Clinical trial results:
A Phase 2, Double-Blind, Randomized Safety and Efficacy Study of Glasdegib (PF-04449913) versus Placebo in Patients with Myelofibrosis Previously Treated with Ruxolitinib

Summary

EudraCT number	2014-001048-40
Trial protocol	GB ES AT FR
Global end of trial date	31 January 2018

Results information

Result version number	v2 (current)
This version publication date	18 January 2019
First version publication date	03 December 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	B1371013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02226172
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the lead-in cohort was to assess the safety and tolerability of glasdegib in patients with primary or secondary myelofibrosis (MF) who had been previously treated with 1 or more Janus kinase inhibitors (JAKis).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects. The final protocol and any amendments were reviewed and approved by the Institutional Review Board(s) and/or Independent Ethics Committee(s) at each of the investigational centers participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	21
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	4

From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In this study, 2 cohorts were involved lead-in and randomized cohort. Lead-in cohort was followed by randomized cohort. Though the drug was considered safe and tolerable in Myelofibrosis, but a key secondary efficacy end point was not met. Therefore, continuation into the randomized cohort did not proceed.

Pre-assignment

Screening details:

Subjects were screened at 1 visit or over multiple visits across a 4 week period. Following this, subjects entered the treatment phase of the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Glasdegib Lead-in

Arm description:

Glasdegib administered orally at a daily starting dose of 100 mg on a continuous regimen of 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Glasdegib
Investigational medicinal product code	PF-04449913
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Glasdegib administered orally at a daily starting dose of 100 mg with approximately 8 ounces (240 mL) of water (in the morning, at the same time each day) on a continuous regimen of 28-day cycles. Subjects requiring dose reduction(s) were administered multiples of 25 mg tablets

Number of subjects in period 1	Glasdegib Lead-in
Started	21
Completed	4
Not completed	17
Death	1
Study terminated by sponsor	1
Unspecified	5
Adverse Events	6
Lost to follow-up	4

Baseline characteristics

Reporting groups	
Reporting group title	Glasdegib Lead-in
Reporting group description:	
Glasdegib administered orally at a daily starting dose of 100 mg on a continuous regimen of 28-day cycles.	

Reporting group values	Glasdegib Lead-in	Total	
Number of subjects	21	21	
Age categorical			
Units: Subjects			

Age Continuous			
Units: Years			
arithmetic mean	69.3		
standard deviation	± 7.0	-	
Gender, Male/Female			
Units: Subjects			
Female	8	8	
Male	13	13	

End points

End points reporting groups

Reporting group title	Glasdegib Lead-in

Reporting group description:

Glasdegib administered orally at a daily starting dose of 100 mg on a continuous regimen of 28-day cycles.

Primary: Percentage of Subjects Achieving Spleen Volume Reduction (SVR) ≥35% as Measured by Magnetic Resonance Imaging (MRI)/Computed Tomography (CT) Scan at Week 24 in the Randomized Cohort

End point title	Percentage of Subjects Achieving Spleen Volume Reduction (SVR) ≥35% as Measured by Magnetic Resonance Imaging (MRI)/Computed Tomography (CT) Scan at Week 24 in the Randomized Cohort[1]

End point description:

The double blind, randomized, placebo controlled phase of the study was not enrolled after the study was terminated early so no data were collected to assess this endpoint.

End point type	Primary

End point timeframe:

Week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: percentage of subjects				

Notes:

[2] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment –Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs): Lead-in Cohort

End point title	Number of Subjects With Treatment –Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs): Lead-in Cohort[3]

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to 28 days after last dose of study drug (up to Week 131) that were absent before treatment or that worsened relative to pretreatment state.AEs included both serious and non-serious adverse event.All subjects treated in the lead-in portion of the study.

End point type	Primary

End point timeframe:

Baseline up to Week 131

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
AEs	21			
SAEs	5			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment Emergent Treatment –Related Adverse Events (AEs) and Serious Adverse Events (SAEs): Lead-in Cohort

End point title	Number of Subjects With Treatment Emergent Treatment –Related Adverse Events (AEs) and Serious Adverse Events (SAEs): Lead-in Cohort[4]

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 28 days after last dose of study drug (up to Week 131) that were absent before treatment or that worsened relative to pre-treatment state. Relatedness to study drug was assessed by the investigator. AEs included both serious and non-serious adverse event. All subjects treated in the lead-in portion of the study.

End point type	Primary

End point timeframe:

Baseline up to Week 131

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
AEs	19			
SAEs	5			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment Emergent Adverse Events (AEs) According to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03: Lead-in Cohort

End point title	Number of Subjects with Treatment Emergent Adverse Events (AEs) According to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03: Lead-in Cohort[5]

End point description:

AE was untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. SAE was AE resulting in any outcomes or deemed significant for any other reason: death;initial or prolonged inpatient hospitalization;life-threatening experience; persistent or significant disability.Treatment-emergent were events between first dose of study drug and up to 28 days after last dose of study drug (up to Week 131) that were absent before treatment or that worsened relative to pretreatment state.AE were assessed according to maximum severity grading based on NCI CTCAE Version 4.03.Grade 1=mild;Grade 2=moderate:within normal limits:Grade 3=severe or medically significant but not immediately life-threatening:Grade 4=life-threatening or disabling:urgent intervention indicated;Grade 5=death.Only categories with at least 1 subject with event were reported. All subjects treated in lead-in portion of the study.

