Date	4/27/2018
PDUFA Goal Date **(Internal Goal Date)**	12/27/2018 (11/27/2018)
Review Classification	Priority
Proposed Indication (or current indication if unchanged)	Daurismo is a hedgehog pathway inhibitor (b) (4) [redacted]
Dosing Regimen	100 mg orally once daily
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

Documents Reviewed:

In this review, I propose labeling recommendations and edits in the DAURISMO labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of DAURISMO.

The following pages contain the working version of the DAURISMO labeling with my recommended edits and comments (identified as 'KV3' through 'KV47') and includes comments and edits from other review team members. Given that the scientific review of the labeling is ongoing, my labeling

recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the DAURISMO labeling.

22 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

VIRGINIA E KWITKOWSKI
09/13/2018

CLINICAL INSPECTION SUMMARY

Date	August 29, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Kelly Norsworthy, M.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Clinical Team Leader Thomas Iype, Regulatory Project Manager Division of Hematology Products
NDA	210656
Applicant	Pfizer, Inc.
Drug	glasdegib (PF-04449913)
NME	Yes
Therapeutic Classification/Status	oral Hedgehog inhibitor
Proposed Indication	(b) (4)
Consultation Request Date	May 8, 2018
Summary Goal Date	September 20, 2018 (CDER priority review)
Action Goal Date	November 27, 2018 (revised)
PDUFA Date	December 27, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Study B1371003 conducted by the sponsor (Pfizer, Inc.) was inspected in support of NDA 210656. The sponsor appeared to have adequate oversight and the study data, as reported by the sponsor to the NDA, are considered to be reliable in support of the requested indication.

The regulatory classification for the sponsor is Voluntary Action Indicated.

2. BACKGROUND

The Hedgehog (Hh) signaling pathway regulates cell differentiation and self-renewal in the developing embryo, but not in adult tissues. Aberrant Hedgehog signaling has been identified in human leukemia; specifically, upregulation of the Hedgehog pathway has been observed in acute myeloid leukemia (AML) stem cell lines. Inhibition of the Hedgehog pathway has been a strategy pursued in combination treatments for high-risk myelodysplastic syndrome and acute myeloid leukemias.

Glasdegib is an oral Hedgehog inhibitor proposed as combination chemotherapy with low-dose cytarabine [redacted] (b) (4)

Study B1371003

B1371003 is an ongoing Phase 1b to Phase 2, open-label, international, multi-center, safety and efficacy study of glasdegib in combination with intensive chemotherapy (cytarabine and daunorubicin), low dose Ara-C (LDAC), or decitabine in previously untreated patients with AML or high-risk MDS.

The primary objective was to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of PF-04449913 (glasdegib) in combination with low dose Ara-C (cladribine given in combination with low-dose cytarabine (LDAC), Arm A), decitabine (Arm B) or cytarabine/daunorubicin (Arm C) when administered to adults with previously untreated AML or high-risk MDS. Glasdegib was administered once daily (QD) and orally on a continuous basis for all patients. A cycle was defined as 28 days unless the cycle was prolonged due to toxicity.

The primary study endpoint (Phase 2) was Complete Response rate (P2 Fit) and Overall Survival (P2 Unfit), where: (A) P2 Unfit (Non-intensive) was defined as the efficacy of glasdegib in combination with LDAC assessed in a randomized, open-label cohort of LDAC with or without glasdegib in approximately 132 unfit patients, and (B) P2 Fit (Intensive) was defined as the efficacy of glasdegib in combination with cytarabine with daunorubicin was assessed in a single-arm cohort of approximately 70 fit patients.

The study was conducted at 21 centers in the United States (US), 2 centers in Canada, 10 centers in Germany, 3 centers in Poland, 8 centers in Spain, and 4 centers in Italy. The first subject's first visit was on June 25, 2012. The Primary Completion Date was on January 3, 2017. The study is ongoing for these 255 enrolled study patients.

3. RESULTS (by site):

Name of Sponsor Address	Protocol #/ # Subjects enrolled	Inspection Dates	Classification
Pfizer, Inc. 445 Eastern Point Rd. Groton, CT 06340	Study B1371003 255 total patients	June 11-21, 2018	VAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are 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. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Sponsor

1. Pfizer, Inc.

Records reviewed included but were not limited to: organizational charts; vendor list; vendor oversight plans; transfer of obligations; investigator agreements; financial disclosures; monitoring plans; monitoring reports; safety reports; adverse events; protocol deviations; and standard operating procedures. A total of 48 study sites world-wide participated. Three clinical sites with recurring issues noted during study conduct were selected from the investigator listings for review of monitoring reports and monitor qualifications, as chosen by ORA at random during Pfizer's inspection. No study sites were closed.

At the end of the inspection, a Form FDA 483 was issued due to failure to ensure proper monitoring of the study and ensure that the study was conducted according to the investigational plan. This List of Inspectional Observations was shared with the DHP. Specifically, from June 27, 2014 through April 2016, ongoing safety issues were noted consecutively in every monitoring visit at Site 1033 such as late Serious Adverse Event (SAE) reporting for four of eight subjects (ranging from 24 hours to seven days late), SAE follow up, and incomplete collection of SAE documentation. SAE reporting issues continued to occur despite escalation to Pfizer. The sponsor failed to ensure the site met compliance/protocol standards despite consecutive reports of late safety reporting and documentation concerns raised by the site monitor.

The sponsor responded to the Form FDA 483 adequately on July 12, 2018, with a corrective and preventive action plan. In addition to the site study monitor, the Pfizer Study Team took steps during the conduct of the study to improve timeliness of reporting of SAEs and conducted study-specific training focused on SAE reporting and related required follow-up actions at all sites. An ongoing continuous improvement project was implement in 2018 to enhance processes and procedures with respect to repeat noncompliance with requirements by study sites.

Despite the observation noted above regarding delayed reporting of SAEs, study monitor at the site detected, and was able to request documentation of the SAEs. Overall, it appears that the study site monitor and the sponsor were able to obtain necessary safety data. Data reliability for the study was not compromised.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}
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/s/

ANTHONY J ORENCIA
08/30/2018

JANICE K POHLMAN
08/30/2018

KASSA AYALEW
08/30/2018

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:	August 20, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 210656
Product Name and Strength:	Daurismo (glasdegib) tablets, 25 mg, 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Pfizer, Inc.
FDA Received Date:	April 27, 2018
OSE RCM #:	2018-890
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container labels and Prescribing Information (PI) for Daurismo (glasdegib) tablets, 25 mg and 100 mg (NDA 210656) for areas of vulnerability that could lead to medication errors. The Division of Hematology Products (DHP) requested this review as part of their evaluation of the 505(b)(1) submission for Daurismo (glasdegib) tablets.

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
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

Pfizer submitted a 505(b)(1) application to obtain marketing approval of Daurismo tablets. Daurismo is a hedgehog pathway inhibitor (b) (4) Daurismo will be supplied as 25 mg and 100 mg tablets. The recommended dose is 100 mg once daily; however, dose modifications may be required based on individual safety and tolerability to 50 mg once daily.

We performed a risk assessment of the proposed container labels and PI for Daurismo (glasdegib) to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we recommend replacing symbols with their intended meaning. For the Applicant, we recommend changes to the container labels to improve readability and prominence of important information. Specifically, we recommend differentiation between the product's

strengths, revision of the usual dosage statement, and defining the format of the expiration date on the labeling.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the labels to promote the safe use of the product. We provide recommendations below in Section 4.1 and Section 4.2 to address our concerns. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    1. Dosage and Administration
        a. In Section 2.1, revise the last paragraph on missed doses to increase clarity and remove unnecessary information. We recommend revising to "If a dose of DAURISMO is missed, take as soon as possible unless more than 10 hours have passed. Do not take 2 doses of DAURISMO at the same time to make up for the missed dose."
        b. In Section 2.1, include the following statement, "Do not cut, crush, or chew the tablets." We recommend this to mitigate the risk of administration errors.
    2. Warnings and Precautions Section
        a. In Section 5.2, replace the symbol, ">" with the intended meaning "greater than" to prevent misinterpretation and confusion.
    3. Use in Specific Populations
        a. In Section 8.1 *Pregnancy* and Section 8.4 *Pediatric Use*, replace the symbol "≥" with the intended meaning "greater than or equal to" to prevent misinterpretation and confusion.
    4. Nonclinical Toxicology
        a. In Section 13.1 *Carcinogenesis, Mutagenesis, Impairment of Fertility*, replace the symbol "≥" with the intended meaning "greater than or equal to" to prevent misinterpretation and confusion.

