30 April 2020
EMA/CHMP/284008/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Daurismo

International non-proprietary name: glasdegib

Procedure No. EMEA/H/C/004878/0000

Note

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

Administrative information

Name of the medicinal product:	Daurismo
Applicant:	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles BELGIUM
Active substance:	GLASDEGIB MALEATE
International Non-proprietary Name/Common Name:	glasdegib
Pharmaco-therapeutic group (ATC Code):	other antineoplastic agents, other antineoplastic agents (L01XX63)
Therapeutic indication(s):	Daurismo is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	25 mg and 100 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/alu) and bottle (HDPE)
Package size(s):	30 and 60 tablets

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List of abbreviations

ASAP	Accelerated Stability Assessment Program
BCS	Biopharmaceutics Classification System
CHMP	Committee for Medicinal Products for Human use
CM	Continuous Manufacturing
CFU	Colony Forming Units
CPP	Critical process parameter
CQA	Critical Quality Attribute
DoE	Design of experiments
DSC	Differential Scanning Calorimetry
EC	European Commission
EI	elemental impurities
EU	European Union
FA	Focus Area
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
JP	Japanese Pharmacopoeia
LC	Liquid chromatography
LDPE	Low density polyethylene
MVTR	Moisture Vapor Transmission Rate
NMR	Nuclear Magnetic Resonance
NMT	Not more than
PACMP	post-approval change management protocol
PCMM	Portable, Continuous, Miniature and Modular
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
PVC	Polyvinyl chloride
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative Humidity
RTD	Residence time distribution
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
tmax	Time to achieve Cmax
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 29 April 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Daurismo, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 July 2017.

Daurismo, was designated as an orphan medicinal product EU/3/17/1923 on 16 October 2017 in the following condition: Treatment of acute myeloid leukaemia.

The applicant applied for the following indication: Daurismo is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Daurismo as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Daurismo

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0239/2018 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance glasdegib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The Applicant received Protocol Assistance on the development relevant for the approved indication from the CHMP on 21 April 2017 (EMEA/H/SA/2898/4/2017/II) and 28 February 2019 (EMEA/H/SA/2898/5/2019/PA/I). The Scientific Advice pertained to the following quality and clinical aspects of the dossier:

- the proposed strategy to provide some of the quality data during the review process;

- the proposed clinical development plan to support registration for glasdegib in the treatment of previously untreated adult patients with AML in combination with chemotherapy, in particular:

  whether the results of randomised phase 2 study B1371003 of glasdegib + LDAC vs LDAC alone in elderly patient's ineligible for intensive chemotherapy could be used to support full approval,

  whether the design of the proposed randomized, placebo-controlled Phase 3 Study B1371019 (i.e. eligibility criteria, comparator, stratification factors, SAP, PRO) in patients with AML, "fit" and "unfit" for intensive treatment, with or without the addition of glasdegib in both settings, is adequate to support marketing authorisation.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Sinan B. Sarac

The application was received by the EMA on	29 April 2019
The procedure started on	23 May 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 August 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 August 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	27 August 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	3 February 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2020

The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 February 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 April 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Daurismo on	30 April 2020
The CHMP adopted a report on similarity of Daurismo with Dacogen, Mylotarg, Rydapt, Vyxeos liposomal, Xospata on treatment of AML	30 April 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

AML is a haematopoietic system malignancy characterized by increased proliferation of bone marrow and peripheral blasts, pancytopenias causing infections and bleeding, and reduced survival.

2.1.2. Epidemiology

Acute myeloid leukaemia (AML) accounts for approximately 80% of acute leukaemias diagnosed in adults. It has been estimated that 19,950 people were diagnosed with AML in the US, with a similar incidence in the EU.

Literature reports estimated prevalence rates for AML in the EU ranging between 9.0 to 15.4 per 100,000 population. Countries within Europe report varied AML incidence rates per 100,000 population: 2.7 in Serbia, 3.0 in Switzerland and the Netherlands, 4.7 in Italy, 5.1 in the United Kingdom (UK), and 5.4 in Denmark. The median age at diagnosis is approximately 68 years for AML.

2.1.3. Biologic features

AML is generally characterized by aberrant differentiation and proliferation of malignantly transformed myeloid progenitor cells but can be considered a heterogeneous disease state with various molecular and genetic aetiologies that result in variable clinical outcomes. When untreated or refractory to available treatments, AML results in the accumulation of these transformed cells within the bone marrow, suppression of the production of normal blood cells (resulting in severe neutropenia and/or thrombocytopenia), as well as infiltration of these cells into other organs and tissues, and can be rapidly fatal.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

AML is a genetically heterogeneous malignancy characterized by multiple genetic mutations at the time of diagnosis that evolve with treatment, resulting in treatment resistance, disease relapse, and reduced survival. Diagnosis is made via bone marrow assessment.

2.1.5. Management

Treatment of AML with standard intensive chemotherapy of an anthracycline plus cytarabine induction therapy followed by cytarabine consolidation therapy and/or allogeneic stem cell transplantation results in long-term remissions in up to 60% of patients. However, treatment-related mortality of 5.5% for younger patients and 17.7% for elderly patients limits effectiveness. Given that the majority of patients are older and unable to tolerate the more intensive chemotherapy treatment, less intensive therapies such as LDAC, azacitidine, or decitabine are used. While less toxic non-intensive therapies may prolong OS versus the best supportive care, there are fewer complete remissions and shorter OS, with little chance for a cure compared to more intensive chemotherapies such as induction chemotherapy with cytarabine (7 days) plus daunorubicin (3 days) (7+3). None of the less intensive treatments are curative.

About the product

Glasdegib is an inhibitor of SMO, a key protein in the hedgehog (Hh) pathway. Aberrant Hh signalling has been identified in many solid tumour types and in haematological malignancies. As an inhibitor of the Hh signalling pathway, glasdegib may act as an anti-leukaemic stem cell agent.

In this application, glasdegib is proposed for regulatory approval in combination with LDAC chemotherapy for the treatment of newly diagnosed de novo or secondary AML in adult patients who are not candidates for standard induction chemotherapy.

The proposed regimen is 100 mg once daily by oral administration.

The product is supplied as film-coated tablets; 25 mg and 100 mg.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 25 or 100 mg of glasdegib. The product contains the maleate salt.

Other ingredients are:

Tablet core
Sodium starch glycolate
Microcrystalline cellulose (E460(i))
Calcium hydrogen phosphate (anhydrous) (E341ii)
Magnesium stearate (E470b)

Film-coating
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Triacetin (E1518)
Iron oxide yellow (E172)
Iron oxide red (E172) (100 mg tablets only)

The product is available in PVC (polyvinyl chloride) blister sealed with aluminium foil or high-density polyethylene (HDPE) bottle with polypropylene closure as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of glasdegib maleate is 1-((2R,4R)-2-(1H-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea maleate corresponding to the molecular formula C25H26N6O5.It has a relative molecular mass of 490.51 Daltons and the following structure:

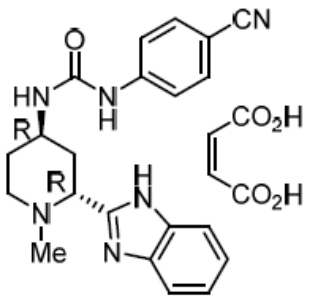


Figure 1: active substance structure

The chemical structure of glasdegib maleate was elucidated by a combination of IR, ^{1}H and ^{13}C NMR and UV spectroscopy, mass spectrometry and specific rotation. Single crystal X-Ray diffraction was used for the characterization of the asymmetric carbons and the determination of the absolute stereochemical configuration. The solid state properties of the active substance were measured by DSC and TGA.

Glasdegib maleate is a non-hygroscopic white to pale coloured powder. It is slightly soluble in water, over a range of pH 2.31 to 7.24, with a trend of decreasing solubility with increasing pH. It is very soluble in dimethylsulfoxide, sparingly soluble in methanol, tetrahydrofuran and has low solubility in acetone and ethanol.

Glasdegib has two asymmetric centers, giving four possible stereoisomers. The absolute configuration is 2*R*, 4*R*. There are no geometrical isomers or atropisomers for glasdegib maleate Enantiomeric purity is controlled routinely by chiral HPLC.

A comprehensive polymorph and hydrate screening for glasdegib maleate was conducted using diverse crystallization techniques at different temperatures (including those present in the crystallization process) and slurries, solvent evaporations, and solvent free methods. Glasdegib maleate (Form 1) was the only crystalline anhydrous form identified from these studies. No new polymorphs of anhydrous glasdegib maleate were isolated. Additionally, no hydrated forms of glasdegib maleate were found through extensive screening.

An amorphous form and four solvated forms were found.

Glasdegib maleate Form 1 is physically and chemically stable under normal manufacturing and storage conditions as well as under accelerated conditions. This form was selected for Daurismo and has been consistently manufactured and used to support commercial development.

Manufacture, characterisation and process controls

The proposed active substance is manufactured by a single manufacturer.

The active substance is synthesized in five main steps using well defined starting materials with acceptable specifications. The justification for selection of the starting materials is found acceptable and follows ICH Q11 and its questions and answer document.

Critical steps and critical process parameters (CPP) have been identified and justified.

The ranges and limits stated in the description of the manufacturing process were based on the ranges evaluated during the development of the manufacturing process. The Design of Experiments (DoE) studies performed demonstrated that no additional impurities are formed when quantities within these ranges are

used, and that the selected ranges can limit the formation of impurities. The manufacturing process as described in section 3.2.S.2.2. of the dossier constitutes a design space.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials, reagents and solvents have been presented. Maleic acid is used in the last step of the synthesis to create the salt, which is the final active substance. It is a significant part in the composition of the active substance, however, in accordance to ICH Q11, it can be considered a reagent. Its quality is justified.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed. This included information on the source of the impurity, the controls in the starting materials, the possible transformations and the controls in the intermediates, the possible purge during the manufacturing process and the controls in the active substance.

Since the medicinal product is intended to be used for the treatment of patients with advanced cancer, ICH M7 is not applicable for the control of the impurities and the ICH Q3A qualification threshold of 0.15% was applied for the control of the specified impurities.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program.

Two main synthetic pathways were used during the development of the active substance manufacturing process. Glasdegib dihydrochloride salt was used in early development and Phase I and Phase II clinical studies. This salt was deemed unsuitable for commercial development

Four different routes were used throughout development. The reaction scheme for each of the synthetic routes was provided.

Overall, changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be supportive to that produced by the proposed commercial process.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of Quality by Design (QbD) such as risk assessment, and DOE studies.

The selection of the Critical Quality Attributes (CQAs) of the active substance was based on its intended use in the formulation of the finished product. The active substance attributes that could have an impact on the quality of the tablets were identified as critical.

A quality risk management assessment was performed to identify potential CPPs and critical material attributes. The process inputs, material attributes, process operating parameters and potential links to CQAs were identified.

The active substance manufacturing process was divided into nine focus areas closely related to the active substance quality attributes, and especially those responsible for the formation, fate and purge of the impurities. An experimental plan was subsequently developed and DoE studies and univariate studies executed in order to establish the impact of the identified parameters on the quality attributes, determine the extent of this impact and identify the ranges within which the process can be operated and determine the appropriate analytical testing strategy. Particular attention was given to the discussion of the possible impurities that could be present at each step and their transformations and purge.

The DoE studies performed are considered acceptable. Scale dependency was discussed in each step. The conclusions obtained were further confirmed by the controls performed on batches manufactured at pilot and commercial scale, which demonstrated that the quality of the intermediates/active substance was compliant with the specifications.

Based on these studies, and following a query raised during the review, the applicant confirmed that the operational ranges of the critical process parameters as described in section 3.2.P.3.3. of the dossier constitute a design space. The design space has been developed at lab and pilot scale, but the scale independency of the different steps was justified. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

The active substance is packaged in a container which complies with the requirements EU regulation 10/2011 on plastic and articles for food use.

Specification

The active substance specification includes tests for: appearance, identification (IR, chiral HPLC), particle size (laser diffraction), assay (HPLC), maleic acid counterion content (HPLC), impurities (HPLC), chiral purity (HPLC), residue on ignition (Ph. Eur.), residual solvents (GC), water content (KF).

The active substance specification includes relevant tests for its use in the finished product. The proposed acceptance criteria were based on the observations made on the release and stability batches, as requested during the evaluation procedure.

The limits initially proposed for the control of the related substances were not considered acceptable. The applicant justified the proposed limits by toxicological qualifications for the specified impurities and by the fact that ICH M7 is not applicable for this product. These justifications were not considered adequate, the expectation being that impurities should be limited in line with ICH Q3A, and wider limits proposed only when justified by the batch results. Consequently, tighter limits in line with batch results were proposed for the control of the specified and unspecified impurities.

A suitable justification for not including the control of polymorphic form, residual solvents (ethyl acetate, n-heptane, isopropylamine, dimethyl sulfoxide, triethylamine, 4-methyl-2-pentanone and benzene), elemental impurities, specific rotation, reagents and the microbiological quality was provided.

The absence of control of certain residual solvents used in the manufacturing process was justified by the batch history.

The absence of testing of elemental impurities was justified based on scientific rationale and batch analysis data.

Specific rotation was not included in the specification, since glasdegib has a fixed stereochemistry derived from the proposed commercial process which is confirmed using a chiral LC identity. The enantiomer content is assayed using a chiral LC purity method included in the active substance specification. Additionally, the diastereomers of glasdegib are quantified in the achiral purity method.

The absence of control of microbiological quality was justified based on low risk of microorganism contamination, risk assessment and batch analysis data.

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

Batch analysis were provided for 32 batches of the active substance, which included 8 process validation batches manufactured at the proposed manufacturing site using the commercial synthesis route SR4. Batch analyses for three batches of glasdegib maleate used to support toxicology studies were also provided. The results were very similar between the batches and were compliant with the acceptance criteria in the specification.

Stability

Stability data from three commercial scale batches of active substance manufactured at one of the development sites using the commercial process and stored in the intended commercial packaging for up to 18 months under long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The stability batches were evaluated for appearance, assay, degradation products, water content, solid form, particle size and microbial quality. The analytical methods used for the analysis were the same as for release.

All tested parameters were within the specifications and no particular trends were observed.

Supportive stability data from one batch of the active substance obtained through each of the previous manufacturing routes, packed in a container similar to the one proposed for the commercial batches were also provided. These batches were stored under ICH climatic zone II conditions of 25°C/60%RH and 30°C/75% RH as long term conditions and, 40°C/75% RH as accelerated conditions. Results at 36 months under long term conditions and 6 months under accelerated conditions were provided. Samples were tested for appearance, assay, chiral and achiral purity, water content, solid form. All results met the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch. After exposure the samples were analysed for appearance, assay, related substances (specified, individual unspecified, total impurities) and chiral purity. No changes were observed, and it was concluded that the active substance is not light sensitive and does not require a 'protect from light' restriction.

Results under stress conditions were also provided. Solid samples of active substance were exposed to elevated temperature (with and without humidity) and simulated sunlight filtered through window glass and were analysed for assay and purity. Solutions of drug substance were exposed to acid, base, hydrogen peroxide, auto-oxidation, Fe (III), and Cu (II) and were analysed for assay and purity. Degradation was observed after exposure to base and hydrogen peroxide. No significant degradation was observed under the other conditions. Mass balance was achieved in all conditions. The results show that the method proposed for the analysis of the related substances is stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 30 months at 30°C/75% RH in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as immediate-release round film-coated tablets. The tablets are available in two strengths: 25 mg and 100 mg of glasdegib, equivalent to 32.8 mg glasdegib maleate and 131.1 mg glasdegib maleate, respectively.

The tablet strengths are differentiated by colour (yellow for 25 mg and pale orange for 100 mg), debossing and size.

The finished product may be packaged in heat induction sealed high density polyethylene (HDPE) bottles or PVC/foil blisters.

Glasdegib maleate is a salt of the active compound, glasdegib, with maleic acid. It is a white to pale coloured powder that is classified as a BCS Class IV compound (i.e., low solubility and low permeability) based on the Biopharmaceutics Classification System. Glasdegib maleate salt, Form 1, has a high melting point, is non-hygroscopic, and exhibits excellent physical and chemical stability.

Active substance particle size studies were focused to understand the impact of material properties on dosage form quality attributes, such as potency, content uniformity, dissolution and tablet physical properties with statistically designed multivariate experimental trials (DoEs). Various active substance lots with a wide range of particle size distributions were evaluated throughout the finished product development process, during clinical manufacturing, and with the manufacture of registration batches. The impact of active substance particle size on bioavailability, finished product stability, and manufacturability was also evaluated. Based on the results, the specification of the active substance particle size was defined.

Excipients chosen are compendial (microcrystalline cellulose and dibasic calcium phosphate anhydrous as diluents, sodium starch glycolate type A as disintegrant, magnesium stearate NF VG (impalpable powder) as lubricant) and not compendial (colour mixture yellow Opadry® II 33G120011 and color mixture beige Opadry® II 33G170003).

All excipients are well known pharmaceutical ingredients. All of them other than the film-coating mixtures (Opadry® II yellow and Opadry® II beige) are of Ph. Eur quality. The film-coating mixtures are not compendial, but their individual constituents comply with Ph. Eur., except the colouring agents iron oxides. The iron oxides comply with Commission Regulation (EU) No 231/2012.

The functionality-related characteristics of the excipients and their controls have been discussed. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The amount of excipients used in the composition has been properly justified by different studies performed during the development.

An excipient compatibility screening with conventional immediate release formulation excipients was completed using binary mixtures of the active substance and excipient. No significant degradation was observed. Supporting development data and registration stability studies showed that these excipients are suitable to enable a stable finished product.

An enhanced development approach was used for the design and development of glasdegib maleate film-coated tablets. It was based on a risk-based approach incorporating statistically DoEs to evaluate the impact of raw material variability and process parameters variability on the CQAs of the finished product.

In order to select the commercial formulation a material risk assessment was performed to identify properties of the formulation components which could have an impact on tablet core quality attributes.

As mentioned above, a dihydrochloride salt of glasdegib was used in early development and all of Phase 1 and Phase 2 clinical studies. This salt was deemed unsuitable for commercial development Following extensive salt screening, the glasdegib maleate salt was developed as the preferred form due to its physical properties and stability and was shown to have equivalent exposure to glasdegib dihydrochloride in a relative bioavailability study (B1371014). The maleate salt was selected for commercial tablet formulation development. A pivotal bioequivalence study (B1371026) was conducted to compare a single 100mg dose of glasdegib commercial maleate tablet formulation to a single 100mg dose of a glasdegib dihydrochloride. The results indicated that the proposed commercial glasdegib maleate tablet was bioequivalent to the glasdegib dihydrochloride tablet.

The commercial glasdegib maleate film-coated tablet has been manufactured to support registration stability and clinical studies.

In addition to immediate-release tablets, various clinical trial formulations were developed for the clinical studies: an oral solution, oral suspension and intravenous solution.

The development of the commercial glasdegib maleate film-coated tablet included evaluations of drug loading, active substance particle size, excipients concentration and grade, and the film- coating formulation.

A material risk assessment followed by statistically designed experiments (DoEs) were performed to optimize the commercial formulation. Based on the risk assessment, the components with the highest potential to impact finished product quality attributes were identified and defined as critical.

Based on the results from the DOE studies, the formulation was developed.

Studies evaluating the impact of excipients on finished product manufacturing and performance were also conducted.

The impact of excipient lot-to-lot variability on glasdegib maleate tablets was assessed. The potential impact of lot-to-lot variability was deemed to be low.

The impact of variations in formulation composition on finished product quality attributes was also evaluated.

Glasdegib tablet cores of both 25 mg and 100 mg strength were evaluated for assignment of the holding times in accordance with "Annex 4: General guidance on hold-time studies". The applied holding times using commercial bulk packaging configuration for glasdegib tablet cores showed no negative effect on manufacturing performance (subsequent film-coating operation) and product quality. Based on these results the total holding time, beginning with packaging into the commercial bulk packaging configuration until start of film-coating was defined.

The dissolution method selection has been described, including apparatus, pH and agitation speed. The discriminatory power of the dissolution method has been demonstrated.

The glasdegib maleate tablets core are manufactured by direct compression, using a continuous manufacturing (CM) platform designed by Pfizer called Portable, Continuous, Miniature and Modular (PCMM). The continuous manufacturing process involves the first three steps: (1) continuous feeding and (2)

continuous mixing, followed by (3) tablet compression using a conventional rotary tablet press. The final unit operation is a film-coating process which is performed as a batch process using conventional equipment. The process flow and equipment train used at the manufacturing site proposed to supply the EU market is the same that was used in the manufacture of registration stability and clinical batches.

Adequate discussion around the equipment design and configuration, and its impact on the process performance, has been provided.

The process development of glasdegib maleate film-coated tablets has focused on the product and quality attributes identified in the Quality Target Product Profile (QTPP) that ensure the quality, efficacy, stability and safety of the product, and are defined in the product specification.A combination of risk-based assessments, laboratory studies, computational models, and manufacturing experience resulted in a comprehensive understanding of the formulation and process conditions and their impact on these quality attributes.

This risk assessment was performed based upon prior knowledge as well as the knowledge that had been gained throughout the development of the manufacturing process. Attributes and parameters were categorized as either critical or non-critical, based on their impact to the product quality.

A multivariate experimental plan was developed to gain further process understanding across the manufacturing process steps and evaluate the impact of the identified process parameter ranges on dosage form quality attributes.

Feeding performance has been adequately addressed. Experimental studies demonstrated the ability of an individual gravimetric feeder to deliver raw material at a target mass flow rate with minor fluctuations in instantaneous mass flow rate based on an overall target mass flow rate. These gravimetric feeder studies included a broad range of active substance and excipient lots, in order to evaluate the impact of material attribute variability on feeder performance. The gravimetric feeder set point (in kg/h), for each formulation component has been described. Each gravimetric feeder is continuously monitored and controlled to a target mass feed rate. For the mixing, a risk assessment was conducted to guide the creation of experimental activities to characterize the residence time distribution (RTD). The results of the broad range of formulation compositions studied provided the foundation to establish control and alarm limits for the gravimetric feeders and CMT and ensure that the formulation composition remains within compositional ranges. The dampening capacity of the system has been demonstrated. Complementing the RTD characterization work, three representative step-change experiments were conducted to demonstrate the overall process system dynamics.

A NIR in-process control (IPC) system that allows monitoring and potential real-time diversion of nonconforming material has been developed. The model post-approval changes have been described in a post-approval change management protocol (PACMP). This PACMP was revised during the evaluation procedure to bring it in line with the EMA guideline on NIR and its addendum.

A contingency plan to be used when the NIR is not available (e.g. NIR model update) consisting of stratified sampling of tablet cores with off-line testing by the HPLC reference method has been established.

The multiple layers of control and alarm ensure that variation in tablet core concentration will be detected and non-conforming material will be rejected.

The primary packaging is a PVC (polyvinyl chloride) blister sealed with aluminium foil, or a high-density polyethylene (HDPE) bottle with polypropylene closure. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The commercial glasdegib maleate immediate release 25 mg and 100 mg tablet cores are manufactured using Pfizer's PCMM manufacturing line. The CM concerns the first three steps of glasdegib film-coated tablet manufacturing process: feeding, mixing and compression. Core tablets manufactured from this continuous process are then coated in a traditional batch tablet coating process.

Given the continuous mode of operation, the process is considered to be a non-standard manufacturing process.

The batch size has been defined by the amount of input raw materials to make a predetermined amount of tablet cores.

The continuous feeders and continuous mixer are operated to deliver material to the tablet press at a fixed total mass throughput. Start up and shut down processes, as well as strategy for controlled process pause that may be required following process events that may occur during routine manufacture, and the strategy for material diversion have been described.

There is no rework procedure for glasdegib maleate film-coated tablets.

Following a query raised during the review, the applicant confirmed that the operational ranges of the critical process parameters constitute a design space. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

The control strategy for Daurismo tablets comprises material attributes, process parameters, in-process controls, GMP controls and the finished product specification.

Taking into account that the proposed manufacturing process involves continuous manufacturing and that all the development was conducted at a manufacturing site which will not manufacture the product for the EU market, the data from the process validation at the EU manufacturing site was requested during the review.

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

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and comprises appearance, identification (LC retention time and UV spectra), assay (HPLC), impurities (HPLC), dissolution (Ph. Eur.), uniformity of dosage units by content uniformity (Ph. Eur.) and microbial limits: TAMC, TYMC, *E. coli* (Ph. Eur.)

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The potential presence of elemental impurities (EIs) in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The risk assessment concluded that none of the excipients used in the finished product formulations poses a risk of contributing Class 1 and Class 2A EIs, at levels above the 30% control threshold of their oral permitted daily exposures (PDEs), in the finished product. To confirm this, four batches each tablet strength manufactured according to the commercial process were screened for EIs identified during the risk assessments using a validated ICP-MS

method. The individual Class 1 and Class 2A EIs were all below the 30% control threshold values, with respect to their individual oral PDEs and/or concentration limits. Based on this, no controls or acceptance criteria for individual elemental impurities are proposed for the 25 mg or 100 mg glasdegib maleate immediate release film-coated tablets. The information on the control of elemental impurities is satisfactory.

A justification for not including a test for water content has been provided. This is acceptable.

Chiral purity has also been omitted, since it is controlled in the active substance and no increase in its level were observed in glasdegib 25 mg and 100 mg tablets exposed to high temperature and humidity conditions and light exposure under forced degradation conditions. This is in line with decision tree #5 of Q6A guidance.

Following the request from the CHMP during the review, a risk assessment for the potential presence of nitrosamine impurities was provided. This risk assessment followed the EFPIA workflow for active substance manufacturing process risk assessment for presence of N-nitrosamines. It included the risk assessment of all raw material used in the synthesis. No risk of nitrosamine formation (no nitrosating agents used in the manufacturing process) or source of contamination was identified within the active substance manufacturing process. The finished product formula (active substance, excipients and degradants) does not contain a secondary amine functional group, no risk has been identified for the glasdegib finished product. Furthermore, it was noted that glasdegib is intended to treat advanced cancer patients and the usual criteria for genotoxic impurities does not apply.

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

Batch analysis results obtained throughout development are provided for 58 batches of pilot or commercial scale (which include 7 commercial scale batches manufactured at the proposed manufacturing site) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three commercial scale batches of each tablet strength stored for up to 24 months under long term (25 ºC / 60% RH) and intermediate (30 ºC / 75% RH) 25 ºC / 60% RH, and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of glasdegib 25 mg and 100 mg are identical to those proposed for marketing and were packed in the primary packagings proposed for marketing (i.e. HDPE bottles or PVC/foil blisters). They were manufactured at one of the manufacturing sites used during the development program, which is not the site proposed for EU manufacture, but uses the same process flow and equipment train.

A bracketing design was applied to the testing for the HDPE bottles based on Moisture Vapor Transmission Rate (MVTR) principles. This is acceptable considering the number of tablets included in the commercial presentations (30 for the 100 mg tablets, 60 for the 25 mg tablets).

Samples were tested for appearance, assay, degradation products, dissolution, water content and microbiological quality. The analytical procedures used are stability indicating.

There were no significant trends observed in the stability results under any of the storage conditions. Although a minor increasing trend for the water content was observed under some storage conditions (e.g.

higher humidity conditions), the increases did not impact chemical or physical stability or quality and performance of the product.

Additional stability data from three commercial scale batches of each tablet strength manufactured at the site proposed for commercial manufacture for the EU market packaged in HDPE bottles and PVC/foil blisters stored for up to 6 months at the long term storage conditions of 25°C/60% RH and 30°C/75% RH and 6 months at the accelerated storage condition of 40°C/75% RH were also presented during the evaluation procedure. The samples were evaluated for appearance, assay, degradation products, and dissolution. The stability data were consistent with the results from the primary stability batches, with all results meeting the acceptance criteria.

An in-use open bottle study was carried out on two batches of each tablet strength. At the initial point of the stability study and following storage in sealed bottles for 9 and 21 months at 30°C/75%RH, bottles were opened, the cap and seal were removed and the bottles were stored without closure at 30°C/75% RH for 90 days. Samples were tested for appearance, assay, degradation products, dissolution and water content. No significant changes were observed in any of the attributes measured (other than an expected increase in water content) during the in-use study and all results met the acceptance criteria. As discussed earlier, the increase in water content did not adversely impact stability, quality or performance of the product.

Supportive stability studies were performed, consisting of (1) an open bottle thermal cycle and short term accelerated thermal/humidity study, (2) an Accelerated Stability Assessment Program (ASAP) challenge, (3) a comparative study assessing the stability performance of glasdegib maleate tablet cores produced at the development and EU commercial manufacturing sites following short term, accelerated studies and (4) forced degradation studies. These are summarized below.

To support minor shipping excursions, open bottle thermal cycle and short term accelerated thermal/humidity studies were completed on one batch of each strength of both the film-coated tablets and the intermediate tablet cores. Samples were stored in 60 cc HDPE bottles without closure or heat-induction seal and exposed to two cycles of 40°C/75% RH and -20°C, or 50°C /75% RH for 3 days.

The appearance, assay, degradation products and dissolution performance of the 25 mg and 100 mg tablets and the intermediate tablet core remained essentially unchanged through both the open bottle thermal cycle study and the open bottle 3-day 50°C/75% RH exposure. There were no reportable degradation products. As expected in an open bottle study, the water content in the samples increased. This increase did not have a negative impact on the quality attributes mentioned above and, glasdegib maleate film-coated tablets and tablet cores are not shipped in open containers, therefore the increase in water content is not of concern. These data are supportive of minor shipping excursions for the glasdegib maleate film-coated tablets and tablet cores.

For the ASAP study, 25 mg and 100 mg film-coated tablets were stored in open glass containers and exposed to various temperature, humidities and durations. The model predicted the shelf-life limiting degradant would remain below the proposed specification limit after 36 months.

A short-term, supportive stability study was conducted to compare the stability performance of tablet cores produced at the site proposed for EU manufacture and those produced at the development facility used to manufacture the primary stability batches The assessment of a single strength of tablet cores produced per site was justified and considered sufficient for the comparison. The results confirmed the equivalent stability performance of tablets manufactured at the two sites.

Forced degradation experiments were performed on 25mg and 100 mg primary stability batches to establish the extent and nature of potential degradation pathways and to confirm the suitability of the assay and purity method. The experiments included thermal, thermal humidity, and photolysis studies No degradation was observed under thermal stress conditions and under photolysis stress condition. The studies under thermal humidity stress conditions showed an increase in degradation. The liquid chromatographic assay and purity method for glasdegib maleate immediate release film-coated tablets was shown to be specific, selective and stability indicating.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were tested for appearance, assay, degradation products, and water content. No significant changes were observed in any of the parameters tested. Therefore, it is concluded that glasdegib maleate 25 mg and 100 mg immediate release film-coated tablets are stable to light and no precautionary packaging or labeling is required.

Based on available stability data, the proposed shelf-life of 2 years for Daurismo 25 mg and 100 mg immediate release film-coated tablets, as stated in the SmPC (section 6.3), is acceptable. This medicinal product does not require any special storage conditions.

Adventitious agents

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

No other excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A quality-by-design approach has been followed for the development of the active substance and finished product. A design space for the active substance and the finished product manufacture have been defined. The film-coating tablets are manufactured using a continuous direct compression process comprising feeding, blending and compression, followed by a conventional film-coating batch process. The product is released based on end-product testing. Multiple layers of control and alarm have been established ensure adequate tablet composition. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

n/a

2.3. Non-clinical aspects

2.3.1. Introduction

Glasdegib (PF-04449913) is small molecule inhibitor of Smoothened (SMO), a key transmembrane protein in the Hedgehog (Hh) signaling pathway. Aberrant activation of the Hedgehog pathway can occur by different mechanisms and result in cancer. Aberrant Hh signalling has been identified in a variety of human leukaemia and leukaemia stem cells (LSC).

2.3.2. Pharmacology

Primary pharmacodynamic studies

Table 1. Summary of key pharmacological properties of glasdegib.

In Vitro Activity	
PF-04449913 Inhibition in a Biochemical Assay	**Potency**
^{3}H-PF-03451358 competition for human SMO	IC50 = 7.7 nM
PF-04449913 Inhibition in Cell-based Assays	
Shh-induced Gli-luciferase reporter in C3H10T1/2 cells	IC50 = 5.2 nM
Inhibition of Shh-induced Gli1 mRNA in human fibroblasts	>75% at 40 nM
In Vivo Activity	
$Ptc^{+/-}p53^{+/-}$ medulloblastoma tumor growth inhibition (IC50)	73.2 nM (6.8 nM free)
Gli1 expression in medulloblastoma tumor (IC50)	101.8 nM (9.4 nM free)
Gli1 expression in the skin of non-tumor bearing mice (IC50)	675.7 nM (62.9 nM free)

Gli1 = zinc finger transcription factor; IC50 = Half maximal inhibitory concentration; mRNA = messenger RNA; Ptc = Patched; Shh = Sonic Hedgehog; SMO = Smoothened; TGI = Tumor growth inhibition.

Source: PF-04449913_10Dec08_191616.

In vitro, glasdegib bind to human SMO (amino acids 181-787) with an IC50 of 7.7 ± 7.2 nM. Glasdegib inhibited Shh-induced Gli reporter activity with an IC50 of 5.22 ± 1.65 nM (n=12). Glasdegib, at 40 nM, inhibited >75% of the Shh-induced Gli1 levels assessed in human fibroblasts. The effect of glasdegib was tested on a panel of kinases, only 3 kinases were weakly inhibited: cRAF, GRK4 and ALK4. No information is reported relative to potential effects of those kinase inhibition.

Glasdegib demonstrated antitumor efficacy in a Ptc+/-p53+/- GEM tumour model of medulloblastoma, specific model for the Hh pathway. A dose-dependent regression of tumour was demonstrated with maximal effect at ≥ 25 mg/kg. Glasdegib-induced tumour regression persisted over time with a lack of measurable tumour regrowth over 45 days following a 10-day course of once daily dosing (100 mg/kg).

Glasdegib was also tested on 3 AML patient derived xenograft models (AML009, AML183 and BM2407) as monotherapy and in combination with low dose cytarabine (LDAC) (AML183 and 009) and daunorubicin (DA)

and cytarabine (BM2407). In tested models, glasdegib has no antileukemic effect alone on CD45+/CD33+ blasts compared to vehicle group while LDAC alone or DA alone have effect. As a combination, a proof of efficacy was provided on AML 183 with LDAC but not on AML009, in which the combination with glasdegib showed no additional benefits on CD45+/CD33+ cells. In the BM2407 model, the combination of glasdegib and DA enhanced the anti-leukemic effect compared to DA treatment. As monotherapy, no proof of efficacy of glasdegib was brought in AML models.

Glasdegib produced a dose- and time-dependent reduction of Gli1 mRNA levels in medulloblastoma tumour and skin following a similar time course (IC50 = 73.2 nM for TGI, 101.8 nM; 9.4 nM free for Gli1 mRNA suppression in tumours and 675.7 nM for Gli1 mRNA suppression in the skin).

Secondary pharmacodynamic studies

The effect of glasdegib was tested against a panel of enzymes, receptors and ion-channels in vitro using a Cerep battery. Glasdegib produced a concentration-dependent inhibition of the Nav1.5 peak current, with an IC50 value of 2.6 µM.

Table 2. Off-target secondary pharmacology of glasdegib.

Type of target Model	Tests item concentration	Findings
Nav1.5 sodium current CHO cells ref 17GR212 no GLP	PF-04449913-00 1.18;3.5; 10.6; 32 and 96 µM	Inhibition 29.8 ± 3.7 at 1.18 µM 57.7 ± 2.2 at 3.5 µM 84.4 ± 2.4 at 10.6 µM 99.9 ± 1.3 at 32 µM 101.6± 0.7 at 96 µM IC_{50}=2.6 µM
A1 receptor Human recombinant, CHO cells ref 8850718	PF-04449913-01	Antagonist IC_{50}=2,6 10^{-6}M
µ opioid receptor CHO-β-arrestin-EA cells ref SP1008	PF-04449913-01-0010 3,30,300 µM	Antagonist KB 31.6 µM
histamine receptor (H1) isolated guinea pig ileum ref 17GR318	PF-04449913 1, 10, 100 µM	Antagonist KB 40 nM
Panel of receptors and enzymes assays ref 7570637 and 7571398	PF-04449913-01	Inhibition/antagonist A1, alpha 2 adrenergic, alpha 2c H1, µ, Na+ chanel

Glasdegib demonstrated activity (response > 50% of a maximal response) against a number of targets: human adenosine A1 receptor (binding assay) Ki = 370 nM, human alpha 2a adrenoceptor (binding assay) Ki = 1900 nM, human alpha 2c adrenoceptor (binding assay) Ki = 1600 nM, human mu opioid receptor (binding assay) Ki = 3500 nM, human histamine H1 (binding assay) Kb = 40 nM, sodium channel site 2 (Nav 1.5) (binding assay) Ki = 470 nM. PF-04449913 produced a concentration-dependent inhibition of the Nav1.5 peak current, with an IC50 value of 2.6 µM. PF-04449913 is an antagonist of the adenosine receptor A1 and mu opioid receptor and histamine H1 receptor.

Safety pharmacology programme

The effects of glasdegib were tested on the potassium hERG currents.

Table 3. In vitro safety pharmacology studies with glasdegib.

Type of Channel Model	Tets item concentration	Findings
hERG Potassium Channels Cloned hERG-HEK 293 cells ref 161203.QHJ GLP	PF-04449913-11 1, 3, 10 and 30 µM	Inhibition 25.3 ± 2.8% at 1 µM 51.9 ± 2.2% at 3 µM 80.0± 0.9% at 10 µM 92.8± 0.3% at 30 µM IC_{50}=2.8 µM
hERG Potassium Channels Cloned hERG-HEK 293 cells ref PF4449913/ESD/1108/HERG	PF-04449913-11 1, 3, 10 µM	Inhibition 20.4 ± 6.4% at 1 µM 49.7 ± 4.6% at 3 µM 78.5 ± 3.7% at 10 µM IC_{50}=3.1 µM
Nav1.5 sodium current HEK293 cells ref PF04449913NA15	PF-04449913-01-0010 10, 30, 100, 300 µM	Inhibition 15.6 ± 4.4% at 10 µM 49.1 ± 3.3% at 30 µM 81.3 ± 2.9% at 100 µM 97.0 ± 1.9% at 300 µM IC_{50}=32 .2 µM

It showed statistically significant inhibition from 1µM (IC50 estimated 2.8 µM). A second hERG study also demonstrated glasdegib inhibited HERG currents in a concentration-dependent manner, with an IC50=3.1 µM. Glasdegib also produced a significant concentration-dependent inhibition of Nav1.5 current (IC50=32.2 µM) at all concentrations tested.

Table below shows results of safety pharmacology studies with glasdegib.

Table 4. Glasdegib in vivo safety pharmacology studies.

Type of Study Study reference	Purpose	Test system	Main findings
Cardiovascular system			
Cardiovascular Assessment of PF-04449913 in Beagle Dogs ref 08SN238 GLP	to evaluate the potential acute pharmacological effects of PF-04449913 on the hemodynamic and electrocardiographic parameters	telemetered Beagle dog (n=4) Oral gavage, single dose Time interval follow up: 0.5-h, 7-14h, 14-22h post dose 1, 5, 30 mg/kg	1 mg/kg: nothing to note 5 mg/kg: significant increase in Qtc (5 msec) compared to vehicle, during 7-14h interval post dose 30 mg/kg: significant increase in HR (10 bpm) and QRS (3 msec), Qt, QTc (24 msec) intervals during 0.5 to 14 h post dose and Qt and Qtc until 14 to 22h post dose Emesis Cmax at 5 mg/kg: 1972ng/ml 0.5-1h post dose
Respiratory system			

Pulmonary Assessment of PF-04449913 in Males Rats ref 08SN229 GLP	to determine the effects of PF-04449913 on pulmonary function	male SD rats Oral gavage Whole body plethysmography 1, 5, 50 mg/kg	1 mg/kg: increase (7%) in tidal volume 120 min post dose 5 mg/kg: increase (6%) in tidal volume 160 min post dose 50 mg/kg: no significant effects on tidal volume, respiratory rate or minute volume
Central nervous system			
Neurofunctional Assessment of PF-04449913 in Male Rats ref 08SN228 GLP	to determine the effects of PF-04449913 in a neurofunctional assessment	male rats Oral gavage FOB, body temperature, locomotor activity 1, 5, 50 mg/kg	No statistically significant effects on any behaviour, no change in body temperature, no effect on grip strength, and locomotor activity

In telemetered dogs (5 and 30 mg/kg), glasdegib produced increases in QT and QTc intervals until 22 hours after dosing and statistically significant increase in QRS interval (30 mg/kg) up to 14 hours after dosing as well as heart rate decrease. This effect was consistent with the inhibition observed on Nav1.5. No effect on blood pressure were reported. A safety margin between the Cmax plasma concentration of 1972.5 ng/mL achieved after dosing with 5 mg/kg corresponds to approximately 13x the predicted clinically efficacious total concentration of approximately 150 ng/mL.

Regarding respiratory system, significant effects were observed on tidal volume (increase) but were not dose related or linked to respiratory rate / minute volume. In the 26-week repeat dose GLP rat toxicity study, laboured breathing was observed in some animals administered 50 mg/kg/day but this dose was not tolerated and resulted in several adverse clinical signs and moribundity. There were no microscopic findings in the lungs of any animals.

Concerning central nervous system, glasdegib had no effect on locomotor activity, behaviour and body temperature until 50 mg/kg at 4x the observed unbound Cmax at the 100 mg QD clinical dose. Additionally, FOB and locomotor activity assessment was added on to the repeat dose 26-week chronic toxicity study in rats. Several effects were observed at doses ≥50 mg/kg/day. There were no microscopic findings noted in the brain of any animals.

Pharmacodynamic drug interactions

Non-clinical pharmacodynamic drug interaction studies have not been conducted.

2.3.3. Pharmacokinetics

The ADME profile of glasdegib has been evaluated in in vitro assays and in vivo in rat, dog and rabbit.

Analytical methods

Concentrations of glasdegib in animal plasma were determined by LC-MS/MS validated in rat, dog and rabbit plasmas over the range 1-1000 ng/ml for the 3 species. The full validation of measurement included selectivity, linearity, LLOQ, carry-over, intra-and inter-assay precision and accuracy, stock solution stability, short-term matrix stability, freeze-thaw and long-term matrix stability and dilution integrity. All the results met the acceptance criteria.

Absorption

The PK profile of glasdegib following intravenous or oral administration has been assessed in rats and dogs.

Table 5. Plasma PK parameters for glasdegib following single dosing.

Study ID		Species n	Dose (mg/kg) Route	C_{max} (ng/ml)	T_{max} (h)	AUC_{0-inf} (ng.h/ml)	Cl (ml/min/kg)	Vss (l/kg)	$t_{1/2}$ (h)	F (%)
143627		Rat SD 3M/gp	1 mg/kg, PO, Fasted (0.5% methylcellulose)	38.6	0.33	109				33.2
			1 mg/kg, IV (bolus) Solution (10% ethanol/20% PEG400/70% PBS)			329	50.9	4.78	1.4	
PF-04449913/12Nov08/161811		Rat SD PO;4M/gp IV:5M/gp	5 mg/kg, PO, Fed Solution (0.5% methyl cellulose and 0.25 equiv HCl)	53.8	1.3	356				18.9
			5 mg/kg, PO, Fasted Solution (0.5% methyl cellulose and 0.25 equiv HCl)	172	1.75	655				34.9
			5 mg/kg, IV (50% glycerol formal: 50% water)			2430	39.6	4.22	1.2	
PF-04449913/14nov08/143412		Beagle dog 2M/gp	3 mg/kg, PO, Fasted 0.5% methylcellulose	1070	0.5	3860				68
			0.5 mg/kg, IV, Fasted (10% ethanol/20% PEG400/70% PBS)			368	22.9	4.21	2.3	

Terminal half-life after IV administration was 1.2 to 1.4 hours in rat and 4.2 hours in dog. Volume of distribution was 4.2 to 4.8 L/kg in rat and 4.2 L/kg in dog, hence glasdegib appear to be mainly distributed to tissues. Oral bioavailability was 68% in dog and 19 to 35% in rat. Bioavailability was higher in fasted rats. Food effect of glasdegib oral bioavailability was evaluated in a clinical study.

The PK of glasdegib was characterized in rats and dogs, following consecutive daily oral administration in repeat dose toxicity studies and fetal development (EFD) toxicity. In rats, during repeat-dose toxicity studies (1-month, 13-week and 9-month), no apparent sex-related differences in exposure were demonstrated. Mean systemic exposure to glasdegib (AUC24) increased with dose in a greater than dose proportional manner. In the 26-week repeat-dose study, apparent accumulation of glasdegib was observed (AUC24 and Cmax), ranging from 2.0x to 6.2x when compared to the exposures on Day 1, while steady-state exposures on Weeks 13 and 26 were similar to those observed in previous studies. Glasdegib was rapidly absorbed in dogs with mean Tmax occurring <3 hours post dose for all dose groups across all studies.

Distribution

Glasdegib appeared to be moderately to highly protein bound, in plasma , with the overall mean fraction unbound of 0.0470 (CD-1 mice), 0.0932 (SCID mice), 0.110 (SD rats), 0.0203 (NZW rabbit), 0.141 (Beagle dog), 0.0899 (human) across all evaluated concentrations. The binding to human serum albumin and alpha 1-acid glycoprotein was moderate with fu of 0.204 and 0.478, respectively.

Glasdegib demonstrated species dependent blood partitioning with a modest preferential distribution into the blood cells of rats and humans, a limited distribution into the blood cells in rabbits, over a concentration range of 0.2 to 50 µM and a marked, concentration-dependent and saturable preferential distribution into the blood cells of dogs.

In vivo, glasdegib was widely distributed to tissues in a QWBA study in rats after oral gavage. Maximum concentration was reached 0.5 hour post-dose in the majority of tissues. The highest concentrations of radioactivity in tissues were found in uveal tract, liver, kidney and renal substructures, adrenal gland, and pancreas. Elimination was quite complete except for the eyes and uveal tract (until 672 h). Glasdegib penetrate the blood:brain barrier, at low levels and for short duration after oral dosing and exhibited an affinity for pigmented ocular tissues containing melanin. This association was slowly reversible, with a slower elimination rate (t1/2 values of 717 and 1656 hours) than observed for non-pigmented skin.

Metabolism

In vitro studies were performed on HLM and human enzymes (UGT, CYP), a comparative study was performed on rat, dog, monkey, human and mouse liver microsomes, human hepatocytes, rat bile and rat and dog plasma.

Table 6. Glasdegib in vitro metabolite profiling.

Type of Study/Test system reference	Concentration/ Dose	Assay	Metabolite profiling and identification
Enzymes phenotyping			
UGT enzymes			
Enzyme kinetics and identification of UDP-UGT isoforms involved in the in vitro metabolism of PF-04449913 Study 050630	PF-04449913 5 to 1000 µM	human liver microsomes	PF-04449914 glucuronidation was only mediated by UGT1A9.
Glucuronide conjugates of PF-04449913 in human liver microsomes and recombinant UGT1A9 and in human urine (single administration) Study 153629	[^{14}C]PF-04449913 1µM	human liver microsomes LC-MS	Same single glucuronide conjugate formed in both in vitro systems and present in human urine (M8) following oral administration of PF-04449913.
Preliminary *in vitro* recombinant UDP-UGT phenotyping of PF-04449913 Study 163216	PF-04449913 10-250µM and 1000µM	recombinant human UGTs	➢formation of glucuronide metabolite (M8 N glucuronide) of PF-04449913 observed during rUGT1A9 incubations ➢glucuronide metabolite not detected in incubations with recombinant UGTs 1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A10, 2B4, 2B7, 2B10, 2B15 or 2B17.
CYP enzymes			
Phenotyping of PF-04449913 using human hepatocyte relay method Study 081555	PF-044499131 1 µM	human hepatocyte relay method LC-MS/MS	Contribution of enzymes to PF-04449913 metabolism: 76% by CYP3A and 15% by CYP2C8. Total CYPs' contribution to PF-04449913 metabolism> 91% and contribution of non-CYPs < 9%
In vitro cytochrome P450 reaction phenotyping of PF-04449913 Study 172724		recombinant cytochrome P450 enzymes LC-MS/MS	Among 11 recombinant cytochrome P450 (CYP) enzymes, CYP3A4 primarily responsible for PF-04449913 metabolism (99.9%) with minor contribution from CYP2D6 (0.1%) and negligible contributions from the 9 others P450s
Enzyme kinetics and identification of cytochrome P450 insoforms involved in the in vitro metabolism of PF-04449913 Study 112959	PF-04449913 1 or 30 µM	human liver microsomes LC-MS/MS	➢CYP 3A4 major isoform involved in the formation of all 4 metabolites, M1, M2, M3, and M9 accounting for 60% to 80% of the total PF-04449913 metabolism in vitro ➢lesser contributions from CYPs 2C8 (2-20%), 2C9 (≤ 1%), and 1A2 (≤ 1%)
Biotransformation			
Biotransformation of PF-04449913 in rat, dog, monkey, human and mouse liver microsomes, human hepatocytes, rat bile and rat and dog plasma Study 130612	PF-04449913	human hepatocyte microsomes rat and dog plasma LC/MS chromatography	Low metabolism of PF-04449913 in non clinical species and human matrices, NADPH-dependent 5 metabolites identified, identical metabolites with varying abundance between species (table below) <u>In rat plasma</u> M2 (25%), M1, M3, M4, and M5 (<5% of PF-04449913) <u>In dog plasma</u> only M4 observed at 30 mg/kg No metabolites identified at lower doses Based on the relative abundance of metabolites observed in rat urine, bile, and plasma, it appears that the primary metabolic pathway in rat involves hydroxylation of the benzimidazole ring followed by conjugation with glucuronic acid.

The metabolism of glasdegib was low and qualitatively similar across species with varying abundance in liver microsomes and human hepatocytes. Predominantly oxidative metabolites were detected in vitro and included M1, M2, M3, and M4.

Considering CYP P450 phenotyping, total CYPs' contribution to glasdegib metabolism is > 91% and contribution of non-CYPs is < 9% and CYP3A4 major isoform is mainly involved with minor contributions from remaining CYPs. The metabolism was NADPH dependent in non-clinical species and human matrices with 5 metabolites identified. UGT1A9 was identified as the enzyme responsible for metabolizing glasdegib to M8 N glucuronide observed in vitro and present in human urine.

In vivo metabolism studies were conducted in rat and dog plasmas and excreta and compared to humans after oral administration.

Table 7. Metabolite profiling and identification.

Species	Model	Type of Study, Study reference	Route and dose (mg/kg)	Assay	Metabolite profiling and identification
Rat	SD male and female naïve and bile-duct cannulated	Study 090256	[^{14}C]PF-04449913 PO 10 mg/kg (single dose)	LC-MS	➢ similar metabolism for male and female naïve and bile-duct cannulated rats ➢ unchanged PF-04449913 : major component of naïve rat plasma (63.4% and 82.5% of the total drug-related material in M and F rats) major component of naïve rat excreta (41.1% of the total dose in M and 51.0% in F) major component of bile-duct cannulated rat excreta (62.2% in M and 41.1% in F) ➢ primary metabolic pathways for [^{14}C]PF-04449913 : N-demethylation, oxidation, dehydrogenation and nitrile hydrolysis. ➢ in plasma, a product of N-demethylation of the N-methylpiperidine group: major metabolite (18.0% and 4.4% in male and female naïve rats) ➢ in naïve rat excreta: a product of mono-oxidation in the benzimidazole group most abundant metabolite (38.3% and 32.5% of the dose in M and F) ➢ in bile-duct cannulated rat excreta, a product of mono-oxidation and subsequent glucuronidation the most abundant metabolite (10.4% and 28.1% of the dose in male and female rats) ➢ Additional sites of metabolism identified in rat plasma and excreta included mono-oxidation and dehydrogenation in the piperidine ring and hydrolysis of the nitrile group to form a primary amide. M1 mono-oxidation in the benzimidazole ring, M1 accounted for 38.3% and 32.5% of the dose respectively in male and female naïve rat excreta, 7.0% and 12.2% of the dose respectively in male and female bile-duct cannulated rat excreta, minor component in male and female naïve rat plasma. M2 dehydrogenation in the piperidine ring. minor component in male and female naïve rat plasma and excreta and in male and female bile-duct cannulated rat excreta. M3 N-demethylation of the N-methylpiperidine ring. M3 accounted for 18.0% and 4.4% of the total radioactivity respectively in male and female naïve rat plasma, 6.1% and 2.4% of the dose respectively in male and female naïve rat excreta and 3.0% and 2.9% of the dose respectively in male and female bile-duct cannulated rat excreta. M4 product of N-oxidation of the N-methylpiperidine ring. minor component in male and female naïve rat plasma and excreta and in male and female bile-duct cannulated rat excreta. M5 mono-oxidation and subsequent glucuronidation in the benzimidazole ring, although the specific sites of oxidation and conjugation could not be determined. minor component in male and female naïve rat plasma and excreta (detected in female rat urine only) but accounted for 10.4% and 27.4% of the dose respectively in male and female bile-duct cannulated rat bile.

					M9 mono-oxidation in the benzimidazole ring, although the specific site of oxidation could not be determined. trace component in male and female naïve rat plasma and a minor or trace component in male and female naïve rat excreta and male and female bile-duct cannulated rat excreta. M10 aliphatic mono-oxidation (proposed on the basis of dehydrated ions at m/z 241 and 198) and N-demethylation in the N-methylpiperidine moiety, although the specific site of oxidation could not be determined. trace component in male and female naïve rat plasma and a minor component in male bile-duct cannulated rat urine. M12 hydrolysis of the nitrile group to yield a primary amine. minor or trace component in male and female naïve rat feces and a minor component in male and female bile-duct cannulated rat feces M13 N-demethylation in the N-methylpiperidine group and mono-oxidation in the benzimidazole moiety. minor or trace component in male and female naïve rat feces and a trace component in male bile-duct cannulated rat feces
Rat	Long Evans	Study 122431	[^{14}C]PF-04449913 PO 10 mg/kg (single dose)	QWBA	➢ PF-04449913 (32.1% and 49.5% of radioactivity recovered in feces and urine) and 3 metabolites identified in feces and urine. M1,benzimidazole ring hydroxylated metabolite: major fecal component (49.9% of fecal radioactivity and 12.7% of urinary radioactivity) M2, piperidine ring desaturated metabolite: minor component in both matrices at 1.7% and 3.4% of fecal and urinary radioactivity M3, N-demethylated metabolite, major urinary component at 22.8% of urinary radioactivity and 6.6% of fecal radioactivity.
Dog	Beagle FORMULATION	Study 090417	[^{14}C]PF-04449913 PO 5 mg/kg (single dose)	LC-MS	➢ similar metabolism for male and female dogs. ➢ unchanged PF-04449913: major component of dog plasma (83.7% and 80.1% of the total drug-related material in M and F), and excreta, (22.3% of the total dose (comprising 1.8% of the total dose in urine and 20.5% of the total dose in feces) in male dogs and 28.0% of the total dose (comprising 1.9% of the total dose in urine and 26.1% of the total dose in feces) in female dogs . ➢ primary metabolic pathways: N-demethylation, oxidation, dehydrogenation and nitrile hydrolysis. In plasma, an unknown metabolite and a product of mono-oxidation in the benzimidazole group were the most abundant metabolites in male and female dogs, although all metabolites in plasma individually accounted for ≤5% of the circulating radioactivity. A product of mono-oxidation in the benzimidazole group : most abundant metabolite in excreta, (51.0% and 45.4% of the dose in M and F dogs respectively). The N-desmethyl metabolite accounted for 4.3% and 3.9% of the dose in the excreta of male and female dogs respectively, whilst all other metabolites in the excreta individually accounted for <2% of the dose. Additional sites of metabolism identified in dog plasma and excreta included mono-oxidation and dehydrogenation in the piperidine ring, mono-oxidation in the benzonitrile group and hydrolysis of the nitrile group to form a primary amide.

In vivo, unchanged glasdegib is the major component of naïve rat plasma and excreta and either bile-duct cannulated rat excreta. Nine metabolites were identified in rat (M1, M2, M2, M4, M5, M9, M10, M12, M13), the first 5 being predominant and the remaining ones existing as minor components. Unchanged glasdegib is also the major component retrieved in dog plasma and excreta. M2 was predominant in rat plasma (25%) and M4 only was observed in dog (high dose). In plasma, an unknown metabolite and a product of mono-oxidation in the benzimidazole group were the most abundant metabolites in male and female dogs, although all metabolites in plasma individually accounted for ≤5% of the circulating radioactivity. The major metabolic pathways of glasdegib seem to be oxidation (N-demethylation, hydroxylation and dehydrogenation), primary glucuronidation, and secondary N-glucuronidation of oxidative metabolites in both rats and dogs.

Glasdegib and radioactivity related to glasdegib is mainly excreted through faeces and bile in rat and dog. Metabolic profiles in plasma, urine and faeces were overall considered to be similar among non-clinical species and humans. Three glucuronidated metabolites were identified as unique for human plasma and urine. Two of those (M6, M7) were below 2% of total radioactivity in plasma. The third (M8) comprised of 7.2% in plasma and were not an acyl glucuronide and therefore not of toxicological concern. UGT1A9 was suggested to be responsible for formation of M8.

Excretion

The excretion of glasdegib was investigated in rat and dog and compared to humans using [14C]-glasdegib (study 8309181 and 182).

In male and female beagle dogs after a single oral dose of [14C]PF-04449913 monohydrate-2HCl (5-mg/kg dissolved in 0.5% methylcellulose). Blood was collected through 24 hours postdose and excretion profiles of total radioactivity were determined through 168 hours postdose. Cmax in blood and plasma occurred at 2 h postdose for males and at 1 h postdose for females. Blood and plasma radioactivity concentrations were quantifiable in all dogs through 24 hours postdose and were generally at least 2-fold lower in plasma than blood at the corresponding time points over this duration. After reaching Cmax, plasma total radioactivity concentrations declined, with an average terminal plasma elimination t1/2 of 4.8 hours for males and 4.5 hours for females. The predominant elimination route of radioactivity was fecal excretion and the majority of the radioactivity was eliminated within 48 h postdose for both genders. Through 168 hours postdose, average recoveries in feces accounted for 82.4% and 83.0% of the dose for males and females, respectively. The average recovery in urine accounted for 7.20% and 7.50% of the dose in males and females, respectively. The average total recoveries of the administered dose were 93.0% for males and 92.5% for females.

In SD rats, excretion profiles of total radioactivity were determined in intact male and female rats through 168 hours postdose, and in BDC male and female rats through 48 hours postdose. For males and females, after a single oral dose of [14C]PF-04449913 (10-mg/kg in 0.5% methylcellulose), Cmax in plasma occurred at 1 hour postdose and plasma radioactivity concentrations were quantifiable in all rats through 24 hours postdose. After reaching Cmax, plasma total radioactivity concentrations declined, with a terminal plasma elimination t1/2 of 5.9 hours for males and 3.3 hours for females. The predominant elimination route of radioactivity was faecal excretion. The majority of the radioactivity was eliminated within 24 and 48 hours postdose for male and female rats, respectively. Through 168 hours postdose, average recoveries in faeces accounted for 93.7% and 89.2% of the dose for males and females, respectively. For males, the average recovery in urine accounted for 5.66% of the dose. For females, the average recovery in urine accounted for 5.88% of the dose. Total average recoveries of the dose were 100% and 96.7% for male and female rats, respectively. After oral administration of [14C]PF-04449913 to BDC male and female rats, biliary excretion of radioactivity through 48 hours postdose accounted for 26.0% and 45.7% of the dose for the male and female rats, respectively. Recoveries of radioactivity in faeces were 67.6% for the male rat and 41.0% for the

female rat. Recoveries of radioactivity in urine from male and female rats were 2.82% and 13.9%, respectively. Total recovery of the dose was 101% for the male BDC rat and 102% for the female BDC rat. Bile and urine recovery data indicated that a minimum of 29% and 60% of the orally-administered radioactivity was absorbed in male and female BDC rats through 48 hours postdose, respectively.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies with glasdegib have not been conducted.

Repeat dose toxicity

Six pivotal repeat-dose toxicity studies were performed in SD rats and Beagle dogs from 29-day to 26 and 39-week studies, respectively. Glasdegib was administered in 0.5% methylcellulose across studies. The non-pivotal 7 and 10-day and pivotal 1-month studies were conducted using the dihydrochloride salt form (lot#121675-119-8); all other pivotal studies were conducted using the maleate salt form (lot#705848-213-00) which is the form that will be commercially available. Similar exposures were achieved between the two salt forms in repeat-dose toxicity studies and there were no sex related differences in exposure.

Table 8. Repeat dose toxicity studies.

Study reference/ GLP compliance	Species (number, sex)	Route Dose (mg/kg/d) Duration	NOAEL (mg/kg/day)	Major findings

RAT				
1-month toxicity rat 1-Month Oral Toxicity Study of PF-04449913 in Rats with 1-Month Recovery with Micronucleus Assessment GLP ref 08LJ094	SD rats 10-15/sex/gp	Oral gavage 0.5% (w/v) methylcellulose 1, 10, or 50 mg/kg/day 29 days	NOAEL 10 mg/kg	● **Mortality** 1 female dead at day 2, 10 mg/kg, not related to test article (urogenital tract inflammation) ● **Clinical signs and BW** Oral discharge 1 animal (50 mg/kg) BW ↓ and food consumption ↓ (50 mg/kg) and did not reverse ● **Ophtalmology** Nothing to note ● **Haematology** ↑ WBC ● **Serum chemistry** ➢creatinine higher in M and F, globulin higher in males, and inorganic phosphorus in females (50) ➢red cell mass lower (i.e., red blood cell count, hb and hematocrit) in M, minimally higher red distribution wid (RDW) and absolute reticulocyte count in males and females, ➢minimally higher absolute neutrophil count in males, ➢minimally lower albumin resulting in a lower albumin-to-globulin ratio in females, and minimally high cholesterol and lower calcium and alkaline phosphatase activity observed in males and females (50 mg/kg/da All clinical pathology findings exhibited reversibility at the end of the recovery phase, except lower albumin whi persisted ● **Urinalysis** presence of granular casts in the urine (50) ● **Organ weights** ➢ ↑kidney weight (absolute and organ/body weight ratio) of females (50 mg/kg/day, end of dosing) ➢ ↓ heart and liver weight in males and females, ↓ spleen weight in males, and ↓ kidney weight in female and these decreases were considered related to the decreased terminal body weight (at recovery) ● **Histopathology** ➢kidney: tubular cell regeneration (often with cytomegaly/karyomegaly), degeneration/necrosis of tubul epithelial cells, and increased lymphocyte/macrophage infiltrate.) from 10 to 50, dose related ➢bones : epiphysis alteration (decreased chondrocytes and disorganization of chondrocytes) and ↓ in medulla trabeculae of femur and sternum bone sections (50 mg/kg) The femur and sternum epiphysis alteration decrease in medullary trabeculae persisted in animals that had be given 50 mg/kg/day. The decrease in the group incidence and severity of findings suggest the kidney changes a reversible but not completely reversed after the 1-month recovery period. ● **TK** no marked gender-related differences in exposure, no apparent drug accumulation. Systemic exposure increase with dose, Cmax and AUC_{0-24} increased greater than dose proportional for both ma and female rats on Days 1 and 86, possible intrinsic sex difference Evidence for accumulation with repeated daily dosing $t_{1/2}$ 5.05 to 8.75 h day 1 , $t_{1/2}$ 9.44 to 15.3 h day 86

13-week toxicity rat 13-Week Oral Gavage Toxicity and Toxicokinetic Study with PF-04449913 in Rats GLP ref 14LJ052	SD rats **10-15/sex/gp**	Oral gavage, once daily 0.5% (w/v) methylcellulose 10, 50, 100 mg/kg/day 92 days	NOAEL 10 mg/kg Cmax and AUC24 1060 ng/mL and 10,000 ng·hr/mLon Day 87	• **Mortality** 2 females 50 kg/day died following clinical pathology blood collection on Day 53, cause accidental • **Clinical signs and BW** >50 mg/kg/day: tremors; twitching (entire body); malocclusions; discolored (white) or missing teeth; swoll gingiva; clear oral discharge; rough haircoat; and thinning haircoat in the perioral, ventral cervical, or ventral thor regions lower mean BW and BW gains for M and F at at >50 mg/kg/day for F • **Ophtalmology** Nothing to note • **Clinical pathology** ➢≥50 mg/kg/day: Mildly lower red cell mass (i.e., red blood cell count, hb and hematocrit) in M (100) and (50), mildly to moderately higher red cell distribution width and absolute reticulocyte count for males a females ➢Mildly higher WBC count due to higher absolute neutrophil and/or lymphocyte counts for males and femal given 100 mg/kg/day ➢mildly lower albumin:globulin ratio for males and females given 100 mg/kg/day were consistent with a m inflammatory response. ➢Minimally higher urea nitrogen and creatinine concentrations and higher incidence and/or severity of granul casts, white blood cells, and epithelial cells present in the urine sediment for males and females given ≥ mg/kg/day ➢mildly to moderately lower alkaline phosphatase activity for males given ≥50 mg/kg/day and females giv 100 mg/kg/day (reduced osteoblast activity) 10 mg/kg/day had no effect • **Histopathology** ➢kidney: tubular epithelial cell degeneration/regeneration discolored tan and/or brown kidney ≥50 mg/kg/da ➢bone and marrow of the femur and sternum, minimal to moderate and minimal to mild disorganization chondrocytes ≥50 mg/kg/day, hypercellularity of marrow ➢thymus, decreases in lymphocytes ≥50 mg/kg/day ➢one or more incisor teeth, mild to marked degeneration/necrosis/absence of the apical portion and minimal marked neutrophil infiltrates, discolored or not present incisor ≥50 mg/kg/day ➢oral mucosa, erosion/ulcer 100 mg/kg ➢peripheral nerve coincidentally present in the mesentery adjacent to the mesenteric lymph node. axon degeneration in the nerve adjacent to the mesenteric lymph node ≥50 mg/kg/day • **TK** No apparent sex-related differences, Tmax 2-6h (day 87), AUC and Cmax increase with dose

26-week toxicity rat 26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with PF-04449913 in Rats with a 13-Week Recovery Phase GLP Ref 14LJ108	SD rats 10-20/sex	Oral gavage, once daily 0.5% (w/v) methylcellulose 10, 50, 100 mg/kg/day 26 weeks	NOAEL 10 mg/kg Cmax and AUC24 1050 ng/mL and 7,800 ng•hr/mL, respectively, on Week 26.	• **Mortality** At 100 mg/kg/day: treatment was terminated at 18 weeks due to mortality in M and F (≥50 mg/kg/day) andear scheduled euthanasia of all surviving toxicity animals administered 100 mg/kg/day occurred The cause of PF-04449913-related mortality: dental abnormalities or renal tubule cell necrosis noted histologicall • **Clinical signs and BW** ≥50 mg/kg/day : continuous or intermittent tremors (various body regions or whole body); malocclusions; missi teeth; thin appearance; clear oral discharge; squinting eyes; rough haircoat and piloerection; rough, thinning discolored (red, yellow, black, or brown) haircoat in various body regions; and alopecia. labored respiration and Hypoactivity 100 mg/kg/day: hunched posture, nonformed feces, red or clear nasal discharge, and pale feet or ears Clinical observations that persisted through the recovery phase at 50 or 100 mg/kg/day included malocclusion missing teeth, and discolored or thinning haircoat. ≥50 mg/kg/day: dose-dependent lower mean body weights and body weight gains (little evidence of recovery) a lower mean food consumption • **FOB** ≥50 mg/kg/day excessive salivation; exophthalmos; piloerection (also in females administered 10 mg/kg/day tremors; barbered or stained fur; clonus (100 mg/kg/day only); reduced forelimb and hindlimb grip strength, a decreased mean locomotor activity (reverted at recovery except piloerection, tremors, reduced grip strength, a mean locomotor activity) • **Ophtalmology** Nothing to note • **Haematology/Clinical pathology** ➢≥50 mg/kg/day: red blood cell loss and inflammation (↓ RBC, Hb, Ht), ↑ reticulocytes, platlets and leukocy (Differences in hematology parameters of animals administered ≥50 mg/kg/day were reversed by Day 95 of t recovery phase in animals administered 50 mg/kg/day or by Day 151 of the recovery phase in animals administe 100 mg/kg/day.) ➢↑ urea nitrogen, creatinine, phosphorus, lower albumine • **Histopathology** ➢hypercellularity of marrow in the femur and sternum, disorganization of chondrocytes in the physis of t femur and sternum and erosion/ulcer in the oral mucosa ≥50 mg/kg/day ➢kidney: tubular epithelial cell degeneration/regeneration discolored kidney ≥50 mg/kg/day ➢one or more incisor teeth: degeneration/necrosis/absence apical portion and minimal to moderate mixed c infiltrates (corresponded with the macroscopic finding of not present incisor teeth, and clinical observations missing teeth, malocclusions, and clear oral discharge) ≥50 mg/kg/day ➢nerve (other; nerve found adjacent to the mesenteric lymph node region and associated adipose tissue ≥ mg/kg/day ➢testis severe hypospermatogenesis in males administered ≥50 mg/kg/day (partial to complete loss spermatogonia, spermatocytes, and spermatids; some animals also exhibited degeneration of seminifero tubules) At recovery necropsies, PF-04449913-related microscopic observations persisted in the teeth, femur, and sternu of animals and testis of males administered 50 or 100 mg/kg/day, indicating a lack of recovery. The kidn

				degeneration/necrosis and axonal degeneration nerve (other) observed at the terminal euthanasia were n observed at the recovery euthanasia. ● **TK** No apparent sex-related differences Tmax 3.3-4.8h day 1 and 1.4 -4.1h week 26 Systemic exposure increase with dose 10 to 100 mg/kg/day on Day 1 and during Week 13 and from 10 to 5 mg/kg/day during Week 26. Exposure was 2.0x to 6.2x during Weeks 13 and 26 when compared with Day 1.
DOG				
1-month toxicity in dog Oral Toxicity and Toxicokinetic Study of PF-04449913 in Dogs with 1 Month Recovery GLP ref 08LJ093	Beagle dog **3-5/sex/gp**	Oral gavage 0.5% methylcellulose 1, 5, 30/15 mg/kg/day **30 days**	NOAEL 1 mg/kg (AUC0-24)= 1020 ng.h/ml in M 427 ng.h/ml in F Cmax 201 ng/ml in M 100ng/ml in F	● **Mortality** 2 M (30/15 mg/kg/day) sacrificed on Day 11, and 1 (30/15 mg/kg/day) sacrificed on Day 19 1 F (30/15 mg/kg/day) sacrificed on Day 15, and 2 F (30/15 mg/kg/day) on day 19 Treatment-related kidney changes contributed to the moribund condition of these animals, and the deaths we considered treatment-related. marked azotemia in animals sacrificed ● **Clinical signs and BW** dehydration, tremors, hypoactivity, excessive salivation, vomitus, discoloured feces, and liquid feces (30/ mg/kg/day) no significant BW loss (reverse) and ↓ food consumption (reverted in F and partly in M) ● **Ophtalmology** Nothing to note ● **Electrocardiograhy** Nothing to note ● **Clinical pathology** At 30/15 mg/kg/day: azotemia (↑ urea nitrogen, creatinine, phosphorus) (partly reverted ↓ sodium and chloride ● **Histopathology** ➢ kidney findings 30/15 mg/kg/day: necrosis/degeneration of cortical tubules, granular/mineralized casts, a dilated tubules and were generally more severe in males 5 mg/kg/day: minimal to slight necrosis/degeneration and lacked granular mineralized casts and dilated tubul ➢increased incidence and mean severity score of lymphocyte/macrophage infiltrates, cortical tubul regeneration, and proteinaceous casts. Renal findings and lymphocyte/macrophage infiltrates partly reverted in females and reverted in males ● **TK:** Gender-related differences in exposure at 1 mg/kg/day only (males X2 compared to females), Tmax=0.5-1h Systemic exposure increase with dose, greater than proportional , possible drug accumulation

13-week toxicity in dog 13-Week Oral Gavage Toxicity and Toxicokinetic Study with PF-04449913 in Dogs GLP Ref 14LJ055	Beagle dog 3/sex/gp	Oral gavage 0.5% methylcellulose 1, 5, 10 mg/kg/day 13 weeks	NOAEL 1 mg/kg/day 65.5 ng/mL and 487 ng.hr/mL Combined Cmax and AUC	• **Mortality** no • **Clinical signs and BW** thin appearance (females given >5 mg/kg/day, and males given 10 mg/kg/day), abnormal (liquid or nonformed feces (animals given 10 mg/kg/day), and perioral alopecia 10 mg/kg/day: Transient individual body weight loss, decreases in mean body weight gain, and decreased food consumption • **Haematology, coagulation, ophthalmology, ECG:** nothing to note • **Clinical pathology** ➢≥5 mg/kg/day mildly to moderately increased urea nitrogen and/or creatinine ➢granular casts in the urine sediment of one female given 10 mg/kg/day ➢mildly increased ALT on Day 92 of the dosing phase for one male given 5 mg/kg/day ➢mildly to moderately increased cholesterol 10 mg/kg/day • **Organ weights** nothing to note • **Histopathology** ➢ kidney ≥5 mg/kg/day: degeneration/necrosis of renal cortical tubules and granular/hyaline casts, dilatation of the tubules, and/or infiltrates of lymphocytes/macrophages. ➢ liver 1 or 5 mg/kg/day: mixed cell inflammation, iron pigment in Kupffer cells In general, males were affected more severely than females and findings were considered adverse at ≥5 mg/kg/day due to the severity of the renal and liver findings and evidence of clinical pathology changes. • **TK:** Cmax and AUC_{0-24} increased with dose, no apparent sex difference, Tmax 2-2.3 h day 89
39-week toxicity in dog 39-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with PF-04449913 in Dogs with a 16-Week Recovery Phase GLP	Beagle dog 4-6/sex/gp	Oral gavage 0.5% methylcellulose 1, 5, 10 mg/kg/day 39 weeks Once daily	NOAEL Not established	• **Mortality** Mortality at ≥1 mg/kg/day: euthanasia (BW loss, ↓ food consumption, thin appearance, dehydration, hypoactivity, periodic vomitus, abnormal feces, thinning hair coat, ocular discharge, discolored red skin, excessive salivation, clenched teeth, and/or cold to touch, test article-related microscopic findings in the kidney (tubular degeneration/necrosis, tubular regeneration, granular/cellular casts, and tubular dilatation), and liver (centrilobul

Ref 14LJ109				to midzonal mixed cell inflammation, single cell necrosis of hepatocytes, centrilobular hepatocyte vacuolation, ar Kupffer cell/macrophage pigment) Euthanasia of surviving animals (5 and 10 mg/kg/day) ● **Clinical signs and BW** thin appearance, hypoactivity, periodic vomitus, evidence of dehydration (as noted by a veterinarian), and cold touch ≥1 mg/kg/day: body weight loss and reduced food consumption ● **Organ weights, ophthalmology, ECG, haematology, coagulation** nothing to note ● **Clinical pathology** ➢mildly to moderately increased AST, ALT, ALP, GGT (1 and 5 mg/kg/day transient, reverted -) ➢increased cholesterol (10 and >5 mg/kg/day (F): (transient, reverted) ● **Urinalysis** 5 and 10 mg/kg presence of granular casts in the urine sediment (reverted) ● **Histopathology/macroscopic observations** ➢ kidney (≥5 mg/kg/day): discoloration, degeneration/necrosis/ regeneration (reverted) ➢ skin/subcutis alopecia (≥1 mg/kg/day) hair shaft atrophy (reverted) ➢ gastrointestinal tract (>1 mg/kg/day): discoloration (red, dark red, black, or brown) of 1 or more segmen (stomach, duodenum, jejunum, ileum, and colon) ➢ liver (≥5 mg/kg/day): hepatocyte necrosis, centrilobular/midzonal mixed (partly reverted), cell inflammatio Kupffer cell/macrophage pigment, and centrilobular hepatocyte vacuolation ➢thymus, mesenteric lymph node ➢pancreas and prostate. In general, males were affected more severely than females and findings were considered adverse at ≥5 mg/kg/da due to the severity of the renal and liver findings and evidence of clinical pathology changes. ● **TK:** Toxicokinetic parameters were calculated for Groups 2-4 on Day 1, during Week 13, and on Day 160 and for Gr during Week 39 due to mortality Cmax and AUC0-24 increased with dose, no apparent sex difference in exposure, exposure similar along time Tmax 0.9-1.3 h day week 13 and day 160

In rats, the main target organs were kidney (mild to marked tubular degeneration/necrosis, cytomegaly, inflammation, regeneration, increased creatinine, increased kidney weight), bone physis (femur, sternum mild to moderate disorganized and hypertrophic chrondrocytes; partial closure of epiphysis), abnormal mouth and incisor teeth (mild to marked incisor tooth degeneration/necrosis; complete loss of apical portion of teeth, swollen gingiva, and clear oral discharge, malocclusions), peripheral nerve (minimal to mild axonal degeneration swollen axons, and multifocal relative increases in Schwann cell numbers) and testis (severe hypospermatogenesis at 50 mg/kg/day, partial to complete loss of spermatogonia, spermatocytes, and spermatids; degeneration of seminiferous tubules in some animals). The NOAEL was 10 mg/kg/day for all studies. Regarding longer duration studies, at recovery necropsies, glasdegib-related microscopic observations persisted in the teeth, femur, and sternum of animals and testis of males administered 50 or 100 mg/kg/day, indicating a lack of recovery. The kidney degeneration/necrosis and axonal degeneration nerve observed at the terminal euthanasia were not observed at the recovery euthanasia.

Concerning dog, glasdegib was well tolerated up to 5 mg/kg/day during 1 month except microscopic kidney findings. The NOAEL was established at 1.0 mg/kg for 1- and 3-month administration and was not established for chronic study. The target organs were similar to rat species: kidney (tubule degeneration/necrosis tubular dilatation increased urea nitrogen and creatinine concentrations, and/or granular casts in the urine), liver (mixed cell inflammation centrilobular/midzonal, single cell necrosis of hepatocytes, Kupffer cell/macrophage pigment, and centrilobular hepatocyte vacuolation, increased ALT/AST, ALP, GGT). Evidence of partial recovery was noted for microscopic liver findings after a 16-week recovery phase in animals administered 10 mg/kg/day. No test article-related microscopic findings were present in the kidney of recovery animals. Non-adverse test article-related findings in the skin/subcutis included mild atrophy of hair shafts and minimal to mild follicular ectasia; these findings corresponded with clinical and macroscopic observations of alopecia. Other non-adverse, test article-related findings were present in the GALT/Peyer's Patch (minimal to mild decreased cellularity of lymphocytes), thymus (increased severity of decreased cellularity of lymphocytes), mesenteric lymph node (minimal decreased cellularity of lymphocytes), pancreas (minimal to mild decreased zymogen granules), and prostate (mild decreased secretion). No test article-related microscopic findings were present in the skin/subcutis, GALT/Peyer's Patch, thymus, mesenteric lymph node, pancreas, or prostate of recovery animals.

A study (09LJ058/Non-GLP) in rats was a study to explore the mechanism of the renal findings and suggest biomarkers to be used in the clinical setting. This study was conducted at one active dose-level, namely 250 mg/kg/day for 7 days. Again, renal findings were evident. In 4 out of 4 rats on Day 3, mild renal tubular degeneration correlated with increased Kim-1 urine levels. This was also the case for αGST, another biomarker for early detection of kidney injury. These two biomarkers were suggested as sensitive early biomarkers for renal injury (i.e. acute tubular necrosis, Han et al, 2002, or cisplatin kidney injury, Saleena et al, 2012). These two biomarker were not used in clinical studies to monitor early signs for kidney injury because 1) Assays were not validated at the time of Phase 1 and 2 clinical studies, 2) No signs of glasdegib induced kidney injury was observed in clinical studies, 3) The population included in the clinical studies presents multiple confounding factors making interpretation of biomarker data difficult and finally 4) No clinically relevant dose-dependent changes in serum creatinine were reported in monotherapy studies including supratherapeutic doses of glasdegib.

The main identified target organs of glasdegib are kidney, bones, teeth, testis, liver, skin, and GI. Additional clinical observations of alopecia, weight loss, and muscle tremors/twitching, known class effects of SMO inhibitors, were observed in both species.

Genotoxicity

Glasdegib underwent a complete genotoxicity tests battery in vitro and in vivo, included the definitive microbial reverse mutation assay, human lymphocyte assay and the in vivo rat micronucleus assay.

Table 9. Summary of genotoxicity studies.

Type of test/ Study reference /GLP status	Test system	Product/ Concentrations range/ Metabolising system	Results Positive/negative/equivocal
Bacterial Reverse Mutation Assay with a Confirmatory Assay Ref 08GR352 GLP	Salmonella; TA98, TA100, TA1535, and TA1537) tryptophan locus of Escherichia coli (E. coli) strain WP2uvrA(pKM101	PF-04449913 10 to 5000 µg/plate, +/- metabolic activation	No positive increases in the mean number of revertants per plate in the presence or absence of S9 mix **Negative**
Human lymphocyte assay of PF-04449913-01 Ref 09GR016 GLP	human peripheral lymphocytes	PF-04449913-01 74.2 to 177 and 37.1 to 219 µg/ml, +/- metabolic activation	47 and 53% mitotic suppression at the highest test concentration evaluated in the 3-hour tests with and without metabolic activation 58% mitotic suppression at the highest concentration, in the 24-hour test PF-04449913-01 did not induce significant increases in numerical chromosome changes and did not induce significant increases in chromosome damage at any concentration. **Negative**
1-Month Oral Toxicity Study of PF-04449913 in Rats with 1-Month Recovery with Micronucleus Assessment GLP ref 08LJ094	Rats (10/sex/dose)	Oral gavage 0.5% (w/v) methylcellulose 1, 10, or 50 mg/kg/day 29 days	The administration of PF-04449913, at the dose levels tested, did not alter the number of micronucleated polychromatic erythrocytes (PCEs), polychromatic erythrocyte-to-normochromatic erythrocyte ratios (PCE:NCE), or micronuclei. samples at sacrifice day 29; treated for 1 month **Negative**

Glasdegib was negative in the Bacterial Reverse Mutation Assay and did not induce significant structural chromosome aberrations in human lymphocyte cultures when tested up to concentrations that produced marked mitotic suppression (i.e., 58%). The micronucleus assay was conjunction with the 1-month toxicity study in rats, no clastogenic activity and/or disruption of the mitotic apparatus by counting micronuclei in polychromatic erythrocytes (PCEs) in rat bone marrow was detected.

Carcinogenicity

Carcinogenicity studies with glasdegib have not been conducted.

Reproduction Toxicity

Fertility and pre-and post-natal development studies were not conducted with glasdegib.

Embryofoetal development (pEFD) studies were conducted in rats and rabbits according to GLP regulations on a lower number of animals than in conventional studies, and included: assessments of foetal survival and body weight, as well as external, visceral and skeletal examinations.

Table 10. Summary of preliminary embryo-foetal (pEFD) studies.

Study type/ Species Study ID / GLP	**Route, duration, doses**	**Major findings**
pEFD (Pivotal) Rat (SD) – 8 pregnant F/group (7 for controls) 15GR056 (CRO no.20069225) GLP: Yes	Oral (gavage) GD 7-17 (C-section GD21) 0, 10, 50, 100 mg/kg/day	**F0** • ≥50 mg/kg: ↓BW (GD18-21) and ↓BWG (GD 12-18, GD 7-18, GD 7-21) due to postimplantation loss and/or ↓fetal bw with correlating ↓gravid uterine wt and no effect on corrected maternal BW and BWG **F1** • 10 mg/kg: **skeletal variations** (incompletely ossified / unossified metacarpals, metatarsals, ischium, pubes, ribs, squamosal bones, zygomatic arches, cervical/lumbar arches, thoracic centra; nodulated and wavy ribs), **skeletal malformations** (absent ribs, fused lumbar/ thoracic vertebra) • 50 mg/kg: **total litter loss** (3/8), ↑**postimplantation loss** (↑early and late resorptions), ↓no. live fetuses ⇒ only 9 live fetuses from 5 litters available for further fetal examination ➢ ↓**fetal wt**, **external variation** (whole body edema), **visceral variations** (malpositioned subclavian/carotid artery, absent innominate artery, large spleen), **skeletal variations** (incompletely ossified / unossified skull bones, long bones, pelvic bones, scapula, sternebrae, phalanges, metacarpals, metatarsals, ischium, pubes; misshapen ilium/scapula; mishappen/malpositioned/partially fused skull bones; fused/misshappen sternebrae) ➢ **External malformations*:** eye (depressed eye bulge), face (small mouth, mishappen snout, absent tooth), head (rhinocephaly), fore/hindlimbs (short), digits (absent, short), tail (short, threadlike), trunk (short) ➢ **Visceral malformations*:** adrenal gland (small), aorta (malpositioned), arteries (narrow pulmonary trunk, retroesophageal subclavian artery), brain (severe dilation of lateral ventricle), esophagus (narrow), heart (ventricular septum defect), kidney (absent, malpositioned), lung (absent, small), nasopharynx (interrupted), ovary (large), trachea (absent), ureter (absent) ➢ **Skeletal malformations*:** fore/hindlimb (absent phalanges, absent metacarpals/ metatarsals, unossified/ incompletely ossified/ short/ misshapen long bones [humerus, radius, ulna, femur, fibula, tibia]), ribs (incomplete ossification, multiple abnormalities), scapula (small), skull (fused mandible/ maxilla, absent premaxilla), vertebrae (incomplete ossification of cervical and lumbar arches) • 100 mg/kg: total litter loss (8/8) with 100% postimplantation loss (with ↑early resorptions) ⇒ no live fetus available for further examination
pEFD (Pivotal) Rabbit (NZW) – 8 pregnant F/group 15GR057 (CRO no.20069230) GLP: Yes	Oral (gavage) GD 7-19 (C-section GD29) 0, 5, 10, 50, 100 mg/kg/day	**F0** • 5 mg/kg: BW loss due to embryofetal toxicity (↓gravid uterine wt related to postimplantation loss and ↓fetal wt, but no effect on corrected BW), ↓food consumption • ≥10 mg/kg: **mortality** (elective euthanasia of 2/8 on GD23, 5/8 on GD18-20, and 8/8 on GD14-17 at 10, 50, and 100 mg/kg; 1 found dead on GD19 at 10 mg/kg) and **abortion** (5/8 on GD19-21 and 3/8 on GD18-20 at 10 and 50 mg/kg) due to maternal **BW loss and**

Study type/ Species Study ID / GLP	Route, duration, doses	Major findings
		adverse clinical signs (mostly ↓fecal output, presence of red liquid material) **F1** • 5 mg/kg: ↑**postimplantation loss** (↑late resorptions), ↓no. live fetuses ⇒ only 22 fetuses/6 litters available for further examination (vs. 68/7 in control group ➢ ↓**fetal wt**, **external variation** (localized subcutaneous edema on hindpaws), **visceral variations** (notably: moderate dilation of the third and lateral ventricles of the brain, absent innominate artery, malpositioned subclavian artery origin, absent lung lobe), **skeletal variations** (delayed ossification or unossified skull bones/ pubes/ vertebrae/ phalanges/ metacarpals, structural changes in clavicles/pelvic bones/ribs/ scapula/ skull bones/ fontanelle/ hyoid/ vertebrae) ➢ **External malformations***: eye (open, malpositionned), face (proboscis, absent teeth, fused nares, misshapen palate, short/misshapen snout, protruding tongue), head (domed), fore/hindlimb (malrotated, hyperextension), tail (short) ➢ **Visceral malformations***: arteries (persistent truncus arteriosus, retroesophageal subclavian artery), diaphragm (hernia), heart (malpositioned atrium, absent chordae tendinae, absent papillary muscle, ventricular septum defect), intestine (malpositioned), lung (small), trachea (absent) ➢ **Skeletal malformations***: skull (absent palatine/ premaxilla, fused/ short maxilla), vertebra (multiple anomalies, fused cervical centrum) • 10 mg/kg: **total litter loss** (early resorption) of 5/7 litters, ↑post-implantation loss in the remaining 2/7 litters (62.5-83.3%) ⇒ no live fetus available for further examination • ≥50 mg/kg: **total litter loss** (early resorption) of all litters ⇒ no live fetus available for further examination

The embryo-foetotoxic and teratogenic potential of glasdegib in rats and rabbits has been observed. In rats, this developmental toxicity occurred at non-maternotoxic dose levels. Treatment-related embryolethality (early and late resorptions) in both species, and abortions in rabbits were reported in most treated groups but not in low dosed groups. In both species, multiple treatment-related external, visceral and skeletal malformations were observed. They consisted mainly in craniofacial malformations, malformed limbs, paws/digits, trunk and tail, dilation of brain, malpositioned/malformed eyes, misshapen head, small tongue, absent palate, teeth and viscera, diaphragmatic hernia, oedema, persistent truncus arteriosus, heart defects, small/absent lung, absent trachea, rib and vertebral abnormalities, malformed or absent structures in the appendicular skeleton (notably in the long bones). No developmental NOAEL was identified in any species. At the lowest embryotoxic and teratogenic dose levels, exposure ratios based on unbound AUC levels reached 0.8 and 0.6 in rats and rabbits, respectively. It is noted that the TK data obtained from the 1-month toxicity rat study was used, since TK investigations were limited to the measure of drug concentration at 4 hours post-dose in the rat pEFD study.

Reports of 3 alternative non-GLP developmental toxicity tests were submitted: a rat whole embryo culture assay, a zebrafish embryo-developmental assay, and a murine embryonic stem cell assay. Cyclopamine, a known SMO inhibitor, was used as a positive control.

Table 11. Statistical prediction models for developmental toxicity.

	LDA	MHD	RF3
Glasdegib	**Moderate**	Low: 27.6% probability	Low: 30.2% probability

		Moderate: 72.4% probability High: 0% probability	**Moderate**: 56.0% probability High: 13.8% probability
Cyclopamine	 **High**	Low: 31.2% probability **Moderate**: 43.2% probability High: 25.6% probability	Low: 1.0% probability Moderate: 20.2% probability **High**: 78.8% probability

Glasdegib was identified as a developmental toxicant in these assays. Results were similar to those obtained with cyclopamine, and were confirmed further in rats and rabbits.

Toxicokinetic data

A summary of toxicokinetics data obtained during repeat-dose toxicity studies is provided below. The calculation of exposure margin between animals and humans is based on a human dose of 100mg/man resulting in an AUC0-24: 17200 ng.h/ml for glasdegib.

Table 12. Summary of toxicokinetics studies with glasdegib in rats and dogs and animal-to-human exposure ratios from repeat-dose toxicity studies.

Species (Study)	Doses (mg/kg/d)	Day and sex	C_{max} (ng/mL) (Mean)	T_{max} (h) (Mean)	AUC_{0-24} (ng-hr/mL) (Mean)	Animal/Human Exposure Multiple based on glasdegib AUC total
Rat VO **1 month** ref 08LJ094	1	1-M	23	2.5	228	0.01
		1-F	39	3.3	384	0.02
		29-M	22	2.8	7920	0.46
		29-F	49	2.1	8340	0.48
	10	1-M	491	3.8	4700	0.27
		1-F	996	3.1	9350	0.54
		29-M	708	1.5	6740	0.39
		29-F	1060	1.5	10700	0.6
	50	1-M	3860	3.6	48900	2.8
		1-F	4710	3.6	57900	3.3
		29-M	4670	3.0	60700	3.5
		29-F	6550	1.6	73000	4.2
Rat VO **13 weeks** ref 14LJ052	10	1-M				
		1-F				
		87-M	942	2	7170	0.4
		87-F	1350	0.5	12900	0.7
	50	1-M				
		1-F				
		86-M	5110	6	70900	4.1
		86-F	8310	2	101000	5.8
	100	1-M				
		1-F				
		86-M	13700	6	192000	11.1
		86-F	15100	6	237000	13.7
Rat	10	1-M	121	3.3	1180	0.06

VO **26 weeks** ref 14LJ108		1-F	219	3.3	2300	0.1
		Wk26-M	641	2.5	5290	0.3
		Wk26-F	968	1.8	8870	0.5
	50	1-M	2740	5.0	35200	2.0
		1-F	4370	4.5	58100	3.3
		Wk26-M	6000	3.8	78000	4.5
		Wk26-F	8910	3.3	107000	6.2
	100	1-M	5210	5.0	68600	3.9
		1-F	7420	4.5	95300	5.5
		Wk26-M	14400	4.3	182000	10.5
		Wk26-F	12800	4.5	174000	10.1
Dog VO **1 month** ref 08LJ093	1	1-M	145	1	701	0.04
		1-F	77	1	318	0.01
		28-M	201	0.83	1020	0.06
		28-F	100	1	427	0.02
	5	1-M	3000	0.5	9730	0.5
		1-F	2720	0.5	6850	0.3
		28-M	3690	0.67	14000	0.8
		28-F	3000	0.83	13000	0.7
	30 Notes: Due to toxicity in Group 4 animals, dosing was stopped after Day 19 of the dosing phase.	1-M	13200	0.9	116000	6.7
		1-F	15700	0.6	115000	6.6
		28-M	nd	nd	nd	
		28-F	nd	nd	nd	
Dog VO **13 weeks** ref 14LJ055	1	1-M				
		1-F				
		89-M	81	1.2	518	0.03
		89-F	49	3.3	455	0.02
	5	1-M				
		1-F				
		89-M	988	2.0	7740	0.4
		89-F	1210	2.0	8290	0.4
	10	1-M				
		1-F				
		89-M	3210	1.7	29500	1.7
		89-F	2900	2.7	22200	1.2
Dog VO **39 weeks** ref 14LJ109	1	1-M	132	1.1	823	0.04
		1-F	142	0.75	561	0.03
		Wk39-M	74	0.83	355	0.02
		Wk39-F	117	0.5	390	0.02
	5	1-M	1860	0.83	10100	0.5
		1-F	1800	1.0	8030	0.4
		Wk39-M			10500	0.6
		Wk39-F			4220	0.2
	10	1-M	5100	1.0	37500	2.1

		1-F	5010	1.0	32900	1.9
		Wk39-M			16400	0.9
		Wk39-F			21900	1.27

Local Tolerance

Glasdegib was evaluated for the potential to cause local irritation when administered intravenously (IV) or perivascularly (PV) as a parenteral formulation to the ear of New Zealand White rabbits (Study 16GR159). Glasdegib and its parenteral vehicle formulation were well-tolerated when administered as a single IV or PV dose at 1 and 0.05 mg (at 1 mg/mL), respectively. Glasdegib, as well as vehicle and saline did not cause local irritation or macroscopic and microscopic findings in rabbits when administered IV or PV at the doses tested.

Other toxicity studies

Phototoxicity

An in vivo phototoxicity assay was conducted on pigmented rat in accordance with ICHS10 for API that bind to melanin. There were no test article-related effects on survival, clinical signs, skin reaction observations in pigmented and non-pigmented skin, body weights or ophthalmology observations. Mean systemic exposure (as assessed by mean Cmax and AUC24) increased with increasing dose of glasdegib in a greater than dose-proportional manner. Once daily oral administration of glasdegib for 3 days to female Crl:LE (Long-Evans) rats at doses as high as 100 mg/kg/day followed by UVR exposure was not phototoxic based on the absence of effects in pigmented rats. At 100 mg/kg/day on Day 3, the mean Cmax was 14200 ng/mL and the mean AUC24 was 137000 ng•hr/mL. The irradiation of animals was conducted at the approximate Tmax and the dose that covers the range of NOAEL and MTD. Glasdegib absorbs at 290 and 320 nm in the range of natural sunlight and MEC value is above the threshold (1000 L mol-1 cm-1) only at 290 nm (study 2011045).

Haemolysis

In vitro haemolysis compatibility assay was performed with glasdegib (report 17GR182) to assess the whole blood and plasma compatibility with human donor blood, evaluating haemolysis and precipitation. There was no haemolysis of the whole blood and no precipitation of the plasma in the undiluted and diluted tubes. Glasdegib (0.01-1.0 mg/mL) does not cause haemolysis in human whole blood and is compatible with human donor plasma.

2.3.1. Ecotoxicity/environmental risk assessment

Table 13. Summary of main study results

Substance (INN/Invented Name): Daurismo (glasdegib)			
CAS-number (if available): 1095173-27-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 5: 2.59 pH 7: 3.64 pH 9: 3.98	Potential PBT: No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**

Bioaccumulation	log K_{ow}	pH 7: 3.64	Bioaccumulation study /justification required (see below)
PBT-statement:	No PBT potential		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (based on prevalence of 1.1 in 10000 in EU, literature)	0.0055	µg/L	> 0.01 threshold: No
Other concerns (e.g. chemical class)			No

In order to justify omission of a Phase II ERA assessment of glasdegib, a thorough discussion on glasdegib teratogenic effects in terms of risk to organisms in the environment e.g. aquatic life was presented.

1) Glasdegib is a known teratogen and nonclinical studies show that glasdegib does not directly interact or interfere with receptors of estrogens, androgens or other steroid hormones including thyroid and therefore cannot be classified as a classical endocrine disrupting substance.