4.2 RECOMMENDATIONS FOR PFIZER, INC.

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

A. Container Labels

(b) (4)


(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Daurismo received on April 27, 2018 from Pfizer, Inc.

Table 2. Relevant Product Information for Daurismo	
Initial Approval Date	N/A
Active Ingredient	Glasdegib
Indication	(b) (4) [redacted]
Route of Administration	Oral
Dosage Form	Tablets
Strength	25 mg, 100 mg
Dose and Frequency	The recommended dose of Daurismo is 100 mg taken orally once daily in combination with low-dose cytarabine. Dose modifications may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of Daurismo should be reduced to 50 mg taken orally once daily.
How Supplied	Daurismo is supplied as: • 30 count bottle with 100 mg tablets • 60 count bottle with 25 mg tablets
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).
Container Closure	Daurismo will be packaged in high-density polyethylene (HDPE) bottle (b) (4) [redacted]

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 23, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Daurismo. Our search did not identify any previous reviews.

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,[a] along with postmarket medication error data, we reviewed the following Daurismo labels and labeling submitted by Pfizer, Inc.

- Container labels received on April 27, 2018
- Medication Guide received on April 27, 2018
- Prescribing Information (Image not shown) received on April 27, 2018

G.2 Label and Labeling Images

Container labels

(b) (4)

Medication Guide and Prescribing Information

Application 210656 - Sequence 0001 - 1.14.1.2 Annotated Draft Labeling Text -

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

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/s/

NICOLE B GARRISON
08/20/2018

HINA S MEHTA
08/22/2018

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

IND or NDA	NDA 210656
Brand Name	DAURISMO
Generic Name	Glasdegib (PF-04449913)
Sponsor	Pfizer, Inc.
Indication	(b) (4)
Dosage Form	Film-coated tablet, 25 mg and 100 mg
Drug Class	Inhibitor of smoothened (SMO), a key protein in the hedgehog (Hh) pathway
Therapeutic Dosing Regimen	100 mg QD (in combination with low-dose cytarabine)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	400 mg QD in advanced hematological malignancies; 320 mg QD in advanced solid tumors
Submission Number and Date	SDN 001; 27 Apr 2018
Review Division	DHP

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

A QTc prolongation effect of glasdegib (single dose of 150 mg and 300 mg) was detected in the TQT Study B1371023 and the effect was dose-/concentration-dependent. The largest upper bounds of the 2-sided 90% CI for the mean difference between glasdegib (150 mg and 300 mg) and placebo were above 10 ms (Table 1). These findings are consistent with the preclinical studies and suggests that glasdegib prolongs the QTc interval via inhibition of the hERG potassium channel.

In this randomized, blinded, four-period crossover study, 36 healthy male subjects were randomized to receive a single dose of glasdegib 150 mg, glasdegib 300 mg, placebo, and a single oral dose of moxifloxacin 400 mg. 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 1, indicating that assay sensitivity was established. 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 Glasdegib (150 mg and 300 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	LS Mean ΔΔQTcF (ms)	90% CI (ms)
Glasdegib 150 mg single dose	4	8.0	(5.8, 10.2)
Glasdegib 300 mg single dose	3	13.4	(11.2, 15.6)
Moxifloxacin 400 mg*	3	13.9	(11.7, 16.0)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 3 timepoints was 11.1 ms.

A single 150 mg dose of glasdegib in this study represents the steady state exposure observed with the intended clinical dose of 100 mg QD. The supratherapeutic dose (300 mg) produces mean C_{max} which is 2.1-fold (2218 vs. 1071 ng/mL) of that with 150 mg dose and it covers the predicted worst case scenario exposure (increase in C_{max} by 1.4-fold and increase in AUC by 2.4-fold due to CYP3A4 inhibition).

1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

Question from the Division: The TQT study is identified as Study B1371023, and in Section 6.2 of the ISS there is a cross-study analysis of the clinical cardiac conduction abnormalities. Please assess the potential clinical impact of glasdegib on cardiac repolarization. Please assess the proposed text in Sections 5.2 and 12.2 of the Prescribing Information.

QT-IRT's response:

Glasdegib prolongs the QTc interval in a dose/concentration-dependent manner; however, the mean QTc increase at the high clinical exposure scenario is less than 20 ms. Nonclinical data shows that glasdegib inhibits the hERG potassium channel and prolongs the QTc interval in dogs.

Patients in clinical trials experienced QTc prolongation. In the S1 cohort of study B1371013, 5 (6%) patients in the glasdegib 100 mg + LDAC arm and 2 (12%) in the LDAC arm had QTcF values >500 ms. In the glasdegib + LDAC arm, 3 of the 5 patients also had an increase from baseline >60 ms. These cases are confounded by other risk factors that could also prolong the QTc interval such as concomitant use of other QT prolonging drugs or CYP3A4 inhibitors, and the presence of electrolyte abnormalities.

Because glasdegib prolongs the QTc interval, we suggest that the findings of the thorough QT study are described in section 12.2 (Phamacodynamics) and the potential risk for patients taking CYPA3 inhibitors and other QT prolongers are described in section 5.2 (Warnings and Precautions). Our specific comments on the proposed QT-language in the label are presented below.

2 PROPOSED LABEL

The sponsor included the following QT-related language in their current proposed label. The QT-IRT's suggested edits are shown in red on top of the sponsor's proposal. The QT-IRT's proposed labeling language is a suggestion only and we defer final labeling decisions to the Division.

Reviewer's comments: The proposal is acceptable.

5.2 QT Interval Prolongation

(b) (4)

Reviewer's comments: We do not agree (b) (4)

(b) (4)

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of glasdegib administration on corrected QT interval (QTc) was evaluated in a randomized, single-dose, double-blind, 4-way crossover, placebo- and open-label moxifloxacin-controlled study in 36 healthy subjects. At therapeutic plasma concentrations (b) (4)

(b) (4)

Reviewer's comments: We recommend keeping the results of the thorough QT study because it was designed to characterize the effects of glasdegib on the QTcF interval.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Glasdegib is an inhibitor of SMO, a key protein in the hedgehog (Hh) pathway. Glasdegib is being developed for the treatment of patients with AML (b) (4) As an inhibitor of the Hh signaling pathway, glasdegib may act as an anti-leukemic stem cell agent. Two other SMO inhibitors (vismodegib and sonidegib) have been approved

for advanced basal cell carcinoma but, unlike glasdegib, they have not been shown to be effective against myeloid malignancies.

3.2 MARKET APPROVAL STATUS

Glasdegib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Glasdegib was evaluated in-vitro for its effect on binding to the Human Ether-à-go-go-Related Gene (hERG) potassium channel stably expressed in human embryonic kidney cells 293(HEK-293). The hERG half maximal inhibitory concentration (IC_{50}) for glasdegib was 3.1 μM, which was approximately 14-fold above the projected human free efficacious maximum observed plasma concentration within the dosing interval (C_{max}) at the 100 mg dose (215 nM).