2) Although it cannot be concluded for certain, that fish full lifecycle studies of glasdegib will show that no feminisation will occur in the presence of glasdegib, a partial lifecycle early development study in zebrafish larvae incubated with glasdegib or cyclopamine from 6 hours post fertilisation for 5 days, showed a relatively low potency for morphological adverse effects for glasdegib compared with cyclopamine (study 15gr263). LOEC concentration for glasdegib was 30 µM and 0.78 µM for cyclopamine. It should be noted that tissue concentration at the LOEC was 291.8 ng/mL (30 µM or 11.2 mg/L in media) and 485.3 ng/mL (0.78 µM in media) for glasdegib and cyclopamine, respectively. Hence, bioaccumulation appeared much more pronounced for the naturally occurring steroid alkaloid cyclopamine as compared to glasdegib and tissue concentrations are in line with glasdegib plasma concentrations leading to malformation in rat embryofetal development studies (495 ng/mL).

3) Glasdegib is much less potent than e.g. the known endocrine disruptor ethinylestradiol, which was shown to lead to feminisation of male zebrafish larvae at media concentrations as low as 1 ng/L (Örn et al, 2003) compared to 14.7 mg/L of glasdegib leading to developmental malformations in zebrafish larvae.

4) Glasdegib PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

2.3.2. Discussion on non-clinical aspects

The non-clinical development program for glasdegib was designed in accordance with ICH S9 guideline, regarding the treatment of patients with advanced cancer and is considered sufficient to support the claimed indication for marketing authorization.

The pharmacological profile of glasdegib was demonstrated in in vitro assays and in vivo model xenografted in rodents. The proof of concept was demonstrated, an anti-tumour activity is obvious as a combination of glasdegib with LDAC, however the mechanism of action of the combination is not fully known. The process of cell death could also not be completely demonstrated. Clinical data are currently collected to address these two points (see clinical part of the AR).

Absorption, distribution, metabolism and excretion of glasdegib have been thoroughly evaluated following intravenous and oral administration in rats and dogs, species used for pharmacology and toxicology studies. The non-clinical pharmacokinetic studies for this application are considered sufficient for the proposed indication.

The toxicological profile of glasdegib has been evaluated during repeat-dose toxicity studies in rats and dogs, genotoxicity studies, reproductive and developmental toxicity studies and phototoxicity. No further non-clinical studies are requested in accordance with ICH S9 guideline. The toxicities observed in the general toxicity studies were consistent across studies and species and concerns kidney, liver, bone physis, teeth, skin, reproductive organs (testis) and peripheral nerves. Moreover, Qt prolongation was clearly demonstrated in vivo (see SmPC section 5.3). The telemetric study in beagle dogs highlighted cardiac effects and confirmed in vitro results by demonstrating a QTc prolongation in a dose-dependent manner. Heart rate corrected QT (QTc) interval prolongation has been observed in patients treated with Daurismo at supratherapeutic dose (> 270 mg) and therapeutic dose (100 mg with low-dose cytarabine), QTcF interval greater than 500 msec was reported in 6% of patients. Monitoring and dose modifications are recommended in the SmPC (see sections 4.2, 4.4 and 4.5).

Regarding reproductive and developmental toxicity studies, male patients treated with Daurismo are now advised to have sperm sample preserved and stored before treatment (see SPC sections 4.4 and 4.6) since non-reversible hypospermatogenesis was reported in rats without safety margin, a finding possibly driven by the pharmacological activity of glasdegib. A potential pharmacologically-mediated effect on female fertility with glasdegib is expected since nonclinical and clinical data available with other SMO inhibitors approved in Europe indicate potential adverse effects on this aspect. The Applicant's approach to conduct GLP-compliant pEFD studies in rats and rabbits instead of full EFD studies is acceptable. Indeed, adverse embryo-foetal effects were expected in view of the significant role of hedgehog signalling in embryonic development, and the teratogenic potential of other authorized SMO inhibitors. These pEFD studies confirmed the embryo-foetotoxic (including lethality) and teratogenic potential of glasdegib in both species. These malformations were reported at exposure levels lower than those reached in patients at the recommended dose of 100 mg/day. This is reflected in the SmPC section 4.4, 4.6 and as an important potential risk in the RMP / RMMs.

Since glasdegib is intended for treatment of adult patients with relapsed or refractory AML, no additional studies are requested in accordance with ICH S9.

In general, the non-clinical findings are adequately addressed in the SmPC and RMP and reported in the non-clinical part of the RMP.

An ERA was performed for glasdegib, the Log Kow of glasdegib exceeds 3 at pH 7; hence according to Q & A on Guideline on the environmental risk assessment of medicinal products for human use (CHMP, 2016), the Applicant was requested to provide evaluation of bioaccumulation or justification for not submitting such a study. In order to justify omission of a Phase II ERA assessment of glasdegib, a thorough discussion on glasdegib teratogenic effects in terms of risk to organisms in the environment, e.g. aquatic life was presented. The justification was accepted by the committee.

2.3.3. Conclusion on the non-clinical aspects

The pharmacodynamics studies demonstrate anti-proliferative effects of glasdegib in combination with LDAC. The ADME profiles of glasdegib is well documented and performed in relevant species. The toxicological

program, designed in accordance with ICH S9 guideline, allowed to draw main target organs toxicities in rodent and non-rodent species. The adverse effects are clearly identified in animals and reported in the RMP. The safety information is adequately reported in the SmPC 4.4, 4.6 and 5.3.

Overall, the non-clinical package available with glasdegib, in line with ICH S9 guideline, is considered sufficient to support the marketing authorization for the proposed indication.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 14: Overview of included studies

Study Number	Study Design	Study Population	Glasdegib Therapy	Number of Patients[a]	Status
B1371001	Dose-escalation	AML, MDS, CML, CMML, MF	Monotherapy	47	Complete
B1371013	Phase 2 safety and efficacy	MF	Monotherapy	21	Complete
B1371002	Safety and efficacy	Solid tumours	Monotherapy	23	Complete
B1371003	Phase 1b Arm A Arm B Arm C Phase 2 randomised Phase 2 single arm	AML, MDS	 + LDAC + Decitabine + 7+3 + LDAC LDAC alone + 7+3	 23 7 22 88 randomised 84 treated 44 randomised 41 treated 69	Ongoing
B1371012	Phase 1b safety and efficacy	AML, MDS, CMML	+ Azacitidine	12 in LIC 29 in expansion[e]	Ongoing
B1371005	Arm 1 Arm 2 Arm 3 Combination Continuation	AML, MDS, CML, CMML, MF AML, MDS AML, MDS AML Rollover[d]	Monotherapy + LDAC + 7+3 + Azacitidine Monotherapy	13 6 6 6 1[d]	Ongoing
B1371009	Human ADME	HV	Monotherapy	6	Complete
B1371010	Ketoconazole DDI/Food effect	HV	Monotherapy	14	Complete
B1371014	Relative BA/PPI/ Food effect	HV	Monotherapy	35	Complete
B1371015	Rifampin DDI	HV	Monotherapy	12	Complete
B1371017	Renal impairment	HV	Monotherapy	18	Complete
B1371022	Absolute BA	HV	Monotherapy	12	Complete
B1371023	TQT	HV	Monotherapy	36	Complete
B1371026	BE/PPI/Food effect	HV	Monotherapy	24	Complete
B1371019[b]	Safety and efficacy	AML	Glasdegib or placebo + 7+3 + azacitidine	 31 13	Ongoing
WI171861	IIR	MDS	Monotherapy	35	Complete
WI220403[c]	IIR	AML post HSCT	Monotherapy	35	Ongoing
WI204578	IIR	Sclerotic Chronic Graft-Versus-Host Disease	Monotherapy	6	Ongoing
WI218564	IIR	Glioblastoma	+ radiation and temozolomide	3	Ongoing
WI216382-1	IIR	AML	+ gemtuzumab ozogamycin	2	Ongoing

2.4.2. Pharmacokinetics

Pharmacokinetics of glasdegib have been studied in 7 studies in healthy volunteers (absorption, distribution, metabolism, and excretion, drug-drug interaction, QT, food effect and bioavailability). One study was

performed in subjects with renal impairment (B1371017). Single- and multiple-dose PK of glasdegib have been evaluated in 5 studies in adult patients with haematologic malignancies and solid tumours (B1371001, B1371002, B1371003, B1371005, and B1371012). Several bioanalytical methods were developed for the quantification of glasdegib in human plasma, in urine and human plasma:PBS matrix. In addition, for each drug product used in association with glasdegib during the clinical development program, a specific bioanalytical method was developed.

Absorption

The absolute bioavailability of glasdegib was estimated in Study B1371022 after oral administration of the proposed commercial maleate tablet formulation of glasdegib relative to glasdegib IV infusion administered to healthy adult volunteers after an overnight fast.

The absolute oral bioavailability of the glasdegib-proposed commercial maleate tablet formulation was 77.12% (71.83%, 82.81%) based on the AUCinf. Therefore, approximately 77% of the administered oral dose of glasdegib reached the systemic circulation after oral administration.

Table 15. Study B1371022, Descriptive summary of plasma Glasdegib PK parameters.

Parameter (units)	Parameter Summary Statistics[a] for Glasdegib by Treatment	
	Glasdegib 50 mg IV	Glasdegib 100 mg Oral Tablet
N	11	12
AUC_{inf} (ng•hr/mL)	4879 (38)	7628 (38)
AUC_{last} (ng•hr/mL)	4778 (39)	7488 (38)
C_{max} (ng/mL)	664.6 (27)	668.0 (23)
T_{max} (hr)	1.27 (1.00-1.27)	1.52 (1.00-4.00)
CL/F (L/hr)	NA	13.10 (38)
CL (L/hr)	10.25 (38)	NA
V_z/F (L)	NA	265.9 (26)
V_{ss} (L)	151.6 (22)	NA
$t_{½}$ (hr)	13.78 ± 2.97	14.26 ± 2.45

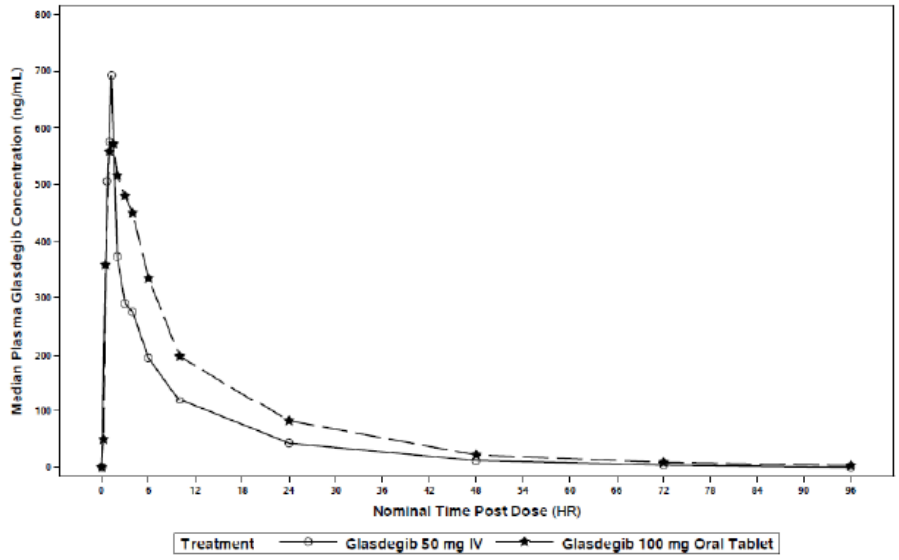
Source: Table 14.4.5.1
PK parameters are defined in Table 5.
Abbreviations: %CV= percent coefficient of variation; hr = hour(s); IV = intravenous; N = number of subjects in the treatment group and contribution to the means; NA = not applicable; PK = pharmacokinetic(s); SD = standard deviation.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean (±SD) for $t_{½}$.

Table 16. Study B1371022, Statistical summary of treatment comparison for Glasdegib absolute bioavailability assessment.

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Glasdegib 100 mg Oral Tablet (Test)	Glasdegib 50 mg IV (Reference)		
AUC_{inf}(dn) (ng•hr/mL/mg)	76.28	98.90	77.12	(71.83, 82.81)
AUC_{last}(dn) (ng•hr/mL/mg)	74.88	96.98	77.21	(71.72, 83.12)

Source: Table 14.4.5.3
PK parameters are defined in Table 5.
Values have been back-transformed from the log scale.
The model was a mixed effects model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect.
Abbreviations: CI = confidence interval; IV = intravenous; PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.

Figure 3. Median Plasma Glasdegib Concentration-Time Profiles Following Single Oral and IV Doses (Study B1371022)



Bioequivalence

Immediate-release di-HCl tablet formulations were the initial product presentation and were used in early clinical studies for clinical pharmacology, safety, and efficacy (B1371001, B1371002, B1371003, B1371005, B1371010, B1371012, B1371013, B1371014, and B1371026). An immediate-release maleate film-coated tablet formulation (Generation-1 maleate tablet), one with a drug loading of 13.11% maleate to provide a 10 mg active dose and the other with a drug loading of 26.21% maleate to provide 25 and 100 mg were developed to support the phase I studies B1371014 (food effect and BE) and B1371015 (DDI). The formulation was further changed and the proposed commercial maleate formulation (to be marketed formulation) now contains 21.84% glasdegib maleate to make 25 mg an\d 100 mg active tablets and was used in the QTc study BE (B1371023) and in multiple dose study in patients with MDS/AML (B1371012) but not in the pivotal E/S trial.

In total the applicant submitted 3 bioavailability and bioequivalence studies (B1371014, B1371026 and B1371022) in healthy subjects to allow bridging of the earlier data (generated with earlier formulations) to the to be marketed product. Two of these BE studies were intended to bridge the data from the phase 1/2b study B1371003 study.

Study B1371014 bridges the HCL salt formulation and the intermediary maleate formulation.

Table 17. Study B1371014, Descriptive summary of plasma Glasdegib Pharmacokinetic Parameters.

Parameter Summary Statistics[a] for Glasdegib by Treatment					
Parameter (Units)	100 mg Glasdegib di-HCl	100 mg Glasdegib MFS	100 mg Glasdegib MFL, Fasted	100 mg Glasdegib MFL, Fed	50 mg Glasdegib Solution
N	33	34	34	13	6
AUC_{inf} (ng·h/mL)	8333 (26)	8871 (25)	9051 (30)	8059 (20)	4130 (18)
AUC_{last} (ng·h/mL)	8239 (27)	8760 (25)	8957 (30)	7954 (21)	4013 (18)
C_{max} (ng/mL)	712.9 (23)	772.4 (25)	775.3 (28)	576.2 (34)	338.7 (17)
T_{max} (h)	1.00 (0.500-3.02)	1.00 (0.500-3.02)	1.50 (0.500-4.07)	2.02 (0.500-4.00)	1.25 (0.500-2.07)
CL/F (L/h)	12.00 (26)	11.28 (25)	11.05 (30)	12.40 (20)	12.10 (18)
Vz/F (L)	268.4 (30)	249.4 (25)	237.7 (25)	306.1 (18)	258.6 (20)
$t_{½}$ (h)	15.99 ± 4.14	15.59 ± 2.77	15.10 ± 2.42	17.28 ± 2.48	14.83 ± 0.82

Source: Study B1371014 CSR, Table 14.
Study drugs were administered under fasted condition unless otherwise specified.
AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; AUC_{last} = area under the plasma concentration-time curve from time 0 to last measurable concentration; %CV = percent of coefficient of variation; CL/F = apparent oral clearance; C_{max} = maximum-observed plasma concentration; di-HCl = dihydrochloride; MFL = large high-shear, wet-milled particle size of maleate; MFS = small jet-milled particle size of maleate; N = number of subjects receiving in the treatment group; SD = standard deviation; $t_{½}$ = terminal plasma half-life; T_{max} = time for first occurrence of C_{max}; V_z/F = apparent volume of distribution.
a. Geometric mean (geometric %CV) for all parameters except: median (range) for T_{max}; arithmetic mean (±SD) for $t_{½}$.

For the MFS tablet, the ratio (Test/Reference) of adjusted geometric means (90% CI) of glasdegib AUCinf and Cmax were 105.10% (101.20%, 109.14%) and 107.42% (102.41%, 112.66%), respectively, relative to the di-HCl reference tablet. The corresponding 90% CI for the adjusted geometric mean AUCinf and Cmax ratios were wholly contained within the acceptance range for bioequivalence (80%, 125%). The median Tmax values were 1.0 hour each for both the MFS tablet and the di-HCl reference tablet. The mean apparent terminal plasma half-life (t½) was similar for the 2 treatments with mean values of 15.6 hours and 16.0 hours for MFS tablet and di-HCl tablet, respectively.

For the MFL tablet, the ratio (Test/Reference) of adjusted geometric means (90% CI) of glasdegib AUCinf and Cmax were 107.51% (103.67%, 111.48%) and 107.77% (101.32%, 114.64%), respectively, relative to the di-HCl reference tablet. The corresponding 90% CI for the adjusted geometric mean AUCinf and Cmax ratios were contained within the acceptance range for bioequivalence (80%, 125%).

Study B1371026 compares the final 100 mg maleate tablet against the 100 mg di-HCl tablet.

Table 18. Study B1371026, Statistical summary of treatment comparison for plasma Glasdegib Pharmacokinetic Parameters – Bioequivalence.

	Adjusted Geometric Means			
Parameter (units)	ICH Maleate Glasdegib 100 mg (Test)	di-HCl Glasdegib 100 mg (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng•hr/mL)	8704	8368	104.02	(99.74, 108.48)
AUC_{last} (ng•hr/mL)	8612	8275	104.07	(99.73, 108.60)
C_{max} (ng/mL)	764.3	752.0	101.63	(96.13, 107.44)

Source: Table 14.4.3.3.1

PK Parameters are defined in Table 6.

Values have been back-transformed from the log scale. The model is a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect.

Abbreviations: CI=confidence interval; di-HCl = dihydrochloride; ICH = International Council for Harmonisation; PK = pharmacokinetic.

a. The ratios (and 90% CIs) are expressed as percentages.

Studies **B1371014** and **1026** showed bioequivalence between glasdegib maleate salt tablet with small particle size (MFS) relative to di-HCl tablet for the first study, and between glasdegib 100 mg ICH commercial maleate tablet formulation and 100 mg di-HCl tablet formulation for the second study.

Distribution

Study **B1371009** was the mass balance study. The overall mean mass balance of the dosed radioactivity in the excreta was 90.64% over the 288-hour study, with recovery in individual subjects ranging from 89.1% to 93.5%.

The glasdegib geometric mean (geometric percent coefficient of variation [%CV]) apparent volume of distribution (Vz/F) was 188 (20) L following single dose of 100 mg glasdegib in patients with haematologic malignancies. Distribution volume ranged from 270 L to 455 L, with population estimates of a steady state apparent volume of distribution of approximately 282.5 L. In humans, Glasdegib mean fu was 0.0899, and mean Cb/Cp values was 1.38 (1.36 to 1.49 in Study B1371009).

This data suggests that glasdegib demonstrated a modest preferential distribution into the blood cells.

Elimination

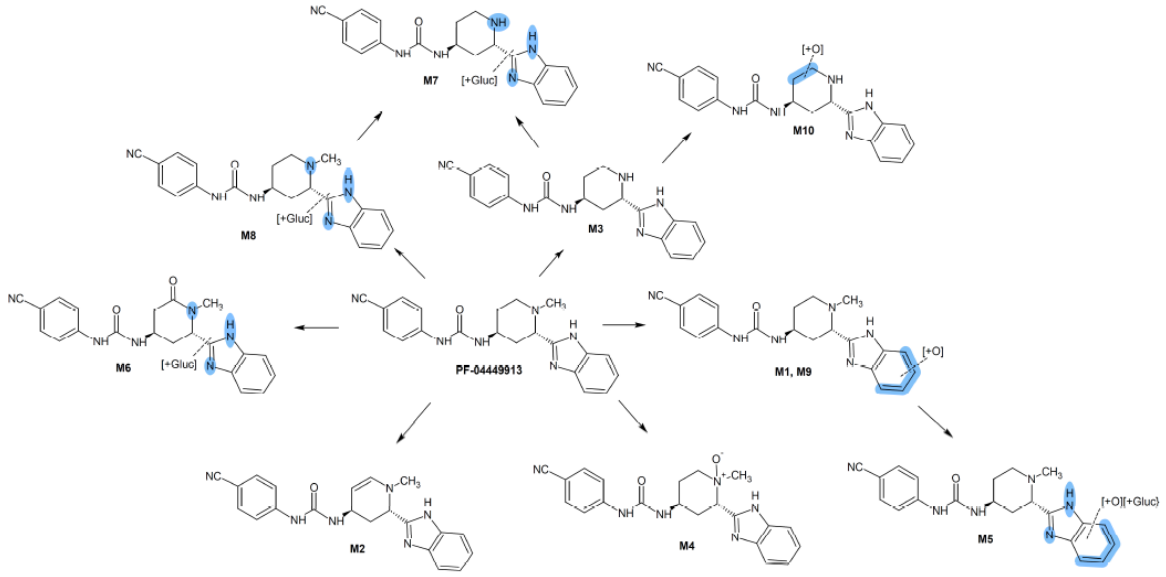
Average CL/F ranged from 5.22 to 14.81 L/h, terminal half-life averaged 20 – 24 hours. The geometric mean (geometric %CV) apparent oral clearance (CL/F) of glasdegib was 7.63 (20) L/hr after single dose administration of 100 mg glasdegib and 6.45 (25) L/hr after multiple doses of 100 mg QD of glasdegib. The mean ± standard deviation (SD) terminal plasma half-life was 17.4 ± 3.66 hours after single dose of 100 mg glasdegib in patients with selected haematologic malignancies.

The overall mean mass balance of the dosed radioactivity in the excreta was 90.64% over the 288-hour study, with recovery in individual subjects ranging from 89.1% to 93.5%. Excretion was shared between urinary and faecal pathways, 48.9% and 41.7% of elimination respectively. Unchanged glasdegib recovered in the urine and feces accounted for 17.2% and 19.5% of the dose, respectively, indicating that excretion plays a role in elimination of glasdegib.

Following oral administration of a single dose of [14C] glasdegib to healthy subjects in Mass balance study B1371009, glasdegib was extensively metabolized, with the primary metabolic pathways comprising of N-demethylation, glucuronidation, oxidation, and dehydrogenation. The primary CYP enzymes involved in the oxidative metabolism of glasdegib were CYP3A4 (60% to 80%) and CYP2C8 (2% to 20%). For the minor glucuronidation pathway, UGT1A9 was the predominant enzyme involved in the glucuronidation of glasdegib.

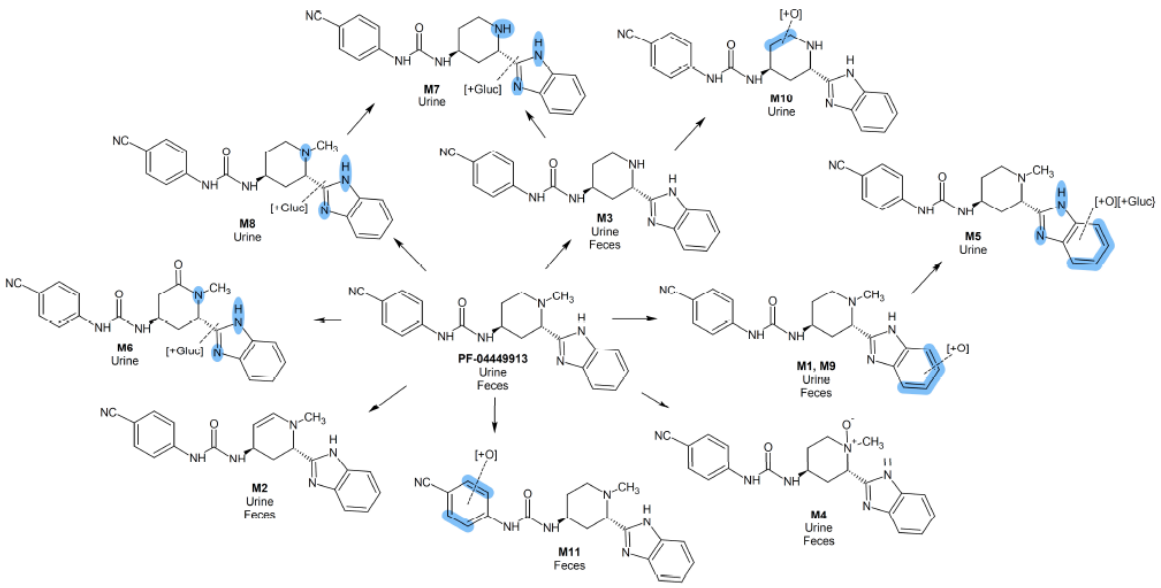
In plasma, the N-desmethyl and N-glucuronide metabolites of glasdegib accounted for 7.9% and 7.2% of the circulating radioactivity, respectively. Other metabolites in plasma individually accounted for <5% of circulating radioactivity. The N-desmethyl metabolite of glasdegib was the most abundant metabolite in urine and faeces, accounting for 16.8% and 9.2% of dose respectively. The N-glucuronide metabolite of glasdegib was observed in urine, accounting for 4.2% of dose. Other metabolites in the excreta individually accounted for ≤5% of dose.

Figure 4. Proposed pathway for glasdegib in vivo metabolites present in plasma.



Source: Study B1371009 CSR Section 16.2.5.10.4.

Figure 5. Proposed pathway for glasdegib in vivo metabolites present in excreta



Source: Study B1371009 CSR Section 16.2.5.10.4.

Additional sites of metabolism identified in human plasma and excreta included mono-oxidation in the benzimidazole ring, mono-oxidation and dehydrogenation in the piperidine ring and mono-oxidation in the benzonitrile group.

Dose proportionality and time dependencies

Dose proportionality

Dose proportionality following single and multiple escalating glasdegib doses was evaluated in the Phase 1 dose-escalation trials in patients with select advanced hematologic malignancies (Studies B1371001 and B1371005) and advanced solid tumors (Study B1371002).

Plasma exposure of glasdegib is dose proportional over the dose range of 5 mg to 640 mg QD, indicating dose-linear PK.

Figure 6. Relationship between the glasdegib geometric mean Cmax and AUCinf and dose (single oral dose) in patients with advanced haematologic malignancies (Study B1371001).

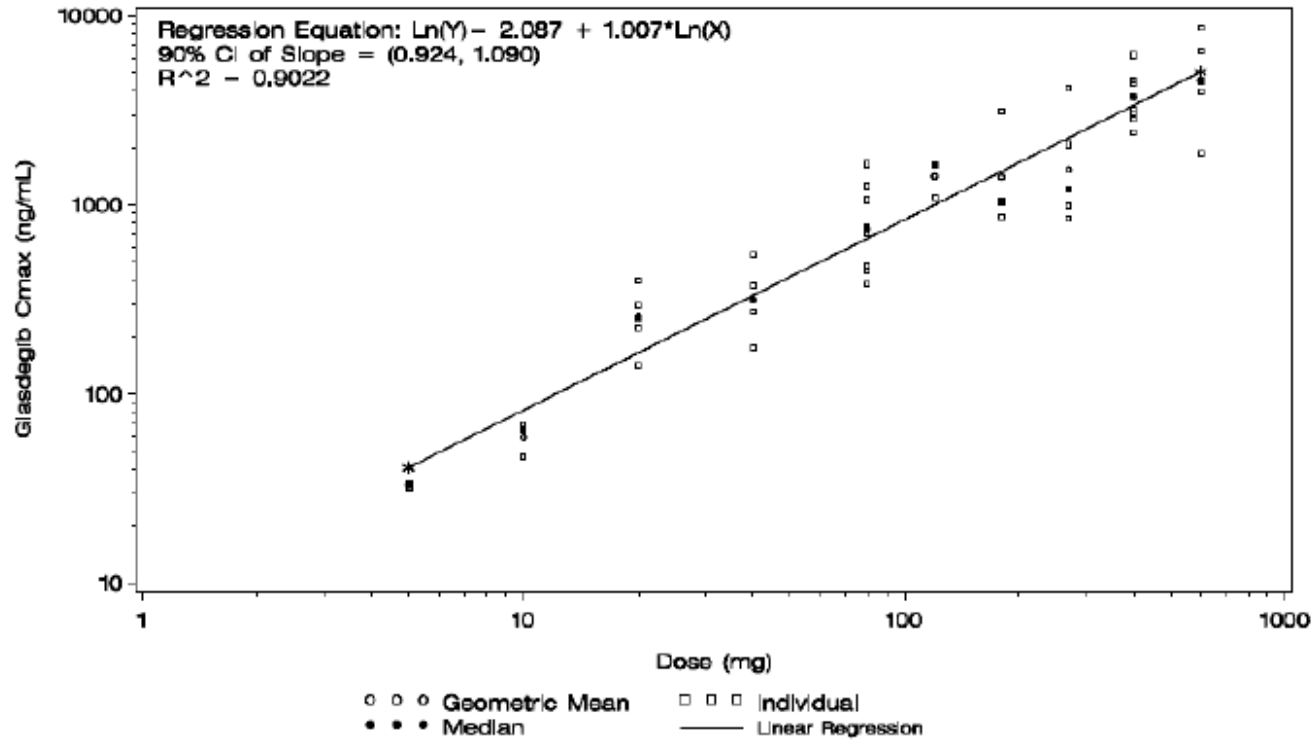
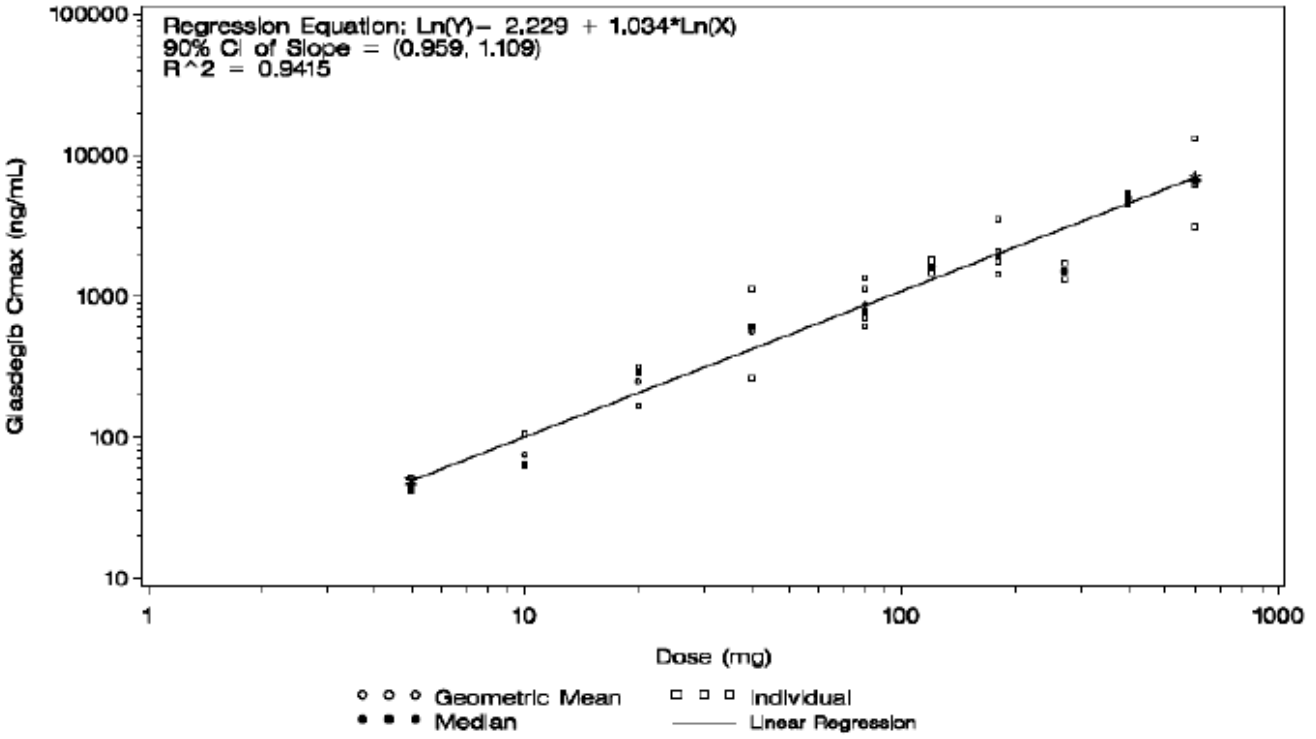


Figure 7. Relationship between the glasdegib geometric mean Cmax and AUCinf and dose (multiple oral doses) in patients with advanced haematologic malignancies (Study B1371001).



Time dependency

In Study B1371001, CL/F stayed similar after multiple dosing, showing time independence. Rss indicated no unexpected accumulation. In Study B1371002, steady state was reached at Day 8, and the accumulation ratio from 1.35 to 1.75 was consistent with a T1/2 around 20h. In Study B1371005: the accumulation ratio was also as expected.

There is no time dependency of glasdegib PK, and a QD dosing should result in 1.6 to 2.6 fold accumulation.

Intra and Inter-individual variability

For the di-HCl tablet formulation, inter-subject variability ranged from 26% to 35% for AUCinf and from 23% to 41% for Cmax, across the studies assessed here. For the maleate tablet formulations (Generation-1 and proposed commercial maleate tablets), inter-subject variability ranged from 20% to 42% for AUCinf and from 25% to 34% for Cmax, across the studies.

PK in target populations

Single and multiple dose PK in patient population has been evaluated in 5 studies, including 4 in patients with haematological malignancies (B1371001, B1371003, B1371005 and B1371012) and 1 study in patients with solid tumours (B1371002). Following repeated 100 mg QD dosing to steady state, glasdegib median time to first occurrence of the maximum observed plasma concentration (Tmax) ranged from approximately 1.3 hours to 4.1 hours (Studies B1371003, B1371005, and B1371012).

In study B1371003 the PK was evaluated in the AML patient population in combination with LDAC as proposed in the label. At the 100 mg once daily glasdegib dose, the geometric mean (geometric coefficient of variation, %CV) of glasdegib Cmax was 1,252 ng/mL (44%) and AUCtau was 17,210 ng•hr/mL (54%) in phase 2 of this study. The mean plasma half-life of glasdegib was 17.4 ± 3.66 hours after a single dose of 100 mg glasdegib in patients.

The POPPK dataset contains data from 2 studies in adult patients with selected advanced haematologic malignancies (n=47 in Study B1371001 and n=202 in Study B1371003) and 1 study in patients with advanced solid tumours (n=23 in Study B1371002). Glasdegib PK was well characterized by a 2-compartment model with first order absorption. Baseline percent bone marrow blasts (BPBL), weight normalized clearance (WNCL), and use of moderate or strong CYP3A4 inhibitors were statistically significant covariates on CL/F retained in the final model. Tumour type (i.e., solid tumours) was a statistically significant covariate on Vp/F and apparent intercompartmental clearance (Q/F).

In order to evaluate the magnitude of effect of BPBL on CL/F, values of CL/F were calculated at extreme BPBL values (i.e., 10th and 90th percentiles in the analysis population) and compared with their typical values at a median BPBL of 38.2%. A 1% change in BPBL from the median value would result in an estimated 0.4% change in glasdegib CL/F, which is not clinically meaningful. Relative to the typical value of CL/F of 6.27 L/hr, CL/F increased by approximately 9% for an individual with 15% BPBL (10th percentile). CL/F decreased by approximately 17% for an individual with 83% BPBL (90th percentile).

Tumour type was also identified as a statistically significant covariate on both Vp/F and Q/F in the final POPPK model. Patients with solid tumours had approximately 83% and 65% lower glasdegib Vp/F and Q/F compared to patients with haematologic malignancies.

Special populations

Renal impairment

In the clinical study B1371017, exposure was doubled in subjects with moderate and severe impaired renal function following a single 100 mg dose of glasdegib, 105% and 102% increase in AUCinf and 37% and 20% increase in Cmax were noted in subjects with moderate and severe renal impairment compared to subjects with normal renal function, respectively.

The effect of renal function on the glasdegib CL/F was evaluated using WNCL in a population PK analysis. Data from 269 patients included 105 patients with normal renal function (BCCL ≥90 mL/min), 102 patients with mild renal impairment (BCCL 60-89 mL/min), and 61 patients with moderate renal impairment (BCCL 30-59 mL/min). No patient met the criteria for severe renal impairment (BCCL 15-2 mL/min).

In population PK modeling, baseline creatinine clearance (WNCL) was a statistically significant predictor of variability in CL/F. In order to evaluate the magnitude of effect of WNCL on CL/F, values of CL/F were calculated at extreme WNCL values (i.e., 10th and 90th percentiles in the analysis population) and compared with their typical values at a median WNCL of 71.2 mL/min. Relative to the typical value of CL/F of 6.27 L/hr for a patient with WNCL of 71.2 mL/min, CL/F decreased by approximately 16% for an individual with reduced WNCL of 46.9 mL/min (10th percentile). CL/F increased by approximately 19% for an individual with WNCL of 110 mL/min (90th percentile).

Hepatic impairment

Data from a dedicated pharmacokinetic trial (B13711016) have shown that plasma exposures for total glasdegib (AUCinf and Cmax) were similar between the normal hepatic function group and the moderate hepatic impairment group (Child-Pugh Class B), whilst geometric mean AUCinf and Cmax values were 24% and 42% lower, respectively, for the severe hepatic impairment group (Child-Pugh Class C), compared to the normal hepatic function group. The glasdegib unbound exposure (unbound AUCinf) in subjects with moderate or severe hepatic impairment was increased by 18% and 16%, respectively, relative to subjects with normal hepatic function. Peak glasdegib unbound exposure (unbound Cmax) increased by 1%, for moderate hepatic impairment and decreased by 11% for severe hepatic impairment, relative to subjects with normal hepatic function.

Baseline body weight

Baseline body weight (BW) was incorporated on CL/F and Q/F in the Pop PK model based on the simulated glasdegib exposures data (AUCtau and Cmax), an over-exposure of 1.7-fold is expected for the extreme low BW values of 40 kg and an under-exposure of 0.6 fold is expected for the extreme high BW values of 140 kg compared to a typical patient of 70 kg. However, these exposures differences are found to be within the therapeutic window for glasdegib [the upper boundary threshold was set to 2-fold increase for Cmax and 2.4-fold increase for AUC; and the lower boundary is 0.5-fold for AUC and Cmax]. Furthermore, population PKPD exposure-responses analyses demonstrated no meaningful impact of BW on the efficacy (OS) and key safety endpoints.

Age, sex, race

No clinically relevant effects of age, sex, or race on glasdegib PK were observed.

Children

No data are available in this population.

Elderly

Table 19. Number of elderly patients studied in glasdegib development programme.

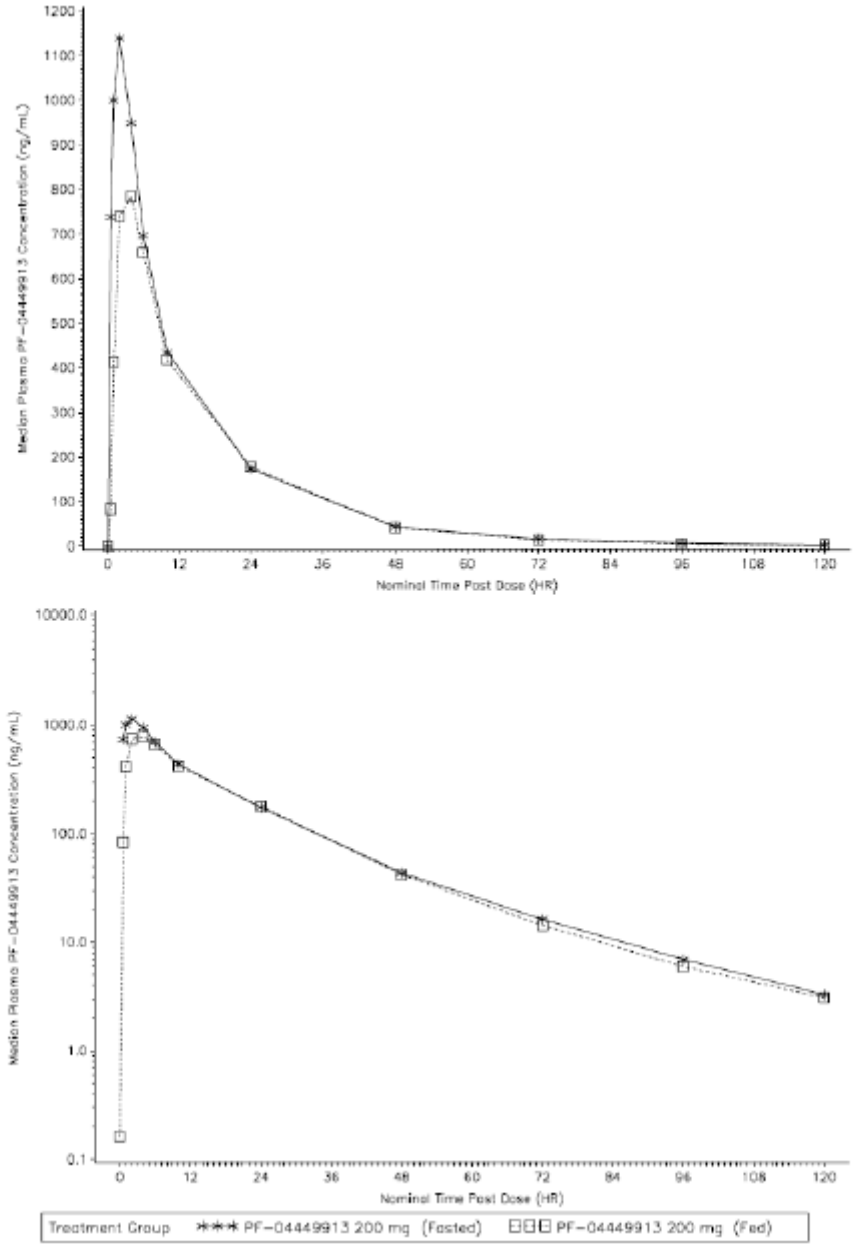
	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials (B1371009, B1371010, B1371014, B1371015, B1371016, B1371017, B1371022, B1371023, B1371026)	21 / 181	1 / 181	0 / 181

Pharmacokinetic interaction studies

Influence of food

Studies B1371010, B1371014, and B1371026 investigated the effect of food on glasdegib PK. The AUCinf and Cmax decreased 0.87 and 0.66 fold, respectively, as compared to administration under overnight fasted conditions, for di-HCl tablets.

Figure 8. Study B1371010, Median Glasdegib plasma concentration time profiles after single oral dose for food effect.



Glasdegib effect on other drugs

Study XT135086 aims to investigate the potential for PF-04449913 (glasdegib) to inhibit cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 activities in vitro, using pooled human liver microsomes (HLM). PF-04449913 did not appear to cause time-dependent or metabolism-dependent inhibition of any CYP enzyme activity examined since there was less than a 20% increase in inhibition observed after 94 µM PF-04449913 was preincubated with human liver microsomes in either the presence or absence of NADPH for 30 minutes.

Study XT133102 aimed to investigate the potential of PF-04449913 to induce CYP3A4 and CYP2B6 in vitro using freshly plated human hepatocytes (Lot H1182) and cryopreserved human hepatocytes (Lots Hu1434 and Hu8148). Induction of CYP3A4 and CYP1A2 were observed for the known CYP3A4 inducer rifampin, as measured by testosterone 6β-hydroxylase activity and CYP3A4 mRNA levels, and the known CYP1A2 inducer omeprazole. Treatment of the human hepatocytes with PF-04449913 did not cause induction of CYP3A4, 2B6 and 1A2.

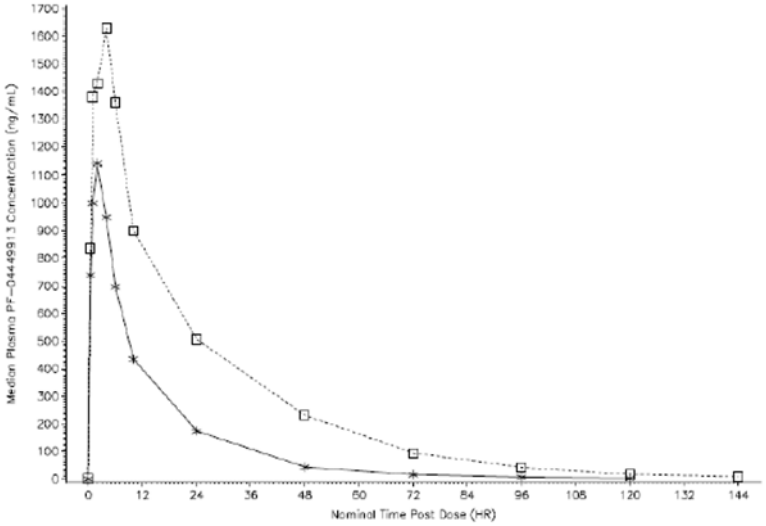
Other drugs on glasdegib PK

Clinical studies in healthy volunteers were conducted to assess the impact of other drugs such as CYP3A4 inhibitor and CYP3A4 inducer on glasdegib PK.

The effect of CYP3A4 inhibitors (Study B1371010) and inducers (Study B1371015) as well as agents that increase gastric pH, was evaluated in studies in HVs. Potential for DDI of glasdegib with LDAC was assessed in the patients with haematologic malignancies.

A 40% increase (geometric mean ratio [90% CI]: 139.54% [123.51%, 157.64%]) in glasdegib Cmax and a 140% increase (geometric mean ratio [90% CI]: 239.84% [214.70%, 267.93%]) in glasdegib AUCinf were noted in a DDI study conducted with ketoconazole (strong CYP3A4 inhibitor), confirming the involvement of CYP3A4 in glasdegib metabolism (Study B1371010).

Figure 9. Median plasma glasdegib concentration-time profiles (single oral dose) for ketoconazole treatment effect.



A 35% decrease (geometric mean ratio [90% CI]: 64.71% [57.21%, 73.19%]) in glasdegib Cmax and a 70% decrease (geometric mean ratio [90% CI]: 29.66% [26.17%, 33.62%]) in glasdegib AUCinf were noted in clinical DDI study conducted with rifampin (strong CYP3A4 inducer), confirming the involvement of CYP3A4 in glasdegib metabolism (Study B1371015).

Table 20. Descriptive summary of plasma glasdegib PK parameter in the absence and presence of rifampin (Study B1371015).

	Parameter Summary Statistics[a] for Glasdegib by Treatment	
Parameter (units)	Glasdegib 100 mg SD	Rifampin 600 mg QD + Glasdegib 100 mg SD
N	12	12
AUC_{inf} (ng•hr/mL)	8145 (23)	2416 (25)
AUC_{last} (ng•hr/mL)	8051 (23)	2385 (26)
C_{max} (ng/mL)	703 (19)	455 (26)
T_{max} (hr)	1.50 (1.00-4.05)	1.25 (1.00-2.07)
CL/F (L/hr)	12.3 (23)	41.4 (25)
V_z/F (L)	233 (18)	299 (23)
$t_{½}$ (hr)	13.4±2.76	5.11±1.06

Source: Study B1371015 CSR Table 10.
Pharmacokinetic parameters are defined in Table 3.
%CV = percentage confidence interval; N = Number of subjects in the treatment group and contributing to the mean; SD = single dose/standard deviation; QD = once daily
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean (±SD) for $t_{½}$.

Coadministration of multiple 40 mg QD doses of rabeprazole, a PPI, resulted in a 20% decrease in glasdegib Cmax (geometric mean ratio [90% CI]: 80.46% [70.68%, 91.59%]) relative to those when glasdegib was administered alone. However, no change in glasdegib AUCinf (geometric mean ratio [90% CI]: 100.58% [93.19%, 108.55%]) was observed (Studies B1371014, B1371026).

Table 21. Statistical summary of treatment comparisons for plasma glasdegib PK parameters – PPI effects assessment (Study B1371014).

	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Parameter (Unit)	MFL+PPI (Test)	MFL, fasted (Reference)		
AUC_{inf} (ng•hr/mL)	10130	9051	111.93	(102.76, 121.92)
AUC_{last} (ng•hr/mL)	10030	8957	111.93	(102.70, 121.99)
C_{max} (ng/mL)	676	775	87.21	(75.86, 100.26)

Source: Study B1371014 CSR Table 18.
Pharmacokinetic parameters are defined in Table 3.
CI = confidence interval; MFL = large High Shear Wet Milled particle size of maleate salt; MFS = small Jet Milled particle size of maleate salt; PK = pharmacokinetic; PPI = proton pump inhibitor (rabeprazole).
Values have been back-transformed from the log scale. The model was a mixed effects model with treatment as fixed effects and subject within sequence as a random effect.
a. The ratios (and 90% CIs) are expressed as percentages.

In Study B1371014, a food effect was observed: decrease of Cmax by 0.75 fold on MFL formulation in fed state. In Study B1371026, food effect and PPI effect could be detected: decrease of 0.7 fold of Cmax in fed state as compared to fasted state, and with coadministration of PPI as compared as without PPI, for 100 mg ICH commercial maleate tablet formulation.

There was no evidence of DDI between glasdegib and LDAC when the 2 drugs were coadministered as non-intensive treatment in patients with previously untreated AML or high-risk MDS (Study B1371003).