In vivo, in conscious telemeterized dogs at dose levels of 5 (maximum tolerated dose [MTD]) and 30 mg/kg, glasdegib produced a statistically significant and dose-dependent increase in the time from the beginning of the Q wave to the end of the T wave corresponding to electrical systole (QT) and QT interval corrected for heart rate (QTc) normalized to 75 beats per minute (bpm) (QTc^{75}) which was apparent up to at least 14 hours post-dosing. The maximum observed QTc^{75} prolongation was 5 and 24 milliseconds (msec) at 5 and 30 mg/kg, respectively. There were no statistical or remarkable changes in dogs treated with 1 mg/kg glasdegib. At 5 mg/kg, the Day 1 free plasma concentration in male dogs was 420 ng/mL (from the 1-month dogs). This represented a >4-fold margin above the projected free Cmax (about 100 ng/mL) at the clinical dose of 100 mg.

Reviewer's Comment: A hERG safety margin of 14x was observed in the in vitro hERG assay, which suggests a possibility for direct inhibition of hERG. Additionally, a QTc effect was observed in the dog study at the 5 and 30 mg/kg dose levels.

3.4 CLINICAL EXPERIENCE

Based on the B1371001 Phase 1 study in hematology cancer patients, 400 mg once daily (QD) of glasdegib was determined to be the MTD. A Phase 1 study (B1371002) in solid tumor patients determined the MTD to be 320 mg QD. The clinical dose for glasdegib was 100 mg QD. QT interval prolongation with glasdegib treatment was observed in the Phase 1 program, mainly at doses of glasdegib >100 mg (doses >270 mg QD), and was considered an adverse drug reaction for glasdegib. In Study B1371003, glasdegib 100 mg QD was administered in combination with chemotherapy in patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). At a dose of 100 mg glasdegib QD cases of QTc using Fridericia's formula (QTcF) prolongations >500 msec or change in QTcF >60 msec from baseline occurred in settings of multiple confounders. Therefore, this current study (B1371023) aimed to estimate the potential of glasdegib, at therapeutic and supra-therapeutic exposures, to affect cardiac repolarization.

A preliminary analysis was conducted to provide characterization of exposure-response relationship between QTc and glasdegib plasma concentration values in patients with advanced cancer. Pooled data from 2 open-label Phase 1 studies (B1371001 and B1371002) in 70 patients with advanced cancer (dose range of 5-640 mg QD), where both electrocardiograms (ECGs) and PK samples were collected, were used for analysis.

The analysis showed that the slope describing the QTcF-concentration relationship was positive (4.297 msec per 1,000 ng/mL increase in glasdegib plasma concentration) and the mean predicted change in the QTc interval at the mean Cmax of the therapeutic dose was 5.30 msec, which would be the anticipated QTc change for the 150 mg single dose with an approximate doubling at a single dose of 300 mg.

As of 15 July 2015, glasdegib had been administered chronically to over 300 advanced cancer patients in Pfizer sponsored clinical trials at doses ranging from 5 - 640 mg per day.

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 105453 on 23 May 2017. The QT-IRT protocol review noted that because the study only included four sequences and moxifloxacin was administered open-label that there was a potential for study unblinding. The sponsor did not address this comment in their protocol and it is therefore possible that the study could have been unblinded. However, given that the study results are positive the potential unblinding is not of concern. The sponsor submitted the study report B1371023 for glasdegib (PF-04449913), including electronic datasets and waveforms to the ECG warehouse.

A separate concentration-QTc report based on the data from B1371023 was also submitted.

4.2 TQT STUDY

4.2.1 Title

A Phase 1, Single Center, Randomized, 4-Way Crossover, Double Blinded, Placebo and Moxifloxacin Controlled Study to Evaluate the Effect of Glasdegib on the Cardiac Repolarization in Healthy Subjects

4.2.2 Protocol Number

B1371023

4.2.3 Study Dates

09 Jun 2017 – 16 Oct 2017

4.2.4 Objectives

Primary Objective:

- To estimate the effect of glasdegib on QT/QTc interval after single dose oral administration relative to time-matched placebo in healthy subjects.

Secondary Objectives:

- To evaluate study sensitivity by evaluating the effect of moxifloxacin on QTc interval relative to time-matched placebo at moxifloxacin historical time for C_{max} (T_{max}).
- To assess the safety and tolerability of single doses of glasdegib when administered to healthy adult volunteers.

Other Objectives:

- To evaluate the PK of glasdegib.
- To evaluate the relationship of the QTc interval with plasma concentrations of glasdegib.

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 a washout period of at least 6 days.

4.2.5.2 Controls

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

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded. All the other treatments were double-blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 4 treatments in the study:

- A = Glasdegib 150 mg (tablet)
- B = Glasdegib 300 mg (tablet)
- C = Moxifloxacin 400 mg (tablet)
- D = Placebo (tablet)

4.2.6.2 Sponsor's Justification for Doses

In this study, glasdegib single doses of 150 mg and 300 mg and moxifloxacin single doses of 400 mg (standard recommended dose of moxifloxacin positive control) were administered to healthy subjects under fasted conditions.

With doses as high as 640 mg/day given to patients, no acute safety concerns were noted after the initial single-dose. Based on clinical activity, biomarker modulation and safety/tolerability data, the recommended Phase 2 dose (RP2D) of glasdegib for future clinical development was 100 mg QD. Additionally, in Study B1371010, 14 healthy volunteers had received 3 single 200 mg oral doses of glasdegib, with an 8-day washout between doses, without safety concerns. This study also included the ketoconazole drug-drug interaction (DDI) arm with higher exposures observed in the presence of ketoconazole. In the presence of ketoconazole, a 2.4-fold increase in area under the plasma concentration-time curve (AUC) was observed with a 200 mg single dose, which

would be the equivalence of exposures obtained after a 480 mg single dose. There were no safety concerns in this DDI cohort of healthy subjects. Three additional studies had been conducted in healthy subjects using the 100 mg dose with a washout in between.

Based on the safety data of glasdegib and prior clinical experience as described above, a single dose of 150 mg or 300 mg administered with a washout in this study was expected to pose little risk to healthy adult volunteers.

Reviewer's Comment: The dosing is acceptable.

4.2.6.3 Instructions with Regard to Meals

In this study, glasdegib single doses of 150 mg and 300 mg and moxifloxacin single doses of 400 mg (standard recommended dose of moxifloxacin positive control) were administered to healthy subjects under fasted conditions following an overnight fast of at least 10 hours.

Reviewer's Comment: The dosing in fasted state in this study is acceptable as the high fat meal results in 24% decrease in C_{max} over fasted state.

4.2.6.4 ECG and PK Assessments

ECG Assessments: A single 12-lead ECG will be taken at Screening. Triplicate ECGs will be obtained on Day 1 pre-dose at -1, -0.5 and 0 hours (immediately preceding dosing) and at 0.5, 1,1.5, 2, 3, 4, 6 and 24 h post-dose. All assessments will be made after at least a 10-minute supine rest prior to collection of blood draws.

PK Assessments: Blood samples for glasdegib PK analysis were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 24, 72, 96, and 120 h after dosing. Plasma PK samples for moxifloxacin were to be analyzed for the 1, 2, 3, 4, and 6 hour time points if a positive signal (QTc prolongation) is not observed.

Reviewer's Comment: As per the protocol review, "ECG/PK sampling timepoints can cover the effects near T_{max} (median of ~1-2 h following a single dose) and any potential delayed effects up to 24 hours."

4.2.6.5 Baseline

The average of predose QT/QTc values in each period was used as baseline for that period.

4.2.7 ECG Collection

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 36 healthy adult males were randomized to the study. Thirty-five of the 36 subjects completed all study periods. All 36 subjects were included in the ECG analysis population and safety population; 35 of the 36 subjects were included in the PK population.

4.2.8.2 Statistical Analyses

Reviewer's Comments: The sponsor's analysis showed largest mean QTc difference between glasdegib and placebo was greater than 10 ms. Please see the reviewer's independent analysis in section 5.2.

4.2.8.3 Safety Analysis

No death, serious adverse events (SAEs), or other significant adverse events (AEs) were reported in the study. There were no permanent discontinuations from the study or study treatment due to AEs. There were no dose reductions or temporary discontinuations due to AEs.

Reviewer's Comments: None of the events identified to be of clinical importance per the ICH E14 guidelines, i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death, occurred in this study.

4.2.8.4 Clinical Pharmacology

Reviewer's comment: The reviewer's results for concentration-QTc analysis are presented in Section 5.3 and are consistent with the sponsor's results that there is a concentration-dependent increase in QTc

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

Since no large mean changes (≥10 bpm) in heart rate were observed (Section 5.2.2), QTcF is used for primary analysis. No assessment of the QT/RR correction methodology is necessary. The sponsor also used QTcF for primary analysis.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Glasdegib

The statistical reviewer used mixed model to analyze the ΔQTcF and ΔΔQTcF 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 the following tables.

Table 2: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = A: Glasdegib 150 mg

	□QTcF (ms) Glasdegib 150 mg (N=35)	ΔQTcF (ms) Placebo (N=36)	ΔΔQTcF (ms) Glasdegib 150 mg	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0.5	-0.1	-0.0	-0.1	(-2.3, 2.1)
1	1.3	-0.8	2.1	(-0.1, 4.2)
1.5	3.5	-1.6	5.1	(3.0, 7.3)

	□QTcF (ms) Glasdegib 150 mg (N=35)	ΔQTcF (ms) Placebo (N=36)	ΔΔQTcF (ms) Glasdegib 150 mg	
Time (hour)	LSmean	LSmean	LSmean	90% CI
2	4.0	-1.9	6.0	(3.8, 8.1)
3	5.5	-2.2	7.8	(5.6, 9.9)
4	6.7	-1.3	8.0	(5.8, 10.2)
6	0.8	-4.3	5.1	(2.9, 7.3)
24	4.4	-1.5	5.9	(3.7, 8.1)

Table 3: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = B: Glasdegib 300 mg

	ΔQTcF (ms) Glasdegib 150 mg (N=35)	ΔQTcF (ms) Placebo (N=36)	ΔΔQTcF (ms) Glasdegib 300 mg	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0.5	0.6	-0.0	0.6	(-1.5, 2.8)
1	4.4	-0.8	5.1	(2.9, 7.3)
1.5	8.2	-1.6	9.8	(7.6, 12.0)
2	9.1	-1.9	11.1	(8.9, 13.2)
3	11.2	-2.2	13.4	(11.2, 15.6)
4	12.1	-1.3	13.4	(11.2, 15.6)
6	6.5	-4.3	10.8	(8.6, 13.0)
24	7.4	-1.5	8.9	(6.7, 11.1)

The largest upper bounds of the 2-sided 90% CI for the mean differences between glasdegib 150 mg and placebo, and between glasdegib 300 mg and placebo were 10.2 ms and 15.6 ms, respectively.

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 4. The largest unadjusted 90% lower confidence interval was 11.7 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 11.1 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 4: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

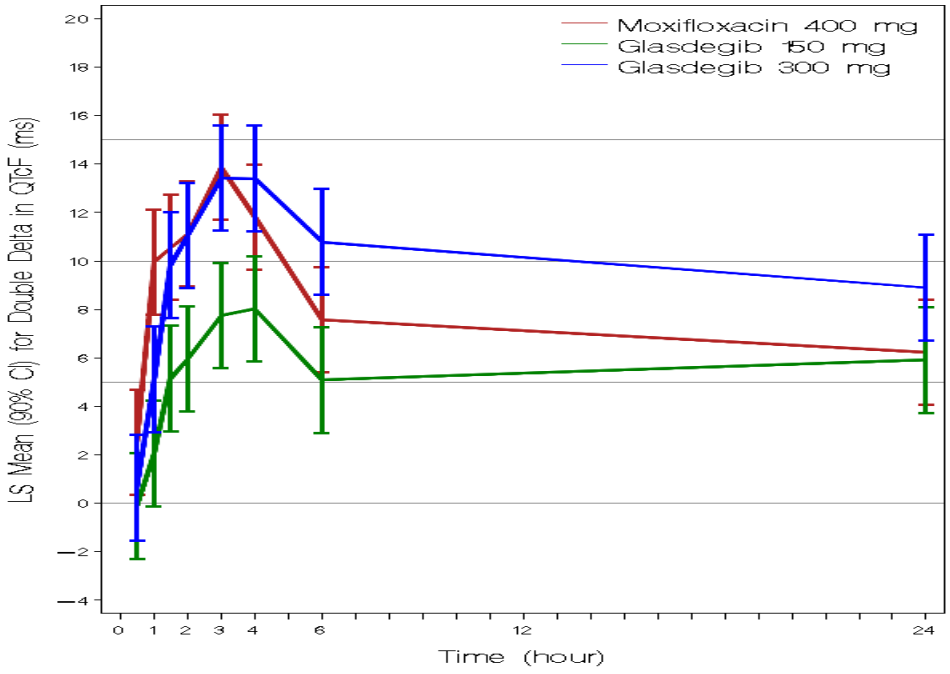
	ΔQTcF (ms) Moxifloxacin 400 mg (N=36)	ΔQTcF (ms) Placebo (N=36)	ΔΔQTcF (ms) Moxifloxacin 400 mg		
Time (hour)	LSmean	LSmean	LSmean	90% CI	Adjusted 90% CI*
0.5	2.5	-0.0	2.5	(0.3, 4.7)	(-0.3, 5.3)
1	9.2	-0.8	10.0	(7.8, 12.1)	(7.1, 12.8)
1.5	8.9	-1.6	10.6	(8.4, 12.7)	(7.8, 13.4)
2	9.2	-1.9	11.1	(9.0, 13.3)	(8.3, 13.9)
3	11.6	-2.2	13.9	(11.7, 16.0)	(11.1, 16.7)
4	10.5	-1.3	11.8	(9.7, 14.0)	(9.0, 14.6)
6	3.3	-4.3	7.6	(5.4, 9.7)	(4.8, 10.4)
24	4.7	-1.5	6.2	(4.1, 8.4)	(3.4, 9.0)

* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 3 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. It should be noted that CIs are all unadjusted, including those for moxifloxacin.

Figure 1: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 5 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 5: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<=480 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	36	426	36 (100%)	426 (100%)	0 (0.0%)	0 (0.0%)
Placebo	36	297	36 (100%)	297 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	36	297	35 (97.2%)	296 (99.7%)	1 (2.8%)	1 (0.3%)
Glasdegib 150 mg	35	288	35 (100%)	288 (100%)	0 (0.0%)	0 (0.0%)
Glasdegib 300 mg	35	289	33 (94.3%)	286 (99.0%)	2 (5.7%)	3 (1.0%)

No subject's change from baseline in QTcF was above 30 ms.

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 6. The largest upper limits of 90% CI for the HR mean differences between glasdegib 150 and placebo and glasdegib 300 mg and placebo were 2.8 bpm and 5.4 bpm, respectively.

Table 6: Analysis Results of ΔHR and ΔΔHR

	Glasdegib 150 mg			Glasdegib 300 mg		
	ΔHR (bpm)		ΔΔHR (bpm)	ΔHR (bpm)		ΔΔHR (bpm)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.5	-0.7	-0.8	0.2 (-1.3, 1.6)	-0.0	-0.8	0.8 (-0.6, 2.2)
1	-0.6	-1.5	0.9 (-0.5, 2.4)	-0.6	-1.5	0.9 (-0.5, 2.4)
1.5	-0.8	-2.2	1.4 (-0.0, 2.8)	-0.8	-2.2	1.5 (0.0, 2.9)
2	-1.4	-2.4	1.1 (-0.4, 2.5)	0.1	-2.4	2.5 (1.1, 4.0)
3	-0.9	-1.8	0.9 (-0.6, 2.3)	0.2	-1.8	2.0 (0.6, 3.4)
4	0.1	-0.6	0.8 (-0.7, 2.2)	1.5	-0.6	2.1 (0.7, 3.6)
6	7.4	6.0	1.4 (-0.1, 2.8)	10.0	6.0	4.0 (2.5, 5.4)
24	2.7	2.8	-0.1 (-1.5, 1.3)	2.6	2.8	-0.2 (-1.7, 1.2)

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 7. The largest upper limits of 90% CI for the PR mean differences between glasdegib 150 mg and placebo and glasdegib 300 mg and placebo were 3.0 ms and 2.6 ms, respectively.