Pharmacokinetics using human biomaterials

Study PF04449913_28Jul15_154108 aimed to determine the inhibitory potency of glasdegib for human multi-drug resistance protein 1 (MDR 1, P-gp), human breast cancer resistance protein (BCRP), human hepatic organic anion transporting polypeptides (OATP) 1B1 and 1B3, human organic anion transporter (OAT) 1 and 3, human organic cation transporter (OCT) 2, human multidrug and toxin extrusion proteins (MATE) 1 and 2K when stably expressed in a mammalian cellular system.

The used biomaterial and the probe substrates are summarized in Table 22.

Table 22. Used biomaterial, probe substrates, and control inhibitor used to evaluate glasdegib inhibitory potential for BCRP, P-gp, OATP1B1/1B3, OAT1/3, OCT2, MATE1 and MATE2K from study PF04449913_28Jul15_154108.

	Transporters	Test system	Probe substrate (µM)	Control inhibitor
Efflux transporter (brain, testes, placenta, GIT)	BCRP	MDCKII-BCRP	Pitavastatin (2 µM)	PSC833
	P-gp	MDCKII-P-gp	Digoxin (12 µM)	Ko143
Hepatic uptake	OATP1B1/1B3	HEK293-OATP1B1/1B3	Rosuvastatin (5 µM)	rifamycin SV
Renal uptake	OAT1	HEK293-OAT1	[3H]-Para-aminohippurate (PAH) (2 µM)	probenecid
	OAT3	HEK293-OAT3	[3H]-Estrone Sulfate (0.2 µM)	probenecid
	OCT2	HEK293-OCT2	[14C]-Metformin (10 µM)	quinidine
Hepatic and renal efflux	MATE1	HEK293-MATE1	[14C]-Metformin (10 µM)	cimetidine
Renal efflux	MATE2K	HEK293-MATE2K	[14C]-Metformin (10 µM)	cimetidine

Table 23. Summary of glasdegib inhibition potential for BCRP, P-gp, OATP1B1/1B3, OAT1/3, OCT2, MATE1 and MATE2K from study PF04449913_28Jul15_154108.

Summary Result	Assessment of risk for in vivo DDIs between glasdegib and co-administered substrates of various transporters, based on the EMA Guideline (2012).[a]					
	Transporter	K_i[b] (μM)	50 × $C_{max,u}$[c] (μM)	25 × $I_{max,u,inlet}$[d] (μM)	0.1 × Dose/ 250 mL[e]	Threshold Cutoff For Potential DDI
Systemic	P-gp	16.7	15.0	--	--	$K_i \leq (50 \times C_{max,u})$
	BCRP	2.3	15.0[f]	--	--	$K_i \leq (50 \times C_{max,u})$
	OATP1B1	13.2	--	7.78	--	$K_i \leq (25 \times I_{max,u,inlet})$
	OATP1B3	13.0	--	7.78	--	$K_i \leq (25 \times I_{max,u,inlet})$
	OCT2	>50	15.0	--	--	$K_i \leq (50 \times C_{max,u})$
	OAT1	>25	15.0	--	--	$K_i \leq (50 \times C_{max,u})$
	OAT3	>50	15.0	--	--	$K_i \leq (50 \times C_{max,u})$
	MATE1	4.9	15.0[f]	--	--	$K_i \leq (50 \times C_{max,u})$
	MATE2K	1.2	15.0[f]	--	--	$K_i \leq (50 \times C_{max,u})$
Intestinal	P-gp	16.7	--	--	106.8[f]	$K_i \leq (0.1 \times dose/250)$
	BCRP	2.3	--	--	106.8[f]	$K_i \leq (0.1 \times dose/250)$

Glasdegib inhibits MDR1/P-gp and BCRP with an estimated Ki (16.7 μM for P-gp and 2.3 μM for BCRP), and IC50 of 33.3 μM and 4.6 μM respectively. There was concentration-dependent inhibition of hepatic OATP1B1 and OATP1B3 by glasdegib up to 300 μM. The estimated IC50 for OATP1B1 and OATP1B3 was 26.3 and 25.9 μM, respectively. There was no concentration-dependent inhibition of renal OAT1, OAT3, and OCT2 by glasdegib from 0.012 up to 50 μM. The estimated IC50 for glasdegib against OAT1, OAT3, and OCT2 was >50, >50, and >50 μM, respectively. There was concentration-dependent inhibition of renal efflux transporter MATE1 and MATE2K by glasdegib from 0.012 up to 50 μM. The estimated IC50 for glasdegib against MATE1 and MATE2K was 4.9 and 1.2 μM, respectively.

Glasdegib potential for inhibition of selected UGTs was evaluated in human liver microsomes. Glasdegib showed a minor potential for inhibition of UGT1A1 and UGT1A9.

The extent of in vitro binding of glasdegib to human plasma proteins and non-clinical species was determined using an equilibrium dialysis method at concentrations ranging from 1 to 50 microM, depending on the species. Glasdegib was moderately to highly bound to plasma proteins in all species evaluated. Binding was independent of drug concentration. The glasdegib mean fu values are 0.0899 in human.

The in vitro binding of glasdegib (at 2 μM) to human serum albumin (HSA) and alpha-1 glycoprotein (AAG) was determined at physiological concentrations for these proteins. Glasdegib was moderately bound to both HSA (mean fu of 0.204) and AAG (mean fu of 0.478), which suggests that glasdegib likely binds to both HSA and AAG in human plasma

The extent of glasdegib partitioning into blood cells was determined in human whole blood and other species over a concentration range of 0.2 to 50 microM. In human whole blood the partitioning of glasdegib was independent of concentration and the mean Cb/Cp value was 1.38, respectively.

Exposure relevant for safety evaluation

Relevant data on exposure of Glasdegib after repeated dose of 100 mg once daily, at steady state, in patients, could be found in Studies B1371003, B1371005, B1371012 and B1371013.

Average AUC0-tau,ss ranged from 13150 ng/mL (CV 50%) to 19170 (CV 61%), and Cmax,ss ranged from 996.8 ng.hr/mL (CV 45%) to 1718 ng.hr/mL (CV 28%).

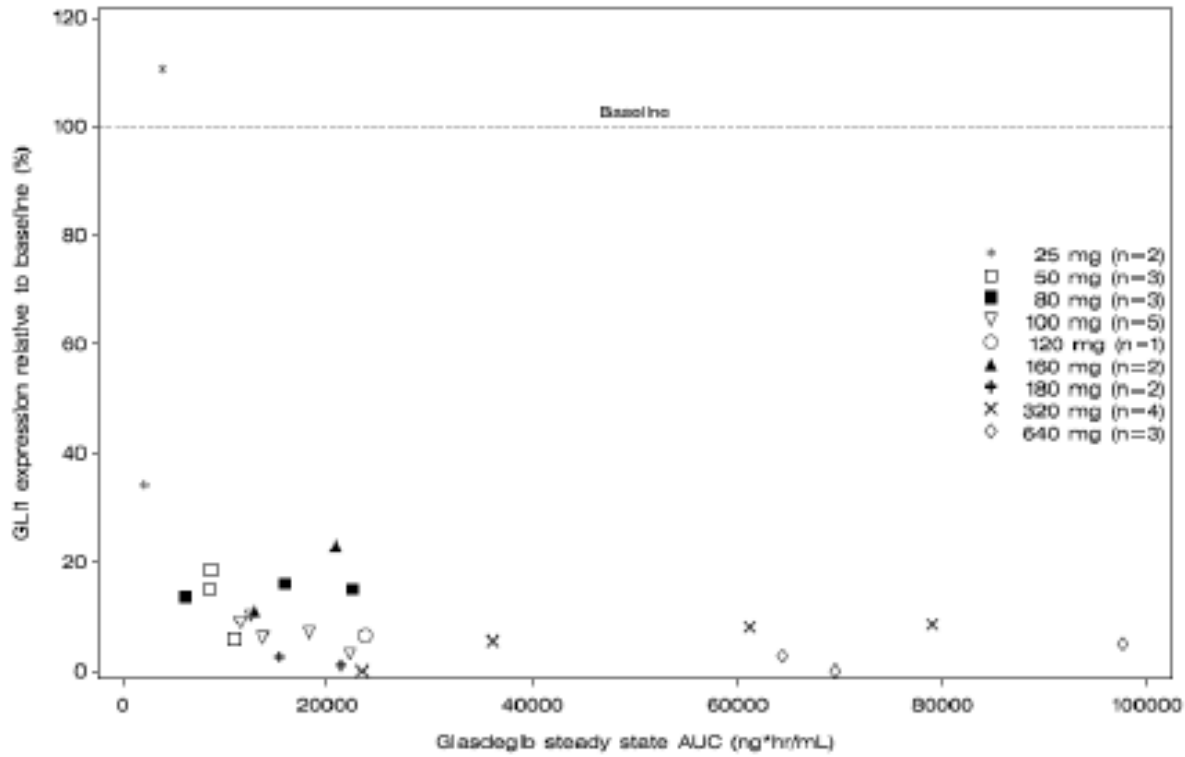
2.4.3. Pharmacodynamics

Mechanism of action

Glasdegib is a small molecule inhibitor of the hedgehog pathway, administered orally. Binding of the Sonic, Indian, or Desert Hh ligands to the transmembrane receptor patched allows activation of the glioma-associated oncogene homolog 1 and 2 (GLI1 and GLI2) transcriptional regulators, and modulation of target gene expression through SMO-mediated signalling. Glasdegib is an inhibitor of the Hh signaling pathway through binding to the target, SMO (Smoothened), resulting in down-regulation of GLI1, a marker of pathway activation.

Skin biopsies were obtained from patients in 3 studies (B1371001, B1371002 and B1371005). Samples were collected at different doses of glasdegib (25 mg to 640 mg QD). Normal skin punch biopsies were obtained from patients at Screening and following repeated daily dosing to steady state. Skin samples were analyzed for treatment related changes in the ribonucleic acid transcript levels of Hh pathway regulated genes.

Figure 210. Down-regulation of gli1 expression in skin versus glasdegib steady state plasma exposure (Studies B1371001, B1371002 and B1371005).



The results of this analysis showed down-regulation of GLI1 expression at most dose levels, with similar effect on expression observed at 100 mg QD and higher dose levels, up to 640 mg. Consistent down regulation of GLI1 expression was also observed at the 50 mg QD dose.

No dedicated primary PD study has been submitted.

Secondary pharmacology

Dose rationale - Maximum Tolerated Dose and Recommended Phase 2 Dose determination

The number of DLTs reported at each glasdegib dose-escalating level during Cycle 1 of the first in man (FIH) study in patients with selected advanced haematologic malignancies (Study B1371001) is summarized in Table 24.

Table 24. Summary of Dose-Limiting Toxicities (Study B1371001).

Number of Patients (%)	5 mg	10 mg	20 mg	40 mg	80 mg	120 mg	180 mg	270 mg	400 mg	600 mg
Patients treated	3	3	4	4	8	3	3	5	9	5
Patients evaluable for DLTs	3	3	4	4	6	3	3	3	7	5
Patients with DLTs	0	0	0	0	1 (16.7)	0	0	0	0	1 (20.0)

Source: Study B1371001 CSR Table 26.
Patients who took less than 80% of the planned dose in Cycle 1 due to reasons other than study-related toxicities were not evaluable for DLTs.
DLT = dose-limiting toxicity.

Out of the 41 DLT evaluable patients, 2 patients (1 patient each in the 80 mg and the 600 mg groups) experienced DLTs during Cycle 1. The patient in the 80 mg group experienced non-hematologic DLTs of hypoxia and pleural effusion. In response to the hypoxia DLT, which was also considered as an SAE, dosing with the study drug was interrupted temporarily, and then the dose reduced. The patient also received a blood transfusion. The patient in the 600 mg group experienced a non-haematologic DLT of peripheral oedema which was also considered as an SAE. In response to the SAE, the study drug was stopped temporarily. All the 3 DLTs experienced by both patients were Grade 3 in severity and considered to be related to the study drug.

In addition, 3 patients (1 patient in the 400 mg group and 2 patients in the 600 mg group) had a post-baseline maximum QTcF interval of ≥500 msec and 6 patients (1 from the 5 mg group and 5 from the 600 mg group) had a maximum QTcF increase from baseline of ≥60 msec.

The MTD was defined as 400 mg once daily after considering the DLT and QTc prolongation data.

The RP2D of glasdegib was defined as 200 mg once daily (or less) based on the following factors:

- Efficacy observed across a broad range of doses (10 to 600 mg once daily).
- Confirmation of the MTD as 400 mg once daily.
- An oedema DLT event and QTc prolongation events observed at 600 mg once daily.
- In the FIH study (B1371001), PD data in surrogate tissue was available at the 120 mg, 180 mg and 270 mg dose levels. The data showed down regulation of GLI1 expression at all three dose levels. Additionally, comparable PD data from solid tumour study B1371002 showed pathway knockdown at doses of 80 mg and above.
- To provide additional safety margin with respect to possible increased exposures resulting from potential drug-drug interactions.

Genetic differences in PD response - Mutational analysis

Pharmacodynamics data relative to the claimed population have been assessed in the pivotal B1371003 Phase 1b/2 study. In the part 2 phase, 88 unfit patients were included in baseline mutational analyses of bone marrow and/or peripheral blood, including 61 patients who received glasdegib 100 mg + LDAC and 27 patients who received LDAC alone (Table 24).

For the glasdegib 100 mg + LDAC arm, clinical responses were evident across patients with diverse mutational profiles, including mutations in all 12 genes reported, with the exception of KRAS (only 2 instances in non-responders). The most commonly mutated genes in responding patients were RUNX1, IDH1 and TET2 (10 of 21 [47.6%], 5 of 21 [23.8%] and 7 of 21 [33.3%] responding patients, respectively), which likely reflects their overall high incidence in this patient population (28/61 [45.9%], 10/61 [16.4%] and 15/61 [24.6%] patients, respectively, in the glasdegib 100 mg + LDAC arm). No significant correlations were evident between mutational status of any of the individual 12 reported genes and clinical response, although there was non-significant trend suggesting a relationship between DNMT3A mutations and lack of response (DNMT3A mutations in 2/21 [9.5%] responders and 13/40 [32.5%] non-responders, p-value = 0.063 using Fisher's Exact test). This trend may reflect the known association of DNMT3A mutations with poor outcome in AML. For the LDAC alone arm, the overall spectrum of mutations evidence was similar to the glasdegib 100 mg + LDAC arm, but no meaningful assessment of potential correlations with response was feasible, since there was only 1 responding patient among 27 patients evaluable for mutational status.

Table 25. Summary and analysis of baseline gene mutation frequency and clinical response category by treatment arm (AML/MDS) – phase 2 unfit (non-intensive)

Gene name	Mutation Status	Glasdegib 100 mg+LDAC N=61		LDAC Alone N=27	
		Responder	Non-Responder	Responder	Non-Responder
		n (%)	n (%)	n (%)	n (%)
CEBPA	mutated	3 (4.9)	5 (8.2)	0	3 (11.1)
	non-mutated	18 (29.5)	35 (57.4)	1 (3.7)	23 (85.2)
DNMT3A	mutated	2 (3.3)	13 (21.3)	0	6 (22.2)
	non-mutated	19 (31.1)	27 (44.3)	1 (3.7)	20 (74.1)
FLT3	mutated	1 (1.6)	4 (6.6)	0	0
	non-mutated	20 (32.8)	36 (59.0)	1 (3.7)	26 (96.3)
FLT3-ITD	mutated	1 (1.6)	2 (3.3)	0	2 (7.4)
	non-mutated	20 (32.8)	38 (62.3)	1 (3.7)	24 (88.9)
IDH1	mutated	5 (8.2)	5 (8.2)	0	2 (7.4)
	non-mutated	16 (26.2)	35 (57.4)	1 (3.7)	24 (88.9)
IDH2	mutated	2 (3.3)	10 (16.4)	0	5 (18.5)
	non-mutated	19 (31.1)	30 (49.2)	1 (3.7)	21 (77.8)
KIT	mutated	1 (1.6)	2 (3.3)	0	1 (3.7)
	non-mutated	20 (32.8)	38 (62.3)	1 (3.7)	25 (92.6)
KRAS	mutated	0	2 (3.3)	0	2 (7.4)
	non-mutated	21 (34.4)	38 (62.3)	1 (3.7)	24 (88.9)
NPM1	mutated	2 (3.3)	3 (4.9)	0	1 (3.7)
	non-mutated	19 (31.1)	37 (60.7)	1 (3.7)	25 (92.6)
NRAS	mutated	1 (1.6)	4 (6.6)	0	3 (11.1)
	non-mutated	20 (32.8)	36 (59.0)	1 (3.7)	23 (85.2)
RUNX1	mutated	10 (16.4)	18 (29.5)	0	7 (25.9)
	non-mutated	11 (18.0)	22 (36.1)	1 (3.7)	19 (70.4)
TET2	mutated	7 (11.5)	8 (13.1)	1 (3.7)	8 (29.6)
	non-mutated	14 (23.0)	32 (52.5)	0	18 (66.7)
WT1	mutated	1 (1.6)	2 (3.3)	0	1 (3.7)
	non-mutated	20 (32.8)	38 (62.3)	1 (3.7)	25 (92.6)

Source: Table 14.4.7.3.1
The baseline of gene mutation was selected from the combined results from both bone marrow and blood: use bone marrow results if available, blood results if bone marrow results not available, with results unknown if neither available.

- Correlation of glasdegib pharmacokinetics with efficacy endpoints

Treatment-Response (T-R) and Exposure-Response (E-R) analysis have been done on data from the patients randomized in the non-intensive chemotherapy arm in the part 2 of the B1371003 pivotal study.

For the Treatment-Response (T-R) analysis, glasdegib + LDAC treatment arm appeared to be a statistically significant predictor of OS globally. The absence of glasdegib treatment (eg., LDAC alone) was associated with shorter OS. Indeed, the hazard ratio (HR) was 0.47 (95% CI: 0.32-0.67) for glasdegib + LDAC arm versus LDAC alone arm. Additional exploratory T-R for the AML subpopulation was also conducted for OS. The median HR (95% CI) was 0.42 (0.28-0.66) for glasdegib + LDAC treatment versus LDAC alone which is similar to the HR for OS calculated using a Cox proportional hazard model and reported in Study B1371003 [HR 0.46 (95% CI: 0.30-0.72)]. These results support the benefit of adding glasdegib to non-intensive chemotherapy, LDAC, in patients with AML who are not eligible to receive intensive chemotherapy. Patient demographic characteristics (e.g., age, sex, baseline weight), disease characteristics (e.g., de novo or secondary, cytogenetic risk, baseline ECOG performance status), prior treatment with a hypomethylating agent, and baseline safety laboratory values (e.g., BCCL, BAST, baseline white blood cells [BWBC], BPBL, baseline percent peripheral blasts [BBPL]) were formally evaluated as potential predictors of OS. No other covariates, aside from treatment arm, were identified as significant predictors of OS in this analysis.

For the Exposure-Response (E-R) analysis in the AML subpopulation, patients with AML in the Phase 2 glasdegib + LDAC treatment arm were randomized to receive 100 mg of glasdegib; dose reductions were permitted. Time- independent exposure metrics were selected for formal evaluation in the E-R analysis for OS (e.g., cycle 1 first dose maximum concentration, end of Cycle 1 maximum concentration, end of Cycle 1 minimum trough concentration, overall average concentration) based on the distribution of the average glasdegib dose administered during treatment and glasdegib plasma exposure parameters. None of the tested glasdegib exposure metric was identified as a significant predictor of OS. Patient demographic characteristics (e.g., age, sex, baseline weight), disease characteristics (e.g., de novo or secondary, cytogenetic risk, baseline ECOG performance status), prior treatment with a hypomethylating agent, and baseline safety laboratory values (e.g., BCCL, BAST, BWBC, BPBL, BBPL) were also formally evaluated as potential predictors of OS with none identified as significant predictors of OS.

No dedicated study assessing relationship between plasma concentration and effect has been submitted. Treatment-Response (T-R) and Exposure-Response (E-R) analysis have been done on data from the patients randomized in the non-intensive chemotherapy arm in the part 2 of the B1371003 pivotal study. Therefore, only the dose of glasdegib of 100 mg was assessed. No E-R relationship was observed between glasdegib plasma exposure and efficacy endpoint (OS) in patients with previously untreated AML with the glasdegib dose evaluated.

- Correlation of glasdegib pharmacokinetics with safety endpoints

Exposure-Response relationships for safety endpoints were examined using data from studies in patients with advanced hematologic malignancies or solid tumours treated with glasdegib over a dose range of 5 to 640 mg once daily (Studies B1371001, B1371002 and B1371003) (PMAR-783). The population consisted of 181 males and 91 females with a median (range) age of 69.0 (25.0-92.0) years old and median (range) baseline body weight of 78.6 (43.5-146) kg. The following E-R relationships for safety endpoints were identified: dysgeusia, muscle spasms, renal toxicity, and QT interval prolonged.

- Correlation of glasdegib pharmacokinetics with electrocardiogram data

In the thorough QT (TQT) study in 36 healthy subjects treated with glasdegib, at steady state therapeutic plasma concentrations (achieved with a 150 mg single dose), the largest mean QTc interval change was 8.03 msec. The highest 90% CI upper bound for the largest, placebo- and baseline-adjusted QTcF change was 10.22 msec at 4 hours post dose. At supra-therapeutic exposure, the highest 90% CI upper bound for the largest, placebo and baseline-adjusted QTcF change was 15.61 msec at 3 hours post dose. The upper bound of the 2-sided 90% CIs for all time-matched least square (LS) mean differences between glasdegib and placebo was below 20 msec.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetics of glasdegib has been studied in 7 studies in healthy volunteers (absorption, distribution, metabolism, and excretion, drug-drug interaction, QT, food effect and bioavailability), and in 1 study in subjects with renal impairment (B1371017). Single- and multiple-dose PK of glasdegib has been evaluated in 5 studies in adult patients with haematologic malignancies and solid tumours (B1371001, B1371002, B1371003, B1371005, and B1371012). The overall pharmacology package is considered sufficiently extensive to allow for a detailed assessment of PK in the populations studied.

As the Applicant developed 3 glasdegib formulations, two bridging studies have been performed to demonstrate bioequivalence between the generation 1 maleate tablet and the reference di-HCl tablet, and between the commercial maleate tablet (to be marketed) and the reference di-HCl tablet. The three different formulations are well bridged, and as PK of glasdegib can be proven linear from 5 to 680 mg, this can extend to tablets of lower strengths (studies used di-HCl tablet at 5, 10, 25, 100g strength, and maleate tablets at 20 and 100 mg). Bioequivalence to the di-HCl formulation is shown and is considered of critical importance, as all early clinical studies as well as the pivotal B1371003 study have only been performed with this formulation and results from these studies are considered valid also for the commercial formulation.

Studies in healthy subjects following single dose and studies in patients following single- and multiple dose administrations showed that glasdegib AUCinf and Cmax increased in a dose-proportional manner over the dose range of 5 mg to 600 mg (the proposed dose is 100 mg taken orally once daily).

Following 100 mg oral administration absolute bioavailability was 77%. Glasdegib is highly bound to human plasma proteins. In line with applicant's responses in can be agreed that no significant impact on the unbound systemic exposures of glasdegib in e.g. patients with renal and hepatic impairment (mean free fraction of 9%) is expected. The glasdegib mean apparent volume of distribution (Vz/F) was 188 L (20%) following a single dose of 100 mg glasdegib. The primary metabolic pathways for glasdegib are comprised of N-demethylation, glucoronidation, oxidation and dehydrogenation. CYP3A4 is the primary metabolizing enzyme (60 to 80%) with minor contributions by CYP2C8 (2 to 20%) and UGT1A9. A mass balance study B1371009 investigated metabolism and metabolites of glasdegib, showing that unchanged glasdegib was the major component in human plasma (69.4%), with N-desmethyl and N-glucoronide glasdegib metabolites accounted for 7.9% and 7.2% of the circulating radioactivity, respectively and other metabolites accounted for less than 5% individually. Oxidative metabolism was the major route of glasdegib elimination with minor contributions from glucuronidation. Inter-conversion is not a risk for glasdegib.

The geometric mean (geometric %CV) oral clearance (CL/F) of glasdegib was 7.63 (20) L/hr after single dose administration of 100 mg glasdegib and 6.45 (25) L/hr after multiple doses of 100 mg QD of glasdegib. About 17.2% and 19.5% of the administered dose were excreted unchanged in urine and faeces. The geometric mean CL is 1.97 L/hr and mean half-life is 17.4 ± 3.7 hours. Accumulation of glasdegib observed in human plasma following continuous QD dosing was consistent with the plasma half-life of the drug (see SmPC section 5.2).

PK parameters were also evaluated in an adequate number of patients, treated with multiple doses of glasdegib. In patients, median tmax following a single dose of glasdegib is around 2 hrs and after multiple doses between 1.3 and 1.8 hrs (Study B1371003), which is comparable to results from the healthy volunteers (HV) studies. The exposure was higher in the patient population with higher Cmax and AUC values, while a lower Cl was found in patients compared to HV; ~12L/hr compared to ~6L/hr in HV. The glasdegib geometric mean plasma Cmax values in healthy volunteers ranged from 561 ng/mL to 890 ng/mL across studies, while the geometric mean AUCinf values ranged from 7628 ng•hr/mL to 9599 ng•hr/mL after a single 100mg dose. In study B1371005 the geometric mean Cmax and AUCinf in patients were 1019 ng/mL and 13119 ng•hr/mL, respectively.

Differences in exposure between the target patient population and healthy volunteers are likely due to subject characteristics; the patient population is comprised of elderly subjects with a naturally lower kidney function. Due to the decreased renal function, clearance of glasdegib is likely lower which could result in higher exposure.

PK characterisation in the target population is considered essential for this submission and relevant pharmacology studies were conducted with patients, the PK data generated in healthy volunteers are considered supportive with this regard. Of note, 98% of patients included in the PK studies were > 65 years of age. According to the proposed indication (section 4.1 of the SmPC) glasdegib is indicated for adult AML patients, not only elderly patients. While it could be speculated that PK characteristics of glasdegib in younger AML patients are comparable to the HV PK profiles, this has not been formally investigated or discussed by the Applicant and also only mainly considers underlying differences in renal clearance as underlying cause, but not other possible (disease) characteristics. However, it is acknowledged that, for the assessment of safety (of exposure), it has advantages to investigate it in a 'worst case' population. The ADME of glasdegib in patients > 65 years has been characterised and is adequately reflected in the SmPC.

PK curve characteristics are comparable between HVs and patients, also for combination therapy with LDAC.

The population modelling is well detailed. During assessment timeline, some deficiencies were addressed. Although the inclusion of BPBL on CL/F was statistically significant, the effect of BPBL is not considered to be clinically relevant and dose adjustment based on this laboratory value is not warranted. While the reason for this difference is not known, the impact of this difference is not clinically relevant given that the exposure observed in solid tumour versus haematologic patients was similar. Hence, glasdegib dose adjustment based on tumour type is not warranted. A residual variability of 59.5 and 65.7% (proportional error) was estimated for glasdegib in patients. Moreover, a high shrinkage is observed for Vp/F, Q and Ka. However, taking into account the overall model adequacy (GOF, VPC, precision of PK parameter estimates) and the fact that the model parameter estimates were in line with parameters reported through non-compartmental analyses in formal PK studies, the issues are not pursued. PK in the target population appears to be not significantly different from PK in healthy volunteers. Overall, the final POPPK model described the observed data reasonably well, and the predictive capability of the final POPPK model was validated through different approaches. The inter-subject variability is around 30% with the proposed dose.

Food intake decreased plasma exposure of glasdegib, AUCinf by 16% and Cmax by 31%. Tmax was delayed between 0-3 hrs, while half-life time was similar. According to the proposed SmPC section 5.2 glasdegib can be administered irrespective of food intake and this rule was also applied in the clinical studies as the impact of food on the pharmacokinetics of glasdegib is not considered clinically relevant.

Possible genetic polymorphisms are not expected to have a clinically relevant influence, as the prevalence of CYP3A4*22 polymorphism is low and the safety margin of glasdegib was established up to doses of 400mg. Glasdegib is not metabolised by pathways that are at risk for possible genetic polymorphism.

Five modelling reports were submitted to support various aspects of the submission; one pop-PK model to describe the kinetic behaviour of glasdegib, two PK/PD models to assess the effect of glasdegib on QT intervals (one in HVs and one in patients), one PK/PD model for Exposure-Response Analysis for Efficacy and one PK/PD model for Exposure-Response Analysis for safety. The models are built based on data generated (and submitted) by the Applicant for this development. They serve as additional source of information to describe glasdegib properties and performance for regulatory scrutiny and are considered as supporting documentation.

Special populations

One study has been performed in patients with renal impairment (Study B1371017). Glasdegib plasma exposure was about 2-fold higher in subjects with moderate and severe renal impairment compared to subjects with normal renal function. The applicant justified that the 2-fold increase in AUCinf for glasdegib 100 mg observed in Study B1371017 was similar for subjects with moderate and severe renal impairment

which corresponds to equivalent plasma exposures as the 200 mg dose, which is still 50% lower than the MTD for glasdegib. Peak glasdegib exposure (Cmax) increased by 37%, and 20% for subjects with moderate, and severe renal impairment, respectively, relative to subjects with normal renal function (see SmPC section 5.2). These changes are not considered to be clinically relevant. PK results from the renal impaired study are comparable to the studies in AML patients, these patients were largely elderly patients, also with slightly decreased renal function. No dose adjustment is recommended by the Applicant which is accepted.

Data from a dedicated pharmacokinetic trial have shown that plasma exposures for total glasdegib (AUCinf and Cmax) were similar between subjects with normal hepatic function and subjects with moderate hepatic impairment (Child-Pugh Class B), whilst geometric mean AUCinf and Cmax values were 24% and 42% lower, respectively, for subjects with severe hepatic impairment (Child-Pugh Class C), compared to the normal hepatic function group. The glasdegib unbound exposure (unbound AUCinf) is increased by 18% and 16% in subjects with moderate and severe impairment, respectively, relative to subjects with normal hepatic function. Peak glasdegib unbound exposure (unbound Cmax) increased by 1%, for moderate hepatic impairment and decreased by 11% for severe hepatic impairment, relative to subjects with normal hepatic function. These changes are not considered to be clinically relevant (see SmPC section 5.2).

In the pooled POP-PK analysis, no clinically relevant effects of age, sex, race, or body weight on glasdegib PK were observed, supporting the fixed dose approach. Simulated data (popPK) support the assumption that results are applicable also for patients < 65 years, however, the amount of observed data is small. The proposal of the applicant that no dose modifications are necessary based on BW are acceptable.

Daurismo should not be used in paediatric patients, therefore no additional data are necessary.

The exposure-response relationship between glasdegib and selected safety endpoints including dysgeusia, muscle spasms, renal toxicity, and QT interval prolongation needs to be further discussed.

In a QT study glasdegib exhibited concentration dependent QT-prolongation. The highest 90% CI upper bound for the largest, placebo- and baseline-adjusted QTcF change was 10.22 msec at 4 hours post dose. A negative QTc study according to ICH E14 criteria shows an upper one-sided 95% CI of the QTc effect of less than 10 msec. At supra-therapeutic exposure, the highest 90% CI upper bound for the largest, placebo and baseline-adjusted QTcF change was 15.61 msec at 3 hours post dose (i.e. an effect on QTc of less than 20, but more than 10 msec). In categorical terms, none of the subjects met the criterion of absolute QTcF interval of ≥480 msec or increase from baseline in QTcF interval ≥30 msec after receiving any treatment; but 2 subjects on glasdegib and 1 on moxafloxacin had a QTcF interval between 450 and 480 msec. ECG QT prolonged has been added to the ADR table in the SmPC section 4.8 and section 4.2 and 4.4 for dose modification and management of adverse reactions, respectively; this is considered sufficient. The TQT study has been added in section 5.1 of the SmPC and QT prolongation has been identified as potential risk in the RMP.

Interactions

Two DDI studies (B1371014 & B1371026) have been performed in healthy volunteers to investigate the effect of CYP3A4 modulators on glasdegib PK. AUCinf of glasdegib increased 140% and Cmax 40% in combination with a strong CYP inhibitor, while AUCinf decreased 70% and Cmax 35% in combination with a CYP inducer. Based on data from the in-vivo studies, a Pop-PK model was used to test the influence of CYPs on glasdegib PK, and again it was found to be a significant co-variate. Results from the clinical studies are summarised in the SmPC section 4.5. As concomitant use of CYP inhibitors is medically necessary, the influence was considered in the dose finding. Caution should be used when administering concomitantly with

strong CYP3A4 inhibitors (e.g., boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, telaprevir, troleandomycin, voriconazole, ritonavir, grapefruit or grapefruit juice) as an increase in glasdegib plasma concentration may occur. If possible, alternate concomitant medicinal product with no or minimal CYP3A4 inhibition potential is recommended. Concomitant use with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's Wort) should be avoided, as this is likely to decrease glasdegib plasma concentrations. If concomitant use of moderate CYP3A4 inducers cannot be avoided, the dose of Daurismo should be increased (see SmPC section 4.2). In addition to in vivo investigations, the potential for glasdegib to inhibit or induce CYP enzymes was investigated in vitro (see SmPC section 5.2).

The PI wording specifies that glasdegib may have the potential to inhibit P-gp (GI tract) and BCRP (systemically and at the GI tract) mediated-transport at clinically relevant concentrations, and caution should be exercised in administration of narrow therapeutic index substrates of P-gp and BCRP in combination with glasdegib (see SmPC section 4.5). Clinically relevant DDIs are not expected following coadministration of glasdegib with MATE1 or MATE2K substrates (see SmPC section 4.5).

In two studies (B1371014 & B1371026) the effect of a PPI on glasdegib PK was investigated. Although glasdegib Cmax decrease 20% in combination with a PPI, there was no change in glasdegib AUCinf. Concomitant administration of glasdegib with acid-reducing agents (including PPIs, H2-receptor antagonists, and locally acting antacids) is permitted (see SmPC section 4.5).

Pharmacodynamics

Glasdegib is a protein-kinase inhibitor targeting SMO in the hedgehog signalling pathway. The theoretic pharamacodynamic principles have been sufficiently described by the Applicant. The choice of GLI-1 as PD marker is endorsed as it is an important downstream target in the Hh signalling pathway and a commonly used marker in the investigation of Hh inhibitors. Since the primary pharmacology, assessment of the inhibitor effect of glasdegib on expression of the GLI1 gene (transcriptional regulator of the Hh pathway), was assessed on a small size of patient samples from various studies, these data can only be considered as a proof of concept. The number of patients evaluated in the studies was very limited (n= 25), with only 3 patients in study B1371001 and 12 patients in study B1371002. In study B1371005, biomarker analysis were performed; the downregulation of GLI1 expression was not observed at the 25-mg dose level, it was observed at 50 mg and above. This observation suggests that at the clinically recommended dose of 100 mg, glasdegib reduces GLI1 expression relative to baseline levels. Additional preliminary exploratory analyses showed no pharmacodynamic modulation of the expression of other pathway-relevant genes. Preliminary data from a mutational analysis suggest that glasdegib could induce a therapeutic response in various mutated AML and MDS. However, no clear conclusion could be drawn without mutational dedicated studies.

Although the data are sparse, treatment with glasdegib reduced GLI-1 expression over 80%, supporting the proposed mode of action. Choice of the proposed 100mg QD dose seems rational, regarding downregulation of GLI-1 expression over 90% with the proposed dose. However, no dedicated study assessing relationship between plasma concentration and effect has been done. Treatment-Response (T-R) and Exposure-Response (E-R) analysis have been done on data from the patients randomized in the non-intensive chemotherapy arm in the part 2 of the B1371003 study where the dose of glasdegib of 100 mg was assessed. Finally, the MTD was defined as 400 mg QD after considering the DLT and QTc prolongation data observed in the FIH study - Study B1371001. The RP2D of glasdegib of 200 mg QD (or less) has been selected based on preliminary efficacy results from the FIH study taking into account an additional safety margin.

Exposure-response relationships with safety endpoints identified some adverse effects: dysgeusia, muscle spasms, renal toxicity, and QT interval prolonged. It is mentioned in the section 4.9 of the SmPC that "Glasdegib has been administered in clinical studies up to a dose of 640 mg/day. At the highest dosage the dose-limiting toxicities reported were nausea, vomiting, dehydration, hypotension, fatigue and dizziness".

2.4.5. Conclusions on clinical pharmacology

In general, the data presented enable conclusive description of the pharmacokinetic profile of oral glasdegib in patients with acute myeloid leukaemia. The information on pharmacokinetics is considered adequately reflected in the SmPC.

The mechanism of action of glasdegib in the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy, seems plausible. Taken together, the presented data to characterise pharmacodynamic profile of glasdegib in AML patients support the postulated mechanism of action and inform the dose finding.

2.5. Clinical efficacy

Efficacy of glasdegib + LDAC is supported by the pivotal, randomised portion of Study B1371003 (see Table 21). The assessment focuses on the claimed indication: "in combination with low-dose cytarabine (LDAC) chemotherapy for the treatment of newly diagnosed *de novo* or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy".

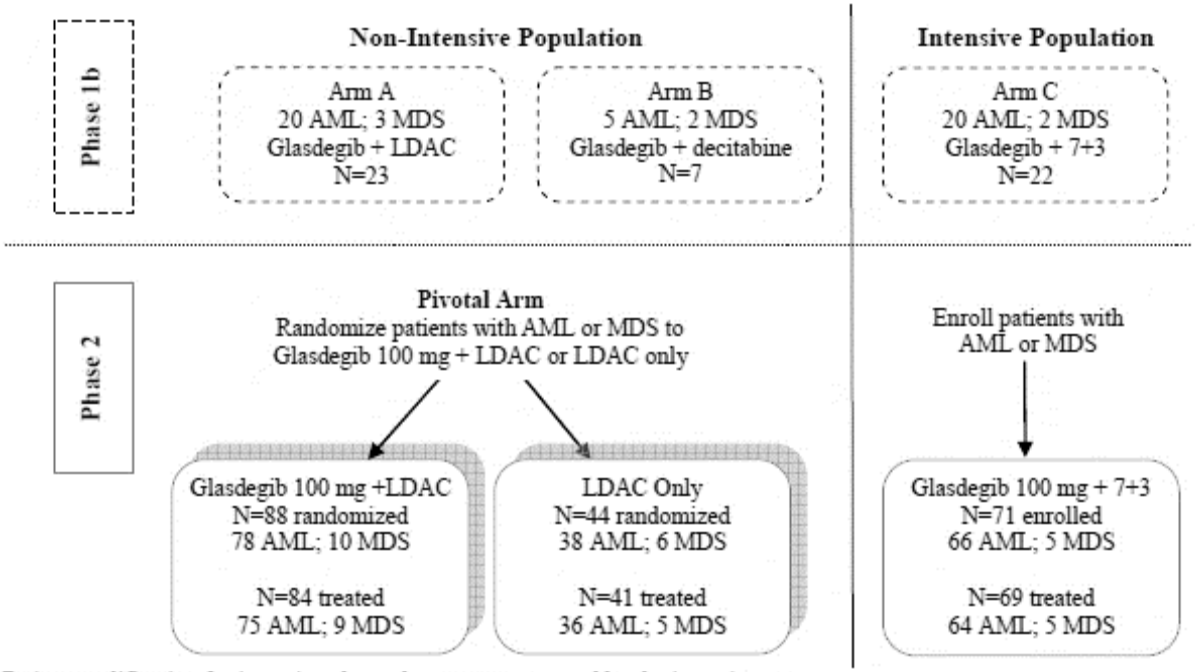
Study B1371003 is a multi-centre, open-label Phase 1b/2 study to evaluate the safety and efficacy of glasdegib when administered in combination with first-line treatment regimens for AML and high-risk MDS. This study was divided into a Phase 1b portion and a Phase 2 portion. A schematic of this study is provided in Figure 12.

Only data of patients treated by glasdegib and LDAC have been assessed in this application: data from the arm A of the phase 1b are presented in the section on dose-response, and data from the 'pivotal arm' including unfit (non-intensive population) in the phase 2 are discussed in the section on main study results below.

In the Phase 1b portion, patients participated in a dose-escalation phase aimed at estimating the maximum tolerated dose of glasdegib in combination with 1 of 3 different chemotherapy options (Arms A [LDAC], B [decitabine], and C [7+3 intensive chemotherapy regimen]).

The Phase 2 portion consisted of 2 parts. In the first Phase 2 part, patients who were not candidates for standard induction chemotherapy (unfit population, "P2 Unfit") were randomised to receive either glasdegib + LDAC or LDAC alone. Randomization of this non-intensive population used a 2:1 allocation ratio and was stratified by prognostic risk factor (good/intermediate or poor) based on cytogenetics. In the second Phase 2 part, patients who were candidates for intensive chemotherapy (intensive/fit population) received glasdegib in combination with 7+3 chemotherapy.

Figure 12. Schematic of study B1371003 and identification of efficacy analysis cohorts.



Patient qualification for intensive chemotherapy was assessed by the investigator.
AML=acute myeloid leukaemia; LDAC=low-dose cytarabine; MDS=myelodysplastic syndrome; N=number of patients treated except where indicated; 7+3=chemotherapy with cytarabine (7 days) plus daunorubicin (3 days); CSR=clinical study report; SCE=summary of clinical efficacy

2.5.1. Dose response study(ies)

No dedicated dose-response study has been submitted in this application. In the Phase 1b portion of study B1371003, patients participated in a dose escalation phase aimed at estimating the maximum tolerated dose of glasdegib in combination with LDAC in Arm A. Clinical efficacy of glasdegib + LDAC in adults with previously untreated AML or high-risk MDS was assessed as secondary endpoint.

Phase 1b: methodology

Primary Objective: To determine the MTD and RP2D of glasdegib in combination with LDAC (Arm A), decitabine (Arm B) or cytarabine/daunorubicin (Arm C) when administered to adults with previously untreated AML or high-risk MDS – primary endpoint: DLT.

Secondary Objectives: In arm A, to assess the efficacy of glasdegib when administered in combination with LDAC to adults with previously untreated AML or high-risk MDS – endpoints: CR/Cri.

Design of part 1b

For each arm separately, a 3+3 dose escalation design was applied in 3-6 patient cohorts until identification of the MTD or maximum administered dose (MAD) of glasdegib when given in combination with each standard therapy. MTD was determined separately within each arm and was associated with the occurrence of DLTs in <33% of patients. In practice, the MTD estimate was the dose level at which 0/6 or 1/6 evaluable patients experienced a DLT during the DLT observation period with the next higher dose having at least 2 of 3 to 6 patients experiencing DLTs.

In arm A, LDAC was administered twice daily subcutaneously for the first 10 days of each 28-day cycle. In each safety dose escalation cohort, glasdegib administration began on Cycle 1/Day 3 for PK assessment purposes and continued with no interruptions thereafter. In the Phase 1b portion of the study, glasdegib was initially administered at a starting dose of 100 mg once daily. Starting doses for subsequent patient cohorts were to be 50 or 200 mg once daily, based on DLT.

For the Phase 1b portion, an external Data Monitoring Committee was not established. During this portion, the sponsor procedures for periodic safety review were applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases.

Phase 1b: results

Disposition of patients: 23 patients were assessed in the full analysis set; 17 received 100 mg of glasdegib + LDAC and 6 received 200 mg of glasdegib + LDAC.

Baseline data: The mean (range) age for Arm A was 75.8 (60 to 85) years. The majority of patients had good/intermediate cytogenetic risk, specifically 14 (60.9%) patients in Arm A. Most patients (50/52) received drugs prior to study treatments. In Arm A specifically, 12/23 (52.2%) patients received prior hypomethylating agents (HMA: decitabine or azacitidine).

Dose limiting toxicity: A total of 28 patients were enrolled in the 3 arms. Out of these 28 patients, there were 26 patients evaluable for DLTs; Patient 10031003 died from disease progression before receiving at least 80% planned dose and Patient 10211014 refused to continue study treatments for reason other than AE. Therefore, the 2 patients were not evaluable for DLTs. 1 patient was reported to have a DLT in the Arm C (Grade 4 polyneuropathy reported during the first induction cycle). The MTD was not reached for Arm A, B or C. A MTD of 400 mg was confirmed in the B1371001 FIH study.

Analysis of efficacy: 2 out of 23 patients (8.7% [80% CI: 2.3%, 21.5%]) patients in Arm A achieved CR/CRi based on investigator-reported responses. 21 deaths were reported, and the estimated median OS was 4.4 [80% CI: 2.5, 6.6] months. Limited efficacy of glasdegib has been shown in these preliminary results.

2.5.2. Main study(ies)

A Phase 1b/2 Study to Evaluate the Safety and Efficacy of PF-04449913, an Oral Hedgehog Inhibitor, in Combination With Intensive Chemotherapy, Low Dose Ara-C or Decitabine in Patients With Acute Myeloid Leukaemia or High-Risk Myelodysplastic Syndrome - B1371003 study

Methods

Study Participants

Main inclusion criteria

1. AML or refractory anaemia with excess blasts (RAEB)-2 high-risk MDS newly diagnosed according to the WHO 2008 Classification and previously untreated. Patients with MDS, and patients with AML arising from an antecedent hematologic disease (AHD) or MDS, may have had 1 prior regimen (e.g., azacitidine or decitabine) for the treatment of their prior haematologic disease. The patients may not have had any prior therapy for AML. Patients in the P2 Unfit arms had to have a known cytogenetic profile at study entry.

2. AML patients included de-novo AML, AML evolving from MDS or other AHD and AML after previous cytotoxic therapy or radiation (secondary AML).

- For a diagnosis of AML, a bone marrow blast count of 20% or more was required.
- For AML defined by cytogenetic aberrations t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia, the proportion of bone marrow blasts could be <20%.
- In AML FAB M6a (erythroid leukaemia), ≥20% of non-erythroid cells in the bone marrow had to be leukaemic blasts and ≥50% of the cells erythroid precursors.
- In AML with monocytic or myelomonocytic differentiation, monoblasts and promonocytes, but not abnormal monocytes, were counted as blast equivalents.

3. For high-risk MDS RAEB-2: 10-19% bone marrow blasts (protocol refers to WHO Classification of MDS[1]).

4. Age: ≥18 years old for patients enrolled in Phase 1b and P2 Fit arm.

5. Eastern Cooperative Oncology Group (ECOG) Performance Status 0, 1, or 2.

6. Patients with AML or high-risk MDS who had 1 or more of the criteria below were considered unfit for intensive chemotherapy[2] and were eligible for Phase 1b Arms A and B or P2 Unfit arms: Age ≥75 years; ECOG of 2; Serum creatinine >1.3 mg/dL; Severe cardiac disease (e.g., left ventricular ejection fraction [LVEF] <45% by multi-gated acquisition [MUGA] or echocardiography at screening).

7. Adequate organ function (AST and ALT ≤3 × ULN, or AST and ALT ≤5 × ULN if liver function abnormalities were due to underlying malignancy; Total serum bilirubin ≤2 × ULN [except patients with documented Gilbert's Syndrome]; Serum creatinine ≤1.5 × ULN or estimated creatinine clearance ≥60 mL/min.

8. All anti-cancer treatments (unless specified) discontinued ≥2 weeks from study entry, for example: targeted chemotherapy, radiotherapy, investigational agents, hormones, anagrelide or cytokines.

- For control of rapidly progressing leukaemia, hydroxyurea or leukapheresis could be used before and for up to 1 week after first dose of glasdegib.
- Patients with controlled CNS leukaemia (2 consecutive assessments of 0 blast count in cerebrospinal fluid) receiving intra-thecal therapy at study entry were eligible and continued intra-thecal therapy.

Main exclusion criteria

1. APL with t(15;17) or patients with a t(9:22) cytogenetic translocation for any component of the study.

2. Hyperleukocytosis (leukocytes ≥30 × 10^9/L) at study entry. These patients may have been treated with hydroxyurea or received leukapheresis treatment according to routine practice, and enrolled in the study when the leukocyte count fell below 30 × 10^9/L.

1 Vardiman, JW, Harris, NL, Brunning RD: The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;(100):2292-2302.62

2 Kantarjian H, O'brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer 2006;106:1090-8.

3. Patients known to be refractory to platelet or packed red cell transfusions per Institutional Guidelines, or refusing blood product support.

4. Myocardial infarction, congenital long QT syndrome, Torsades de Pointes (TdP) or ventricular arrhythmias.

5. QTc using Fridericia's formula (QTcF interval) >470 milliseconds (msec).

6. Current use at study entry or anticipated need for drugs that were known strong CYP3A4/5 inducers.

Treatments

Both agents (glasdegib, LDAC) were to be started together on Cycle 1/Day 1.

Glasdegib 100 mg once a day has been administered in the morning at approximately the same time as the first LDAC subcutaneous injection on days these agents are dosed together. LDAC has been administered at a dose of 20 mg (not adjusted for the patients' weight) SC twice daily (morning and evening; approximately 12 hrs apart) on Days 1-10 days of the 28 day cycles.