Table 7: Analysis Results of ΔPR and ΔΔPR

	Glasdegib 150 mg			Glasdegib 300 mg		
	ΔPR (ms)		ΔΔPR (ms)	ΔPR (ms)		ΔΔPR (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.5	-0.8	-1.0	0.2 (-1.5, 1.9)	-1.2	-1.0	-0.2 (-1.9, 1.5)
1	-0.1	-0.9	0.8 (-0.9, 2.5)	-0.6	-0.9	0.3 (-1.4, 2.1)
1.5	-0.9	-2.2	1.3 (-0.4, 3.0)	-1.7	-2.2	0.5 (-1.2, 2.3)
2	-1.9	-2.4	0.6 (-1.2, 2.3)	-1.6	-2.4	0.8 (-0.9, 2.6)
3	-1.6	-1.5	-0.2 (-1.9, 1.6)	-1.7	-1.5	-0.3 (-2.0, 1.5)
4	-1.2	-2.2	1.0 (-0.7, 2.7)	-2.4	-2.2	-0.2 (-1.9, 1.6)
6	-6.6	-7.5	0.9 (-0.9, 2.6)	-8.9	-7.5	-1.4 (-3.2, 0.3)
24	-1.9	-0.4	-1.5 (-3.2, 0.2)	-2.5	-0.4	-2.1 (-3.8, -0.3)

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 8. The largest upper limits of 90% CI for the QRS mean differences between glasdegib 150 mg and placebo and glasdegib 300 mg and placebo were 2.1 ms and 0.7 ms, respectively.

Table 8: Analysis Results of ΔQRS and ΔΔQRS

	Glasdegib 150 mg			Glasdegib 300 mg		
	ΔQRS (ms)		ΔΔQRS (ms)	ΔQRS (ms)		ΔΔQRS (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.5	-0.5	-0.2	-0.4 (-1.3, 0.6)	-0.5	-0.2	-0.3 (-1.3, 0.7)
1	-0.2	0.3	-0.5 (-1.5, 0.5)	-1.0	0.3	-1.3 (-2.3, -0.3)
1.5	-0.9	-0.1	-0.8 (-1.8, 0.2)	-0.6	-0.1	-0.5 (-1.5, 0.5)
2	-0.6	-0.8	0.2 (-0.8, 1.2)	-1.3	-0.8	-0.5 (-1.5, 0.5)
3	-0.1	-0.5	0.3 (-0.7, 1.3)	-1.2	-0.5	-0.7 (-1.7, 0.3)
4	-0.3	-0.7	0.3 (-0.7, 1.3)	-1.7	-0.7	-1.0 (-2.0, -0.0)
6	-1.9	-1.4	-0.5 (-1.5, 0.5)	-2.2	-1.4	-0.8 (-1.8, 0.2)
24	-0.7	-1.8	1.1 (0.1, 2.1)	-2.1	-1.8	-0.3 (-1.3, 0.7)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The objective of the clinical pharmacology analysis is to assess the relationship between drug concentration and ΔQTcF.

Prior to evaluating the relationship using a linear model, the following key assumptions of the model were evaluated: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship. There were no large changes in heart rate (>10 bpm) with treatment as described earlier in Section 5.2.2.

An evaluation of the time-course of drug concentration and changes in ΔΔQTcF is shown in Figure 2, which seems to suggest delayed effects, with the T_{max} occurring ~2 h post-dose and the maximum QTc effects occurring ~3-4 h. Furthermore, the increase in QTcF

appears to be present at the 24 h time-point as well, suggesting the presence of delayed effects. However, a similar pattern was observed in both control arms (Figure 3), suggesting that the observation at the 24 h-time point suggesting the presence of delayed effects is spurious and a result of limited ECG/PK collection during the terminal phase.

Figure 2: Time course of drug concentration (top), and QTcF effects (bottom) following single oral doses of glasdegib

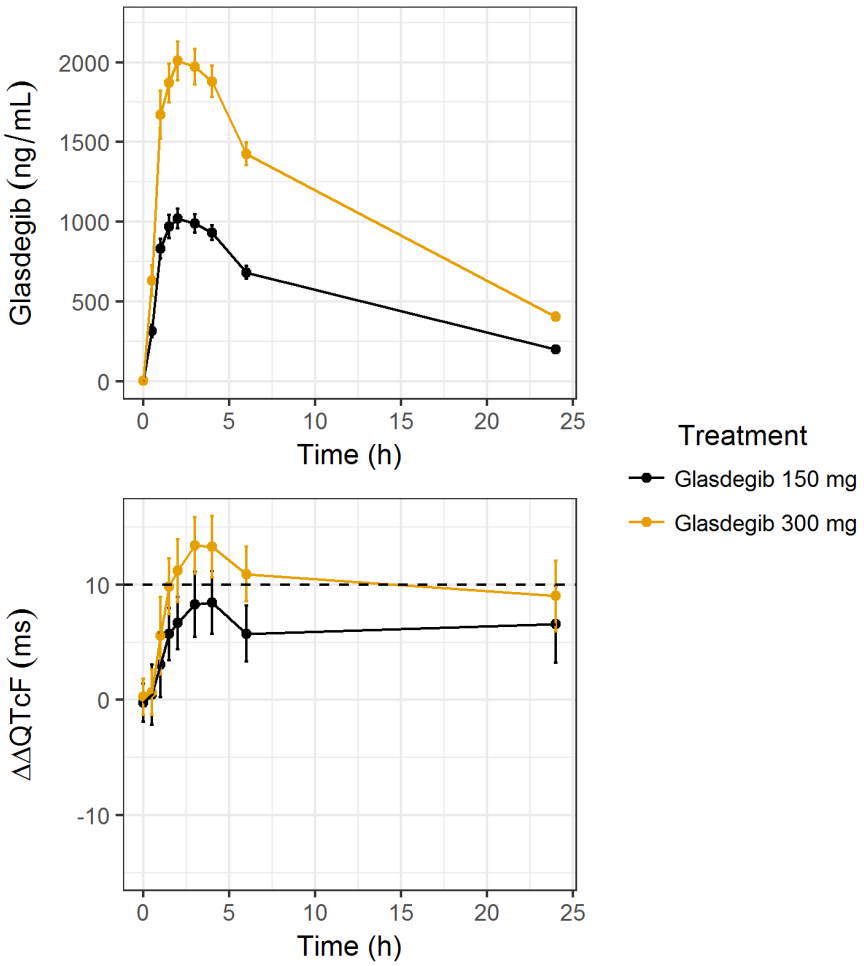
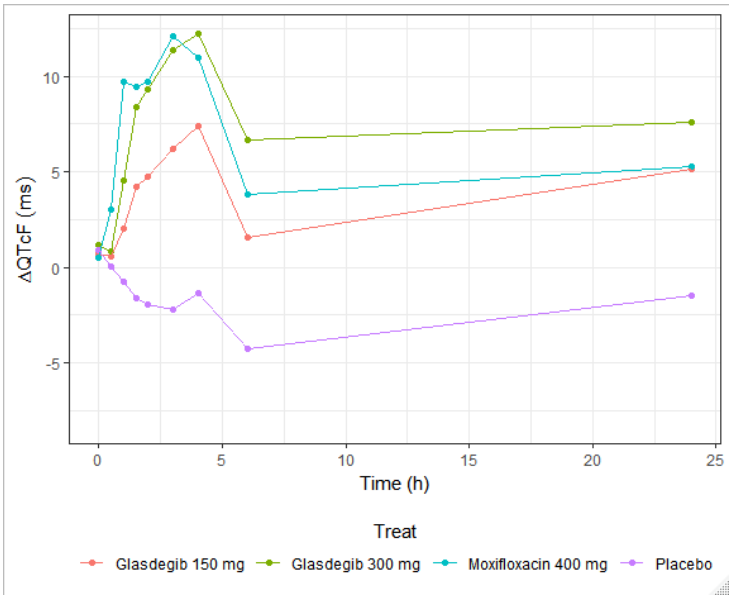
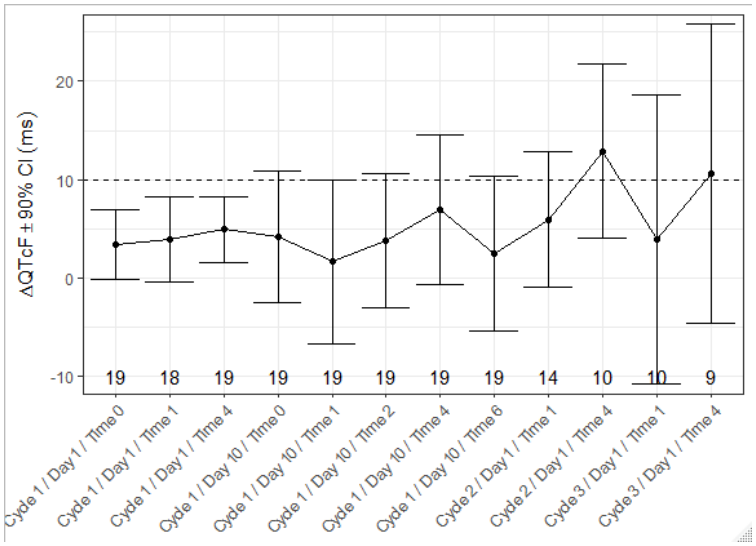