Treatment with glasdegib in combination with LDAC could continue for up to 1 year (12 cycles) from start of therapy or until disease progression or relapse, patient refusal, or occurrence of unacceptable toxicity (whichever came first). Patients who completed treatment for 1 year (12 cycles) with LDAC were considered to have completed treatment on the trial. Patients who completed the maximum number of cycles/months on study treatment, demonstrated clinical benefit with manageable toxicity, and who were willing to continue receiving assigned treatment could be given the opportunity to do so upon agreement between investigator, sponsor and pending study drug availability. For patients on trial longer than the specified period, the schedule of activities continued to be followed.

After discontinuation of study treatment (all arms), post-treatment survival status was to be collected every month for the first 2 months and thereafter every 2 months until death or until termination of the study by the sponsor. All patients would be followed for 4 years from the first dose. Patients who were randomized but did not start treatment would be followed for survival on this schedule from the date of randomization.

The study was to be considered complete once all patients have been followed for 4 years from first dose (or randomization date if applicable), which means the last enrolled patient has been followed for 4 years from his/her first dose (or randomization if applicable).

Objectives

Primary objective

- To compare the overall survival (OS) for glasdegib + LDAC versus LDAC alone in unfit patients with previously untreated AML or high-risk MDS.

Secondary objectives

- To assess clinical efficacy measures (including disease-specific measures) of glasdegib + LDAC versus LDAC alone in unfit patients with previously untreated AML or high-risk MDS.
- To assess the safety and tolerability of glasdegib + LDAC versus LDAC alone in unfit patients with previously untreated AML or high-risk MDS.
- To evaluate the pharmacodynamics of glasdegib + LDAC versus LDAC alone in unfit patients with previously untreated AML or high-risk MDS.

- To evaluate the PK of glasdegib.
- To characterize the effects of glasdegib on QTc interval.

Outcomes/endpoints

Primary Endpoint: Overall survival (OS).

Secondary Endpoints:

- Complete remission response (CR)
- For AML patients: CRi, Morphologic Leukaemia-Free State, Partial Remission (PR), Partial Remission with incomplete blood count recovery (PRi), Minor Response (MR), Stable Disease (SD), Cytogenetic Complete Response (CRc), and Molecular Complete Response (CRm).
- For MDS patients: marrow CR, Partial Remission (PR), Stable Disease (SD), Partial or Complete Cytogenetic Response, and CRi.
- Type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0), timing, seriousness, and relatedness of adverse events.
- Pharmacodynamic biomarkers.
- Pharmacokinetic parameters of PF-04449913 (glasdegib).
- QTc interval.

Response assessment

Assessment of response was made using response criteria for MDS and AML derived and defined by the disease specific International Working Groups and WHO Guidelines[3,4].

Investigator responses are the Investigator's assessment of morphologic disease response per patient based on locally analysed bone marrow aspirates or biopsies, blood samples, and other clinical assessments. Based on clinical judgment, the investigator entered a disease response for each patient in the CRF according to the criteria cited above.

Derived responses are the Sponsor's assessment of morphologic disease responses determined programmatically. Algorithms based on AML and MDS response criteria used the same patient data in the CRF recorded by the investigator to derive each patient’s response.

3 Cheson BD, Greenberg PL, Bennett JM et al. Clinical application and proposal for modification of the international working group (IWG) response criteria in myelodysplasia. Blood 2006; 108(2) 419-25.63

4 Cheson, BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working group for diagnosis, standardization of response criteria, treatment on outcomes and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003; 21(24)4642-4649

Sample size

The null hypothesis was that the OS HR = 1, and the treatment effect was hypothesised to result in HR = 0.625 (considering a historic median OS for LDAC of 5 months and the expected median OS for glasdegib + LDAC of 8 months). The significance level was set to one-sided alpha 10%. Accordingly, a total of 92 OS events were to be observed for the final analysis to provide 80% power to detect the mentioned treatment difference.

Randomisation

In the unfit arm of the portion 2 of the study, the randomization used a 2:1 allocation ratio (glasdegib+LDAC : LDAC alone) and was stratified by cytogenetic risk factor (good/intermediate, or poor).

Randomisation was stratified in the IVRS based on prognosis (cytogenetic risk factor of good/intermediate or poor risk). Any one of the following cytogenetic features (which were required prior to enrolment) classified the patient as having poor-risk disease: inv(3), t(6;9), 11q23, -5, -5q, -7, abnl (17p), complex karyotype (≥3 clonal abnormalities). Patients with none of these features were classified as having good/intermediate-risk disease. The patient risk was captured in IVRS, and the factor(s) characterizing the patient risk were captured on the case report forms (CRFs) (Table 26).

Table 26: Cytogenetic risk classification in study B1371003.

Disease	Risk Group per Case Report Form	Stratification Factor for Randomisation
AML	Favourable	Good/intermediate risk
	Intermediate-I	Good/intermediate risk
	Intermediate-II	Good/intermediate risk
	Adverse	Poor risk
MDS	Good	Good/intermediate risk
	Intermediate	Good/intermediate risk
	Poor	Poor risk

Source: Study B1371003 Protocol in-text Table 6
AML=acute myeloid leukaemia, MDS=myelodysplastic syndrome

Blinding (masking)

The overall study was an open-label study (not blinded).

Statistical methods

The hypothesis of the randomized cohort of the phase II part of this study was that patients with previously untreated AML and MDS and scheduled for non-intensive chemotherapy (unfit population) would have an improved OS when glasdegib was used in combination with LDAC.

The study investigated the difference in survival between glasdegib + LDAC and LDAC alone in a clinical scenario that includes all patients regardless of their treatment compliance (similar to treatment policy estimand). Patients who were lost to follow-up were assumed to be comparable in terms of survival to those who remained in the study.

The primary endpoint was OS, defined as time from randomization to death from any cause. A Cox model using the stratification factor prognosis (good/intermediate *vs* poor) and treatment as covariates was implemented to calculate the hazard ratio (HR).

At the final analysis (planned at a total of 92 OS events observed), an observed HR of 0.76 or below (i.e., observed nominal one-sided $\alpha \leq 0.1$) will reject the null hypothesis of HR = 1.

The proportion of patients who achieved CR with 80 % CI (normal approximation) for each arm was also calculated. A Pearson $\chi 2$ test (unstratified) and Cochran-Mantel-Haenszel (CMH) test stratified by prognosis were presented.

The full analysis set included all randomized patients of the P2 Unfit arms. No Per Protocol Analysis Set has been defined in part 2 of the study.

Patients' treatment arm assignment in the Phase 2 portion was based on the fit or unfit status at screening and an Interactive Registration System (IRS) has been used. Patients in the Phase 2 Unfit randomized component have been analysed in the arm they were randomized for the efficacy analyses, and in the arm they were treated for the safety analyses.

For primary and secondary efficacy analyses, no values were to be imputed for missing data. Patients not known to have died at the time of the last follow-up were censored on the date they were last known to be alive. In the assessment of CR/CRi rate in phase 1b and CR rate in phase 2 portion of the study, patients who were not known to have achieved the endpoint of interest (CR/CRi or CR) were counted as non-responders.

One futility interim analysis (IA) was planned when 46 OS events have been observed. The futility boundary was calculated accordingly using an alpha spending function.

The primary analysis for efficacy endpoints was based on Derived response, and the secondary analysis on the investigator data. The interim analysis was based on investigator's assessments.

The SAP was version 5, dated 11 March 2016. The SAP was amended several times while the study was ongoing to reflect the changes made in the protocol. The changes made in the SAP include updating the study design to a phase 1b/2 study, clarification of definitions and removal of some exploratory endpoints.

Results

Participant flow

The patient disposition for the P2 Unfit arms is summarized in Table 27. All 132 randomized patients (88 and 44 patients in the glasdegib 100 mg + LDAC and LDAC alone arms, respectively) were included in the efficacy analyses.

Table 27. Patient disposition Phase 2 Unfit (non-intensive).

	AML + MDS N=132		AML N=116		MDS N=16	
	Glasdegib + LDAC	LDAC	Glasdegib + LDAC	LDAC	Glasdegib + LDAC	LDAC
Number (%) of patients:						
Assigned to study treatment	88	44	78	38	10	6
Treated	84	41	75	36	9	5
Treatment completed[f]	0	0	0	0	0	0
Analysed for efficacy[c]	88 (100.0)	44 (100.0)	78 (100.0)	38 (100.0)	10 (100.0)	6 (100.0)
Discontinued treatment[a,b]	80 (95.2)	41 (100.0)	71 (94.7)	36 (100.0)	9 (100.0)	5 (100.0)
Insufficient clinical response	37 (44.0)	15 (36.6)	32 (42.7)	12 (33.3)	5 (55.6)	3 (60.0)
AE[d]	13 (15.5)	10 (24.4)	12 (16.0)	10 (27.8)	1 (11.1)	0
AE[e]	8 (9.5)	2 (4.9)	6 (8.0)	1 (2.8)	2 (22.2)	1 (20.0)
Patient died	10 (11.9)	11 (26.8)	10 (13.3)	11 (30.6)	0	0
Global deterioration of health status	3 (3.6)	1 (2.4)	3 (4.0)	0	0	1 (20.0)
Other	3 (3.6)	0	3 (4.0)	0	0	0
Protocol violation	1 (1.2)	0	1 (1.3)	0	0	0
Patient refused continued treatment for other than AE	5 (6.0)	2 (4.9)	4 (5.3)	2 (5.6)	1 (11.1)	0
Treatment ongoing at cutoff date[a,b]	4 (4.8)	0	4 (5.3)	0	0	0
Completed study[g]	0	0	0	0	0	0
Discontinued from study[c]	72 (81.8)	43 (97.7)	63 (80.8)	37 (97.4)	9 (90.0)	6 (100.0)
Patient died	68 (77.3)	41 (93.2)	59 (75.6)	35 (92.1)	9 (90.0)	6 (100.0)
Lost to follow-up	1 (1.1)	0	1 (1.3)	0	0	0
Patient refused further follow-up	3 (3.4)	2 (4.5)	3 (3.8)	2 (5.3)	0	0
Ongoing in study at cutoff date[a]	16 (18.2)	1 (2.3)	15 (19.2)	1 (2.6)	1 (10.0)	0

Source: Study B1371003 CSR P2unfit Table 14.1.1.1.3, 14.1.1.3.3, 14.1.1.4.3; SCE Tables 1.1.E1A, 1.2.E1A, 1.3.E1A; SCE Tables 1.1.E1M, 1.2.E1M, 1.3.E1M

In the P2 Unfit population, 2.3-fold more patients discontinued the treatment because of death in arm LDAC alone compared to the arm glasdegib + LDAC was observed. However, a higher proportion of patients in the combination arm (44.0% *vs* 36.6%) discontinued treatment because of an insufficient clinical response.

The number of patients in the MDS arm is very small. No assessment could be done based on MDS efficacy data.

Recruitment

Study B1371003 was conducted from 2012 to 2019 at 81 study sites in Europe (Germany, Italy, Poland, Spain) and North America.

Conduct of the study

Changes in the protocol

The original protocol (version date: 28 October 2011) was amended 5 times. The submission is based on the protocol with Amendment 5 (version date: 08 February 2016). Inter alia, the independent assessment of bone marrow samples had been removed, and no bone marrow samples in the study were analysed by independent review.

Protocol deviations

The most frequently reported important protocol deviations were SAE not reported within 24 hours of awareness (26 [19.7%] patients) and randomization related: patient not stratified correctly at randomization in IVRS (21 [15.9%] patients), and patient randomization in error (6 [4.5%] patients). Any of the other important protocol deviations was reported in ≤3 patients.

Baseline data

The demographic and other baseline characteristics for patients in the P2 Unfit arms are summarized in Table 28. Demographic and baseline characteristics were similar between treatment arms for median age and baseline cytogenetic risk. Of note, a higher proportion of male patients were randomized to the glasdegib 100 mg + LDAC arm versus LDAC alone arm.

All patients had ECOG score of 0-2 (except for 1 untreated patient in the glasdegib 100 mg + LDAC arm without reported record) and the score distribution was generally similar between the glasdegib 100 mg + LDAC and LDAC alone arms.

Fifty-two (52 [59.1%]) and 25 (56.8%) patients had good/intermediate cytogenetic risk (IVRS based) in the glasdegib 100 mg + LDAC and LDAC alone arms, respectively.

Table 28: Demographic baseline characteristics (Full Analysis Set) – Phase 2 Unfit (Non-intensive).

	AML + MDS N=132		AML N=116		MDS N=16	
	Glasdegib + LDAC n=88	LDAC n=44	Glasdegib + LDAC n=78	LDAC n=38	Glasdegib + LDAC n=10	LDAC n=6
Age; years; n(%)						
18-44	0	0	0	0	0	0
45-64	2 (2.3)	1 (2.3)	1 (1.3)	1 (2.6)	1	
≥65	86 (97.7)	43 (97.7)	77 (98.7)	37 (97.4)	9	6
≥75	53 (60.2)	24 (54.5)	48 (61.5)	23 (60.5)	5 (50.0)	1 (16.7)
Mean (stdev)	76.2 (6.2)	74.5 (4.9)	76.4 (6.0)	74.8 (4.9)	74.3 (7.7)	73.0 (4.8)
Range	63-92	58-83	64-92	58-83	63-84	69-82
Sex; n (%)						
Female	19	18	19	15	0	3
Male	69	26	59	23	10	3
Race; n (%)						
White	85 (96.6)	44 (100.0)	75 (96.2)	38 (100.0)	10	6
Black	1 (1.1)	0	1 (1.3)	0	0	0
Asian	2 (2.3)	0	2 (2.6)	0	0	0
Other	0	0	0	0	0	0
Weight (kg)						
Mean (stdev)	79.1 (13.6)	77.7 (14.2)	78.0 (13.3)	78.0 (13.9)	87.3 (13.1)	75.6 (17.2)
Range	50.1-119.6	52.2-118.0	50.1-119.6	52.2-118.0	66.0-110.7	58.5-104.5
BMI (kg/m^2)						
Mean (stdev)	27.4 (4.2)	28.2 (5.5)	27.3 (4.2)	28.3 (5.7)	28.2 (3.9)	27.5 (4.5)
Range	17.5-41.9	20.0-48.2	17.5-41.9	20.0-48.2	23.0-35.0	22.6-33.1

Source: Study B1371003 CSR P2unfit Table 14.1.2.1.1.3; SCE Table 2.1.3.E1AM; SCE Table 2.1.E1A, SCE Table

Table 29. Disease Baseline Characteristics (Full Analysis Set) – Phase 2 Unfit (Non-intensive).

	AML + MDS N=132		AML N=116		MDS N=16	
	Glasdegib + LDAC n=88	LDAC n=44	Glasdegib + LDAC n=78	LDAC n=38	Glasdegib + LDAC n=10	LDAC n=6
Duration since diagnosis (mo.)						
Mean	--	--	0.8	0.8	4.9	4.2
Range	--	--	0.03-3.52	0.07-3.84	0.20-13.63	0.43-14.98
Disease history, n						
De novo	--	--	38	18	8	4
Secondary	--	--	40	20	2	2
ECOG PS[a]						
0	11 (12.5)	3 (6.8)	10 (12.8)	3 (7.9)	1 (10.0)	0
1	29 (33.0)	18 (40.9)	26 (33.3)	17 (44.7)	3 (30.0)	1 (16.7)
2	47 (53.4)	23 (52.3)	41 (52.6)	18 (47.4)	6 (60.0)	5 (83.3)
Not reported[c]	1 (1.1)	0	1 (1.3)	0	0	0
Cytogenetic risk[b], n (%)						
Good/intermediate risk	52 (59.1)	25 (56.8)	49 (62.8)	21 (55.3)	3 (30.0)	4 (66.7)
Poor risk	36 (40.9)	19 (43.2)	29 (37.2)	17 (44.7)	7 (70.0)	2 (33.3)
AML only - Prognostic risk factors[d], n (%)						
Favourable	--	--	5 (6.4)	3 (7.9)	--	--
Intermediate-I	--	--	27 (34.6)	11 (28.9)	--	--
Intermediate-II	--	--	21 (26.9)	8 (21.1)	--	--
Adverse	--	--	25 (32.1)	16 (42.1)	--	--
MDS only - Prognostic risk factors[d]; n (%)						
Good risk	--	--	--	--	3 (30.0)	2 (33.3)
Intermediate risk	--	--	--	--	1 (10.0)	3 (50.0)
Poor risk	--	--	--	--	6 (60.0)	1 (16.7)
MDS IPSS score, n (%)						
0 (Low)	--	--	--	--	0	0
0.5-1 (Intermediate-1)	--	--	--	--	0	2 (33.3)
1.5-2 (Intermediate-2)	--	--	--	--	4 (40.0)	4 (66.7)
≥2.5 (High)	--	--	--	--	6 (60.0)	0

Source: Study B1371003 CSR P2unfit Tables 14.1.2.2.3, 14.2.1.1.3, 14.1.2.1.3.3.1, 14.1.2.1.4.3; 14.1.2.1.5.3; SCE Tables

A higher proportion of patients with an adverse prognostic risk factor for AML has been observed at the baseline in LDAC alone arm compared to glasdegib + LDAC arm (42.1% *vs* 32.1%). The Applicant submitted a subgroup analysis for AML patients with adverse prognostic risk factor, showing OS result (HR=0.51 [95% CI: 0.26, 1.00]) consistent with the primary analysis of OS.

Table 30. Number (%) of patients meeting specified fit inclusion criteria at baseline – Phase 2 Unfit (Non-Intensive).

	AML + MDS N=132		AML N=116		MDS N=16	
	Glasdegib + LDAC n=88	LDAC n=44	Glasdegib + LDAC n=78	LDAC n=38	Glasdegib + LDAC n=10	LDAC n=6
Criteria for non-intensive						
≥75 years old	53 (60.2)	24 (54.5)	48 (61.5)	23 (60.5)	5 (50.0)	1 (16.7)
ECOG PS 2	47 (53.4)	23 (52.3)	41 (52.6)	18 (47.4)	6 (60.0)	5 (83.3)
Serum creatinine >1.3 mg/dL	19 (21.6)	5 (11.4)	15 (19.2)	5 (13.2)	4 (40.0)	0
Severe cardiac disease[a]	58 (65.9)	21 (47.7)	52 (66.7)	20 (52.6)	6 (60.0)	1 (16.7)
Number of criteria met						
Exactly 1	26 (29.5)	22 (50.0)	23 (29.5)	17 (44.7)	3 (30.0)	5 (83.3)
Exactly 2	38 (43.2)	16 (36.4)	34 (43.6)	15 (39.5)	4 (40.0)	1 (16.7)
Exactly 3	21 (23.9)	5 (11.4)	19 (24.4)	5 (13.2)	2 (20.0)	0
Exactly 4	3 (3.4)	1 (2.3)	2 (2.6)	1 (2.6)	1 (10.0)	0

Source: Study B1371003 CSR P2unfit Table 14.1.2.1.1.4; SCE Table 2.5.2.E1A; SCE Table 2.5.2.E1M

A higher proportion of patients in glasdegib + LDAC arm compared to LDAC alone arm with a serum creatinine > 1.3 mg/dl, with a severe cardiac disease and with 2 or more of the unfit criteria in the AML arm was observed.

Table 31. Baseline haematologic and bone marrow parameters (Safety Analysis Set) – Phase 2 Unfit (Non-intensive).

	AML + MDS N=125		AML N=111		MDS N=14	
	Glasdegib + LDAC n=84	LDAC n=41	Glasdegib + LDAC n=75	LDAC n=36	Glasdegib + LDAC n=9	LDAC n=5
Median (range)						
White blood cell ($10^3/mm^3$)	2.3 (0.6-64.0)	3.6 (1.1-45.2)	2.5 (0.6-64.0)	4.1 (1.1-45.2)	1.8 (1.0-51.0)	3.5 (1.4-24.7)
Haemoglobin (g/dL)	9.1 (6.4-14.0)	9.2 (6.0-14.6)	9.1 (6.4-14.0)	9.3 (6.0-14.6)	9.0 (7.9-12.3)	9.1 (7.9-11.0)
Platelets ($10^3/mm^3$)	47.0 (5.0-587.0)	38.0 (7.0-398.0)	47.0 (5.0-587.0)	38.5 (7.0-149.0)	79.0 (7.0-140.0)	36.0 (12.0-398.0)
Peripheral blood blasts (%)	6.6 (0.0-91.0)	13.5 (0-83.0)	9.0 (0-91.0)	13.5 (0-83.0)	0 (0-15.0)	12.5 (0-25.0)
Bone marrow blasts (%)	40.0 (7.5-100.0)	38.5 (10.5-95.0)	41.0 (16.0-100.0)	46.0 (13.0-95.0)	14.0 (7.5-18.0)	16.0 (10.5-19.0)

Source: Study B1371003 CSR P2unfit Table 14.3.4.1.4.5

Table 32. Primary diagnoses and durations (Full Analysis Set) – Phase 2 Unfit (Non-intensive).

	Glasdegib 100 mg+LDAC	LDAC Alone
Number of patients	88	44
Primary diagnosis by MedDRA (version 19.1) preferred term		
Acute myeloid leukaemia		
Number of patients	78	38
Duration since histopathological diagnosis (months)		
Mean	0.8	0.8
Range	0.03-3.52	0.07-3.84
Disease history		
De novo	38	18
Secondary disease	40	20
Myelodysplastic syndrome		
Number of patients	10	6
Duration since histopathological diagnosis (months)		
Mean	4.9	4.2
Range	0.20-13.63	0.43-14.98
Number of patients unspecified		
Disease history		
De novo	8	4
Secondary disease	2	2

Source: Table 14.1.2.2.3

Numbers analysed

Table 33. Patient Evaluation Groups – Phase 2 Unfit (Non-intensive).

Number (%) of patients	Glasdegib 100 mg+LDAC	LDAC Alone
Number of patients randomized	88	44
Number of eligible patients	87 (98.9)	40 (90.9)
Number of ineligible patients	1 (1.1)	4 (9.1)
Analyzed for efficacy		
Full analysis set	88 (100.0)	44 (100.0)
Analyzed for pharmacodynamics		
Biomarker	81 (96.4)	39 (95.1)
Analyzed for PK		
Concentration	83 (98.8)	-
Parameter	69 (82.1)	-
Analyzed for safety		
Safety analysis set	84 (100.0)	41 (100.0)
Adverse events	84 (100.0)	41 (100.0)
Laboratory data	82 (97.6)	40 (97.6)
Analyzed for ECG sub-study	46	-
Evaluable patients from ECG sub-study	19 (41.3)	-

Source: Tables 14.1.1.1.3 and 14.1.1.5.3

The number of patients is very limited considering that only one phase 1b/2 has been submitted.

Outcomes and estimation

- Overall survival

The OS for patients in the Phase 2 Unfit arms is summarized in Table 33 below (IVRS based cytogenetic risk; primary analysis). CRF based cytogenetic risk per ELN criteria data have been submitted as secondary analyses.

Table 34. Summary of overall survival for all patients in the study B1371003 Phase 2 Non-Intensive Population - IVRS based cytogenetic risk.

	AML + MDS N=132		AML N=116		MDS N=16	
	Glasdegib+LDAC	LDAC	Glasdegib+LDAC	LDAC	Glasdegib+LDAC	LDAC
No. of patients randomised	88	44	78	38	10	6
Deaths; n (%)	68 (77.3)	41 (93.2)	59 (75.6)	35 (92.1)	9 (90.0)	6 (100)
Number (%) of patients censored	20 (22.7)	3 (6.8)	19 (24.4)	3 (7.9)	1 (10.0)	0
Reason for censorship, n (%)						
Patients remained in follow-up	16 (18.2)	1 (2.3)	15 (19.2)	1 (2.6)	1 (10.0)	0
Patients no longer being followed for survival	4 (4.5)	2 (4.5)	4 (5.1)	2 (5.3)	0	0
Median follow-up time (80% CI); mo.	21.7 (19.1, 26.5)	20.1 (NE, NE)	--	--	--	--
Median follow-up time (95% CI); mo.	21.7 (18.4, 27.6)	20.1 (NE, NE)	21.7 (18.1, 26.5)	20.1 (NE, NE)	27.6 (NE, NE)	NE
Kaplan-Meier estimate of median time to event (months)						
mOS (80% CI)	8.8 (6.9, 9.9)	4.9 (3.5, 6.0)	8.3 (6.6, 9.5)	4.3 (2.9, 4.9)	--	--
Hazard Ratio[a] (80% CI) [p-value[b]]	0.513 (0.394, 0.666) [0.0004]		0.463 (0.348, 0.616) [0.0002]		--	
mOS (95% CI)	8.8 (5.0, 11.7)	4.9 (2.9, 6.5)	8.3 (4.7, 12.2)	4.3 (1.9, 5.7)	10.9 (0.4, 12.7)	10.3 (4.9, 15.1)
Hazard Ratio[a] (95% CI) [p-value[b]]	0.513 (0.343, 0.766) [0.0004]		0.463 (0.299, 0.717) [0.0002]		0.772 (0.247, 2.414) [0.3280]	

Source: Study B1371003 CSR P2unfit Tables 14.2.3.1.3.2, 14.2.3.1.3.8, SCE Tables 14.2.3.1.3.8.1.E1AM, 14.2.3.1.3.2.1.1 E1AM, 14.2.3.1.3.2.1.1.E1A, 14.2.3.1.3.8.1 E1A, 14.2.3.1.3.2.1.1.E1M, 14.2.3.1.3.8.1 E1M; Study B1371003 CSR P2unfit supp Table 14.2.3.1.3.5

The difference in OS (primary endpoint) for AML + MDS population was statistically significant (8.8 [6.9-9.9] versus 4.9 [3.5-6.0] months; HR = 0.513) and the 80% CIs did not overlap.

Figure 13. Kaplan-Meier Plot of overall survival by IVRS (Full Analysis Set) – Phase 2 Unfit (Non-intensive) AML + MDS patients.

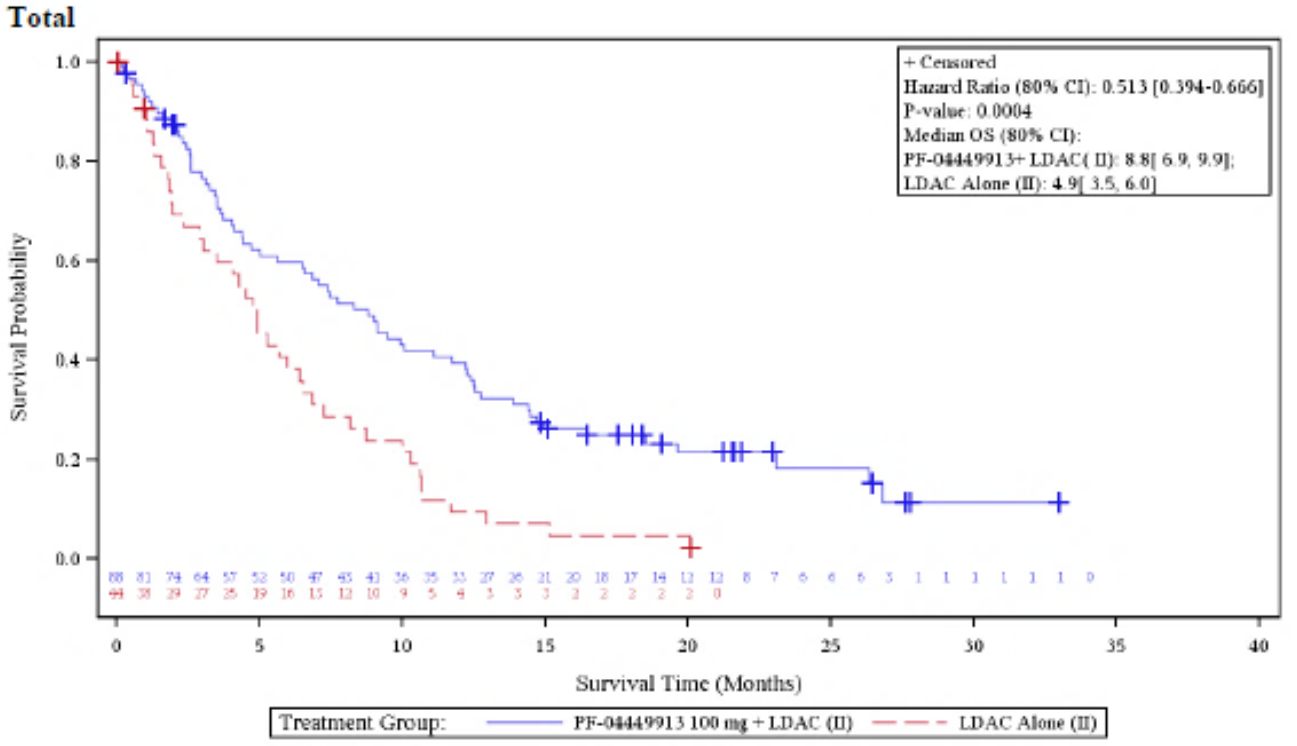
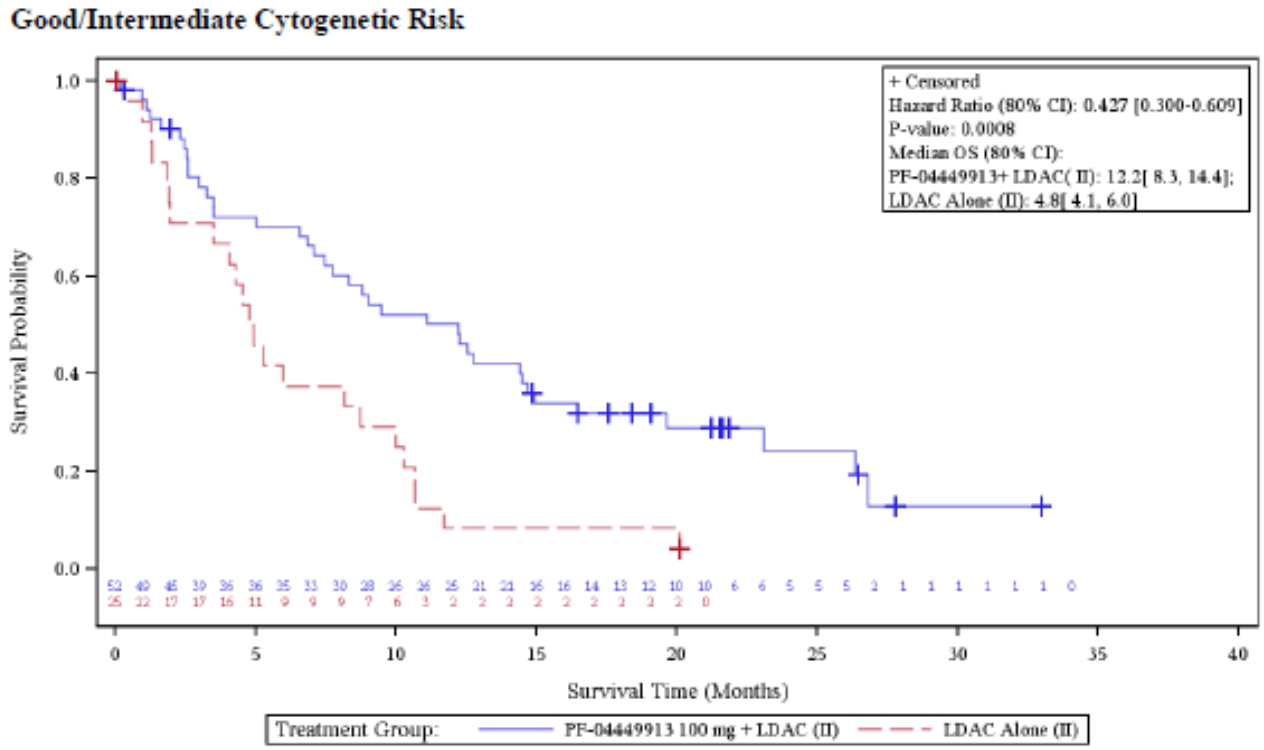


Table 35. Summary of overall survival for patients with good/intermediate cytogenetic risk by IVRS Stratification (Full Analysis Set) - Phase 2 Unfit (Non-intensive).

	AML + MDS N=77		AML N=70		MDS N=7	
	Glasdegib+LDAC	LDAC	Glasdegib+LDAC	LDAC	Glasdegib+LDAC	LDAC
No. of patients randomised[a]	52 (100)	25 (100)	49 (100)	21 (100)	3 (100)	4 (100)
Deaths; n (%)	38 (73.1)	23 (92.0)	35 (71.4)	19 (90.5)	3 (100)	4 (100)
Number (%) of patients censored	14 (26.9)	2 (8.0)	14 (28.6)	2 (9.5)	0	0
Reason for censorship, n (%)						
Patients remained in follow-up	12 (23.1)	1 (4.0)	12 (24.5)	1 (4.8)	0	0
Patients no longer being followed for survival	2 (3.8)	1 (4.0)	2 (4.1)	1 (4.8)	0	0
Median follow-up time (95% CI); mo.	21.7 (18.4, 27.8)	20.1 (NE, NE)	21.7 (18.4, 27.8)	20.1 (NE, NE)	NE	NE
Kaplan-Meier estimate of median time to event (months)						
mOS; mo. (80% CI)	12.2 (8.3, 14.4)	4.8 (4.1, 6.0)	11.1 (7.7, 14.5)	4.4 (1.9, 5.3)	–	–
Hazard Ratio[b] (80% CI) [p-value[c]]	0.427 (0.300, 0.609) [0.0008]		0.417 (0.285, 0.609) [0.0011]		–	
mOS; mo. (95% CI)	12.2 (7.1, 14.7)	4.8 (1.9, 8.7)	11.1 (7.1, 14.9)	4.4 (1.8, 8.7)	12.7 (1.6, 14.4)	8.0 (4.9, 11.7)
Hazard Ratio[b] (95% CI) [p-value[c]]	0.427 (0.248, 0.734) [0.0008]		0.417 (0.233, 0.744) [0.0011]		0.269 (0.029, 2.519) [0.1106]	

Source: SCE Tables 14.2.3.1.3.8.2.1.E1AM, 14.2.3.1.3.3 E1AM, 14.2.3.1.3.3.E1A, 14.2.3.1.3.8.2.1.E1A, 14.2.3.1.3.3.E1M, 14.2.3.1.3.8.2.1.E1M, Study B1371003 CSR Table P2unfit supp 14.2.3.1.3.6; Study B1371003 CSR P2unfit Table 14.2.3.1.3.3

Figure 14. Kaplan-Meier Plot of overall survival in patients with good/intermediate cytogenetic risk.



Source: Figures 14.2.3.2.3.2.1-3
PF-04449913 is the compound number of glasdegib.
Median and 80% CI of OS are expressed in months.
Abbreviations: CI=confidence interval; IVRS= Interactive Voice Response System; LDAC=low dose Ara-C; OS=overall survival.

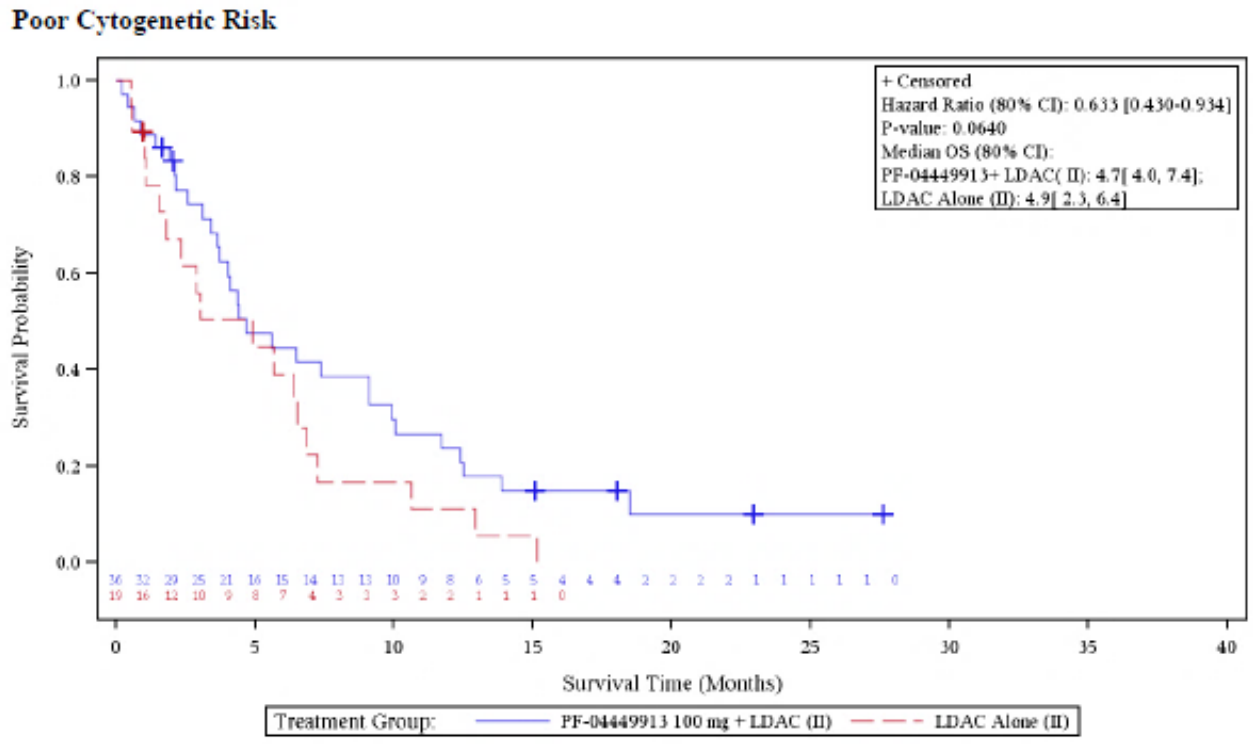
Among the overall population (AML + MDS), the subgroup of patients with good/intermediate cytogenetic risk in the glasdegib 100 mg + LDAC arm had statistically significant improvement in OS as compared to the subgroup of those with good/intermediate cytogenetic risk in the LDAC alone arm (HR = 0.427 [based on IVRS]; p = 0.0008; Table 41). This result is supported by the secondary analysis based on CRF (HR = 0.439; p = 0.0008; Table 41). A significant OS improvement was confirmed in AML patients (HR = 0.417 [based on IVRS]; p = 0.0011; Table 41).

Table 36. Summary of overall survival for patients with poor cytogenetic risk by IVRS Stratification in the Study B1371003 Phase 2 Non-Intensive Population.

	AML + MDS N=55		AML N=46		MDS N=9	
	Glasdegib+LDAC	LDAC	Glasdegib+LDAC	LDAC	Glasdegib+LDAC	LDAC
No. of patients randomised[a]	36 (100)	19 (100)	29 (100)	17 (100)	7 (100)	2 (100)
Deaths; n (%)	30 (83.3)	18 (94.7)	24 (82.8)	16 (94.1)	6 (85.7)	2 (100)
Number (%) of patients censored	6 (16.7)	1 (5.3)	5 (17.2)	1 (5.9)	1 (14.3)	0
Reason for censorship, n (%)						
Patients remained in follow-up	4 (11.1)	0	3 (10.3)	0	1 (14.3)	0
Patients no longer being followed for survival	2 (5.6)	1 (5.3)	2 (6.9)	1 (5.9)	0	0
Median follow-up time (95% CI); mo.	23.0 (15.1, 27.6)	NE	18.1 (15.1, 23.0)	NE	27.6 (NE, NE)	NE
Kaplan-Meier estimate of median time to event (months)						
mOS; mo. (80% CI)	4.7 (4.0, 7.4)	4.9 (2.3, 6.4)	4.4 (3.7, 6.5)	3.1 (1.8, 5.7)	–	–
Hazard Ratio[b] (80% CI) [p-value[c]]	0.633 (0.430, 0.934) [0.0640]		0.528 (0.343, 0.813) [0.0269]		–	
mOS; mo. (95% CI)	4.7 (3.6, 9.1)	4.9 (1.5, 6.5)	4.4 (3.4, 9.1)	3.1 (1.1, 6.4)	10.1 (0.4, 12.5)	12.9 (10.6, 15.1)
Hazard Ratio[b] (95% CI) [p-value[c]]	0.633 (0.350, 1.147) [0.0640]		0.528 (0.273, 1.022) [0.0269]		1.4440 (0.284, 7.318) [0.6709]	

Source: Study B1371003 P2unfit CSR Table 14.2.3.1.3.3; B1371003 CSR P2unfit supp Table 14.2.3.1.3.6; SCE Tables 14.2.3.1.3.3.E1AM, 14.2.3.1.3.8.2.1.E1AM, 14.2.3.1.3.3.E1A, 14.2.3.1.3.8.2.1.E1A, 14.2.3.1.3.3.E1M, 14.2.3.1.3.8.2.1.E1M

Figure 15. Kaplan-Meier Plot of overall survival in patients with poor cytogenetic risk.



Source: Figures 14.2.3.2.3.2.1-3
PF-04449913 is the compound number of glasdegib.
Median and 80% CI of OS are expressed in months.
Abbreviations: CI=confidence interval; IVRS= Interactive Voice Response System; LDAC=low dose Ara-C; OS=overall survival.

For AML + MDS patients with poor cytogenetic risk, there was no statistically difference in OS with 80% CI at the 5% significance level between the glasdegib 100 mg + LDAC arm and the LDAC alone arm (based on IVRS: HR = 0.633 [0.430-0.934], p = 0.0640; based on CRF: HR = 0.613 [0.40-0.916], p = 0.0570).

However, improvement of overall survival has been observed in combination arm [4.4 months (95% CI 3.4, 9.1) vs. 3.1 months (95% CI 1.1. 6.4)].

- Secondary endpoint: Complete Remission

Proportions of patients with derived and investigator-reported CR in the P2 Unfit arms by IVRS based cytogenetic risk are summarized Table 37.

Table 37. Summary of Proportions of Patients with Derived and Investigator-Reported CR (Full Analysis Set) - Phase 2 Unfit (Non-intensive).

	Glasdegib 100 mg+LDAC		LDAC Alone	
Number of patients	88		44	
	Derived	Investigator-reported	Derived	Investigator-reported
Total number (%) of patients with CR	15 (17.0)	15 (17.0)	1 (2.3)	1 (2.3)
80% CI[a]	(11.9, 22.2)	(11.9, 22.2)	(0.0, 5.2)	(0.0, 5.2)
Cytogenetic risk (IVRS based)				
Good/intermediate cytogenetic risk	52	52	25	25
Number (%) of patients with CR	10 (19.2)	10 (19.2)	0 (0.0)	0 (0.0)
80% exact CI[b]	(12.3, 28.1)	(12.3, 28.1)	0.0, 8.8	0.0, 8.8
Poor cytogenetic risk	36	36	19	19
Number (%) of patients with CR	5 (13.9)	5 (13.9)	1 (5.3)	1 (5.3)
80% exact CI[b]	(6.9, 24.2)	(6.9, 24.2)	(0.6, 19.0)	(0.6, 19.0)
Versus LDAC alone				
Pearson Chi-Square test (unstratified)				
p-value	0.0142	0.0142	Not Applicable	
Stratified CMH test based on IVRS[c]				
Odds ratio (80% CI)	5.025 (1.590, 15.884)	5.025 (1.590, 15.884)		
p-value	0.0152	0.0152		

Source: Tables 14.2.2.3.2.1.2 and 14.2.2.3.2.2.2

	AML + MDS		AML		MDS	
	Glasdegib+ LDAC	LDAC	Glasdegib+ LDAC	LDAC	Glasdegib+ LDAC	LDAC
All Patients						
No. of patients randomised	88	44	78	38	10	6
No. (%) with CR	15 (17.0)	1 (2.3)	14 (17.9)	1 (2.6)	1 (10.0)	0
80% CI[c]	11.9, 22.2	0, 5.2	--	--	--	--
95% CI[c]	9.2, 24.9	0, 6.7	9.4, 26.5	0, 7.7	0, 28.6	0, 0
Good/intermediate cytogenetic risk[b]						
No. of patients randomised	52	25	49	21	3	4
No. (%) with CR	10 (19.2)	0 (0)	10 (20.4)	0 (0)	0 (0)	0 (0)
80% exact CI[d]	12.3, 28.1	0, 8.8	--	--	--	--
95% exact CI[d]	9.6, 32.5	0, 13.7	10.2, 34.3	0, 16.1	0, 70.8	0, 60.2
Poor cytogenetic risk[b]						
No. of patients randomised	36	19	29	17	7	2
No. (%) with CR	5 (13.9)	1 (5.3)	4 (13.8)	1 (5.9)	1 (14.3)	0 (0)
80% exact CI[d]	6.9, 24.2	0.6, 19.0	--	--	--	--
95% exact CI[d]	4.7, 29.5	0.1, 26.0	3.9, 31.7	0.1, 28.7	0.4, 57.9	0, 84.2
Glasdegib + LDAC versus LDAC only						
Pearson Chi-Square test (unstratified)[e]						
p-value	0.0142		0.0210		0.4237	
Stratified CMH test based on IVRS data						
Relative risk (95% CI)	7.5992 (1.0080, 57.2880)		7.1034 (0.8879, 56.8281)		NE	
p-value	0.0152		0.0235		0.5930	
Stratified CMH test based on CRF data						
Relative Risk (95% CI)	7.6175 (0.9824, 59.0655)		7.2117 (0.8593, 60.5239)		NE	
p-value	0.0157		0.0249		0.2636	

Source: Study B1371003 CSR P2unfit Table 14.2.2.3.2.1.2; SCE Tables 14.2.2.3.2.2.2.3.E1AM, 14.2.2.3.2.2.2.4.E1AM, 14.2.2.3.2.2.2.3.E1A, 14.2.2.3.2.2.2.4.E1A, 14.2.2.3.2.2.2.3.E1M, 14.2.2.3.2.2.2.4.E1M

In the overall population, higher significant complete remission rates have been observed in the combination arm: 17% vs. 2.3%; p = 0.01. This result is confirmed in AML patients: 17.9% vs. 2.6%; p = 0.02.

A numerically higher CR rate was also observed in the combination arm compared to LDAC alone arm for patients with good/intermediate cytogenetic risk (20.4% vs. 0) and for patients with poor cytogenetic risk patients (13.8% vs. 5.9%).

- Other secondary endpoints

Respectively 22 (25.0% [80% CI: 19.1%, 30.9%]) and 2 (4.5% [80% CI: 0.5%, 8.6%]) patients achieved CR/CRi in the glasdegib 100 mg + LDAC and LDAC alone arms based on derived responses.

Table 38. Derived best overall response for patients with AML (Full Analysis Set) - Phase 2 Unfit

	Glasdegib 100 mg+LDAC		LDAC Alone	
Number of patients	78		38	
	n (%)	80% CI	n (%)	80% CI
Objective response[a]				
Disease status				
Morphologic CR	14 (17.9)	(12.4, 24.8)	1 (2.6)	(0.3, 9.9)
Morphologic CRi	5 (6.4)	(3.2, 11.6)	1 (2.6)	(0.3, 9.9)
MLFS	2 (2.6)	(0.7, 6.7)	0 (0.0)	(0.0, 5.9)
PR	5 (6.4)	(3.2, 11.6)	1 (2.6)	(0.3, 9.9)
PRi	1 (1.3)	(0.1, 4.9)	0 (0.0)	(0.0, 5.9)
MR	5 (6.4)	(3.2, 11.6)	4 (10.5)	(4.7, 19.9)
SD	12 (15.4)	(10.3, 21.9)	8 (21.1)	(12.7, 31.9)
Indeterminate	0 (0.0)	(0.0, 2.9)	1 (2.6)	(0.3, 9.9)
Objective disease progression[a]				
Disease status				
Treatment failure	10 (12.8)	(8.1, 19.1)	6 (15.8)	(8.5, 26.1)
Resistant disease	9 (11.5)	(7.1, 17.6)	6 (15.8)	(8.5, 26.1)
Morphologic relapse	1 (1.3)	(0.1, 4.9)	0 (0.0)	(0.0, 5.9)
Not Evaluable[a]	24 (30.8)	(23.9, 38.4)	16 (42.1)	(31.1, 53.8)
Further endpoints of interest[b]				
CR/CRi	19 (24.4)	(18.1, 30.6)	2 (5.3)	(0.6, 9.9)
Disease modifying response	26 (33.3)	(26.5, 40.2)	3 (7.9)	(2.3, 13.5)
Clinically beneficial response	27 (34.6)	(27.7, 41.5)	3 (7.9)	(2.3, 13.5)

Source: Table 14.2.2.1.1.3

Not evaluable was defined as patients that were not assessed for response.

Disease modifying response: CR, CRi, MLFS, or PR. Clinically beneficial response: CR, CRi, MLFS, PR, or PRi.

Abbreviations: AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; CRi=CR with incomplete blood count recovery; LDAC=low dose Ara-C; MLFS=Morphologic Leukemia-Free State; MR=minor response; n=number of patients in the category; PR=partial remission; PRi=PR with incomplete blood count recovery; SD=stable disease.

a. Using exact method based on binomial distribution and CIs are expressed in percentages.

b. Using normal approximation and CIs are expressed in percentages.