Figure 3: Comparison of ΔQTcF across treatment-arms



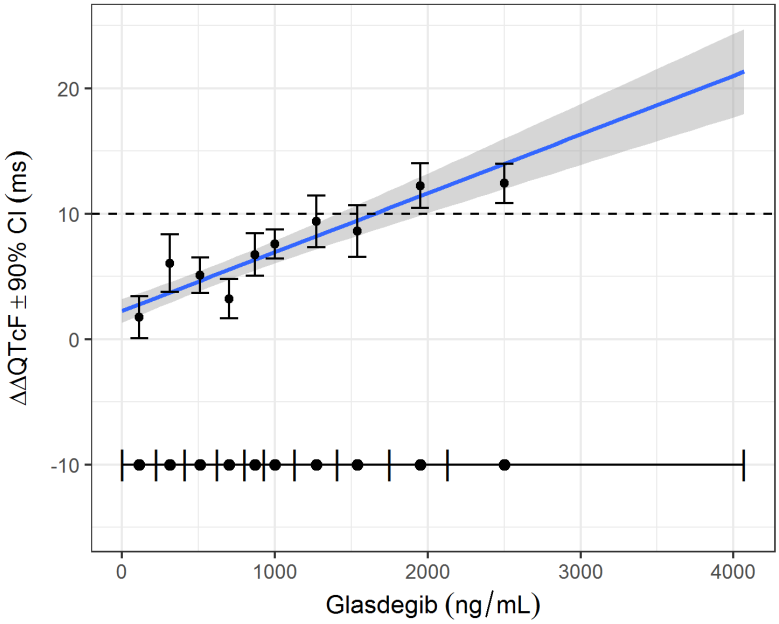
To further assess the possibility of a persistent QTc effect, we assessed the data from an ECG sub-study in their pivotal study (B1371003). This substudy included 19 patients, who had time-matched baseline ECGs collected on cycle 1 days -1 (baseline), 1 and 10 as well as cycle 2 and 3 on day 1. Prior to cycle 1 day 10, subjects were not permitted to take other QT prolongers. The time-course of ΔQTcF is shown in Figure 4 and does not show a trend towards increase over time within cycle 1. However, an increase is observed in cycles 2 and 3 on day 1 around Tmax which could be due to subjects being permitted to take other QT prolongers.

Figure 4: Time-course of ΔQTcF in ECG substudy in B1371003. Numbers in the bottom denote the number of subjects per visit.



The concentration-response relationship (the prespecified LME model shows statistically significant slope [p<0.001]; Figure 5) shows that the QTc effects were dose-/concentration-dependent. Of note, there was a short delay between maximum PK and maximum QTcF as noted above, which could potentially have biased the concentration-QTcF relationship. However, because the primary endpoint for this study is by-time analysis, no further model optimization was done.

Figure 5: ΔΔQTcF vs. Glasdegib concentration



5.4 CLINICAL ASSESSMENTS

Clinical safety assessment was performed for both the thorough QT study as well in the patient studies, because the thorough QT study showed that glasdegib is a QTc prolonger and the review division requested review of the information presented in the ISS.

5.4.1 Thorough QT study

No reports of syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in the TQT study.

5.4.1.1 ECG assessments

ECG acquisition and interpretation in this study appears acceptable.

5.4.1.2 Other ECG Intervals

No clinically relevant changes in PR and QRS were observed in the TQT study.

5.4.2 Patient Studies

The analysis of patient study data is focused on different patient pools from the pivotal patient study (B1371013). Specifically, the S1 cohorts and the S4 pool. The S1 cohorts include glasdegib 100 mg + LDAC (low-dose cytarabine) or LDAC-alone and the S4

pool includes all patients receiving the 100 mg glasdegib dose (see page 28 of ISS for definition of different cohorts and pools).

5.4.2.1.1 Categorical analysis

The sponsor has provided a summary of ECG outliers based on pooled patient data from (combination therapy/pools). The reviewer has repeated the analysis using the cutoffs in the CSRC white paper for PR and QRS (Table 9). There were 5 patients in the glasdegib 100 mg + LDAC arm and 2 in the LDAC arm with a QTcF value > 500 ms. Of these 5 patients, 3 patients had both a QTcF >500 ms and an increase from baseline >60 ms. None of the patients in the LDAC arm met both criteria.

Table 9: ECG outlier analysis

Parameter			S1		S4
			Glasdegib 100 mg + LDAC	LDAC	Glasdegib
			N=83	N=17	N=182
QTc	Absolute	<450	46 (55.4%)	8 (47.1%)	107 (58.8%)
		450 to <480	29 (34.9%)	4 (23.5%)	62 (34.1%)
		480 to <500	3 (3.6%)	3 (17.6%)	7 (3.8%)
		>500	5 (6.0%)	2 (11.8%)	6 (3.3%)
	Change	<30	60 (72.3%)	12 (70.6%)	125 (68.7%)
		>30 to <60	19 (22.9%)	4 (23.5%)	46 (25.3%)
		>60	4 (4.8%)	1 (5.9%)	11 (6.0%)
QRS	Absolute	<110	53 (63.9%)	10 (58.8%)	131 (72.0%)
		>110	30 (36.1%)	7 (41.2%)	51 (28.0%)
PR	Absolute	<220	72 (92.3%)	14 (93.3%)	161 (93.6%)
		>220	6 (7.7%)	1 (6.7%)	11 (6.4%)

Source: Reviewer's analysis of ISS datasets. This analysis only includes patients in the safety population with a baseline ECG.

The reviewer evaluated the narratives for the patients with QTcF >500 ms in study B1371003, S4 population. Overall, these cases are confounded with other risk factors that increase the QTc interval, and the observed QTcF prolongation cannot solely be attributed to glasdegib as described below.

1. Patients with QTcF >500 ms and ΔQTcF > 60 ms:
   - Patient (b) (6) (80 y, white male): Patient was on multiple QT prolonging medication (ondansetron, fluconazole, moxifloxacin, levofloxacin,

voriconazole and posaconazole) and medications that inhibit CYP3A4 (voriconazole and posaconazole).