For the AML population, significant improvement of morphologic CR rate was observed (17.9 vs. 2.6%).

For the other secondary endpoints, 80% CI intervals overlapped. However, the descriptive analyses showed higher rates of morphologic CRi (6.4 vs. 2.6%), MLFS (2.6 vs. 0%), PR (6.4 vs. 2.6%), PRi (1.3 vs. 0) in combination arm compared to LDAC alone arm, which could explain lesser rates of MR (6.4 vs. 10.5%) and SD (15.4 vs. 21.1%) in the combination arm compared to LDAC alone arm.

Of note, 8/78 patients in the glasdegib + LDAC arm and none in LDAC alone arm had cytogenetic response CR, while 12/78 patients in the glasdegib + LDAC arm and 1/38 in LDAC alone arm had molecular CR.

Ancillary analyses

For the pivotal Phase 2 non-intensive population in Study B1371003, the primary endpoint of OS was further evaluated by demographic factors defined in Table 38.

Table 39. Efficacy Subpopulation Analyses.

Demographic Factor	Subpopulation
Cytogenetic risk	Good/intermediate risk and poor risk
Age	<65 versus ≥65 years old; <75 versus ≥75 years old
Race	White, Black, Asian, and Other
Sex	Male, female
Geographic region	United States, Canada, European Union, North America (United States and Canada)
Disease history[a]	De novo, secondary

Source: Glasdegib Integrated Statistical Analysis Plan

For Analysis of OS in the Phase 2 Non-Intensive population by cytogenetic risk: see preceding section.

Analysis of OS in the Phase 2 Non-Intensive Population by age

Table 40. Summary of overall survival for all patients in Study B1371003 Phase 2 Non-Intensive AML + MDS population by age (<75 and ≥75 years old).

	≥75 Years Old		<75 Years Old		All Patients	
	Glasdegib+LDAC N=53	LDAC N=24	Glasdegib+LDAC N=35	LDAC N=20	Glasdegib+LDAC N=88	LDAC N=44
Deaths, n (%)	43 (81.1)	23 (95.8)	25 (71.4)	18 (90.0)	68 (77.3)	41 (93.2)
Patients censored, n (%)	10 (18.9)	1 (4.2)	10 (28.6)	2 (10.0)	20 (22.7)	3 (6.8)
Reason for censorship, n (%)						
Patients remained in follow-up	8 (15.1)	1 (4.2)	8 (22.9)	0	16 (18.2)	1 (2.3)
Patients no longer being followed for survival	2 (3.8)	0	2 (5.7)	2 (10.0)	4 (4.5)	2 (4.5)
mOS (95% CI), mo.	7.7 (4.7, 11.1)	5.1 (1.9, 8.1)	10.1 (3.6, 14.9)	4.8 (1.8, 6.0)	8.8 (6.9, 9.9)	4.9 (3.5, 6.0)
HR (95% CI) [p-value]	0.644 (0.383, 1.082) [0.0467]		0.403 (0.209, 0.780) [0.0027]		0.513 (0.394,0.666) [0.0004]	

Source: SCE Table 14.2.3.1.3.9.1.1.E1AM; Study B1371003 CSR P2unfit Table 14.2.3.1.3.2.

Table 41. Summary of overall survival for all patients in Study B1371003 Phase 2 Non-Intensive AML + MDS population by age (<65 and ≥65 years old).

	≥65 Years Old		<65 Years Old		All Patients	
	Glasdegib+LDAC N=86	LDAC N=43	Glasdegib+LDAC N=2	LDAC N=1	Glasdegib+LDAC N=88	LDAC N=44
Deaths, n (%)	66 (76.7)	40 (93.0)	2 (100)	1 (100)	68 (77.3)	41 (93.2)
Number (%) of patients censored	20 (23.3)	3 (7.0)	0	0	20 (22.7)	3 (6.8)
Reason for censorship, n (%)						
Patients remained in follow-up	16 (18.6)	1 (2.3)	0	0	16 (18.2)	1 (2.3)
Patients no longer being followed for survival	4 (4.7)	2 (4.7)	0	0	4 (4.5)	2 (4.5)
mOS (95% CI), mo.	8.8 (5.0, 11.7)	4.9 (2.9, 6.5)	8.1 (3.6, 12.5)	1.3 (NE, NE)	8.8 (6.9, 9.9)	4.9 (3.5, 6.0)
HR (95% CI) [p-value]	0.522 (0.347, 0.784) [0.0007]		NE (NE) [<0.0001]		0.513 (0.394, 0.666) [0.0004]	

Source: SCE Table 14.2.3.1.3.9.2.1.E1AM; Study B1371003 CSR P2unfit Table 14.2.3.1.3.2.

Deaths were due primarily to the disease under study in both age groups: In ≥75 year old population, 35 [66.0%] in the glasdegib + LDAC arm and 18 [75.0%] in the LDAC-only arm; and the <75 year old population: 21 [60.0%] in the glasdegib + LDAC arm and 17 [85.0%] in the LDAC-only arm).

Analysis of OS in the Phase 2 Non-Intensive population by sex

Table 42. Summary of overall survival for all patients in Study B1371003 Phase 2 Non-Intensive AML + MDS population by sex.

	Male		Female		All Patients	
	Glasdegib+LDAC N=69	LDAC N=26	Glasdegib+LDAC N=19	LDAC N=18	Glasdegib+LDAC N=88	LDAC N=44
Deaths, n (%)	55 (79.7)	25 (96.2)	13 (68.4)	16 (88.9)	68 (77.3)	41 (93.2)
Patients censored, n (%)	14 (20.3)	1 (3.8)	6 (31.6)	2 (11.1)	20 (22.7)	3 (6.8)
Reason for censorship, n (%)						
Patients remained in follow-up	12 (17.4)	0	4 (21.1)	1 (5.6)	16 (18.2)	1 (2.3)
Patients no longer being followed for survival	2 (2.9)	1 (3.8)	2 (10.5)	1 (5.6)	4 (4.5)	2 (4.5)
mOS (95% CI), mo.	8.8 (4.4, 12.4)	4.5 (2.3, 6.9)	7.5 (4.1, 26.8)	6.0 (1.0, 10.7)	8.8 (6.9, 9.9)	4.9 (3.5, 6.0)
HR (95% CI) [p-value]	0.455 (0.277, 0.749) [0.0008]		0.556 (0.256, 1.206) [0.0652]		0.513 (0.394, 0.666) [0.0004]	

Source: SCE Table 14.2.3.1.3.11.1.1.E1AM; Study B1371003 CSR Table P2 unfit 14.2.3.1.3.2.

Deaths were due primarily to the disease under study in both males and females. In males, 45 (65.2%) deaths in the glasdegib + LDAC arm and 22 (84.6%) in the LDAC-only arm were due to disease under study, and in females, 11 (57.9%) deaths in the glasdegib + LDAC arm and 13 (72.2%) in the LDAC-only arm were due to disease under study.

For female patients, the HR was 0.56, not significant (p = 0.065).

Analysis of OS in the Phase 2 Non-Intensive population by race

Of the 132 patients analysed, 129 were White, 1 was Black, and 2 were Asian.

Analysis of OS in the Phase 2 Non-Intensive Population by geographic region

Table 43. Summary of overall survival for all patients in Study B1371003 Phase 2 Non-Intensive AML + MDS Population by Geographic Location.

	North America		European Union		All Patients	
	Glasdegib+LDAC N=33	LDAC N=8	Glasdegib+LDAC N=55	LDAC N=36	Glasdegib+LDAC N=88	LDAC N=44
Deaths, n (%)	28 (84.8)	8 (100)	40 (72.7)	33 (91.7)	68 (77.3)	41 (93.2)
Patients censored, n (%)	5 (15.2)	0	15 (27.3)	3 (8.3)	20 (22.7)	3 (6.8)
Reason for censorship, n (%)						
Patients remained in follow-up	3 (9.1)	0	13 (23.6)	1 (2.8)	16 (18.2)	1 (2.3)
Patients no longer being followed for survival	2 (6.1)	0	2 (3.6)	2 (5.6)	4 (4.5)	2 (4.5)
mOS (95% CI), mo.	7.4 (3.3, 12.4)	4.9 (0.5, 7.2)	9.1 (5.0, 12.5)	4.9 (1.9, 6.5)	8.8 (6.9, 9.9)	4.9 (3.5, 6.0)
HR (95% CI) [p-value]	0.477 (0.205, 1.111) [0.0397]		0.476 (0.295, 767) [0.0009]		0.513 (0.394, 0.666) [0.0004]	

Source: SCE Table 14.2.3.1.3.12.2.1.E1AM; Study B1371003 CSR P2unfit Table 14.2.3.1.3.2.

Analysis of OS in the Phase 2 Non-Intensive AML population by disease history

Table 44. Summary of overall survival for AML patients in the Study B1371003 Phase 2 Non-Intensive Population by *de novo* or secondary disease.

	De Novo Disease		Secondary Disease	
	Glasdegib+LDAC N=38	LDAC N=18	Glasdegib+LDAC N=40	LDAC N=20
Deaths, n (%)	30 (78.9)	16 (88.9)	29 (72.5)	19 (95.0)
Patients censored, n (%)	8 (21.1)	2 (11.1)	11 (27.5)	1 (5.0)
Reason for censorship, n (%)				
Patients remained in follow-up	5 (13.2)	1 (5.6)	10 (25.0)	0
Patients no longer being followed for survival	3 (7.9)	1 (5.6)	1 (2.5)	1 (5.0)
mOS (95% CI), mo.	6.6 (3.7, 12.4)	4.3 (1.3, 10.7)	9.1 (4.4, 16.5)	4.1 (1.5, 6.4)
HR[a] (95% CI) [p-value[b]]	0.670 (0.362, 1.239) [0.0991]		0.287 (0.151, 0.548) [<0.0001]	

Source: SCE Table 14.2.3.1.3.5.E1A

Deaths were due primarily to the disease under study in both subgroups. In the *de novo* history subgroup, 25 (65.8%) deaths in the glasdegib + LDAC arm and 12 (66.7%) in the LDAC-only arm were due to disease under study, and in the secondary history subgroup, 24 (60.0%) deaths in the glasdegib + LDAC arm and 17 (85.0%) in the LDAC-only arm were due to disease under study.

In the glasdegib + LDAC arm, the median OS (mOS) of 9.1 (95% CI: 4.4, 16.5) months for AML patients with secondary disease (n = 40) appeared to be better than the mOS of 6.6 (95% CI: 3.7, 12.4) months for AML patients with de novo (n = 38); however, given the nature of subgroup analysis with limited sample sizes and the overlapping 95% CIs, these two subgroups were considered comparable.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 45. Summary of Efficacy for trial B1371003, A Phase 1b/2 Study to Evaluate the Safety and Efficacy of PF-04449913, an Oral Hedgehog Inhibitor, in Combination With Intensive Chemotherapy, Low Dose Ara-C (LDAC) or Decitabine in Patients With Acute Myeloid Leukemia.

Study identifiers	Protocol number B1371003 EudraCT number 2012-000684-24 NCT01546038		
Design	Multi-center, open-label, study, divided into 2 portions: a phase 1b: dose escalation phase with 3 arms: glasdegib in combination with LDAC [A] or decitabine [B] or 7+3 [C] (not included in this summary of efficacy) a phase 2 consisted of 2 parts: unfit population arm, 2:1 allocation ratio glasdegib + LDAC or LDAC alone stratified by prognostic cytogenetic risk factor (good/intermediate or poor) fit population single arm, receiving glasdegib with 7+3 (not included in this summary of efficacy)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		4.6 years (27/06/2012-03/01/2017) not applicable not applicable
Hypothesis	Superiority		
The following points only refer to the randomized part (unfit arm) of the phase 2 study focusing on the claimed indication.			
Treatments groups		Glasdegib + LDAC	Median treatment duration: 83.0 days, n=84
		LDAC alone	Median treatment duration: 47.0 days, n=41
Treatments groups (AML)		Glasdegib + LDAC	Median treatment duration: 83.0 days, n=75
		LDAC alone	Median treatment duration: 40.5 days, n=36
Primary endpoint	Overall survival	OS	Duration from the date of randomization to the date of death from any cause
Secondary endpoints	(Morphologic) Complete remission	CR	All of: neutros >=1000/µl, thrombos >=100,000/µl,

			<5% bone marrow blasts, no Auer rods, transfusion-independent, no extramedullary disease
	CR with incomplete blood count recovery	CRi	Neutros >=1000/µl or thrombos >= 100,000/µl, and all of: <5% bone marrow blasts, no Auer rods, no extramedullary disease
	Partial remission	PR	All of: neutros >=1000/µl, thrombos >=100,000/µl, 5-25% bone marrow blasts (<5% if Auer rods), >=50% bone marrow blast decrease
	Stable disease	SD	Blasts stable +/-25%
	Complete cytogenetic Response	CRc	All of: neutros >=1000/µl, thrombos >=100,000/µl, <5% bone marrow blasts, cytogenetics normal, no extramedullar disease
	Morphologic leukaemia-free state	MFLS	All of: neutros <1000/µl, thrombos <100,000/µl and all of: <5% bone marrow blasts, no Auer rods, no extramedullary disease
	Partial remission with incomplete blood count recovery	PRi	Neutros >=1000/µl or thrombos >= 100,000/µl, and all of: 5-25% bone marrow blasts (<5% if Auer rods), >=50% bone marrow blast decrease
	Minor response	MR	>25% bone marrow blast decrease
	Molecular complete response	CRm	All of: neutros >=1000/µl, thrombos >=100,000/µl, <5% bone marrow blasts, molecular abnormalities negative, no extramedullar disease
Database lock	03/01/2017		
Results and analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat population The Full Analysis Set (FAS) was defined as all randomized patients.		
Descriptive statistics and estimate variability	Treatment group	Glasdegib + LDAC	LDAC alone
	Number of subjects Overall population AML	 88 78	 44 38
	OS median (months) Overall population AML	 8.8 8.3	 4.9 4.3
	Confidence interval (months, 80% IC) Overall population AML	 [6.9, 9.9] [6.6, 9.5]	 [3.5, 6.0] [2.9, 4.9]

	Complete Remission (%) Overall population AML	 15 (17.0) 14 (17.9)	 1 (2.3) 1 (2.6)
	Confidence interval (80%) Overall population AML	 [11.9, 22.2] [12.4, 23.5]	 [0, 5.2] [0, 6.0]
Effect estimate per comparison	Primary endpoint (OS)	Comparison groups	Glasdegib + LDAC *vs* LDAC alone
		Stratified log-rank test (1-sided, α = 10%): Hazard Ratio (HR) Overall population AML	 All patients: 0.513 Good/intermediate cytogenetic: 0.427 Poor cytogenetic: 0.633 All patients: 0.463 Good/intermediate cytogenetic: 0.417 Poor cytogenetic: 0.528
		Confidence interval (%, 80% CI) Overall population AML	 All patients: [0.394, 0.666] good/intermediate cytogenetic: [0.300, 0.609] Poor cytogenetic: [0.430, 0.934] All patients: [0.348, 0.616] good/intermediate cytogenetic: [0.285, 0.609] Poor cytogenetic: [0.343, 0.813]
		1-sided p-value Overall population AML	 All patients: p= 0.0004 good/intermediate cytogenetic: p=0.0008 poor cytogenetic: p = 0.0640 All patients: p= 0.0002 good/intermediate cytogenetic: p= 0.0011 poor cytogenetic: p = 0.0269
	Complete remission (CR)	Comparison groups	Glasdegib + LDAC vs. LDAC alone
		Number (%) of patients Overall population [80% CI] AML [80% CI]	 15 (17%) [11.9, 22.2] *vs* 1(2.3%) [0, 5.2] 14 (17.9%) [12.4, 23.5] *vs* 1(2.6%) [0, 6.0]
		Pearson Chi-Square test, 2-sided p-value Overall population AML	 0.0142 0.0210
Notes	<free text>		
Analysis description	<Secondary analysis> <Co-primary Analysis> <Other, specify: >		

Analysis performed across trials (pooled analyses and meta-analysis)

No pooling of data among studies was performed due to differences in the patient populations, diagnoses, and combination therapy.

Clinical studies in special populations

	Age < 65 (Older subjects number /total number)	**Age 65-74 (Older subjects number /total number)**	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled trials	N=1/78	N=29/78	N=41/78	N=7/78
Non-controlled trials	Not applicable	Not applicable	Not applicable	Not applicable

Supportive study(ies)

- Study B1371001

Study B1371001 was an FIH, open-label, multi-centre, Phase 1 study of glasdegib administered PO once daily as a single agent to men and women ≥18 years old with selected haematologic malignancies. Patients were eligible if their disease was refractory, resistant, or intolerant to prior therapies, or they were newly diagnosed and previously untreated but not eligible for standard treatment options, or for whom standard therapies were not anticipated to result in a durable response. The primary objectives were to determine glasdegib MTD and RP2D. Efficacy was assessed as a secondary measure.

Forty-seven (47) patients, aged 25-89 years old (mean 64.1 years) with AML (28), CML (5), CMML (1), MDS (6), or MF (7) were treated with glasdegib (5-600 mg once daily). Eleven (11) patients discontinued the study due to death. All treated patients were assessed for PK and safety; 46 patients were assessed for efficacy.

Early signs of efficacy with glasdegib were seen across a range of acute and chronic haematologic malignancies. A total of 3/6 MDS patients and 1/1 CMML patient achieved SD or better, among whom 2 showed hematologic improvement. Two (2) of the 7 MF patients achieved clinical improvement. Among the 2 patients with CML-accelerated phase/blast crisis, 1 had a partial cytogenetic response. None of the patients with CML-chronic phase had a cytogenetic response. Among the 28 AML patients, 1 patient had CRi, 4 patients had PR with incomplete blood count recovery (PRi), and 4 patients had minor response.

Treatment failures occurred in 7 patients due to resistant disease. Clinical benefit [CR + morphologic CRi + PR + PRi + SD + minor response] was shown in 16 patients, including 7 with SD.

Study B1371001 was an FIH study, efficacy assessment was secondary objective. 3/6 MDS patients achieved SD or better. Among the 28 AML patients, 1 patient had CRi, 4 patients had PR with incomplete blood count recovery (PRi), and 4 patients had minor response.

- Study B1371005

Study B1371005 is an ongoing open-label, multi-centre, Phase 1 study in Japan in patients with selected hematologic malignancies to determine the safety, tolerability, PK, and potential DDI of glasdegib in combination with LDAC (non-intensive) or 7+3 (intensive) (AML + MDS in combination arms). The study also

had a monotherapy arm (AML, MDS, CML, CMML, MF). Data are available as of a 20 February 2017 data cut-off date.

Patients in the monotherapy treatment arm received glasdegib once daily (25 mg, 3 patients; 50 mg, 4 patients; 100 mg, 6 patients) for 7 to 167 days. Among the 7 patients with AML, 1 achieved CR, and 4 achieved stable disease (SD). Among the 4 patients with MDS, 1 achieved mCR, and 2 achieved SD. Efficacy data are not available for the non-AML/non-MDS patients.

4 AML patients and 2 MDS patients in the non-intensive treatment arm received glasdegib 100 mg once daily plus LDAC for 29 to 168 days (1 patient was still receiving the treatment as of the data cutoff date). Among the 4 patients with AML, 1 achieved CR, and 1 achieved SD. Among the 2 patients with MDS, both achieved SD.

6 AML patients in the intensive treatment arm received glasdegib 100 mg once daily plus 7+3 for 22 to 342 days (1 patient was still receiving treatment as of the cutoff date). Five (5) of the 6 patients achieved CR/CRi.

Preliminary data from the monotherapy cohort indicate that the PK profile of glasdegib is similar between Japanese patients (Study B1371005) and non-Japanese patients (Study B1371001).

Study B1371005 is not an efficacy dedicated study. Responses to glasdegib with LDAC in AML and MDS patients have been observed in these preliminary efficacy results. No study report has been submitted.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal Study B1371003 is a multi-centre, open-label Phase 1b/2 study to evaluate the efficacy and safety of glasdegib when administered in combination with first-line treatment regimens for AML and high-risk MDS. This study was divided into a Phase 1b portion (a dose escalation phase) and a Phase 2 consisted of 2 parts (assessment in unfit and fit population). Only the unfit Phase 2 part was assessed in the efficacy section as reflecting the claimed population: *in combination with low-dose cytarabine (LDAC) chemotherapy for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy*.

Designs of both parts of the study are considered acceptable:

- a 3+3 dose escalation design was used in the Part1b to characterize the MTD and RP2D of this oncology drug. The starting dose of 100 mg glasdegib was recommended in the Phase 1 study (B1371001) which is acceptable. LDAC has been used with the recommended doses (NCCN 2019);
- patients in the unfit part 2 of the study were randomised to receive either glasdegib + LDAC or LDAC alone. Randomization used a 2:1 allocation ratio and was stratified by prognostic risk factor (good/intermediate or poor) based on cytogenetics.

After the determination of RP2D of glasdegib (100 mg) in the part 1b, the efficacy of glasdegib in combination with LDAC in unfit patient was thus assessed in a randomized, open-label cohort of LDAC ± glasdegib. The hypothesis was that patients with previously untreated AML and MDS and scheduled for non-intensive chemotherapy (unfit population) would have an improved OS when glasdegib was used in combination with LDAC.

The comparator LDAC alone is acceptable as known as standard of care in international recommendation (ESMO, NCCN 2019). The recommended dose modifications to manage haematologic and non-haematologic adverse reactions in the SmPC section 4.2 are aligned with the dose modifications that were followed in the B1371003 trial, which is acceptable.

In this report, assessment mainly focuses on efficacy data of AML patients.

Taking into account the date of protocol writing (1st version 28/10/2011), diagnostic criteria for AML according to the WHO 2008 classification were used in this study. The differences with the latest classification (WHO 2016) should not impact glasdegib efficacy assessment. The criteria relative to the unfit status are acceptable. Finally, the inclusion criteria reflect the claimed population: previously untreated acute myeloid leukaemia.

The efficacy endpoints, overall survival (primary endpoint) and the complete remission (secondary endpoint) were used according to international recommendations (ELN 2017 criteria; IWG 2006). The further secondary AML response endpoints [CR, CRi, Morphologic Leukemia-Free State, Partial Remission (PR), Partial Remission with incomplete blood count recovery (PRi), Minor Response (MR), Stable Disease (SD), Cytogenetic Complete Response (CRc), and Molecular Complete Response (CRm)] were defined according to IWG 2003 criteria. This is acceptable since the criteria defining these are similar to the ELN 2017 criteria.

A protocol amendment resulting in the removal of independent assessment of bone marrow samples and the fact that no bone marrow samples in the study were analysed by independent review, was a concern during the assessment, because independent assessment had been planned as a quality measure for the correct ascertainment of the diagnosis and assessments of bone marrow samples. The concordance of AML diagnostics performed at an institution and by an independent committee is expected to be high, because the diagnosis does not depend on morphological interpretation (and thus to a degree of subjectivity), but in particular on the demonstration of cytogenetic and mutational anomalies and clonal demonstration by flow cytometry. Even though the Applicant did not justify why this procedure was changed, this issue was not further pursued because it is anticipated that diagnostic work-up at pathology units at specialized departments participating in a clinical trial in AML is performed at a satisfactory level of competence.

During the assessment, a major concern was that the proportion of patients non-evaluable for response was 30.8% in the glasdegib + LDAC treatment group and 42.1% in the LDAC group. The Applicant provided a satisfactory explanation and justified that this major concern is applicable to a secondary efficacy endpoint. In the context, the Applicant provided results for AML patients, separately, which reduces the number of patients in both arms for the analysis equally, while numbers of patients are still assessable. The basic principles determining the results by ITT and inclusion of patients as non-responder are acceptable, in particular because the Applicant has clarified the circumstances for response evaluation to reflect common practice. Patients with progressive disease or deteriorating due to complications are not exposed to invasive procedures, with the burden, discomfort and risk for adverse events, like a bone marrow examination without a therapeutic consequence. This decision made by the treating physician together with the individual patient has been guided also by results of peripheral blood analysis (neutrophils, blast-counts, thrombocytopenia, perhaps including microscopy of a smear and flow-cytometry analysis) and the physical signs of remission (no fever, weight gain, Karnofsky performance status etc.). In most cases this integrated sum of information is sufficient to document the response status and to substantiate the therapeutic decisions – if not, a bone marrow examination will be suggested, provided it has a consequence. The relatively high proportion of patients in both arms being non-evaluable is not considered to pose a safety risk for the AML patients in these circumstances, the reasons and extent are acceptable when put in perspective of the management of AML in a palliative setting. The difference of 4 months in the primary endpoint, OS, in patients treated with

LDAC + glasdegib (8.3 months) compared to LDAC monotherapy (4.3 months), supported by higher response rates (17.9% versus 2.6%), are clinically meaningful results when assessed as a single study. The results emphasize the unmet medical need in first-line treatment across the biological spectre of *de novo* and secondary AML in patients, who cannot be administered intensive chemotherapy.

The criteria for inclusion reflect a population of patients who are not candidates for standard induction chemotherapy. However, the age criteria (above 55 or 75 years at enrolment) seems to be arbitrary. The Applicant clarified that age 55 years on the low end and age ≥75 years were included in the Study B1371003 protocol as guidance. It is agreed that age should not be the sole criterion for treating AML with an intensive or non-intensive chemotherapy regimen. Biologically, AML does differ between younger and older adults, due to different driving cytogenetic and mutational aberrations, but these are often more unfavourable in the elderly patients, and the Hedgehog pathway targeting treatment should expectedly be effective also in adults below 50 years of age. Also according to more recent ELN recommendations, age should not be the sole determinant of treatment decisions (Döhner et al. Blood 2017). The criterion of being older than 75 years in particular may cause a bias in relation to the age-independent claimed indication.

Efficacy data and additional analyses

All 132 randomized patients (88 and 44 patients in the glasdegib 100 mg+LDAC and LDAC alone arms, respectively) were included in the efficacy analyses. Among these patients, 116 patients suffered of AML (78 in glasdegib + LDAC arm and 38 in LDAC alone arm) and 16 patients suffered of MDS patients (10 in glasdegib + LDAC arm and 6 in LDAC alone arm). The number of patients in the MDS arm is very small. No assessment could be done based on MDS efficacy data.

The baseline demographic and disease characteristics are similar in both arms. A higher proportion of patients with an adverse prognostic risk factors for AML has been observed at the baseline in LDAC alone arm compared to glasdegib + LDAC arm (42.1% vs. 32.1%). A higher proportion of patients in glasdegib + LDAC arm compared to LDAC alone arm with a serum creatinine > 1.3 mg/dl, with a severe cardiac disease and with 2 or more of the unfit criteria in the AML arm has been observed.

The data were considered as mature, with 109 of 132 (82.6%) of AML + MDS patients having died by the efficacy data cut-off date, with a median follow-up time >20 months for each treatment arm.

The difference in OS in AML+MDS population was statistically significant (8.8 versus 4.9 months; HR = 0.513) and the 80% CI did not overlap ([6.9, 9.9]; [3.5, 6.0]). As planned in the protocol, if an observed HR under 0.76 is observed, the null hypothesis is rejected. Results were similar with the secondary analyses using the stratified Cox proportional hazards model based on patient risk factors as per the CRF. Thus, the results were not impacted by the randomization by IVRS using fewer patient details than documented in the CRF.

The effect of glasdegib on OS in the Phase 2 non-intensive AML + MDS population appeared to be comparable between patients older and younger than 75 years of age. However, reliable conclusions could not be drawn from this OS analysis between patients older and younger than 65 years of age due to the very small numbers of patients <65 years old enrolled in this study. The effect of glasdegib on OS in the Phase 2 non-intensive AML + MDS population appeared to be comparable between male and female patients. Reliable conclusions could not be drawn from the OS analysis by race due to the very small numbers of Black and Asian patients enrolled in this study. Due to the small sample size of patients in North America (8 patients in the LDAC alone arm), no conclusion could be drawn on OS per geographic region.

The significant improvement of OS has been confirmed in patients with AML (8.3 versus 4.3 months; HR = 0.46; 80% CI [6.6, 9.5]; [2.9, 4.9]; p = 0.0002).

Patients with good/intermediate cytogenetic risk in the glasdegib 100 mg+LDAC arm had statistically significant improvement in OS as compared to those with good/intermediate cytogenetic risk in the LDAC alone arm (12.2 [8.3, 14.4] versus 4.8 [4.1, 6.0] months; HR = 0.43 [based on IVRS]; p value=0.0008). This result is supported by the secondary analysis based on CRF (HR = 0.44). Significant OS improvement is confirmed in AML patients (11.1 [7.7, 14.5] versus 4.4 [1.9, 5.3] months; HR = 0.42 [based on IVRS]; p = 0.001).

For patients with poor cytogenetic risk, there was no difference statistically with 80% IC at the 5% significance level between the glasdegib 100 mg+LDAC arm and the LDAC alone arm in OS (based on IVRS: HR = 0.63 [0.43-0.93], p = 0.06; based on CRF: HR = 0.61 [0.410-0.916], p = 0.06).

Ancillary analyses were also performed on the primary endpoint. In the glasdegib + LDAC arm, the median OS (mOS) of 9.1 (95% CI: 4.4, 16.5) months for AML patients with secondary disease (n = 40) appeared to be better than the mOS of 6.6 (95% CI: 3.7, 12.4) months for AML patients with de novo (n = 38); however, given the nature of subgroup analysis with limited sample sizes and the overlapped 95% CIs between these two groups, they were considered comparable.

Rates of both derived and investigator-reported complete remission are similar which is reassuring. In the overall population, higher significant complete remission rates have been observed in the combination arm: 17% vs. 2.3%; p = 0.014. Higher significant CR in combination arm is confirmed in AML patients: 17.9% vs. 2.6%; p = 0.02. Higher numerically CR rate was also observed in combination arm compared to LDAC alone arm for patients with good/intermediate cytogenetic risk (20.4% vs. 0) and for patients with poor cytogenetic risk patients (13.8% vs. 5.9%).

For the other secondary endpoints in AML population, significant improvement of morphologic CR rate was observed (17.9 vs. 2.6%). For the other treatment-response rates, 80% CI intervals overlapped. However, these descriptive data showed higher rates of morphologic Cri (6.4 vs. 2.6%), MLFS (2.6 vs. 0%), PR (6.4 vs. 2.6%), PRi (1.3 vs. 0%) in combination arm compared to LDAC alone arm which could explain lesser rates of MR (6.4 vs. 10.5%) and SD (15.4 vs. 21.1%) in combination arm compared to LDAC alone arm.

The benefit in the combination of glasdegib + LDAC in AML across ages, the ITT and the randomized patients is accepted.

Data of quality of life would be interesting but was not submitted. Only one patient went to transplant after glasdegib treatment and was not anticipated to significantly impact the overall survival in this study.

2.5.4. Conclusions on the clinical efficacy

Clinical efficacy of glasdegib in combination with LDAC is shown by the results of the open-label, randomized Study B1371003 in newly-diagnosed, elderly AML patients who are not candidates for standard induction chemotherapy, in terms of improvement of OS and increase of the potential to achieve CR.

2.6. Clinical safety

Patient exposure

Safety data come primarily from both treatment arms in the randomized Phase 2 portion of Study B1371003 (Safety Analysis Set, S1 Cohort). The S1 Cohort as well as the S2A and S4 Pools included patients receiving the recommended 100 mg glasdegib starting dose (N=186).

Table 46. Patient cohorts and pools used for safety data analyses.

Pool/Cohort	Source	Description[c] and Number of Patients Treated
Primary Patient Cohorts/Pools Presented in the SCS		
S1 Cohort	Study B1371003	Phase 2 randomised portion; glasdegib 100 mg + LDAC (N=84) or LDAC alone (N=41).
S2A[a] Pool		AML patients in the S1 Cohort glasdegib 100 mg + LDAC arm (N=75) plus AML patients in Phase 1b Arm A (100 mg glasdegib starting dose in combination with LDAC; N = 14) (Total N=89).
S4 Pool		The S4 pool includes S2 (N=101) plus S3 (N=69) plus Phase 1b Arm C (100 mg glasdegib starting dose only; N=16) (Total N=186).
Other Patient Cohorts/Pools Presented in the SCS		
S2 Pool	Study B1371003	Glasdegib 100 mg + LDAC arm in S1 (N=84) plus Phase 1b Arm A (100 mg glasdegib starting dose only; N=17) (Total N=101).
S3 Cohort		Phase 2 single-arm portion; glasdegib 100 mg plus 7+3 (N=69).
Phase 1b study arms		Arm A: glasdegib[b] + LDAC (N=23), Arm B: glasdegib[b] + decitabine (N=7); Arm C: glasdegib[b] plus 7+3 (N=22).
Supportive studies presented individually	Study B1371012	Single-arm LIC (N=12) and expansion cohort (13 MDS; 16[e] AML) with glasdegib 100 mg + azacitidine.
	3 Monotherapy studies	Patients received 5-600 mg glasdegib from Study B1371001 (N=47), 80, 160, 320, or 640 mg glasdegib from Study B1371002 (N=23), and 100 mg glasdegib from Study B1371013 (N=21).
	Study B1371019	Patients receiving 100 mg glasdegib or placebo with 7+3 (N=31) or glasdegib 100 mg or placebo with azacitidine (N=13)[f].
	8 HV studies	Study B1371009 (N=6), Study B1371010 (N=14), Study B1371014 (N=35), Study B1371015 (N=12), Study B1371017 (N=18), Study B1371022 (N=12), Study B1371023 (N=36), Study B1371026 (N=24).
	1 Japan study	Study B1371005; patients received 25 mg, 50 mg, or 100 mg glasdegib monotherapy (N=13), glasdegib 100 mg + LDAC (N=6), glasdegib 100 mg plus 7+3 (N=6), and glasdegib 100 mg plus azacitidine (N=6).
	5 IIR studies	Studies WI171861 (N=35), WI220403[d] (N=35), WI204578 (N=6), WI218564 (N=3), WI216382-1 (N=2).

Source: SCS in-text Tables 5 and 6.
a. AML only.
b. Includes 100 mg and 200 mg glasdegib starting doses.
c. Populations studied are provided in Table 1.
d. IIR Study WI220403 was previously Study WS2233096.
e. 1 patient was not treated.
f. Number of patients randomized; 3 of the 44 patients were not treated.
HV=healthy volunteer; IIR=investigator-initiated research; LIC=lead-in cohort; ADR=adverse drug reaction; N=number of patients treated; LDAC=low-dose cytarabine; 7+3=induction chemotherapy with cytarabine (7 days) plus daunorubicin (3 days); AML=acute myeloid leukaemia; MDS=myelodysplastic syndrome

According to Table 45, 101 patients AML + MDS were treated by the combination glasdegib 100 mg + LDAC (84 in the part 2 and 17 in the part 1b). Among these 101 patients, 89 were AML patients (75 treated in part 2 and 14 in part 1b) and 12 were MDS patients (9 treated in part 2 and 3 in part 1b).

The safety profile assessment of glasdegib 100 mg + LDAC in this report focuses on the randomized Phase 2 portion of Study B1371003 (S1 cohort). The S2A pool (including AML patients in part 1b and part 2 unfit), S4 pool have been considered as supportive safety data. Also, the safety profile of glasdegib in monotherapy has been evaluated in 3 monotherapy sponsored-studies (B1371001, B1371002 and B1371013) and 3 investigator-initiated studies (WI171861, WI220403, WI204578).

In the phase 2 unfit arm of the B1371003 pivotal study (S1 Cohort), the safety analysis set was defined as all enrolled patients who received at least 1 dose of any of the study medications.

Table 47: Treatment duration and dose exposure summary for all cycles (Safety Analysis Set, S1 Cohort) - Phase 2 Unfit (Non-intensive).

	Glasdegib 100 mg+LDAC		LDAC Alone
Number of patients	**84**		**41**
Exposure drug name	**Glasdegib**	**LDAC**	**LDAC**
Treatment duration (days), n	84		41
Mean (median)	189.4 (83.0)		66.4 (47.0)
Treatment exposure (days), n	84	Not calculated	Not calculated
Median (range)	75.5 (3, 954)		
Average dose per cycle (mg/day), n	84	84	41
Mean (std)	83.1 (19.71)	36.9 (5.92)	38.4 (3.51)
Median (range)	90.3 (19, 101)	40.0 (8, 40)	40.0 (24, 40)
Number (%) of patients with			
Dose reduction	14 (16.7)	13 (15.5)	0
Temporary dose delay	3 (3.6)	3 (3.6)	0
Dose interruption	65 (77.4)	None	None
Relative dose intensity (%), n	84	84	41
Mean (std)	89.0 (19.69)	95.5 (15.19)	96.1 (8.77)
Median (range)	92.3 (19, 181)	100.0 (20, 154)	100.0 (60, 100)

Source: Tables 14.4.1.1.3.1, 14.4.1.5.1.3.1 and 14.4.1.5.1.3.2

LDAC was given at a dose of 20 mg (not adjusted for the patients weight) subcutaneously twice daily (morning and evening; approximately 12 hours apart) on Days 1-10 days of the 28-day cycles.

The treatment duration (in days) was calculated as (the last dosing date - Cycle 1/Day 1 + 1 day), where the last dosing date was the last non-zero dose date and it included missed doses on unknown dates.

Treatment exposure (in days) of glasdegib was calculated as (the last dosing date - Cycle 1/Day 1 + 1 day), where the last dosing date was the last non-zero dose date and it excluded days with total dose administered of 0 mg.

A cycle delay was defined as ≥8 weeks apart between cycles (from Day 1 of the previous cycle).

A dose reduction was defined as a day when the prescribed dose was less than the previously prescribed dose for any reason with the exception that a day with total dose administered of 0 mg was not considered a dose reduction.

A dose interruption/missed dose was defined as a planned dosing day with 0 mg total dose administered.

Average dose per cycle = actual total dose in this cycle (exclude 0 mg and dose missed on unknown days) / actual dosing days in this cycle (include 0 mg and dose missed on unknown days)

Abbreviations: LDAC=low dose Ara-C; n=number of evaluable patients; std=standard deviation.

The median treatment duration was 1.8-fold longer in the glasdegib + LDAC arm than in the LDAC alone arm (83.0 vs. 47.0 days). The median treatment exposure time of glasdegib was 75.5 days with a large range of exposure time from 3 to 954 days.

Concerning the LDAC treatment, the mean dose per cycle and mean relative dose intensities are similar in both arms (glasdegib + LDAC arm and LDAC alone arm). No dose interruption of LDAC has been observed in either arm.

Dose reductions have been done in 13 (15.5%) patients, and 3 (3.6%) temporary dose delays have been reported in the combination arm.

Adverse events

An overview of all-causality and treatment-related TEAEs for patients in the S4 pool and S1 Cohort (Phase 2 Unfit arms) is provided in tables 48 and 49, respectively.

Table 48. All-Causality Adverse Events (All Grades, Grade 3, Grade 4) (≥5 Patients with Grade 3 or Grade 4 in any arm), by MedDRA PT, maximum CTCAE Grade, sorted by descending frequency of all grade events in the S4 Pool: combination therapy cohort/pools.

MedDRA PT	Number (%) of Patients											
	S1 Cohort						S2A Pool Glasdegib + LDAC N=89			S4 Pool Glasdegib + LDAC or 7+3 N=186		
	Glasdegib + LDAC N=84			LDAC N=41								
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any AE	**84 (100.0)**	**15 (17.9)**	**39 (46.4)**	**41 (100.0)**	**8 (19.5)**	**15 (36.6)**	**89 (100.0)**	**14 (15.7)**	**40 (44.9)**	**186 (100.0)**	**32 (17.2)**	**107 (57.5)**
Diarrhoea	23 (27.4)	4 (4.8)	0 (0.0)	9 (22.0)	1 (2.4)	0 (0.0)	27 (30.3)	4 (4.5)	0 (0.0)	90 (48.4)	6 (3.2)	0 (0.0)
Febrile neutropenia	30 (35.7)	26 (31.0)	4 (4.8)	10 (24.4)	8 (19.5)	2 (4.9)	31 (34.8)	25 (28.1)	6 (6.7)	89 (47.8)	81 (43.5)	8 (4.3)
Anaemia	38 (45.2)	28 (33.3)	7 (8.3)	17 (41.5)	13 (31.7)	2 (4.9)	38 (42.7)	29 (32.6)	6 (6.7)	73 (39.2)	61 (32.8)	7 (3.8)
Pyrexia	23 (27.4)	2 (2.4)	0 (0.0)	9 (22.0)	2 (4.9)	0 (0.0)	24 (27.0)	2 (2.2)	0 (0.0)	72 (38.7)	9 (4.8)	1 (0.5)
Fatigue	26 (31.0)	12 (14.3)	0 (0.0)	8 (19.5)	2 (4.9)	0 (0.0)	27 (30.3)	13 (14.6)	0 (0.0)	64 (34.4)	20 (10.8)	0 (0.0)
Thrombocytopenia	26 (31.0)	3 (3.6)	23 (27.4)	11 (26.8)	0 (0.0)	10 (24.4)	30 (33.7)	4 (4.5)	26 (29.2)	58 (31.2)	7 (3.8)	50 (26.9)
Hypokalaemia	12 (14.3)	4 (4.8)	0 (0.0)	6 (14.6)	0 (0.0)	0 (0.0)	14 (15.7)	4 (4.5)	0 (0.0)	57 (30.6)	12 (6.5)	1 (0.5)
Muscle spasms	19 (22.6)	4 (4.8)	0 (0.0)	2 (4.9)	0 (0.0)	0 (0.0)	19 (21.3)	4 (4.5)	0 (0.0)	45 (24.2)	5 (2.7)	0 (0.0)
Hyponatraemia	11 (13.1)	4 (4.8)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	12 (13.5)	5 (5.6)	1 (1.1)	42 (22.6)	14 (7.5)	1 (0.5)
Neutropenia	13 (15.5)	2 (2.4)	8 (9.5)	8 (19.5)	2 (4.9)	5 (12.2)	17 (19.1)	2 (2.2)	12 (13.5)	41 (22.0)	5 (2.7)	29 (15.6)
Dyspnoea	21 (25.0)	4 (4.8)	2 (2.4)	11 (26.8)	1 (2.4)	1 (2.4)	18 (20.2)	4 (4.5)	1 (1.1)	39 (21.0)	9 (4.8)	2 (1.1)
Pneumonia	24 (28.6)	12 (14.3)	2 (2.4)	10 (24.4)	3 (7.3)	3 (7.3)	23 (25.8)	11 (12.4)	2 (2.2)	37 (19.9)	21 (11.3)	3 (1.6)
WBC count decreased	13 (15.5)	3 (3.6)	8 (9.5)	2 (4.9)	1 (2.4)	0 (0.0)	10 (11.2)	3 (3.4)	5 (5.6)	37 (19.9)	4 (2.2)	31 (16.7)
Platelet count decreased	14 (16.7)	2 (2.4)	12 (14.3)	4 (9.8)	0 (0.0)	4 (9.8)	12 (13.5)	1 (1.1)	11 (12.4)	34 (18.3)	3 (1.6)	31 (16.7)
Hypocalcaemia	4 (4.8)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	6 (6.7)	0 (0.0)	0 (0.0)	33 (17.7)	5 (2.7)	0 (0.0)
Hypotension	12 (14.3)	2 (2.4)	2 (2.4)	4 (9.8)	0 (0.0)	0 (0.0)	10 (11.2)	1 (1.1)	2 (2.2)	32 (17.2)	6 (3.2)	3 (1.6)
Back pain	8 (9.5)	2 (2.4)	0 (0.0)	3 (7.3)	0 (0.0)	0 (0.0)	9 (10.1)	3 (3.4)	0 (0.0)	26 (14.0)	5 (2.7)	0 (0.0)
Neutrophil count decreased	11 (13.1)	4 (4.8)	7 (8.3)	1 (2.4)	1 (2.4)	0 (0.0)	8 (9.0)	4 (4.5)	4 (4.5)	24 (12.9)	7 (3.8)	17 (9.1)
Asthenia	11 (13.1)	2 (2.4)	0 (0.0)	8 (19.5)	2 (4.9)	0 (0.0)	12 (13.5)	4 (4.5)	0 (0.0)	23 (12.4)	5 (2.7)	0 (0.0)
Hypertension	6 (7.1)	4 (4.8)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	5 (5.6)	4 (4.5)	0 (0.0)	21 (11.3)	13 (7.0)	0 (0.0)
Hypophosphataemia	2 (2.4)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.4)	1 (1.1)	0 (0.0)	21 (11.3)	6 (3.2)	2 (1.1)
Hyperglycaemia	3 (3.6)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.4)	2 (2.2)	0 (0.0)	16 (8.6)	7 (3.8)	0 (0.0)
Leukopenia	4 (4.8)	1 (1.2)	2 (2.4)	2 (4.9)	0 (0.0)	1 (2.4)	3 (3.4)	1 (1.1)	1 (1.1)	15 (8.1)	2 (1.1)	12 (6.5)
Hypoxia	3 (3.6)	2 (2.4)	1 (1.2)	1 (2.4)	1 (2.4)	0 (0.0)	4 (4.5)	3 (3.4)	0 (0.0)	14 (7.5)	7 (3.8)	1 (0.5)
Sepsis	5 (6.0)	1 (1.2)	4 (4.8)	6 (14.6)	1 (2.4)	1 (2.4)	6 (6.7)	1 (1.1)	5 (5.6)	14 (7.5)	3 (1.6)	10 (5.4)
Lymphocyte count decreased	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	10 (5.4)	2 (1.1)	6 (3.2)
Syncope	5 (6.0)	5 (6.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	4 (4.5)	4 (4.5)	0 (0.0)	7 (3.8)	7 (3.8)	0 (0.0)

Source: SCS Table 21

AEs=adverse events; CTCAE=Common Terminology Criteria for Adverse Events; LDAC=low-dose cytarabine; 7+3=7 days of cytarabine plus 3 days of daunorubicin; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; N= number of patients treated; WBC=white blood cell; SCS=Summary of Clinical Safety; SOC=System Organ Class.

Patients were counted once in each treatment arm/pool in each row based on the maximum grade of events.

Shading is applied to the meaningfully higher any grade AE or Grade 3 or 4 AE frequencies in the glasdegib + LDAC vs LDAC-alone arms or between S4 Pool and S2A Pool (ie, ≥10% absolute difference in any grade AE frequency or ≥5% absolute difference in Grade 3 or 4 AE frequency between the treatment arms).

Table 49. Overview of Treatment-Related Adverse Events: combination therapy cohort/pools, as-treated patients.

	S1 Cohort		S2A Pool	S4 Pool
	Glasdegib + LDAC N=84	LDAC N=41	Glasdegib + LDAC N=89	Glasdegib + LDAC or 7+3 N=186
Number of TRAEs	521	83	503	1672
Patients with TRAEs	68 (81.0)	24 (58.5)	73 (82.0)	166 (89.2)
Patients with TR SAEs	27 (32.1)	5 (12.2)	31 (34.8)	64 (34.4)
Patients with grade 3 or 4 TRAEs	55 (65.5)	14 (34.1)	61 (68.5)	139 (74.7)
Patients with grade 5 TRAEs	1 (1.2)	1 (2.4)	4 (4.5)	5 (2.7)
Patients permanently discontinued due to TRAEs	9 (10.7)	3 (7.3)	12 (13.5)	32 (17.2)
Patients with glasdegib dose reduced due to TRAEs	13 (15.5)	NA	13 (14.6)	18 (9.7)
Patients with backbone chemotherapy dose reduced due to TRAEs	12 (14.3)	0 (0.0)	11 (12.4)	12 (6.5)
Patients with glasdegib temporary discontinuation due to TRAEs	29 (34.5)	NA	31 (34.8)	54 (29.0)
Patients with backbone chemotherapy temporary discontinuation due to TRAEs	19 (22.6)	2 (4.9)	19 (21.3)	26 (14.0)

Table 50. Treatment-Related Adverse Events (>=10% of patients in any arm) by MedDRA PT, sorted by descending frequency in the S4 pool: combination therapy cohort/pools, as-treated patients.