- Patient [redacted] (71 y, white male): Patient was on multiple QT prolonging medication (citalopram, levofloxacin and voriconazole) and medication that inhibit CYP3A4 (voriconazole). Contribution of glasdegib to observed QTc prolongation on day [redacted] (drug discontinued on day [redacted]) cannot be ruled out because the effective half-life for glasdegib is ~9.3 to 32.6 h.
- Patient [redacted] (65 y, white female): Patient was on multiple QT prolonging medication (ciprofloxacin, ondansetron and voriconazole) and medication that inhibit CYP3A4 (ciprofloxacin, voriconazole).
- Patient [redacted] (67 y, white female): Patient was on multiple QT prolonging medication (citalopram and levofloxacin).
- Patient [redacted] (76 y, white female): Patient was on moxifloxacin (day [redacted] to [redacted]) and ondansetron (day [redacted] till end of study) and experienced an event of QT prolongation 4 days after discontinuation of glasdegib (discontinued on day [redacted]). However, the observed hypocalcemia on day [redacted] likely contributed to the observed QTcF prolongation as well. Contribution of glasdegib to the observed QTc prolongation on day [redacted] cannot be ruled out because the effective half-life for glasdegib is ~9.3 to 32.6 h.
- Patient [redacted] (51 y, white female): Patient was on multiple QT prolonging medication (levofloxacin and ondansetron) and had electrolyte abnormalities during the study (hypokalemia) which could have contributed to the observed QT prolongation.

2. Patients with QTcF > 500 ms:
    - Patient [redacted] (80 y, white male): Patient was on multiple QT prolonging medication (levofloxacin and ondansetron) and had intermittent electrolyte abnormalities during the study (hypocalcemia and hyperkalemia), which could have impacted the QT interval.
    - Patient [redacted] (73 y, white male): The patient was on multiple QT prolonging medication (levofloxacin, fluconazole, ondansetron and voriconazole) as well as CYP3A4 inhibitors (fluconazole and voriconazole).

5.4.2.1.2 Cardiac adverse events

A summary of treatment-emergent adverse events included in the Torsade/QT prolongation SMQ (including seizure) is presented in Table 10. This table shows an imbalance in QT-related adverse events between glasdegib 100 mg + LDAC vs LDAC in the S1 cohort (20.2% vs 9.8% overall).

The sponsor states that the apparent imbalance is due to a difference in the duration of exposure between the treatment arms (glasdegib 100 mg + LDAC: 83 days vs. LDAC: 47 days) and a difference in baseline history of cardiac disease (glasdegib 100 mg + LDAC: 65.9% vs. LDAC: 47.5%).

Table 10: All-causality treatment-emergent adverse events (grade 3, grade 4 or all grades) for QT prolongation SMQ including seizure. Grades are based on CTCAE version 4.0 or 4.03

Number (%) of Patients									
	S1						S4 pool Glasdegib		
	Glasdegib 100 mg + LDAC			LDAC					
	N = 84			N = 41			N = 186		
MedDRA PT	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades
Any AE	8 (9.5)	2 (2.4)	17 (20.2)	2 (4.9)	0 (0.0)	4 (9.8)	13 (7.0)	2 (1.1)	27 (14.5)
Electrocardiogram QT prolonged	2 (2.4)	1 (1.2)	7 (8.3)	1 (2.4)	0 (0.0)	1 (2.4)	4 (2.2)	1 (0.5)	14 (7.5)
Syncope	5 (6.0)	0 (0.0)	5 (6.0)	1[a] (2.4)	0 (0.0)	1 (2.4)	7 (3.8)	0 (0.0)	7 (3.8)
Ventricular Tachycardia	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	3 (1.6)
Cardiac arrest	0 (0.0)	1 (1.2)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.1)
Loss of consciousness	1 (1.2)	0 (0.0)	2 (2.4)	1 (2.4)	0 (0.0)	2 (4.9)	1 (0.5)	0 (0.0)	2 (1.1)
Sudden death	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)
Ventricular fibrillation	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)

a: Per the sponsor this AE was reported as Grade 1. However, given the CTCAE criteria for Syncope this event is reported as grade 3.

Source: Based on table 96 in ISS on page 270

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure

Recommended glasdegib clinical dose: 100 mg Qday (once a day)

Single Dose: Geometric Mean (%CV Geometric mean)				
Dose[a] (mg)	Study B1371001		Study B1371014[c]	
	C_{max} (ng/mL)	AUC_{inf} (ng*hr/mL)	C_{max} (ng/mL)	AUC_{inf} (ng*hr/mL)
80 mg (n=8[b])	746 (56)	8755 (64)	--	--
100 mg (n=34)	--	--	775 (28)	9051 (30)
120 mg (n=3)	1418 (22)	14430 (35)	--	--

[a] Single dose C_{max} and AUC_{inf} data for the 100 mg dose are not available in cancer patients as this dose was not tested in the first-in-patient study. The exposure data for evaluated doses closest to 100 mg is provided. Also the PK exposure data following a single dose in healthy subjects is provided.
[b] For AUC_{inf}, n=7 for the 80 mg dose
[c] B1371014 was a healthy subject study

Multiple Dose: Geometric Mean (%CV Geomean)								
Dose (mg)	Study B1371003[a]						Study B1371012[a] (n=9)	
	Arm A (n=8)		Arm B (n=3)[c]		Arm C (n=15)[d]			
	C_{max} (ng/mL)	AUC_{tau} (ng*hr/mL)	C_{max} (ng/mL)	AUC_{tau} (ng*hr/mL)	C_{max} (ng/mL)	AUC_{tau} (ng*hr/mL)	C_{max} (ng/mL)	AUC_{tau} (ng*hr/mL)
100 mg	1242 (56)	16660 (43)	1718 (28)	17700, 26300	1135 (43)	16300 (46)	991 (57)	14350 (61)

[a] Study B1371003 had three arms in the Phase 1b portion. Arm A: glasdegib + low dose Ara-C (LDAC); Arm B: glasdegib + decitabine; Arm C: glasdegib + daunorubicin/cytarabine. Study B1371012 involved glasdegib dosing in combination with azacitidine. All PK data presented are for 100 mg glasdegib at steady state in the absence of any combination agent.
[b] For AUC_{tau}, tau=24 hours.
[c] n=2 for AUC_{tau}, therefore %CV not presented
[d] n=13 for AUC_{tau}

Maximum tolerated dose	advanced hematological malignancies: 400 mg Qday advanced solid tumors: 320 mg Qday
Principal adverse events	In the clinical development program to date, glasdegib has been studied in patients with hematologic malignancies and advanced solid tumors, including 2 completed Phase 1 monotherapy studies. The safety risk profile of glasdegib is based on an existing clinical safety database that includes over 300 patients with hematological malignancies who received a glasdegib daily dose of 100 mg or higher. The clinical safety profile of single agent glasdegib was established in the completed Phase 1 Study B1371001 where glasdegib was administered PO Qday in doses ranging from 5 mg to 600 mg in patients with selected hematological malignancies (n=47) and in Study B1371002 where glasdegib was administered PO Qday at doses ranging from 80 mg to 640 mg in patients with advanced solid tumors (n=23). The safety profile appears to be consistent with other known SMO inhibitors. In Cycle 1 of Study B1371001, 2/47 patients experienced a dose limiting toxicity (DLT): 1 patient experienced Grade 3 hypoxia and pleural effusion (80 mg) that led to dosing interruption and reduction, and 1 patient experienced a DLT of Grade 3 peripheral edema (600 mg) that led to dosing interruption. The most common treatment-related AEs were dysgeusia (27.7%), decreased appetite (19.1%), and alopecia (14.9%). A total of 3 patients had a post-baseline QTcF $\geq$ 500 msec and 6 patients had a maximum QTcF interval increase from baseline of $\geq$60 msecs: 8/9 patients received glasdegib 400 mg or 600 mg. No ventricular tachycardia, ventricular fibrillation, or Torsades des Pointes were reported. In Study B1371002, 2 patients receiving glasdegib 640 mg Qday experienced DLTs during Cycle 1. One (1) patient developed DLTs of Grade 3 nausea, vomiting, and dehydration that persisted despite optimal supportive care. The second patient developed a DLT of inability to administer 80% of the planned dose of glasdegib during Cycle 1 due to glasdegib-related Grade 2 fatigue, dehydration and dizziness, and Grade 1 dyspepsia and dysgeusia.