MedDRA PT	Number (%) of Patients			
	S1 Cohort		S2A Pool	S4 Pool
	Glasdegib + LDAC N=84	LDAC N=41	Glasdegib + LDAC N=89	Glasdegib + LDAC or 7+3 N=186
Any TRAEs	68 (81.0)	24 (58.5)	73 (82.0)	166 (89.2)
Nausea	24 (28.6)	1 (2.4)	27 (30.3)	79 (42.5)
Diarrhoea	14 (16.7)	1 (2.4)	16 (18.0)	63 (33.9)
Febrile neutropenia	12 (14.3)	3 (7.3)	13 (14.6)	54 (29.0)
Anaemia	26 (31.0)	6 (14.6)	26 (29.2)	53 (28.5)
Dysgeusia	19 (22.6)	0 (0.0)	20 (22.5)	48 (25.8)
Fatigue	19 (22.6)	4 (9.8)	17 (19.1)	48 (25.8)
Decreased appetite	21 (25.0)	2 (4.9)	20 (22.5)	45 (24.2)
Thrombocytopenia	20 (23.8)	5 (12.2)	23 (25.8)	43 (23.1)
Vomiting	14 (16.7)	3 (7.3)	15 (16.9)	38 (20.4)
Muscle spasms	17 (20.2)	0 (0.0)	16 (18.0)	36 (19.4)
Neutropenia	9 (10.7)	4 (9.8)	12 (13.5)	35 (18.8)
Constipation	10 (11.9)	3 (7.3)	9 (10.1)	34 (18.3)
White blood cell count decreased	11 (13.1)	1 (2.4)	8 (9.0)	32 (17.2)
Platelet count decreased	13 (15.5)	1 (2.4)	11 (12.4)	31 (16.7)
Alopecia	9 (10.7)	0 (0.0)	8 (9.0)	30 (16.1)
Stomatitis	3 (3.6)	1 (2.4)	5 (5.6)	23 (12.4)
Pyrexia	5 (6.0)	3 (7.3)	4 (4.5)	22 (11.8)
Abdominal pain	5 (6.0)	1 (2.4)	4 (4.5)	21 (11.3)
Hypokalaemia	4 (4.8)	1 (2.4)	4 (4.5)	21 (11.3)
Alanine aminotransferase increased	2 (2.4)	0 (0.0)	2 (2.2)	20 (10.8)
Neutrophil count decreased	10 (11.9)	1 (2.4)	7 (7.9)	19 (10.2)
Oedema peripheral	6 (7.1)	1 (2.4)	5 (5.6)	19 (10.2)
Weight decreased	12 (14.3)	0 (0.0)	11 (12.4)	19 (10.2)
Dyspnoea	10 (11.9)	1 (2.4)	7 (7.9)	15 (8.1)

Table 51. Treatment-Related Adverse Events (All Grades, Grade 3, Grade 4) (>=5% Patients with Grade 3 or Grade 4 events in Any Arm) by MedDRA PT, maximum CTCAE Grade, sorted by descending frequency of all-grade events in the S4 pool: combination therapy cohort/pools, as-treated patients.

MedDRA PT	Number (%) of Patients											
	S1 Cohort						S2A Pool			S4 Pool		
	Glasdegib + LDAC N=84			LDAC N=41			Glasdegib + LDAC N=89			Glasdegib + LDAC or 7+3 N=186		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any TRAEs	68 (81.0)	20 (23.8)	34 (40.5)	24 (58.5)	3 (7.3)	10 (24.4)	73 (82.0)	23 (25.8)	34 (38.2)	166 (89.2)	41 (22.0)	93 (50.0)
Febrile neutropenia	12 (14.3)	9 (10.7)	3 (3.6)	3 (7.3)	2 (4.9)	1 (2.4)	13 (14.6)	8 (9.0)	5 (5.6)	54 (29.0)	48 (25.8)	6 (3.2)
Anaemia	26 (31.0)	19 (22.6)	3 (3.6)	6 (14.6)	4 (9.8)	1 (2.4)	26 (29.2)	20 (22.5)	2 (2.2)	53 (28.5)	44 (23.7)	3 (1.6)
Fatigue	19 (22.6)	9 (10.7)	0 (0.0)	4 (9.8)	1 (2.4)	0 (0.0)	17 (19.1)	8 (9.0)	0 (0.0)	48 (25.8)	13 (7.0)	0 (0.0)
Thrombocytopenia	20 (23.8)	4 (4.8)	16 (19.0)	5 (12.2)	0 (0.0)	5 (12.2)	23 (25.8)	5 (5.6)	18 (20.2)	43 (23.1)	7 (3.8)	35 (18.8)
Neutropenia	9 (10.7)	0 (0.0)	6 (7.1)	4 (9.8)	0 (0.0)	4 (9.8)	12 (13.5)	0 (0.0)	10 (11.2)	35 (18.8)	3 (1.6)	27 (14.5)
White blood cell count decreased	11 (13.1)	2 (2.4)	8 (9.5)	1 (2.4)	0 (0.0)	0 (0.0)	8 (9.0)	2 (2.2)	5 (5.6)	32 (17.2)	3 (1.6)	28 (15.1)
Platelet count decreased	13 (15.5)	3 (3.6)	9 (10.7)	1 (2.4)	0 (0.0)	1 (2.4)	11 (12.4)	2 (2.2)	8 (9.0)	31 (16.7)	4 (2.2)	26 (14.0)
Neutrophil count decreased	10 (11.9)	3 (3.6)	6 (7.1)	1 (2.4)	1 (2.4)	0 (0.0)	7 (7.9)	3 (3.4)	3 (3.4)	19 (10.2)	5 (2.7)	13 (7.0)
Leukopenia	1 (1.2)	0 (0.0)	1 (1.2)	2 (4.9)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	10 (5.4)	0 (0.0)	10 (5.4)

Safety Analysis Set, S1 Cohort) - Phase 2 Unfit (Non-intensive)

Table 52. Overview of All-Causality Treatment-Emergent Adverse Events (Safety Analysis Set, S1 Cohort) - Phase 2 Unfit (Non-intensive).

	Glasdegib 100 mg+LDAC	LDAC Alone
Patients evaluable for AEs	84	41
Number of AEs	1364	434
Number (%) of patients (with)		
AEs	84 (100.0)	41 (100.0)
SAEs	66 (78.6)	32 (78.0)
Grade 3 or 4 AEs	76 (90.5)	39 (95.1)
Grade 5 AEs	24 (28.6)	17 (41.5)
Discontinued due to AEs	30 (35.7)	19 (46.3)
Glasdegib dose reduced due to AEs	14 (16.7)	NA
LDAC dose reduced due to AEs	13 (15.5)	0
Glasdegib temporary discontinuation due to AEs	47 (56.0)	NA
LDAC temporary discontinuation due to AEs	31 (36.9)	13 (31.7)

Source: Table 14.3.1.2.1.3
Included data up to 28 days after last dose of study drug.
Except for the number of AEs, patients were counted only once per treatment in each row.
AEs were graded in accordance with National Cancer Institute CTCAE version 4.03.
SAEs were according to the investigator's assessment.

Table 53. Overview of glasdegib-related Treatment-Emergent Adverse Events (Safety Analysis Set, S1 Cohort) - Phase 2 Unfit (Non-intensive).

	PF-04449913 100 mg + LDAC (II)		LDAC Alone (II)	
	n	(%)	n	(%)
Number (%) of subjects:				
Subjects evaluable for adverse events	84		41	
Number of adverse events	445		0	
Subjects with adverse events	61	(72.6)	0	
Subjects with serious adverse events	23	(27.4)	0	
Subjects with grade 3 or 4 adverse events	45	(53.6)	0	
Subjects with grade 5 adverse events	1	(1.2)	0	
Subjects discontinued due to adverse events	8	(9.5)	0	
Subjects with PF-04449913 dose reduced due to adverse events	12	(14.3)	0	
Subjects with backbone chemotherapy dose reduced due to adverse events	6	(7.1)	0	
Subjects with PF-04449913 temporary discontinuation due to adverse events	27	(32.1)	0	
Subjects with backbone chemotherapy temporary discontinuation due to adverse events	13	(15.5)	0	

Includes data up to 28 days after last dose of study drug.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
MedDRA (v19.1) coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1.3 Date of Reporting Dataset Creation: 28FEB2017 Date of Table Generation: 20MAR2017 (05:10)

The following special safety topics have been discussed in detail by the Applicant: QT interval prolongation, renal toxicity, cytopenic events, musculoskeletal events, neurological events, skin and other dermal conditions, reproductive and development toxicities.

- QT interval prolongation

Table 54. All-Causality Adverse Events (All Grades, Grade 3, Grade 4) within the AEoSI Cluster Term QT INTERVAL PROLONGATION by MedDRA PT, Maximum CTCAE Grade, sorted by descending frequency of all grade events in the S4 Pool: combination therapy cohort/pools.

MedDRA PT	Number (%) of Patients											
	S1 Cohort						S2A Pool Glasdegib + LDAC N=89			S4 Pool Glasdegib + LDAC or 7+3 N=186		
	Glasdegib + LDAC N=84			LDAC N=41								
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any AE	**17 (20.2)**	**8 (9.5)**	**2 (2.4)**	**4 (9.8)**	**2 (4.9)**	**0 (0.0)**	16 (18.0)	7 (7.9)	1 (1.1)	**27 (14.5)**	**13 (7.0)**	**2 (1.1)**
Electrocardiogram QT prolonged	7 (8.3)	2 (2.4)	1 (1.2)	1 (2.4)	1 (2.4)	0 (0.0)	6 (6.7)	2 (2.2)	0 (0.0)	14 (7.5)	4 (2.2)	1 (0.5)
Syncope	5 (6.0)	5 (6.0)	0 (0.0)	1 (2.4)	1 (2.4)[a]	0 (0.0)	4 (4.5)	4 (4.5)	0 (0.0)	7 (3.8)	7 (3.8)	0 (0.0)
Ventricular tachycardia	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)	0 (0.0)	3 (1.6)	1 (0.5)	0 (0.0)
Cardiac arrest	2 (2.4)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)	1 (1.1)	2 (1.1)	0 (0.0)	1 (0.5)
Loss of consciousness	2 (2.4)	1 (1.2)	0 (0.0)	2 (4.9)	1 (2.4)	0 (0.0)	2 (2.2)	1 (1.1)	0 (0.0)	2 (1.1)	1 (0.5)	0 (0.0)
Sudden death	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)
Ventricular fibrillation	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.1)	1 (0.5)	0 (0.0)	1 (0.5)

Source: SCS Table 52
AE=adverse event; LDAC=low-dose cytarabine; 7+3=7 days of cytarabine plus 3 days of daunorubicin; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; N=number of patients treated; AEoSI=adverse event of special interest; SCS=Summary of Clinical Safety; SMQ=Standardised MedDRA Query.
Patients were counted once in each treatment arm/pool in each row based on the maximum grade of events.
a. In the S1 Cohort LDAC-alone arm, 1 AE of Syncope was reported by the investigator as a Grade 1 event. Given the CTCAE criteria for Syncope, this 1 event is considered to be Grade 3 in severity.
AEoSI cluster term QT INTERVAL PROLONGATION=Torsade de pointes/QT prolongation (SMQ), Seizure.

Table 55. All-Causality Serious Adverse Events Within the AEoSI Cluster Term QT INTERVAL PROLONGATION by MedDRA PT, sorted by descending frequency in the S4 Pool: combination therapy cohort/pools.

MedDRA PT	Number (%) of Patients			
	S1 Cohort		S2A Pool	S4 Pool
	Glasdegib + LDAC N=84	LDAC N=41	Glasdegib + LDAC N=89	Glasdegib + LDAC or 7+3 N=186
Any SAE	**8 (9.5)**	**0 (0.0)**	**7 (7.9)**	**9 (4.8)**
Syncope	4 (4.8)	0 (0.0)	3 (3.4)	5 (2.7)
Cardiac arrest	2 (2.4)	0 (0.0)	2 (2.2)	2 (1.1)
Sudden death	2 (2.4)	0 (0.0)	2 (2.2)	2 (1.1)
Ventricular fibrillation	1 (1.2)	0 (0.0)	1 (1.1)	1 (0.5)

Source: SCS Table 55

SAE=serious adverse event; LDAC=low-dose cytarabine; 7+3=7 days of cytarabine plus 3 days of daunorubicin; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; AEoSI=Adverse Event of Special Interest; SCS=Summary of Clinical Safety; SMQ=Standardised MedDRA Query; N=number of patients treated.
Patients were counted once in each treatment arm/pool in each row based on the maximum grade of events.
AEoSI cluster term QT INTERVAL PROLONGATION=Torsade de pointes/QT prolongation (SMQ), Seizure.

Table 56. All-Causality Grade 5 Adverse Events Within the AEoSI Cluster Term QT INTERVAL PROLONGATION by MedDRA PT, sorted by descending frequency in the S4 Pool: combination therapy cohort/pools.

MedDRA PT	Number (%) of Patients			
	S1 Cohort		S2A Pool	S4 Pool
	Glasdegib + LDAC N=84	LDAC N=41	Glasdegib + LDAC N=89	Glasdegib + LDAC or 7+3 N=186
Any AE	**3 (3.6)**	**0 (0.0)**	**3 (3.4)**	**3 (1.6)**
Sudden death	2 (2.4)	0 (0.0)	2 (2.2)	2 (1.1)
Cardiac arrest	1 (1.2)	0 (0.0)	1 (1.1)	1 (0.5)

Source: SCS Table 54

AE=adverse event; LDAC=low-dose cytarabine; 7+3=7 days of cytarabine plus 3 days of daunorubicin; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; N=number of patients treated, AEoSI=Adverse Event of Special Interest; SCS=Summary of Clinical Safety SMQ=Standardised MedDRA Query; N=number of patients treated.
Patients were counted once in each treatment arm/pool in each row based on the maximum grade of events.
AEoSI cluster term QT INTERVAL PROLONGATION=Torsade de pointes/QT prolongation (SMQ), Seizure.

Table 57. Treatment-Related Adverse Events within the AEoSI Cluster Term QT INTERVAL PROLONGATION by MedDRA PT, Sorted by Descending Frequency in the S4 Pool: combination therapy cohort/pools, as-treated patients.

MedDRA PT	Number(%) of Patients			
	S1 Cohort		S2A Pool	S4 Pool
	Glasdegib + LDAC N=84	LDAC N=41	Glasdegib + LDAC N=89	Glasdegib + LDAC or 7+3 N=186
Any TRAEs	6(7.1)	0(0.0)	6(6.7)	10(5.4)
Electrocardiogram QT prolonged	4(4.8)	0(0.0)	4(4.5)	8(4.3)
Syncope	1(1.2)	0(0.0)	1(1.1)	1(0.5)
Ventricular fibrillation	1(1.2)	0(0.0)	1(1.1)	1(0.5)

- Renal toxicity

Table 58. All-Causality Adverse Events (All Grades, Grade 3, Grade 4) Within the AEoSI Cluster Term RENAL TOXICITY by MedDRA PT, Maximum CTCAE Grade, sorted by descending frequency of all grade events in the S4 Pool: combination therapy cohort/pools.

MedDRA PT	Number (%) of Patients											
	S1 Cohort						S2A Pool Glasdegib + LDAC N=89			S4 Pool Glasdegib + LDAC or 7+3 N=186		
	Glasdegib + LDAC N=84			LDAC N=41								
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any AE	19 (22.6)	5 (6.0)	1 (1.2)	6 (14.6)	1 (2.4)	0 (0.0)	19 (21.3)	4 (4.5)	1 (1.1)	51 (27.4)	6 (3.2)	1 (0.5)
Blood creatinine increased	9 (10.7)	0 (0.0)	0 (0.0)	3 (7.3)	1 (2.4)	0 (0.0)	10 (11.2)	0 (0.0)	0 (0.0)	25 (13.4)	0 (0.0)	0 (0.0)
Acute kidney injury	10 (11.9)	3 (3.6)	1 (1.2)	1 (2.4)	0 (0.0)	0 (0.0)	9 (10.1)	2 (2.2)	1 (1.1)	24 (12.9)	4 (2.2)	1 (0.5)
Proteinuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.7)	0 (0.0)	0 (0.0)
Renal failure	2 (2.4)	1 (1.2)	0 (0.0)	2 (4.9)	0 (0.0)	0 (0.0)	2 (2.2)	1 (1.1)	0 (0.0)	2 (1.1)	1 (0.5)	0 (0.0)
Oliguria	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
Urine output decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

Source: SCS Table 62
AE=adverse event; LDAC=low-dose cytarabine; 7+3=7 days of cytarabine plus 3 days of daunorubicin; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; AEoSI=Adverse Event of Special Interest; SMQ=Standardised MedDRA Query; N=number of patients treated.
Patients are counted once in each treatment arm/pool in each row based on the maximum grade of events.
AEoSI cluster term RENAL TOXICITY=Acute renal failure SMQ.

Table 59. All-Causality Serious Adverse Events Within the AEoSI Cluster Term RENAL TOXICITY by MedDRA PT, sorted by descending frequency in the S4 Pool: combination therapy cohort/pools.

MedDRA PT	Number (%) of Patients			
	S1 Cohort		S2A Pool Glasdegib + LDAC N=89	S4 Pool Glasdegib + LDAC or 7+3 N=186
	Glasdegib + LDAC N=84	LDAC N=41		
Any SAE	**3 (3.6)**	**0 (0.0)**	**2 (2.2)**	**4 (2.2)**
Acute kidney injury	3 (3.6)	0 (0.0)	2 (2.2)	4 (2.2)

Source: SCS Table 64
SAE=serious adverse event; LDAC=low-dose cytarabine; 7+3=7 days of cytarabine plus 3 days of daunorubicin; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; AEoSI=adverse event of special interest; SCS=Summary of Clinical Safety; SMQ=Standardised MedDRA Query; N=number of patients treated.
Patients were counted once in each treatment arm/pool in each row based on the maximum grade of events.
AEoSI cluster term RENAL TOXICITY=Acute renal failure SMQ.

Table 60. Treatment-Related Adverse Events Within the AEoSI Cluster Term RENAL TOXICITY by MedDRA PT, sorted by descending frequency in the S4 Pool: combination therapy cohort/pools, as-treated patients.

MedDRA PT	Number(%) of Patients			
	S1 Cohort		S2A Pool	S4 Pool
	Glasdegib + LDAC N=84	LDAC N=41	Glasdegib + LDAC N=89	Glasdegib + LDAC or 7+3 N=186
Any TRAEs	5(6.0)	0(0.0)	5(5.6)	13(7.0)
Acute kidney injury	3(3.6)	0(0.0)	3(3.4)	6(3.2)
Blood creatinine increased	2(2.4)	0(0.0)	2(2.2)	6(3.2)
Proteinuria	0(0.0)	0(0.0)	0(0.0)	2(1.1)
Oliguria	1(1.2)	0(0.0)	1(1.1)	1(0.5)
Renal failure	1(1.2)	0(0.0)	1(1.1)	1(0.5)

- Cytopenic events

Table 61. All-Causality Adverse Events (All Grades, Grade 3, Grade 4) Within the Blood and lymphatic system disorders SOC and Investigations SOC (≥5% patients with grade 3 or grade 4 events in any arm) by MedDRA SOC and PT, Maximum CTCAE Grade, sorted by descending frequency of all-grade events in the S4 pool combination therapy cohort/pools.

MedDRA SOC/PT	Number (%) of Patients											
	S1 Cohort						S2A Pool			S4 Pool		
	Glasdegib + LDAC N=84			LDAC N=41			Glasdegib + LDAC N=89			Glasdegib + LDAC or 7+3 N=186		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Blood and lymphatic system disorders	**60 (71.4)**	**26 (31.0)**	**32 (38.1)**	**27 (65.9)**	**11 (26.8)**	**15 (36.6)**	**64 (71.9)**	**25 (28.1)**	**37 (41.6)**	**150 (80.6)**	**66 (35.5)**	**79 (42.5)**
Febrile neutropenia	30 (35.7)	26 (31.0)	4 (4.8)	10 (24.4)	8 (19.5)	2 (4.9)	31 (34.8)	25 (28.1)	6 (6.7)	89 (47.8)	81 (43.5)	8 (4.3)
Anaemia	38 (45.2)	28 (33.3)	7 (8.3)	17 (41.5)	13 (31.7)	2 (4.9)	38 (42.7)	29 (32.6)	6 (6.7)	73 (39.2)	61 (32.8)	7 (3.8)
Thrombocytopenia	26 (31.0)	3 (3.6)	23 (27.4)	11 (26.8)	0 (0.0)	10 (24.4)	30 (33.7)	4 (4.5)	26 (29.2)	58 (31.2)	7 (3.8)	50 (26.9)
Neutropenia	13 (15.5)	2 (2.4)	8 (9.5)	8 (19.5)	2 (4.9)	5 (12.2)	17 (19.1)	2 (2.2)	12 (13.5)	41 (22.0)	5 (2.7)	29 (15.6)
Leukopenia	4 (4.8)	1 (1.2)	2 (2.4)	2 (4.9)	0 (0.0)	1 (2.4)	3 (3.4)	1 (1.1)	1 (1.1)	15 (8.1)	2 (1.1)	12 (6.5)
Leukocytosis	6 (7.1)	2 (2.4)	1 (1.2)	3 (7.3)	3 (7.3)	0 (0.0)	7 (7.9)	2 (2.2)	1 (1.1)	10 (5.4)	3 (1.6)	1 (0.5)
Investigations	**51 (60.7)**	**7 (8.3)**	**21 (25.0)**	**20 (48.8)**	**5 (12.2)**	**6 (14.6)**	**50 (56.2)**	**8 (9.0)**	**16 (18.0)**	**119 (64.0)**	**16 (8.6)**	**56 (30.1)**
WBC count decreased	13 (15.5)	3 (3.6)	8 (9.5)	2 (4.9)	1 (2.4)	0 (0.0)	10 (11.2)	3 (3.4)	5 (5.6)	37 (19.9)	4 (2.2)	31 (16.7)
Platelet count decreased	14 (16.7)	2 (2.4)	12 (14.3)	4 (9.8)	0 (0.0)	4 (9.8)	12 (13.5)	1 (1.1)	11 (12.4)	34 (18.3)	3 (1.6)	31 (16.7)
Neutrophil count decreased	11 (13.1)	4 (4.8)	7 (8.3)	1 (2.4)	1 (2.4)	0 (0.0)	8 (9.0)	4 (4.5)	4 (4.5)	24 (12.9)	7 (3.8)	17 (9.1)

Source: SCS Table 69

AE=adverse event; LDAC=low-dose cytarabine; 7+3=7 days of cytarabine plus 3 days of daunorubicin; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SCS=Summary of Clinical Safety; N=number of patients treated; SOC=System Organ Class; WBC=white blood cell.

Patients were counted once in each treatment arm/pool in each row based on the maximum grade of events.

Only the haematology-related values are displayed.

Table 62. Summary of Decreasing Order of Frequency Treatment-Emergent Adverse Events Associated with AEoSI: Cytopenia by MedDRA Preferred Term and Maximum CTCAE Grade (Treatment Related, All Cycles) - Cohort S1AM.

glasdegib 100MG + LDAC

(N=84)

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Gr 3-4		Gr 3-5		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	3	(3.6)	5	(6.0)	9	(10.7)	3	(3.6)	1	(1.2)	0	(0.0)	12	(14.3)	13	(15.5)	21	(25.0)
Pneumonia	0	(0.0)	0	(0.0)	3	(3.6)	0	(0.0)	1	(1.2)	0	(0.0)	3	(3.6)	4	(4.8)	4	(4.8)
Device related infection	1	(1.2)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	3	(3.6)
Epistaxis	2	(2.4)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.6)
Sepsis	0	(0.0)	0	(0.0)	1	(1.2)	2	(2.4)	0	(0.0)	0	(0.0)	3	(3.6)	3	(3.6)	3	(3.6)
Contusion	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)
Gingival bleeding	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)
Haematoma	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)
Petechiae	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)
Purpura	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)
Anal haemorrhage	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Aspergillus infection	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Candida infection	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Clostridium difficile colitis	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Folliculitis	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Gastrointestinal haemorrhage	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Haematemesis	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Haemorrhage intracranial	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Infected dermal cyst	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Infection	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Influenza	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Mouth haemorrhage	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Mucosal infection	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Oral herpes	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Perineal abscess	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Tongue abscess	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Gr 3-4		Gr 3-5		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Upper respiratory tract infection	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Urethral haemorrhage	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)

LDAC Alone

(N=41)

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Gr 3-4		Gr 3-5		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	3	(7.3)	4	(9.8)	0	(0.0)	1	(2.4)	1	(2.4)	0	(0.0)	1	(2.4)	2	(4.9)	9	(22.0)
Mouth haemorrhage	3	(7.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(7.3)
Bronchitis	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Candida infection	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Ecchymosis	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Epistaxis	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Gingival bleeding	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Haematuria	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Haemorrhage	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Oral candidiasis	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Oral herpes	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Petechiae	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	1	(2.4)	1	(2.4)	1	(2.4)
Respiratory tract infection	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Sepsis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	1	(2.4)	1	(2.4)
Urinary tract infection	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
Vulvovaginal candidiasis	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)

Table 63. Treatment-Related Adverse Events (All Grades, Grade 3, Grade 4) Within the AEoSI Cluster Term CYTOPENIC COMPLICATIONS (>=3 Patients in Any Arm) by MedDRA SOC and PT, Maximum CTCAE Grade, sorted by descending frequency of all-grade events in the S4 pool: combination therapy cohort/pools, as-treated patients.

MedDRA SOC/PT	Number(%) of Patients											
	S1 Cohort						S2A Pool			S4 Pool		
	Glasdegib + LDAC N=84			LDAC N=41			Glasdegib + LDAC N=89			Glasdegib + LDAC or 7+3 N=186		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any TRAEs	21(25.0)	9(10.7)	3(3.6)	9(22.0)	0(0.0)	1(2.4)	20(22.5)	9(10.1)	2(2.2)	65(34.9)	26(14.0)	10(5.4)
Infections and infestations	18(21.4)	8(9.5)	2(2.4)	6(14.6)	0(0.0)	1(2.4)	17(19.1)	8(9.0)	2(2.2)	50(26.9)	23(12.4)	8(4.3)
Pneumonia	4(4.8)	3(3.6)	0(0.0)	1(2.4)	0(0.0)	1(2.4)	4(4.5)	3(3.4)	0(0.0)	10(5.4)	8(4.3)	1(0.5)
Device related infection	3(3.6)	1(1.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	3(3.4)	1(1.1)	0(0.0)	7(3.8)	3(1.6)	1(0.5)
Sepsis	3(3.6)	1(1.2)	2(2.4)	1(2.4)	0(0.0)	0(0.0)	3(3.4)	1(1.1)	2(2.2)	7(3.8)	1(0.5)	5(2.7)
Candida infection	1(1.2)	1(1.2)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	2(2.2)	1(1.1)	0(0.0)	4(2.2)	1(0.5)	0(0.0)
Urinary tract infection	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(2.2)	0(0.0)	0(0.0)
Bacteraemia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	3(1.6)	2(1.1)	1(0.5)
Folliculitis	1(1.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)	0(0.0)	0(0.0)	3(1.6)	0(0.0)	0(0.0)
Skin and subcutaneous tissue disorders	4(4.8)	0(0.0)	0(0.0)	2(4.9)	0(0.0)	0(0.0)	4(4.5)	0(0.0)	0(0.0)	15(8.1)	0(0.0)	0(0.0)
Petechiae	2(2.4)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	2(2.2)	0(0.0)	0(0.0)	10(5.4)	0(0.0)	0(0.0)
Purpura	2(2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(2.2)	0(0.0)	0(0.0)	5(2.7)	0(0.0)	0(0.0)
Gastrointestinal disorders	5(6.0)	1(1.2)	0(0.0)	3(7.3)	0(0.0)	0(0.0)	4(4.5)	1(1.1)	0(0.0)	14(7.5)	4(2.2)	0(0.0)
Gingival bleeding	2(2.4)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	1(1.1)	0(0.0)	0(0.0)	5(2.7)	1(0.5)	0(0.0)
Mouth haemorrhage	1(1.2)	0(0.0)	0(0.0)	3(7.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(2.2)	0(0.0)	0(0.0)
Respiratory, thoracic and mediastinal disorders	3(3.6)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	2(2.2)	0(0.0)	0(0.0)	7(3.8)	0(0.0)	0(0.0)
Epistaxis	3(3.6)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	2(2.2)	0(0.0)	0(0.0)	7(3.8)	0(0.0)	0(0.0)
Injury, poisoning and procedural complications	2(2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)	0(0.0)	0(0.0)	5(2.7)	0(0.0)	1(0.5)
Contusion	2(2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)	0(0.0)	0(0.0)	3(1.6)	0(0.0)	0(0.0)

- Musculoskeletal events

Muscle spasms are a known class effect of SMO inhibitors and have been reported with glasdegib and other SMO inhibitors. In the glasdegib program, the majority of AEs within the MUSCLE SPASMS ADR were Grade 1 or 2 in severity but were reported as TRAEs in 20.2% of patients in combination arm and none in LDAC alone arm.

Rhabdomyolysis has been reported with other SMO inhibitors. Neither AEs in the RHABDOMYOLYSIS cluster nor events of Rhabdomyolysis have been reported as of the safety data cutoff dates. Outside of the RHABDOMYOLYSIS cluster, there were no AEs of Blood creatinine phosphokinase (CPK) increased reported in Studies B1371001, B1371002, B1371012 or B1371013. AEs of Blood CPK increased, primarily Grade 1, were reported in Studies B1371003 and Study B1371005, with alternate plausible aetiologies (e.g., infection, physical exertion, resistant disease) and in some instances occurred >28 days after glasdegib dosing had been discontinued. None of these cases were accompanied by other findings suggestive of rhabdomyolysis.

- Neurological events

Peripheral neuropathy AEs have been reported sporadically and were likely related to backbone chemotherapy or factors other than glasdegib. Dysgeusia is a known on-target effect of SMO inhibitors. Dysgeusia as TRAE was reported in 22.6% of patients in combination arm and none in LDAC alone arm.

- Skin and other dermal conditions

Table 64. All-Causality Adverse Events (All Grades, Grade 3, Grade 4) Within the skin and subcutaneous tissue disorders SOC (≥5% patients in any arm) by MedDRA PT, Maximum CTCAE Grade, sorted by descending frequency of all-grade events in the S4 pool combination therapy cohort/pools.

MedDRA SOC/PT	Number (%) of Patients											
	S1 Cohort						S2A Pool			S4 Pool		
	Glasdegib + LDAC N=84			LDAC N=41			Glasdegib + LDAC N=89			Glasdegib + LDAC or 7+3 N=186		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Skin and subcutaneous tissue disorders	**44 (52.4)**	**3 (3.6)**	**0 (0.0)**	**14 (34.1)**	**2 (4.9)**	**0 (0.0)**	**48 (53.9)**	**3 (3.4)**	**0 (0.0)**	**117 (62.9)**	**13 (7.0)**	**0 (0.0)**
Rash	12 (14.3)	2 (2.4)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	12 (13.5)	2 (2.2)	0 (0.0)	31 (16.7)	3 (1.6)	0 (0.0)
Alopecia	9 (10.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (9.0)	0 (0.0)	0 (0.0)	30 (16.1)	0 (0.0)	0 (0.0)
Petechiae	7 (8.3)	0 (0.0)	0 (0.0)	4 (9.8)	0 (0.0)	0 (0.0)	9 (10.1)	0 (0.0)	0 (0.0)	21 (11.3)	0 (0.0)	0 (0.0)
Pruritus	6 (7.1)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	6 (6.7)	0 (0.0)	0 (0.0)	20 (10.8)	1 (0.5)	0 (0.0)
Rash maculo-papular	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	14 (7.5)	3 (1.6)	0 (0.0)
Erythema	7 (8.3)	0 (0.0)	0 (0.0)	2 (4.9)	1 (2.4)	0 (0.0)	7 (7.9)	0 (0.0)	0 (0.0)	11 (5.9)	0 (0.0)	0 (0.0)
Night sweats	4 (4.8)	0 (0.0)	0 (0.0)	2 (4.9)	0 (0.0)	0 (0.0)	6 (6.7)	0 (0.0)	0 (0.0)	11 (5.9)	0 (0.0)	0 (0.0)
Hyperhidrosis	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	10 (5.4)	1 (0.5)	0 (0.0)

Source: SCS Table 84

LDAC=low-dose cytarabine, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, N=number of patients treated; SCS=Summary of Clinical Safety; SOC= System Organ Class.

Patients were counted once in each treatment arm/pool in each row based on the maximum grade of events.

Shading is applied to the meaningfully higher any grade AE or Grade 3 or 4 AE frequencies in the glasdegib + LDAC vs LDAC-alone arms or between S4 Pool and S2A Pool (ie, ≥10% absolute difference in any grade AE frequency or ≥5% absolute difference in Grade 3 or 4 AE frequency between the treatment arms).

Table 65. Treatment-Related Adverse Events (All Grades, Grade 3, Grade 4) Within the Skin and Subcutaneous Tissue Disorders SOC (>=5% of Patients in Any Arm) by MedDRA PT, Maximum CTCAE Grade, sorted by descending frequency of all- grade events in the S4 pool: combination therapy cohort/pools, as-treated patients.

MedDRA SOC/PT	Number (%) of Patients											
	S1 Cohort						S2A Pool			S4 Pool		
	Glasdegib + LDAC N=84			LDAC N=41			Glasdegib + LDAC N=89			Glasdegib + LDAC or 7+3 N=186		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Skin and subcutaneous tissue disorders	25 (29.8)	2 (2.4)	0 (0.0)	3 (7.3)	0 (0.0)	0 (0.0)	28 (31.5)	2 (2.2)	0 (0.0)	73 (39.2)	9 (4.8)	0 (0.0)
Alopecia	9 (10.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (9.0)	0 (0.0)	0 (0.0)	30 (16.1)	0 (0.0)	0 (0.0)
Rash	5 (6.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (6.7)	1 (1.1)	0 (0.0)	14 (7.5)	1 (0.5)	0 (0.0)
Petechiae	2 (2.4)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)	0 (0.0)	10 (5.4)	0 (0.0)	0 (0.0)

There was a higher frequency of skin and subcutaneous disorder SOC TRAEs reported in the glasdegib + LDAC arm (29.8%) compared with the LDAC-alone arm (7.3%). Most of the AEs were Grade 1 or Grade 2 in severity. Alopecia is a known class effect of SMO inhibitors; and was reported in 10.7% of patients in combination arm and none in LDAC alone arm. Also, in the glasdegib + LDAC arm, 6% of rash (including 1 grade 3) were reported as TRAE and none in LDAC alone arm.

There was a single case of Grade 3 Dermatitis exfoliative in a patient receiving glasdegib plus 7+3. Other than that single case, there were no exfoliative AEs reported in clinical trials of glasdegib, and there were no reports of Stevens-Johnson syndrome or Toxic epidermal necrolysis as of the 11 October 2018 data cut-off date.

- Reproductive and developmental toxicity

Hedgehog pathway inhibitors have been demonstrated to be embryotoxic and/or teratogenic in multiple animal species and can cause severe malformations.

Glasdegib safety data used in monotherapy

The safety profile of glasdegib in monotherapy have been evaluated on the provided data from the 3 monotherapy Applicant-sponsored studies (B1371001, B1371002 and B1371013) and the 3 investigator-initiated studies (WI171861, WI220403, WI204578 IIR).

Table 66. Monotherapy Applicant-sponsored studies.

3 Monotherapy studies	Patients received 5-600 mg glasdegib from Study B1371001 (N=47), 80, 160, 320, or 640 mg glasdegib from Study B1371002 (N=23), and 100 mg glasdegib from Study B1371013 (N=21).

B1371001 was A Phase 1 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of glasdegib, an Oral Hedgehog Inhibitor, Administered as Single Agent in Select Hematologic Malignancies.

Table 67. Treatment-Emergent Adverse Events with frequency ≥5% by System Organ Class and Preferred Term (All Cycles, Treatment-Related by Grade) - B1371001 study.

N (%) With AEs by SOC MedDRA Preferred Term[a]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Missing or Unknown	Total (n = 47)
Any AEs	6 (12.8)	11 (23.4)	8 (17.0)	3 (6.4)	0	0	28 (59.6)
Gastrointestinal disorders	6 (12.8)	4 (8.5)	4 (8.5)	0	0	0	14 (29.8)
Diarrhoea	3 (6.4)	3 (6.4)	0	0	0	0	6 (12.8)
Nausea	4 (8.5)	1 (2.1)	1 (2.1)	0	0	0	6 (12.8)
Vomiting	4 (8.5)	0	1 (2.1)	0	0	0	5 (10.6)
General disorders and administration site conditions	3 (6.4)	4 (8.5)	3 (6.4)	0	0	0	10 (21.3)
Fatigue	2 (4.3)	2 (4.3)	1 (2.1)	0	0	0	5 (10.6)
Mucosal inflammation	1 (2.1)	1 (2.1)	1 (2.1)	0	0	0	3 (6.4)
Investigations	2 (4.3)	5 (10.6)	2 (4.3)	0	0	0	9 (19.1)
Electrocardiogram QT prolonged	1 (2.1)	4 (8.5)	0	0	0	0	5 (10.6)
Weight decreased	1 (2.1)	2 (4.3)	2 (4.3)	0	0	0	5 (10.6)
Metabolism and nutrition disorders	2 (4.3)	2 (4.3)	5 (10.6)	0	0	0	9 (19.1)
Decreased appetite	2 (4.3)	2 (4.3)	5 (10.6)	0	0	0	9 (19.1)
Musculoskeletal and connective tissue disorders	4 (8.5)	3 (6.4)	0	0	0	0	7 (14.9)
Muscle spasms	3 (6.4)	1 (2.1)	0	0	0	0	4 (8.5)
Nervous system disorders	7 (14.9)	6 (12.8)	0	0	0	0	13 (27.7)
Dysgeusia	7 (14.9)	6 (12.8)	0	0	0	0	13 (27.7)
Skin and subcutaneous tissue disorders	6 (12.8)	2 (4.3)	0	0	0	0	8 (17.0)
Alopecia	5 (10.6)	2 (4.3)	0	0	0	0	7 (14.9)

Source: Table 14.3.1.3.9.2

B1371002 was a Phase 1 Study to Evaluate the A Phase 1 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of glasdegib, an Oral Hedgehog Inhibitor, Administered as Single Agent in Select Solid Tumors.

Table 68. Treatment-Emergent Adverse Events with frequency ≥5% by System Organ Class and Preferred Term (All Cycles, Treatment –Related by Grade) – B1371002 study.

N (%) With AEs by SOC MedDRA Preferred Term[a]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Any AEs	6 (26.1)	9 (39.1)	5 (21.7)	0	0	20 (87.0)
Blood and lymphatic system disorders	1 (4.3)	1 (4.3)	0	0	0	2 (8.7)
Anaemia	1 (4.3)	1 (4.3)	0	0	0	2 (8.7)
Cardiac disorders	2 (8.7)	0	0	0	0	2 (8.7)
Palpitations	2 (8.7)	0	0	0	0	2 (8.7)
Gastrointestinal disorders	9 (39.1)	6 (26.1)	0	0	0	15 (65.2)
Constipation	2 (8.7)	0	0	0	0	2 (8.7)
Diarrhoea	4 (17.4)	2 (8.7)	0	0	0	6 (26.1)
Gastrooesophageal reflux disease	2 (8.7)	0	0	0	0	2 (8.7)
Nausea	4 (17.4)	4 (17.4)	0	0	0	8 (34.8)
Vomiting	2 (8.7)	3 (13.0)	0	0	0	5 (21.7)
General disorders and administration site conditions	7 (30.4)	4 (17.4)	1 (4.3)	0	0	12 (52.2)
Fatigue	7 (30.4)	4 (17.4)	1 (4.3)	0	0	12 (52.2)
Investigations	3 (13.0)	3 (13.0)	1 (4.3)	0	0	7 (30.4)
Alanine aminotransferase increased	1 (4.3)	0	1 (4.3)	0	0	2 (8.7)
Aspartate aminotransferase increased	1 (4.3)	0	1 (4.3)	0	0	2 (8.7)
Blood alkaline phosphatase increased	2 (8.7)	0	0	0	0	2 (8.7)
Blood bilirubin increased	1 (4.3)	1 (4.3)	0	0	0	2 (8.7)
Blood creatinine increased	2 (8.7)	0	0	0	0	2 (8.7)
Weight decreased	0	2 (8.7)	0	0	0	2 (8.7)
Metabolism and nutrition disorders	2 (8.7)	6 (26.1)	3 (13.0)	0	0	11 (47.8)
Decreased appetite	2 (8.7)	5 (21.7)	1 (4.3)	0	0	8 (34.8)
Dehydration	1 (4.3)	4 (17.4)	1 (4.3)	0	0	6 (26.1)
Musculoskeletal and connective tissue disorders	6 (26.1)	1 (4.3)	0	0	0	7 (30.4)
Muscle spasms	4 (17.4)	1 (4.3)	0	0	0	5 (21.7)
Nervous system disorders	12 (52.2)	3 (13.0)	2 (8.7)	0	0	17 (73.9)
Dizziness	4 (17.4)	2 (8.7)	1 (4.3)	0	0	7 (30.4)
Dysgeusia	14 (60.9)	1 (4.3)	0	0	0	15 (65.2)
Headache	2 (8.7)	0	0	0	0	2 (8.7)
Skin and subcutaneous tissue disorders	2 (8.7)	4 (17.4)	0	0	0	6 (26.1)
Alopecia	1 (4.3)	4 (17.4)	0	0	0	5 (21.7)
Pruritus	2 (8.7)	0	0	0	0	2 (8.7)

Source: Table 14.3.1.3.9.1

B1371013 was a Phase 2, Double-Blind, Randomized Safety and Efficacy Study of glasdegib versus Placebo in Patients with Myelofibrosis Previously Treated with Ruxolitinib. Glasdegib in monotherapy was tested in a lead-in cohort of ≥20 patients previously treated with ≥ 1 licensed or experimental JAKi. Although the drug was considered safe and tolerable in MF, a key secondary efficacy endpoint was not met. Therefore, continuation into the randomized part did not occur.

Table 69. Decreasing order of Frequency of Treatment -Emergent Adverse Events Reported in ≥ 2 Patients by Preferred Term and Maximum CTCAE Grade (Treatment-Related) - B1371013 study.

	Glasdegib Lead-In (N = 21)					
		CTCAE Grade				
Number of Patients Evaluable for AEs	n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Number (%) of patients with AEs by MedDRA (version 20.0) preferred term						
Any AEs	19 (90.5)	1 (4.8)	10 (47.6)	8 (38.1)	0	0
Dysgeusia	13 (61.9)	9 (42.9)	4 (19.0)	0	0	0
Muscle spasms	11 (52.4)	4 (19.0)	5 (23.8)	2 (9.5)	0	0
Alopecia	8 (38.1)	5 (23.8)	3 (14.3)	0	0	0
Decreased appetite	7 (33.3)	6 (28.6)	1 (4.8)	0	0	0
Fatigue	5 (23.8)	0	5 (23.8)	0	0	0
Lipase increased	4 (19.0)	0	0	4 (19.0)	0	0
Weight decreased	4 (19.0)	1 (4.8)	3 (14.3)	0	0	0
Electrocardiogram QT prolonged	3 (14.3)	1 (4.8)	2 (9.5)	0	0	0
Myalgia	3 (14.3)	3 (14.3)	0	0	0	0
Anaemia	2 (9.5)	0	1 (4.8)	1 (4.8)	0	0
Asthenia	2 (9.5)	1 (4.8)	0	1 (4.8)	0	0
Constipation	2 (9.5)	1 (4.8)	1 (4.8)	0	0	0
Diarrhoea	2 (9.5)	2 (9.5)	0	0	0	0
Dizziness	2 (9.5)	1 (4.8)	1 (4.8)	0	0	0
Dry mouth	2 (9.5)	2 (9.5)	0	0	0	0
Fall	2 (9.5)	1 (4.8)	1 (4.8)	0	0	0
Nausea	2 (9.5)	2 (9.5)	0	0	0	0
Neutropenia	2 (9.5)	0	2 (9.5)	0	0	0
Pain in extremity	2 (9.5)	1 (4.8)	1 (4.8)	0	0	0

Source: Table 14.3.1.3.9.1 and Table 14.3.1.3.11.1

Table 70. Investigator-initiated studies (WI171861, WI220403, WI204578 IIR).

WI171861	IIR	MDS	Monotherapy	35	Complete
WI220403[e]	IIR	AML post HSCT	Monotherapy	35	Ongoing
WI204578	IIR	Sclerotic Chronic Graft-Versus-Host Disease	Monotherapy	6	Ongoing
WI218564	IIR	Glioblastoma	+ radiation and temozolomide	3	Ongoing
WI216382-1	IIR	AML	+ gemtuzumab ozogamycin	2	Ongoing

Source: SCS in-text Tables 1 and 2

Based on the individual listing of treatment-related AEs in all cases provided in the SCS:

- In WI171861: One death has been reported in a patient treated by glasdegib at the dose of 50 mg (the causality has not been described). No treatment-related of non-fatal cases has been reported.
- In WI220403: 8 serious events of 3 subjects have been reported: 1 diarrhoea, 2 nauseas, 1 pneumonia, 1 sepsis, 1 appetite disorder, 1 acute kidney injury, 1 pyrexia. Nauseas and appetite disorder have not been recovered; the acute kidney injury recovered with sequel. It was not documented for the sepsis and diarrhoea. No fatal case has been reported. The non-fatal cases were the serious TRAEs reported.
- In WI204578: 2 serious TRAEs have been reported: 1 muscle spasms: the subject temporary withdrawn glasdegib 100 mg and recovered with sequel; 1 cerebrovascular accident resolved after permanently discontinuation of glasdegib 50 mg. No fatal case has been reported. The two non-fatal cases were the serious TRAEs reported.

Serious adverse event/deaths/other significant events

- Serious adverse events

Serious adverse events were reported for 78.6% of patients in the glasdegib + LDAC arm and 78.0% of patients in the LDAC-alone arm. Treatment-related Serious adverse events were reported for 32.1% of patients in the glasdegib + LDAC arm and 12.2% of patients in the LDAC-alone arm.

Table 71. All-causality serious adverse events (≥3 patients in any arm) by MedDRA PT sorted by descending frequency in the S4 pool: combination therapy cohort/pools.

MedDRA PT	Number (%) of Patients			
	S1 Cohort		S2A Pool	S4 Pool
	Glasdegib + LDAC N=84	LDAC N=41	Glasdegib + LDAC N=89	Glasdegib + LDAC or 7+3 N=186
Any SAE	**66 (78.6)**	**32 (78.0)**	**71 (79.8)**	**124 (66.7)**
Febrile neutropenia	24 (28.6)	7 (17.1)	23 (25.8)	42 (22.6)
Pneumonia	19 (22.6)	7 (17.1)	17 (19.1)	25 (13.4)
Disease progression	8 (9.5)	5 (12.2)	10 (11.2)	13 (7.0)
Sepsis	3 (3.6)	5 (12.2)	4 (4.5)	10 (5.4)
Anaemia	6 (7.1)	0 (0.0)	5 (5.6)	6 (3.2)
Syncope	4 (4.8)	0 (0.0)	3 (3.4)	5 (2.7)
Acute kidney injury	3 (3.6)	0 (0.0)	2 (2.2)	4 (2.2)
Bacteraemia	1 (1.2)	0 (0.0)	1 (1.1)	4 (2.2)
Fatigue	3 (3.6)	0 (0.0)	3 (3.4)	4 (2.2)
Haemorrhage intracranial	3 (3.6)	1 (2.4)	2 (2.2)	3 (1.6)
Hyponatraemia	2 (2.4)	0 (0.0)	2 (2.2)	3 (1.6)
Pyrexia	3 (3.6)	1 (2.4)	3 (3.4)	3 (1.6)
Septic shock	2 (2.4)	1 (2.4)	1 (1.1)	3 (1.6)

Source: SCS Table 36

LDAC=low-dose cytarabine; 7+3=7 days of cytarabine plus 3 days of daunorubicin; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; N=number of patients treated; SAEs=serious adverse events; SCS=Summary of Clinical Safety.

Patients were counted once in each treatment arm/pool in each row based on the maximum grade of events.

Shading is applied to the meaningfully higher any grade AE or Grade 3 or 4 AE frequencies in the glasdegib + LDAC vs LDAC-alone arms or between S4 Pool and S2A Pool (ie, ≥10% absolute difference in any grade AE frequency or ≥5% absolute difference in Grade 3 or 4 AE frequency between the treatment arms).

Table 72. Treatment-Related Serious Adverse Events (>=3 Patients in any arm) by MedDRA PT, sorted by descending frequency in the S4 Pool: combination therapy cohort/pools, as-treated patients.

MedDRA PT	Number (%) of Patients			
	S1 Cohort		S2A Pool	S4 Pool
	Glasdegib + LDAC N=84	LDAC N=41	Glasdegib + LDAC N=89	Glasdegib + LDAC or 7+3 N=186
Any TR SAEs	27 (32.1)	5 (12.2)	31 (34.8)	64 (34.4)
Febrile neutropenia	10 (11.9)	2 (4.9)	11 (12.4)	23 (12.4)
Pneumonia	4 (4.8)	1 (2.4)	3 (3.4)	6 (3.2)
Sepsis	2 (2.4)	1 (2.4)	2 (2.2)	6 (3.2)
Anaemia	4 (4.8)	0 (0.0)	3 (3.4)	4 (2.2)
Fatigue	2 (2.4)	0 (0.0)	3 (3.4)	3 (1.6)

- Deaths

The deaths reported in the glasdegib 100 mg+LDAC and LDAC alone arms were 5 (6.0%) and 5 (12.2%) in ≤30 days and 10 (11.9%) and 13 (31.7%) in ≤60 days from the first dose of study treatments, respectively. A summary of deaths for patients in the P2 Unfit arms (S1 Cohort) is provided in Table 73.

Table 73. Summary of deaths (Safety Analysis Set, S1 Cohort) - Phase 2 Unfit (Non-intensive).

	Glasdegib 100 mg+LDAC	LDAC Alone
Number of Patients	84	41
	n (%)	n (%)
Number of deaths from start of treatment to and including 28 days after last dose	25 (29.8)	17 (41.5)
Cause of death on study		
Disease under study	20 (23.8)	15 (36.6)
Study treatment toxicity	0	0
Unknown	4 (4.8)	0
Other	7 (8.3)	8 (19.5)
Number of deaths during follow-up period occurring after 28 days after last dose	39 (46.4)	23 (56.1)
Cause of death during follow-up period		
Disease under study	33 (39.3)	19 (46.3)
Study treatment toxicity	0	0
Unknown	4 (4.8)	1 (2.4)
Other	6 (7.1)	4 (9.8)
Number of deaths	64 (76.2)	40 (97.6)
80% Exact CI[a]	(69.2, 82.2)	(90.8, 99.7)

Source: Table 14.3.2.1.2.3
Patients could have multiple reasons for cause of death.

Over half of the deaths occurred during the follow-up period (after 28 days following the last dose of study treatments): 39 out of 64 and 23 out of 40 deaths in the glasdegib 100 mg + LDAC and LDAC alone arms, respectively. No death due to study treatment toxicity has been reported by the Applicant.

There were 2 Grade 5 AEs that were treatment-related per investigator and reported within 28 days post-dose, 1 in each treatment arm.

- Pneumonia in the glasdegib + LDAC arm,
- Sepsis in the LDAC arm.

Among the "other" deaths derived from the Case Report Form, pneumonia seems to occur more frequently in the glasdegib arm (5 out of 13 patients vs 2 out of 12).

Laboratory findings

Table 74. Haematology Laboratory Test Abnormalities by Maximum CTCAE Grade (All Cycles, Safety Analysis Set, S1 Cohort) - Phase 2 Unfit (Non-intensive).

Laboratory Tests	Evaluated N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
	Glasdegib 100 mg+LDAC				
Anemia	82	1 (1.2)	21 (25.6)	60 (73.2)	0
Lymphocyte count decreased	82	13 (15.9)	25 (30.5)	24 (29.3)	8 (9.8)
Lymphocyte count increased	82	0	11 (13.4)	6 (7.3)	0
Neutrophil count decreased	82	1 (1.2)	3 (3.7)	7 (8.5)	67 (81.7)
Platelet count decreased	82	1 (1.2)	1 (1.2)	10 (12.2)	70 (85.4)
White blood cell decreased	82	3 (3.7)	8 (9.8)	22 (26.8)	39 (47.6)
	LDAC Alone				
Anemia	40	0	11 (27.5)	29 (72.5)	0
Lymphocyte count decreased	40	6 (15.0)	11 (27.5)	9 (22.5)	1 (2.5)
Lymphocyte count increased	40	0	10 (25.0)	3 (7.5)	0
Neutrophil count decreased	40	0	2 (5.0)	5 (12.5)	28 (70.0)
Platelet count decreased	40	1 (2.5)	0	4 (10.0)	35 (87.5)
White blood cell decreased	40	1 (2.5)	6 (15.0)	15 (37.5)	11 (27.5)

Source: Table 14.3.4.1.5.1.3
The data reflect on-study results only.
Severity was graded in accordance with National Cancer Institute CTCAE version 4.03.

Table 75. Abnormal haematology laboratory test findings shifted from grade <=2 to maximum grade 3 or grade 4, sorted in alphabetical order: combination therapy cohort/pools, as-treated patients.

	S1 Cohort Glasdegib + LDAC			S1 Cohort LDAC			S2A Pool Glasdegib + LDAC			S4 Pool Glasdegib + LDAC or 7+3		
		Grades, n (%)			Grades, n (%)			Grades, n (%)			Grades, n (%)	
Haematology Test	**N**	**3**	**4**	**N**	**3**	**4**	**N**	**3**	**4**	**N**	**3**	**4**
Anaemia	82	52 (63.4)	0 (0.0)	40	25 (62.5)	0 (0.0)	87	55 (63.2)	0 (0.0)	184	125 (67.9)	0 (0.0)
Haemoglobin increased	82	0 (0.0)	0 (0.0)	40	0 (0.0)	0 (0.0)	87	0 (0.0)	0 (0.0)	184	1 (0.5)	0 (0.0)
Lymphocyte count decreased	82	21 (25.6)	7 (8.5)	40	8 (20.0)	1 (2.5)	86	20 (23.3)	6 (7.0)	183	67 (36.6)	33 (18.0)
Lymphocyte count increased	82	6 (7.3)	0 (0.0)	40	1 (2.5)	0 (0.0)	86	5 (5.8)	0 (0.0)	183	7 (3.8)	0 (0.0)
Neutrophil count decreased	82	6 (7.3)	14 (17.1)	40	3 (7.5)	8 (20.0)	86	5 (5.8)	17 (19.8)	183	7 (3.8)	53 (29.0)
Platelet count decreased	82	9 (11.0)	26 (31.7)	40	2 (5.0)	8 (20.0)	87	8 (9.2)	28 (32.2)	184	13 (7.1)	67 (36.4)
WBC decreased	82	16 (19.5)	13 (15.9)	40	14 (35.0)	6 (15.0)	87	17 (19.5)	14 (16.1)	184	21 (11.4)	79 (42.9)

Table 76. Abnormal clinical chemistry laboratory test findings shifted from grade <=2 to maximum grade 3 or grade 4, sorted in alphabetical order: combination therapy cohort/pools, as-treated patients.

	S1 Cohort Glasdegib + LDAC			S1 Cohort LDAC			S2A Pool Glasdegib + LDAC			S4 Pool Glasdegib + LDAC or 7+3		
		Grades, n (%)			Grades, n (%)			Grades, n (%)			Grades, n (%)	
Clinical Chemistry Test	**N**	**3**	**4**	**N**	**3**	**4**	**N**	**3**	**4**	**N**	**3**	**4**
ALT increased	80	2 (2.5)	0 (0.0)	40	1 (2.5)	0 (0.0)	84	2 (2.4)	0 (0.0)	180	5 (2.8)	1 (0.6)
Alkaline phosphatase increased	80	0 (0.0)	0 (0.0)	40	1 (2.5)	0 (0.0)	84	0 (0.0)	0 (0.0)	180	1 (0.6)	0 (0.0)
AST increased	80	2 (2.5)	0 (0.0)	40	0 (0.0)	0 (0.0)	84	1 (1.2)	0 (0.0)	180	2 (1.1)	1 (0.6)
Blood bilirubin (total) increased	80	3 (3.8)	0 (0.0)	39	2 (5.1)	0 (0.0)	84	2 (2.4)	0 (0.0)	180	6 (3.3)	0 (0.0)
CPK increased	51	0 (0.0)	0 (0.0)	19	0 (0.0)	0 (0.0)	46	0 (0.0)	0 (0.0)	55	0 (0.0)	0 (0.0)
Creatinine increased	81	3 (3.7)	0 (0.0)	40	2 (5.0)	0 (0.0)	85	3 (3.5)	0 (0.0)	182	3 (1.6)	0 (0.0)
Hypercalcemia	81	0 (0.0)	0 (0.0)	39	0 (0.0)	0 (0.0)	85	0 (0.0)	0 (0.0)	182	0 (0.0)	0 (0.0)
Hyperglycaemia	81	7 (8.6)	0 (0.0)	39	3 (7.7)	0 (0.0)	85	6 (7.1)	0 (0.0)	182	15 (8.2)	0 (0.0)
Hyperkalaemia	81	1 (1.2)	0 (0.0)	40	1 (2.5)	0 (0.0)	85	1 (1.2)	0 (0.0)	182	2 (1.1)	0 (0.0)
Hypermagnesaemia	81	2 (2.5)	0 (0.0)	39	1 (2.6)	0 (0.0)	85	3 (3.5)	0 (0.0)	182	3 (1.6)	0 (0.0)
Hypernatremia	81	0 (0.0)	1 (1.2)	39	0 (0.0)	0 (0.0)	85	0 (0.0)	1 (1.2)	182	0 (0.0)	1 (0.5)
Hypoalbuminemia	80	3 (3.8)	0 (0.0)	40	1 (2.5)	0 (0.0)	84	3 (3.6)	0 (0.0)	180	8 (4.4)	0 (0.0)
Hypocalcaemia	81	0 (0.0)	0 (0.0)	39	1 (2.6)	0 (0.0)	85	0 (0.0)	0 (0.0)	182	3 (1.6)	2 (1.1)
Hypoglycaemia	81	1 (1.2)	0 (0.0)	39	0 (0.0)	0 (0.0)	85	1 (1.2)	0 (0.0)	182	1 (0.5)	0 (0.0)
Hypokalaemia	81	1 (1.2)	0 (0.0)	40	1 (2.5)	0 (0.0)	85	1 (1.2)	0 (0.0)	182	8 (4.4)	0 (0.0)
Hypomagnesemia	81	1 (1.2)	0 (0.0)	39	1 (2.6)	0 (0.0)	85	0 (0.0)	0 (0.0)	182	1 (0.5)	0 (0.0)
Hyponatremia	81	6 (7.4)	1 (1.2)	39	3 (7.7)	0 (0.0)	85	7 (8.2)	1 (1.2)	182	16 (8.8)	2 (1.1)
Hypophosphatemia	80	7 (8.8)	1 (1.3)	39	4 (10.3)	1 (2.6)	84	7 (8.3)	1 (1.2)	180	19 (10.6)	1 (0.6)

No patients in the S4 cohort met the criteria for confirmed Hy's Law cases.

Safety in special populations

Table 77. Adverse events by age group.

MedDRA Terms	Age <65 N=2	Age 65-74 N=32	Age 75-84 N=44	Age 85+ N=6
Total AEs	2 (100.0)	26 (81.3)	36 (81.8)	4 (66.7)
Serious AEs – Total	1 (50.0)	12 (37.5)	13 (29.5)	1 (16.7)
Fatal	0 (0.0)	1 (3.1)	1 (2.3)	0 (0.0)
Hospitalization/prolong existing hospitalization	1 (50.0)	12 (37.5)	12 (27.3)	1 (16.7)
Life-threatening	1 (50.0)	1 (3.1)	0 (0.0)	0 (0.0)
Disability/incapacity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other (medically significant)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to drop-out	0 (0.0)	4 (12.5)	5 (11.4)	0 (0.0)
Psychiatric disorders	0 (0.0)	1 (3.1)	4 (9.1)	0 (0.0)
Nervous system disorders	1 (50.0)	11 (34.4)	15 (34.1)	2 (33.3)
Accidents and injuries	1 (50.0)	1 (3.1)	2 (4.5)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (3.1)	2 (4.5)	0 (0.0)
Vascular disorders	1 (50.0)	2 (6.3)	3 (6.8)	0 (0.0)
Cerebrovascular disorders	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	1 (50.0)	6 (18.8)	10 (22.7)	1 (16.7)
Anticholinergic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	1 (50.0)	5 (15.6)	6 (13.6)	1 (16.7)
Other PTs appearing more frequently in older patients				
Asthenia	0 (0.0)	2 (6.3)	2 (4.5)	0 (0.0)
Constipation	1 (50.0)	2 (6.3)	6 (13.6)	1 (16.7)
Decreased appetite	0 (0.0)	6 (18.8)	15 (34.1)	0 (0.0)
Dizziness	0 (0.0)	2 (6.3)	3 (6.8)	1 (16.7)
Dysgeusia	1 (50.0)	6 (18.8)	10 (22.7)	2 (33.3)
Dyspnea	1 (50.0)	3 (9.4)	6 (13.6)	0 (0.0)
Neutropenia	1 (50.0)	1 (3.1)	7 (15.9)	0 (0.0)
Oedema	0 (0.0)	1 (3.1)	1 (2.3)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	3 (6.8)	1 (16.7)
Rash	0 (0.0)	0 (0.0)	5 (11.4)	0 (0.0)
Weight decreased	1 (50.0)	1 (3.1)	9 (20.5)	1 (16.7)

Numbers displayed are the incidences of reported PTs based on the following searches:
Psychiatric disorders: All PTs in MedDRA SOC Psychiatric disorders
Nervous system disorders: All PTs in MedDRA SOC Psychiatric disorders
Accidents and injuries: All PTs in the Injury, poisoning and procedural complications SOC
Cardiac disorders: All PTs in MedDRA SOC Cardiac disorders
Vascular disorders: All PTs in MedDRA SOC Vascular disorders
Cerebrovascular disorders: PT=Haemorrhage intracranial
Infections and infestations: All PTs in MedDRA SOC Infections and infestations
Anticholinergic syndrome: PT=Anticholinergic syndrome
Quality of life decreased: PT= Quality of life decreased
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures: PTs of Hypotension, Fall, Syncope, Dizziness, Ataxia, Fracture.

Immunological events

No data submitted.

Safety related to drug-drug interactions and other interactions

For interactions related to DDI between glasdegib and other drugs please refer to section 2.4.2. For interactions related to the indicated co-administration of glasdegib with LDAC please refer to sections above.

Discontinuation due to adverse events

- Treatment-related permanent treatment discontinuations

Table 78. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTCAE Grade (Treatment Related, All Cycles, Permanent Discontinuations Due to Adverse Events) - Cohort S1AM.

glasdegib 100MG + LDAC

(N=84)

		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Gr 3-4		Gr 3-5		Total	
System Organ Class	Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs		1	(1.2)	3	(3.6)	4	(4.8)	1	(1.2)	0	(0.0)	0	(0.0)	5	(6.0)	5	(6.0)	9	(10.7)
Blood and lymphatic system disorders		0	(0.0)	0	(0.0)	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	2	(2.4)
	- Febrile neutropenia	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Lymphadenitis	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Gastrointestinal disorders		1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)
	- Nausea	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)
	- Vomiting	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Investigations		0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	2	(2.4)
	- Blood creatinine increased	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Electrocardiogram QT prolonged	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
General disorders and administration site conditions		0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Fatigue	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Infections and infestations		0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Sepsis	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Musculoskeletal and connective tissue disorders		0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Muscular weakness	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Nervous system disorders		0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Dysgeusia	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Skin and subcutaneous tissue disorders		0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Skin toxicity	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)

LDAC Alone

(N=41)

		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Gr 3-4		Gr 3-5		Total	
System Organ Class	Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs		0	(0.0)	0	(0.0)	1	(2.4)	2	(4.9)	0	(0.0)	0	(0.0)	3	(7.3)	3	(7.3)	3	(7.3)
Blood and lymphatic system disorders		0	(0.0)	0	(0.0)	1	(2.4)	2	(4.9)	0	(0.0)	0	(0.0)	3	(7.3)	3	(7.3)	3	(7.3)
	- Febrile neutropenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	1	(2.4)	1	(2.4)	1	(2.4)
	- Granulocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	1	(2.4)	1	(2.4)	1	(2.4)
	- Pancytopenia	0	(0.0)	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)	1	(2.4)	1	(2.4)

- Temporary Discontinuations due to AEs

Table 79. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTCAE Grade (Treatment Related, All Cycles, Temporary Discontinuations Due to Adverse Events) - Cohort S1AM.

glasdegib 100MG + LDAC

(N=84)

System Organ Class	Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Gr 3-4		Gr 3-5		Total	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs		0	(0.0)	2	(2.4)	19	(22.6)	10	(11.9)	0	(0.0)	0	(0.0)	29	(34.5)	29	(34.5)	31	(36.9)
Blood and lymphatic system disorders		1	(1.2)	0	(0.0)	8	(9.5)	4	(4.8)	0	(0.0)	0	(0.0)	12	(14.3)	12	(14.3)	13	(15.5)
	- Febrile neutropenia	0	(0.0)	0	(0.0)	5	(6.0)	2	(2.4)	0	(0.0)	0	(0.0)	7	(8.3)	7	(8.3)	7	(8.3)
	- Anaemia	0	(0.0)	1	(1.2)	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	3	(3.6)
	- Thrombocytopenia	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	2	(2.4)
	- Leukocytosis	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Neutropenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Pancytopenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
General disorders and administration site conditions		0	(0.0)	2	(2.4)	6	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	6	(7.1)	6	(7.1)	8	(9.5)
	- Fatigue	0	(0.0)	0	(0.0)	4	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	4	(4.8)	4	(4.8)	4	(4.8)
	- Pyrexia	0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	2	(2.4)
	- Chest pain	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Mucosal inflammation	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Performance status decreased	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Infections and infestations		0	(0.0)	2	(2.4)	4	(4.8)	1	(1.2)	0	(0.0)	0	(0.0)	5	(6.0)	5	(6.0)	7	(8.3)
	- Pneumonia	0	(0.0)	0	(0.0)	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	2	(2.4)
	- Clostridium difficile colitis	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Device related infection	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Infections and infestations	- Influenza	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Perineal abscess	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Sepsis	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Investigations		0	(0.0)	2	(2.4)	2	(2.4)	3	(3.6)	0	(0.0)	0	(0.0)	5	(6.0)	5	(6.0)	7	(8.3)
	- Electrocardiogram QT prolonged	0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	2	(2.4)
	- Neutrophil count decreased	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	2	(2.4)
	- Alanine aminotransferase increased	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Eastern Cooperative Oncology Group performance status worsened	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- White blood cell count decreased	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Gastrointestinal disorders		0	(0.0)	1	(1.2)	4	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	4	(4.8)	4	(4.8)	5	(6.0)
	- Abdominal pain	0	(0.0)	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)
	- Nausea	0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	2	(2.4)
	- Colitis	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Gastrointestinal haemorrhage	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Gastrooesophageal reflux disease	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Haematemesis	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Gastrointestinal disorders	- Vomiting	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Musculoskeletal and connective tissue disorders		0	(0.0)	2	(2.4)	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	4	(4.8)
	- Muscle spasms	0	(0.0)	2	(2.4)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	3	(3.6)
	- Myalgia	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Renal and urinary disorders		0	(0.0)	0	(0.0)	3	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.6)	3	(3.6)	3	(3.6)
	- Acute kidney injury	0	(0.0)	0	(0.0)	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	2	(2.4)
	- Renal failure	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Cardiac disorders		0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	2	(2.4)
	- Atrial fibrillation	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Ventricular fibrillation	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Metabolism and nutrition disorders		0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	2	(2.4)
	- Hyperuricaemia	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Hyponatraemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Nervous system disorders		0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	2	(2.4)
	- Haemorrhage intracranial	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)

glasdegib 100MG + LDAC

(N=84)

System Organ Class	Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Gr 3-4		Gr 3-5		Total	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	- Peripheral sensorimotor neuropathy	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Presyncope	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Ear and labyrinth disorders		0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- External ear inflammation	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Hepatobiliary disorders		0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Hepatobiliary disease	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Respiratory, thoracic and mediastinal disorders		0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Dyspnoea	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)

LDAC Alone

(N=41)

System Organ Class	Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Gr 3-4		Gr 3-5		Total	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs		0	(0.0)	1	(2.4)	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	1	(2.4)	1	(2.4)	2	(4.9)
Blood and lymphatic system disorders		0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	1	(2.4)	1	(2.4)	1	(2.4)
	- Neutropenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	1	(2.4)	1	(2.4)	1	(2.4)
Infections and infestations		0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)
	- Bronchitis	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.4)

- Dose Reductions due to AEs

Table 80. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTCAE Grade (Treatment Related, All Cycles, Dose Reductions Due to Adverse Events) - Cohort S1AM.

glasdegib 100MG + LDAC

(N=84)

System Organ Class	Preferred Term	Grade 1 n	Grade 1 (%)	Grade 2 n	Grade 2 (%)	Grade 3 n	Grade 3 (%)	Grade 4 n	Grade 4 (%)	Grade 5 n	Grade 5 (%)	Missing or Unknown n	Missing or Unknown (%)	Gr 3-4 n	Gr 3-4 (%)	Gr 3-5 n	Gr 3-5 (%)	Total n	Total (%)
Any AEs		1	(1.2)	4	(4.8)	11	(13.1)	5	(6.0)	0	(0.0)	0	(0.0)	16	(19.0)	16	(19.0)	21	(25.0)
Investigations		1	(1.2)	2	(2.4)	3	(3.6)	1	(1.2)	0	(0.0)	0	(0.0)	4	(4.8)	4	(4.8)	7	(8.3)
	- Electrocardiogram QT prolonged	0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	2	(2.4)
	- Alanine aminotransferase increased	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Blood creatinine increased	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Neutrophil count decreased	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Platelet count decreased	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- White blood cell count decreased	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Blood and lymphatic system disorders		0	(0.0)	1	(1.2)	2	(2.4)	2	(2.4)	0	(0.0)	0	(0.0)	4	(4.8)	4	(4.8)	5	(6.0)
	- Anaemia	0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	2	(2.4)
	- Febrile neutropenia	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	2	(2.4)
	- Pancytopenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
General disorders and administration site conditions		0	(0.0)	0	(0.0)	4	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)	4	(4.8)	4	(4.8)	4	(4.8)
	- Fatigue	0	(0.0)	0	(0.0)	3	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.6)	3	(3.6)	3	(3.6)
General disorders and administration site conditions	- Pyrexia	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Musculoskeletal and connective tissue disorders		0	(0.0)	1	(1.2)	3	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.6)	3	(3.6)	4	(4.8)
	- Muscle spasms	0	(0.0)	1	(1.2)	3	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.6)	3	(3.6)	4	(4.8)
Metabolism and nutrition disorders		0	(0.0)	0	(0.0)	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)	2	(2.4)	2	(2.4)
	- Cachexia	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Hyponatraemia	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Cardiac disorders		0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
	- Cardiac failure	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Gastrointestinal disorders		1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Constipation	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Nausea	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Hepatobiliary disorders		0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Hepatobiliary disease	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
Nervous system disorders		0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Nervous system disorders	- Haemorrhage intracranial	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	1	(1.2)	1	(1.2)
Skin and subcutaneous tissue disorders		0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)
	- Dermatitis exfoliative	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)

Higher proportions of discontinuation due to treatment-related AEs, in the glasdegib 100 mg + LDAC and LDAC alone arms were observed.

Post marketing experience

None available.

2.6.1. Discussion on clinical safety

A total of 101 patients (AML + MDS) were treated with the combination glasdegib 100 mg + LDAC. Among these 101 patients, 89 were AML patients (75 treated in part 2 and 14 in part 1b) and 12 were MDS patients (9 treated in part 2 and 3 in part 1b). The safety profile assessment of glasdegib 100 mg + LDAC in this report has been focused on the randomized Phase 2 portion of Study B1371003 (S1 cohort).

The median treatment duration was 1.8-fold longer in the glasdegib + LDAC arm than in the LDAC alone arm (83.0 vs. 47.0 days). The median treatment exposure time of glasdegib was 75.5 days with a large range of exposure time: 3 to 954 days.

Percentage of patients with treatment-related TEAEs was 1.4-fold higher (81.0 vs. 58.5%) in combination compared to LDAC alone arm. Although the number of patients was 2-fold higher in glasdegib + LDAC arm than in LDAC alone arm, 6.3-fold higher number of TEAEs have been observed in the combination arm (n=521 vs. 83). 85% of TEAEs were glasdegib-related. This overview of treatment-related treatment-emergent AEs logically showed that glasdegib 100 mg + LDAC led to a higher toxicity compared to a treatment of LDAC alone.

Overall TRAEs reported in >=10% patients in any pool (S1 cohort, S2A and S4 Pool) have shown that hematologic disorders were the most frequent TRAEs reported in both arms. All grades included, higher proportions of patients presented with febrile neutropenia (14.3 vs. 7.3%), anaemia (31 vs. 14.6%), thrombocytopenia (23.8 vs. 12.2%), white blood count decreased (11.9 vs. 2.4%) in combination arm compared to LDAC alone arm. Gastrointestinal disorders and general disorders were also observed in higher proportion in combination arm: nausea (28.6 vs. 2.4%), diarrhoea (16.7 vs. 2.4%), constipation (11.9 vs. 7.3%), abdominal pain (6 vs. 2.4%), fatigue (22.6 vs. 9.8%), oedema peripheral (7.1 vs. 2.4%). Higher decreased appetite (25 vs. 4.9%) and dyspnoea (11.9 vs. 2.4%) were observed in the combination arm. Some TRAEs were observed only in combination arm (22.6% dysgeusia, 20.2% muscle spasms, 14.3% weight decreased, 10.7% alopecia, 2.4% ALAT increased).

Globally, higher proportions of patients with grade 3 (23.8 vs. 7.3%) and grade 4 (40.5 vs. 24.4%) TRAEs were reported in combination arm compared to LDAC alone arm. The Applicant was requested to further discuss the higher occurrence of these grade 3/4 events in the combination arm. It is acknowledged that these data could be due to a longer median duration of study treatment in the glasdegib + LDAC arm and may due to mean cumulative dose at time of onset. All treatment-related AEs (including febrile neutropenia, anaemia, thrombocytopenia, neutropenia) have been thus mentioned in Table 6 of the SmPC section 4.8 as requested. A cumulative toxicity due to cumulative dose could not be excluded.

Serious TRAEs were reported in 32.1% patients in glasdegib + LDAC arm compared to 12.2 % patients in LDAC alone arm. In LDAC alone arm, serious TRAEs were reported in two different SOC: 9.8 % in blood and lymphatic system disorders including 4.9% febrile neutropenia; 4.9% of infections and infestations including 2.4% pneumonia and 2.4% sepsis. In combination arm, serious TRAEs were reported in several SOC: blood and lymphatic system disorders (16.7%) including febrile neutropenia (11.9%), anaemia (4.8%); infections and infestations (11.9%) including pneumonia (4.8) and sepsis (2.4%); gastrointestinal disorders (6%) including gastrointestinal haemorrhage (1.2%); general disorders and administration site conditions (3.6%) including fatigue (2.4%); musculoskeletal and connective tissue disorders (3.6%) including muscle spasms (1.2%), muscular weakness (1.2%), myalgia (1.2%); nervous system disorders (3.6%) including haemorrhage intracranial (1.2%); cardiac disorders (2.4%) including cardiac failure (1.2%) and ventricular fibrillation (1.2%). These results showed some of the off target pharmacodynamic effects of glasdegib. One

Grade 5 serious TRAEs was reported in each arm: 1 pneumonia in combination arm and 1 sepsis in LDAC alone arm.

The main cause of deaths was disease under study in both arms. Fewer number of deaths have been described in combination arm compared to LDAC alone arm in the both periods: ≤ 28 days after the last dose (23.8 vs. 36.6%) and > 28 days after the last dose (39.3 vs. 46.3%). The Applicant reported no deaths due to the study treatment. There were 2 Grade 5 AEs that were treatment-related per investigator and reported within 28 days post-dose (1 pneumonia in the combination arm and 1 sepsis in LDAC alone arm).

Among the deaths derived from the Case Report Form, pneumonia seems to occur more frequently in the glasdegib arm (5 out of 13 patients vs 2 out of 12). Based on the available data, pneumonia could not be excluded as related to the treatment, and this AE has been included in the SmPC section 4.8.

Thirty (30 [35.7%]) and 19 (46.3%) patients permanently discontinued study treatments due to AEs in the glasdegib 100 mg + LDAC and LDAC alone arms, respectively. The most common AEs leading to discontinuation were febrile neutropenia, pneumonia and nausea which are common AEs in AML patients due to the disease itself and to chemotherapy treatment (LDAC), although cytopenias including febrile neutropenias were more frequently observed in the glasdegib + LDAC arm. Nine (10.7%) and 3 (7.3%) patients discontinued study treatment due to treatment-related AEs in the glasdegib 100 mg + LDAC and LDAC alone arms, respectively. Although 1 SOC was imputed in the LDAC alone arm (all 3 patients discontinued treatment due to blood and lymphatic system disorders; 2 grade 4 and 1 grade 3), several SOCs were imputed in combination arm. Indeed, among the 9 patients, permanent discontinuations were reported with the following events: 1 grade 4 sepsis, 3 grade 3 ADRs (1 febrile neutropenia, 1 lymphadenitis, 1 QT prolongation, 1 muscular weakness, 1 skin toxicity) and also grade 1/2 ADRs (3 gastrointestinal disorders, 1 blood creatinine increased, 1 fatigue, 1 dysgeusia). In the same way, higher proportions of patients [31 (36.9%) vs. 2 (4.9%)] were reported to have treatment-related AEs that led to temporary discontinuations of study treatments in combination arm and LDAC alone arm respectively. In the combination arm, the same variability of SOCs were imputed. Finally, 21 [25.0%] patients were reported to have treatment-related AEs that led to dose reductions of study treatments in combination arm with 19% of grade 3/4 events. None were reported in LDAC alone arm. Unresolved events have been observed after permanent or temporary treatment discontinuations and dose reductions of glasdegib. Reasonable explanations for unresolved adverse events have been provided by the Applicant.

The following special safety topics have been discussed in detail by the Applicant: QT interval prolongation, renal toxicity, cytopenic events, musculoskeletal events, neurological events, skin and other dermal conditions, reproductive and development toxicities.

According to the ICH E14 recommendation, the thorough QT B1371023 study is positive and an effect on the corrected QTinterval has been demonstrated at the therapeutic and supra-therapeutic doses. This result of this study has been mentioned in section 5.1 of the SmPC. In the B1371003 study, 6 patients (7.1%) in combination arm versus none in LDAC arm reported increased QT interval. Four out of 6 were grade 3/4 ADRs. QT prolonged has been mentioned in the section 4.8 of the SmPC. Management of ECG QT prolongation has been proposed in sections 4.2, 4.4 and 4.8 which is acceptable.

Five (5) renal events related to treatment have been reported in glasdegib + LDAC arm and none in LDAC alone arm in patients with medical history of renal function abnormality. This suggests that glasdegib could worsen renal impairment. Renal toxicity is currently listed in the Risk Management Plan as an important potential risk which is acceptable. Warnings and recommendations for patients with medical history of renal impairment have been added in section 4.4 of the SmPC.

Concerning cytopenic events, the rate of TRAEs was slightly higher in combination arm (25%) compared to LDAC alone arm (22%) in S1 cohort for all grades. However, higher proportions of patients with grade 3/4 (14.3 vs. 2.4%) were reported in combination arm and none in LDAC alone arm. Anaemia, febrile neutropenia, thrombocytopenia, neutropenia have been added in the adverse reaction table in the SmPC section 4.8.

One event of gastrointestinal haemorrhage (Grade 3) and one event haemorrhage intracranial (grade 4) have been observed in glasdegib + LDAC arm. The transfusion-dependent history of the patient who developed the Haemorrhage intracranial could explain this outcome. The gastrointestinal haemorrhage was not further explained. The haematology laboratory test abnormalities were generally similar in the 2 arms. Haemorrhages were reported as treatment-related in B1371003 study and have thus been reported in section 4.8 of the SmPC.

20.2% of muscle spasms, 22.6% dysgeusia and 10.7% alopecia were reported as TRAEs in glasdegib + LDAC arm. These AEs are known class effects of SMO inhibitors. None of these AEs has been reported in LDAC alone arm. Also, 6% of rash (including 1 grade 3) were reported as TRAE in the glasdegib + LDAC arm, and none in LDAC alone arm. Dose modifications and warnings for Muscle-related adverse events have been proposed in SmPC sections 4.2 4.4 and 4.7.

The Applicant submitted data of the S2A Pool (including AML patients in part 1b and part 2 unfit). Proportions of TRAEs, TR SAEs, grade 3/4 TRAEs, doses reduction due to TRAEs, temporary discontinuations due to TRAEs were high and similar between S1 cohort and S2A pool which confirmed the higher toxicity of glasdegib + LDAC in AML patients.

Otherwise, higher proportions of patients with TRAES in combination arm (89.2%) compared to LDAC alone arm (58.5%) was also observed in S4 pool, showing a higher risk of glasdegib also with 7+3 therapy.

Except 1 grade 3 mucosal inflammation and 4 grade 3 lipase increased, these safety data from the monotherapy studies did not show TRAE (with higher severity than grade 3) which was not identified in B1371003 pivotal study. These monotherapy data should be interpreted with cautiun due to the different design of the studies, the different population targeted, the different doses of glasdegib used.

Increased ASAT/ALAT have been observed in glasdegib monotherapy studies. The currently proposed SmPC recommends in Section 4.2 Posology and method of administration (Assessment and monitoring of laboratory abnormalities) that hepatic function be assessed prior to the initiation of glasdegib and at least once weekly for the first month and dose modification in presence of non-haematological toxicity, and this recommendation is considered adequate.

Given that the risk of embryo-foetal toxicity is very limited since the intended population is at a low risk of pregnancy as compared to the approved indication population for the other SMO inhibitors, no pregnancies have been reported, the SmPC has a boxed warning in section 4.4 for the risk of reproductive and developmental toxicity with a cross-reference to section 4.6, according to guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labeling (EMEA/CHMP/203927/2005), the recommendation level proposed by the Applicant "should not be used" is acceptable, and a Pregnancy Prevention Program is considered not necessary. The duration of contraception (30 days = 5 half-lives) post last dose of glasdegib is acceptable. Concerning breast-feeding, there is no argument in particular on bioavailability in favour of a conservative approach imposing a delay of 25 additional days. Therefore, a delay of one week after the last dose is appropriate. The risk minimisation measure in a form of the patient alert card has also been agreed.

Due to the mechanism of action of glasdegib, incidence of treatment-emergent anti-drug antibodies has not been assessed which is acceptable

Long-term safety data are not available in this application. With only 4 patients, all in the glasdegib + LDAC arm, remaining on treatment as of 03 January 2017, additional data collected afterwards have not been provided as they would not be expected to significantly change the efficacy results already observed. Updated data on 14 patients in the glasdegib + LDAC arm treated for >1 year have been provided. No new safety data of clinical concern have been noted. The CHMP considers that submitted information is acceptable.

Since one phase 1b/2 has been submitted to support the MAA, CHMP raised a concern that the relatively low number of AML patients precluded a comprehensive safety assessment. Therefore, the Applicant was requested to justify in detail, how the requirements for a marketing authorisation could be fulfilled. The concern was that despite convincing efficacy results, there could be a risk for more rare and unforeseeable adverse events with the combination of glasdegib and LDAC. The Applicant provided additional data from the additional patients in the glasdegib development program, which did not identify new safety concerns in unfit AML patients. Stomatitis, pyrexia, oedema peripheral, sepsis, urinary tract infection and atrial fibrillation were added to the SmPC section 4.8.

2.6.2. Conclusions on the clinical safety

The safety profile assessment of glasdegib 100 mg + LDAC in this report has been focused on the randomized Phase 2 portion of Study B1371003 (S1 cohort including 75 AML patients and 9 MDS patients).

The safety profile of glasdegib 100 mg PO once daily in combination with LDAC is characterised by a pattern of toxicities typically observed in AML patients treated with chemotherapy and toxicities associated with SMO inhibitor therapy. Generally, the toxicity seems reasonably well manageable as well as acceptable in these poor prognosis, elderly, unfit AML population, given the current treatment options.

2.7. Risk Management Plan

Safety concerns

Table 81. Summary of safety concerns.

Summary of safety concerns	
Important identified risks	None
Important potential risks	Reproductive and Developmental Toxicity
	Renal Toxicity
Missing information	None

Pharmacovigilance plan

Table 82. On-going and planned additional pharmacovigilance activities.

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A	N/A	N/A	N/A	N/A

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities				
N/A	N/A	N/A	N/A	N/A

Risk minimisation measures

Table 83. Risk minimisation measures.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Reproductive and Developmental Toxicity	Routine risk minimisation measures: SmPC Sections 4.4 (boxed warning), 4.6, 5.1, and 5.3; PL Sections 2 and 4 Additional risk minimisation measures: Patient Alert Card for male patients.	Routine pharmacovigilance activities beyond AR reporting and signal detection: None proposed Additional pharmacovigilance activities: None proposed
Renal Toxicity	Routine risk minimisation measures: SmPC Sections 4.2 and 5.3 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None proposed Additional pharmacovigilance activities: None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version V.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21 November 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of glasdegib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers glasdegib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union Product information.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Daurismo (glasdegib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Glasdegib is indicated in combination with LDAC chemotherapy for the treatment of newly diagnosed *de novo* or secondary AML in adult patients who are not candidates for standard induction chemotherapy.

AML is a cancer of the haematopoietic system characterized by increased proliferation of bone marrow and peripheral blasts, pancytopenias causing infections and bleeding, and reduced survival. Given that the majority of patients are older and unable to tolerate intensive chemotherapy, the treatment intention pursued with less intensive therapies such as LDAC, azacitidine, or decitabine, is to prolong the overall survival.

3.1.2. Available therapies and unmet medical need

In patients who care not candidates for standard induction chemotherapy, less toxic non-intensive therapies as LDAC, azacitidine or decitabine may prolong OS versus best supportive care, but there are fewer complete remissions and shorter OS than with intensive chemotherapy, with little chance for cure compared to more intensive chemotherapies such as induction chemotherapy with cytarabine (7 days) plus daunorubicin (3 days) (7+3). Thus, there is a need to improve treatment outcomes in patients who cannot receive intensive chemotherapy.

3.1.3. Main clinical studies

The application is mainly based on Study B1371003, a multi-centre, open-label phase 1b/2 study to evaluate the safety and efficacy of glasdegib when administered in combination with first-line treatment regimens for AML and high-risk MDS. The efficacy of glasdegib + LDAC was investigated in the study's phase 2 part compared to LDAC alone in patients who were not candidates for standard induction chemotherapy (unfit population), more than 95% were 65 years of age or older.

3.2. Favourable effects

The difference in OS (primary endpoint) was statistically significant (8.8 versus 4.9 months median; HR = 0.51, p = 0.0004) between glasdegib + LDAC *vs* LDAC. The data were considered mature, with 109 of 132 (82.6%) of observed events in AML + MDS patients having by the efficacy data cut-off date, and with a median follow-up time >20 months for each treatment arm.

The statistically significant improvement of OS has been confirmed in the subgroup of patients with AML (8.3 versus 4.3 months median; HR = 0.46; p = 0.0002). The number of patients in the MDS arm is very small; efficacy data for MDS could not be assessed.

Patients with good/intermediate cytogenetic risk in the glasdegib 100 mg + LDAC arm had statistically significant improvement in OS as compared to those with good/intermediate cytogenetic risk in the LDAC alone arm (12.2 versus 4.8 months median; HR = 0.43; p = 0.0008) in the AML + MS population. A significant OS improvement is confirmed in the subgroup of patients with AML (11.1 versus 4.4 months median; HR = 0.42; p = 0.001).

In the AML population, subgroup analyses showed improvement in OS in patients with *de novo* disease (6.6 versus 4.3 months median; HR = 0.67; p = 0.099), secondary disease (9.1 versus 4.1 months median; HR = 0.29; p <0.0001) and poor cytogenetic risk (4.1 versus 3.1 months median; HR = 0.53; p = 0.027).

In the AML + MDS population, significantly higher complete remission rates have been observed in the combination arm: 17% vs. 2.3%; p = 0.01. This result was confirmed in AML patients: 17.9% vs. 2.6%; p = 0.02.

3.3. The SmPC section 4.2 recommends that glasdegib should be continued as long as the patient is deriving clinical benefit. Uncertainties and limitations about favourable effects

It is a limitation of study B1371003 that reliable conclusions could not be drawn from an OS analysis between patients older and younger than 65 years of age, due to the very small numbers of patients <65 years old enrolled in this study and this is reflected in the SmPC section 5.2.

Considering the unmet medical need in these patients and the improvement in OS with an oral chemotherapy, an improvement on quality of life was acknowledged.

3.4. Unfavourable effects

The median treatment duration was 1.8-fold longer in the glasdegib + LDAC arm than in the LDAC alone arm (83.0 vs. 47.0 days).

The percentage of patients with treatment-related TEAEs was 1.4-fold higher (81.0 vs. 58.5%) in combination compared to LDAC alone arm. Although the number of patients was 2-fold higher in glasdegib + LDAC arm than in LDAC alone arm, 6.3-fold higher of TEAEs have been observed in the combination arm (n=521 vs. 83). 85% of TEAEs were glasdegib-related. This overview of treatment-related treatment-emergent AEs showed that glasdegib 100 mg + LDAC led to a higher toxicity compared to a treatment of LDAC alone.

Hematologic disorders were the most frequent TRAEs reported in both arms. All grades included, higher proportions of patients with febrile neutropenia (14.3 vs. 7.3%), anaemia (31 vs. 14.6%), thrombocytopenia (23.8 vs. 12.2%), white blood count decreased 11.9 vs. 2.4%) were observed in combination arm compared to LDAC alone arm.

Gastrointestinal disorders and general disorders were also observed in higher proportion in combination arm: nausea (28.6 vs. 2.4%), diarrhoea (16.7 vs. 2.4%), constipation (11.9 vs. 7.3%), abdominal pain (6 vs. 2.4%), fatigue (22.6 vs. 9.8%) and oedema peripheral (7.1 vs. 2.4%). Higher decreased appetite (25 vs. 4.9%) and dyspnoea (11.9 vs. 2.4%) were observed in the combination arm. Some TRAEs were observed only in combination arm (22.6% dysgeusia, 20.2% muscle spasms, 14.3% weight decreased, 10.7% alopecia, 2.4% ALAT increased).

Globally, higher proportions of patients presented with grade 3 (23.8 vs. 7.3%) and grade 4 (40.5 vs. 24.4%) in combination arm compared to LDAC alone arm.

Serious TRAEs were reported in 32.1% patients in glasdegib + LDAC arm compared to 12.2% patients in LDAC alone arm. Although, serious TRAES were reported in only two different SOCs in LDAC alone arm: blood and lymphatic system disorders and infections. Many SOC were implicated in the toxicity of glasdegib + LDAC compared to LDAC alone arm which showed multi-organ toxicities of the combination.

The following special safety topics have been identified by the Applicant: QT interval prolongation, renal toxicity, cytopenic events, musculoskeletal events, neurological events, skin and other dermal conditions which are known effect of SMO inhibitors. Especially, 20.2% of Muscle spasms, 22.6% dysgeusia and 10.7% alopecia were reported as TRAEs in glasdegib + LDAC arm. None of these AEs has been reported in LDAC alone arm. Also, 6% of rash (including 1 grade 3) were reported as TRAEs in the glasdegib + LDAC arm, and none in LDAC alone arm.

Nine (9; 10.7%) and 3; 7.3%) patients discontinued due to treatment-related AEs, in the glasdegib 100 mg + LDAC and LDAC alone arms respectively. In the same way, higher proportions of patients were reported [31 (36.9%) vs. 2 (4.9%)] to have treatment-related AEs that led to temporary discontinuations of study treatments in combination arm and LDAC alone arm respectively. Finally, 21 (25.0%) patients were reported to have treatment-related AEs that led to dose reductions of study treatments in combination arm with 19% of grade 3/4 events. None were reported in LDAC alone arm.

The main cause of deaths was disease under study in both arms. Lesser number of deaths have been described in combination arm compared to LDAC alone arm in the both periods: ≤ 28 days after the last dose (23.8 vs. 36.6%) and > 28 days after the last dose (39.3 vs. 46.3%).

Finally, considering the high number of AML patient in the B1371003 study, the safety profile of glasdegib in AML patient could be considered consistent with the safety profile assessed in the overall population (AML+MDS).

3.5. Uncertainties and limitations about unfavourable effects

Five Renal events related to treatment have been reported in glasdegib + LDAC arm and none in LDAC alone arm in patients with medical history of renal function abnormality. This suggests that glasdegib could worsen renal impairment. Renal toxicity is currently listed in the Risk Management Plan as an important potential risk which is acceptable. Warnings and recommendations for patients with history of renal impairment are in section 4.4 of the SmPC.

One event of gastrointestinal haemorrhage (Grade 3) and one event intracranial haemorrhage (grade 4) have been observed in glasdegib + LDAC arm. The transfusion-dependent history of the patient who developed the intracranial haemorrhage could explain this outcome. The gastrointestinal haemorrhage was not further explained and is included among haemorrhages that are reflected in the SmPC.

Among the deaths derived from the Case Report Form, pneumonia seems to occur more frequently in the glasdegib arm (5 out of 13 patients vs 2 out of 12). Based on the available data, pneumonia cannot be excluded to be related to treatment, this AE has been included in Table 4 of the SmPC.

3.6. Effects Table

Table 84. Effects Table for glasdegib (Daurismo) in combination with low-dose cytarabine, for the treatment of newly diagnosed *de novo* or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy (data cut-off: 3 January 2017).

Effect	Short Description	Unit	Glasdegib + LDAC (N=78)	LDAC (N=38)	Uncertainties/ Strength of evidence	References
Favourable Effects						
OS	Overall survival	median (months) [95% confidence interval]	8.3 [4.7-12.2]	4.3 [1.9-5.7]		B11371003, phase 2, AML patients
CR	Proportion of complete remission	% [95% confidence interval]	17.9 [9.4-26.5]	2.6 [0-7.7]		B11371003 study, phase 2, AML patients
Unfavourable Effects (based on randomized phase 2 portion of study B1371003, S1 cohort including 75 AML patients and 9 MDS patients)						
Grade 3-4 TRAEs	Proportion of patients with serious TRAE	%	62.2	31.7		
QT interval prolongation	Proportion of patients with treatment-related adverse events	%	7.1	0		
Renal Toxicity	Proportion of patients with treatment-related adverse events	%	6	0		
Cytopenic events	Number of patients with		22	25		
Pneumonia	Proportion of patients with treatment-related serious adverse event	%	4.8	2.4		
Febrile neutropenia	Proportion of patients with treatment-related serious adverse event	%	11.9	4.9		
Muscle events	Proportion of patients with treatment-related adverse event	%	20.2	0		
Neurological events	Proportion of patients with treatment-related adverse event	%	22.6	0		
Skin and other dermal conditions	Proportion of patients with treatment-related adverse event	%	29.8	7.3		

Effect	Short Description	Unit	Glasdegib + LDAC (N=78)	LDAC (N=38)	Uncertainties/ Strength of evidence	References
Deaths	Proportion of patients with reported death	%	76	92		

Abbreviations: OS, overall survival; CR, complete remission; TRAE: treatment-related treatment-emergent adverse events.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Newly-diagnosed AML in patients who are not candidates for standard induction chemotherapy, represents a difficult clinical situation to conduct clinical trials due to a poor prognosis, short overall survival and co-morbidity. The phase 2, randomised Study B1371003 is a valid clinical trial to introduce a novel anti-leukaemic agent in combination with standard chemotherapy, in this case low-dose cytarabine (LDAC). The demonstration of a clear benefit in OS treated by the combination compared to monotherapy with the SOC (LDAC) and a concomitant higher frequency of state of remissions in Study B1371003 therefore indicate an important progress in the management of this frail patient group, for which disease-specific therapeutic improvements are lacking.

The supportive care in terms of anti-microbials and transfusion standards have improved over the last two decades. It is essential in this context that the adverse events to treatment are acceptable, well known and manageable. The safety profile of glasdegib may be characterised as relatively benign, but still adds some toxicity to the SOC. The importance of the add-on toxicity effect of glasdegib must not be disregarded, and it had an impact on dose reductions.

3.7.2. Balance of benefits and risks

The B/R of glasdegib is positive in the claimed indication. The main study, B1371003, showed that glasdegib + LDAC resulted in a statistically and clinically significant improvement in OS over LDAC alone in newly-diagnosed patients with AML who are not eligible for intensive chemotherapy. The safety profile was considered acceptable in these poor prognosis, elderly, unfit AML population, given the current treatment options. Therefore, it can be concluded that the benefits outweigh the risks.

The introduction of targeted therapies such as glasdegib in unfit patients with AML is important, because standard induction chemotherapy may be replaced by combinations aiming to spare normal cells, mitigating the treatment burden with standard chemotherapy and creating an option for novel regimens, more effective by a combination of different targets.

3.8. Conclusions

The overall B/R of Daurismo, in combination with low-dose cytarabine, for the treatment of newly diagnosed *de novo* or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Daurismo is not similar to Dacogen, Rydapt, Mylotarg, Vyxeos, Xospata within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Daurismo is favourable in the following indication:

Daurismo is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH shall ensure that in each Member State where DAURISMO is marketed, all male patients are provided via their prescribing physicians with the Patient Alert Card. The Patient Alert Card should contain the following key elements:

- Glasdegib may be present in semen carrying a potential risk of reproductive and developmental toxicity
- Effective contraception (condom with spermicide, if available) should be used, even after vasectomy and for at least 30 days after the last dose due to the potential risk of exposure of male patients' female partners to glasdegib through semen
- The importance of informing a healthcare provider as soon as a pregnancy is suspected, either for a female patient or female partner of a male patient
- A reminder not to donate semen while taking Daurismo and for 30 days after last dose
- The recommendation to seek advice on effective fertility preservation for men prior to initiating treatment with glasdegib.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that glasdegib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.