	In the Phase 1b cohort of Study B1371003 (n=52) , in patients with AML or higher risk MDS who were treated with glasdegib 100 mg or 200 mg PO Qday in combination with chemotherapy, one patient experienced a DLT of grade 4 polyneuropathy. In the randomized Phase 2 cohort in the study B1371003 the most commonly reported AEs were anemia (45.2%), febrile neutropenia (35.7%), nausea (35.7%), decreased appetite (32.1%) and fatigue (31%) and the most commonly reported SAEs were febrile neutropenia (28.6), pneumonia (21.4%) and sepsis (3.6%). The safety profile of glasdegib appears consistent with what has been reported for the smoothened inhibitor class and the backbone chemotherapy. The observed 'on target' toxicities included: muscle spasms, dysgeusia, decreased appetite, and alopecia.	
Maximum dose tested	Single Dose	640 mg
	Multiple Dose	640 mg Qday in advanced solid tumors; 600 mg Qday in advanced hematologic malignancies
Exposures Achieved at Maximum Tested Dose	Single Dose: mean (%CV)	640 mg: N=8; C_{max}: 5887 ng/mL (40) and AUC_{24}: 60310 ng*hr/mL (30)
	Multiple Dose: mean (%CV)	640 mg: N=4; C_{max}: 4840 ng/mL (20) and AUC_{24}: 68670 ng*hr/mL (27)
Range of linear PK	Hematological malignancies: glasdegib pharmacokinetics are linear over the dose range of 5-600 mg Qday Solid tumors: glasdegib pharmacokinetics are linear over the dose range of 80-640 mg Qday	
Accumulation at steady state	In patients with hematologic malignancies, for single agent glasdegib over the dose range tested of 5 – 600 mg Qday, median glasdegib accumulation (R_{ac}) following repeated dosing ranged from 1.2 to 2.5. This is in line with the predicted accumulation based on the half-life and dosing frequency.	
Metabolites	Based on metabolic profiling conducted using samples from the human ADME study (B1371009), the primary metabolic pathways for [^{14}C]glasdegib are believed to comprise of N-demethylation, glucuronidation, oxidation, and dehydrogenation. In plasma, glasdegib was responsible for 69.4% of the circulating radioactivity. The N-desmethyl (M3) and N-glucuronide (M8) metabolites of glasdegib accounted for 7.9% and 7.2% of the circulating radioactivity, respectively. All other metabolites were <5% in circulation. The N-desmethyl metabolite of glasdegib was the most abundant metabolite in urine and feces, accounting for 16.8% and 9.2% of administered radioactivity, respectively. The N-glucuronide metabolite of glasdegib was observed in urine, accounting for 4.2% of dose. Mean recovery of unchanged glasdegib in the urine was approximately 17.2% and the mean recovery in faeces was 19.5%. Assessment of pharmacological activity with the N-desmethyl (M3) metabolite indicated that it was ~200-fold less potent than glasdegib.	
Absorption	Absolute/Relative Bioavailability	No absolute bioavailability information is currently available for glasdegib. A clinical study is planned that will report out in 2018. In nonclinical species (rats and dogs), oral absorption of glasdegib was moderate with a mean absolute bioavailability of 33% and 68% in rats and dogs, respectively.

		In order to confirm that there are no changes in exposure due to a salt change between the clinical and commercializable formulation, a relative bioavailability study was conducted (B1371014). A small particle size based tablet and a large particle size based tablet of the commercializable formulation were tested against the clinical tablet. The ratios of adjusted geometric means (90% CI) of the 100-mg large particle size based commercializable tablet (Test) versus the 100-mg clinical tablet (Reference) for AUC_{inf} and C_{max} were 107.51% (103.67%, 111.48%) and 107.77% (101.32%, 114.64%), respectively. The ratios of adjusted geometric means (90% CI) of the 100-mg small particle size based commercializable tablet (Test) versus the 100-mg clinical tablet (Reference) for AUC_{inf} and C_{max} were 105.10% (101.20%, 109.14%) and 107.42% (102.41%, 112.66%), respectively.
	T_{max}	In subjects with myeloid malignancies and solid tumours treated with glasdegib, the median time to maximum concentration (T_{max}) typically ranged from ~1-4 hours after both single dose and at steady state across the doses tested (5 – 640 mg Qday). In AML patients with glasdegib + non-intensive chemotherapy at the dose of 100 mg Qday, the median T_{max} at steady state was 1.3 hours (0.53-2.0) hours.
Distribution	Vd/F	The mean apparent volume of distribution (V_z/F) of glasdegib in patients ranged from 174 L to 455 L across all dose levels and exceeded the typical plasma volume (3L) suggesting that glasdegib is distributed into tissues from plasma.
	% protein bound in human plasma	Glasdegib unbound fraction information: Nominal Concentration (ng/mL) / % mean unbound (standard deviation) 374 (1 µM) / 7.72 ± 0.29 3744 (10 µM) / 10.3 ± 1.3 Glasdegib protein binding was ~ 91%
Elimination	Route	In a mass balance study (B1371009), the overall median recovery of administered radioactivity was 90.6%. Urine recovery contributed to 48.9% of the recovered radioactivity and fecal recovery contributed to 41.7% of the recovered radioactivity. Approximately 17.2% of the administered dose of glasdegib was excreted unchanged in the urine

		and the mean recovery of glasdegib in feces was 19.5%.
	Terminal t½	In patients with hematologic malignancies, for single agent glasdegib over the dose range tested of 5 – 600 mg Qday, the arithmatic mean terminal half-life ranged from 17.4 – 34.3 hours.
	CL/F	In patients with hematologic malignancies, for single agent glasdegib over the dose range tested of 5 – 600 mg Qday, the glasdegib CL/F ranged from 5.63 to 12.7 L/hour following a single dose and 5.33 to 13.3 L/hour following multiple dosing.
Intrinsic Factors	Age	Preliminary population PK analysis of the data from studies B1371001 and B1371002 (n=70) did not show any significant correlation between age, sex, or race and post hoc estimates of any PK parameter.
	Sex	
	Race	
	Hepatic & Renal Impairment	Formal hepatic or renal impairment studies have not been performed to date. In a mass balance study (B1371009), the overall mean recovery of administered radioactivity was 90.6%. Urine recovery contributed to 48.9% of the recovered radioactivity and fecal recovery contributed to 41.7% of the recovered radioactivity. Approximately 17.2% of the administered dose of glasdegib was excreted unchanged in the urine and the mean recovery of glasdegib in faeces was 19.5%.
Extrinsic Factors	Drug interactions	Strong CYP3A4/5 inhibitor (ketoconazole): 40% increase in mean glasdegib C_{max} and 140% increase in mean AUC_{inf} Strong CYP3A4/5 inducer (rifampin): 35% decrease in mean glasdegib C_{max} and 70% decrease in mean AUC_{inf} pH altering agent (proton pump inhibitor): 13% decrease in mean glasdegib C_{max} and 12% increase in mean AUC_{inf}
	Food Effects	High-fat meal: 24% decrease in C_{max} and 14% decrease in AUC_{inf}
Expected High Clinical Exposure Scenario	Strong CYP3A4 inhibitor mediated increase in glasdegib exposure. 40% increase in mean C_{max} and 140% increase in mean AUC_{inf} was noted in a study with a strong CYP3A4 inhibitor (ketoconazole)	

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