End point type	Primary

End point timeframe:

Baseline up to Week 131

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
Grade 3 or 4	14			
Grade 5	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Laboratory Abnormalities: Lead-in Cohort

End point title	Number of Subjects With Laboratory Abnormalities: Lead-in Cohort[6]

End point description:

Abnormality:hematology:hemoglobin less than(<)0.8*lower limit of normal(LLN),platelets <0.5*LLN greater than(>)1.75*upper limit of normal(ULN),white blood cell count(WBC)<0.6* LLN>1.5*ULN,lymphocytes,total neutrophils<0.8* LLN>1.2* ULN,band Cells, basophils,eosinophils,monocytes>1.2*ULN,blast cells>1.0*ULN.Coagulation:activated partial thromboplastin time,prothrombin international ratio >1.1* ULN.Liver function: bilirubin >1.5*ULN, AST,ALT,lactate dehydrogenase,alkaline phosphatase>3.0*ULN,protein,albumin<0.8* LLN >1.2*ULN. Renal:blood urea nitrogen,creatinine >1.3*ULN,uric acid>1.2*ULN.Electrolytes: sodium<0.95*LLN >1.05*ULN,potassium,chloride,calcium,magnesium<0.9* LLN>1.1*ULN,phosphate<0.8*LLN >1.2*ULN.Chemistry:glucose<0.6*LLN >1.5*ULN,creatine kinase >2.0*ULN,amylase,lipase >1.5*ULN.Urinalysis:protein,blood >1.0*ULN,red blood cells,WBC>=20,epithelial cells >=6,casts,granular casts,hyaline >1,cellular casts,crystals>=1,bacteria>20.All subjects treated in lead-

End point type	Primary

End point timeframe:

Baseline up to Week 131

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects	21			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Laboratory Test Abnormalities According to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 Grade 3 and above Hematological Test Abnormalities: Lead-in Cohort

End point title	Number of Subjects with Laboratory Test Abnormalities According to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 Grade 3 and above Hematological Test Abnormalities: Lead-in Cohort[7]

End point description:

Anemia(grade[g]1:<LLNto10 gram per deciliter[g/dL],g2:<10 to 8g/dL,g3:<8g/dL, g4:lifethreatening);platelet (g1:<LLN to 75*10^3/millimeter[mm]^3, g2:<75*10^3/mm^3 to 50*10^3/mm^3, g3:<50*10^3/mm^3 to 25*10^3/mm^3, g4:<25*10^3/mm^3); lymphopenia (g1:<LLN to 8*10^2/mm^3, g2:<8*10^2 to 5*10^2/mm^3, g3:<5*10^2 to 2*10^2/mm^3, g4:<2*10^2/mm^3);neutrophil (Absolute) (g1:<LLN to 15*10^2/mm^3, g2:<15*10^2 to 10*10^2/mm^3, g3:<10*10^2 to 5*10^2/mm^3, g4:<5*10^2/mm^3); white blood cell count(g1:<LLN to 3*10^3/mm^3, g2:<3*10^3 to 2*10^3/mm^3, g3:<2*10^3 to 1*10^3/mm^3, g4:<1*10^3/mm^3); hemoglobin (g1:increase in hemoglobin level >0 to 2 g/dL above ULN or above baseline if baseline is above ULN, g2:increase in hemoglobin level>2 to 4g/dL above ULN or above baseline if baseline is above ULN,g3: increase in hemoglobin level>4 g/dL above ULN or above baseline if baseline is above ULN). All subjects treated in lead-in portion of study.

End point type	Primary

End point timeframe:

Baseline up to Week 131

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
Grade 3	3			
Grade 4	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Laboratory Test Abnormalities According to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 Grade 3 and above Chemistry Test Abnormalities: Lead-in Cohort

End point title	Number of Subjects with Laboratory Test Abnormalities According to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 Grade 3 and above Chemistry Test Abnormalities: Lead-in Cohort[8]

End point description:

ALT/AST g1:>ULN 3*ULN, g2:>3-5*ULN, g3:>5 20*ULN, g4:>20*ULN);Alkaline Phosphatase(g1:>ULN 2.5*ULN,g2:>2.5-5*ULN, g3:>5 20*ULN, g4:>20*ULN); Creatinine (g1:>ULN-1.5*ULN,g2:>1.5-3*ULN, g3:>3 6*ULN, g4:>6*ULN);hyperglycemia(g1:>ULN-160,g2:>160 250, g3:>250 500, g4:>500mg/dL);bilirubin(total) (g1:>ULN-1.5*ULN, g2:>1.5-3*ULN, g3:>3 10*ULN,g4:>10*ULN);hypoglycaemia(g1:<LLN-55,g2:<55-40, g3:<40 30,g4:<30mg/dL); hyperkalemia (g1:>ULN-5.5,g2:>5.5-6, g3:>6 7,g4:>7mmol/L);hypokalemia (g1:<LLN-3,g2:<LLN-3, g3:<3 2.5, g4:<2.5mmol/L);hypermagnesemia (g1:>ULN-3,g3:>3 8, g4:>8mg/dL);hypocalcemia (g1:<LLN-8,g2:<8-7, g3:<7-6, g4:<6mg/dL); hypercalcemia (g1:>ULN-11.5,g2:>11.5-12.5, g3:>12.5-13.5, g4:>13.5mg/dL); hypomagnesemia (g1:<LLN-1.2,g2:<1.2-0.9,g3:<0.9-0.7, g4:<0.7mg/dL); hyponatremia (g1:<LLN-130,g3:<130-120, g4:<120mmol/L);hypoalbuminemia (g1:<LLN-3,g2:<3 2,g3:<2, g4:lifethreatening);hypophosphatemia(g1:<LLN-2.5,g2:<2.5-2, g3:<2-1, g4:<1mg/dL).All subjects treated in lead-in portion of study.

End point type	Primary

End point timeframe:

Baseline up to Week 131

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: subjects				
Grade 3	5			
Grade 4	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving SVR ≥35% as Measured by Magnetic Resonance Imaging/Computed Tomography Scan at Week 24 in the Lead-in Cohort

End point title	Percentage of Subjects Achieving SVR ≥35% as Measured by Magnetic Resonance Imaging/Computed Tomography Scan at Week 24 in the Lead-in Cohort

End point description:

MRI (CT scan may have been permitted if MRI was contraindicated) of the spleen and the liver was performed at baseline, then every 12 weeks while the subject was on treatment. The same method of assessment used at baseline was used for the duration of the trial to ensure consistency. Spleen volume was assessed by a central, independent blinded reader.

End point type	Secondary

End point timeframe:

Week 24

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percentage of subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving ≥50% Reduction from Baseline in Total Symptom Score (TSS) as Measured by the Myeloproliferative Neoplasm-Symptom Assessment Diary (MPN-SAD) at Week 24 in the Lead-in Cohort

End point title	Percentage of Subjects Achieving ≥50% Reduction from Baseline in Total Symptom Score (TSS) as Measured by the Myeloproliferative Neoplasm-Symptom Assessment Diary (MPN-SAD) at Week 24 in the Lead-in Cohort

End point description:

The MPN-SAD assessed the impact of 9 MF symptoms, at their worst, over the past 7 days and over the past 24 hours on a scale of 0 (absent) to 10 (worst imaginable). The 9 symptoms are early satiety, abdominal discomfort, inactivity, night sweats, pruritus, bone pain, pain below the ribs on the left-hand side, fatigue and shortness of breath. The TSS is the sum of the individual scores, excluding inactivity and shortness of breath. The TSS at Week 24 is the average of the daily total scores from the last 28 days of symptom scores immediately prior to Week 24. A higher score indicates worse symptoms.

End point type	Secondary

End point timeframe:

Week 24

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of subjects				
number (not applicable)	4.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Monthly Mean Change from Baseline in Overall Total Symptom Score (TSS) in the Lead-in Cohort

End point title	Monthly Mean Change from Baseline in Overall Total Symptom Score (TSS) in the Lead-in Cohort

End point description:

The MPN-SAD assessed the impact of 9 MF symptoms, at their worst, over the past 7 days and over the past 24 hours on a scale of 0 (absent) to 10 (worst imaginable). The 9 symptoms are early satiety, abdominal discomfort, inactivity, night sweats, pruritus, bone pain, pain below the ribs on the left-hand side, fatigue and shortness of breath. The TSS is the sum of the individual scores, excluding inactivity and shortness of breath. The TSS at Week 24 is the average of the daily total scores from the last 28 days of symptom scores immediately prior to Week 24. A higher score indicates worse symptoms.
9999 = not applicable, no standard deviation was calculable since n=1.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 36 and 48

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Monthly mean change at Week 12 (n=13)	-2.74 (± 14.07)			
Monthly mean change at Week 24 (n=6)	-4.95 (± 5.78)			
Monthly mean change at Week 36 (n=1)	-4.11 (± 9999)			
Monthly mean change at Week 48 (n=2)	-8.39 (± 11.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Anemia Response (Transfusion Dependent versus Independent) in the Lead-in Cohort

End point title	Percentage of Subjects Achieving Anemia Response (Transfusion Dependent versus Independent) in the Lead-in Cohort

End point description:

Anemia response was defined as transfusion-independent subjects with a ≥20 gram per liter (g/L)

increase in hemoglobin (Hb) level where baseline Hb level was <100 g/L, or baseline transfusion-dependent patients becoming transfusion-independent post-baseline. Transfusion dependency before the start of study treatment was defined as transfusions of ≥6 units of packed red blood cells in the 12 weeks prior to start of study treatment, for a final pre-treatment Hb of <85 g/L. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients required absence of any packed red blood cell transfusions during any consecutive rolling 12-week interval during the treatment phase, capped by a Hb level of ≥85 g/L.

End point type	Secondary

End point timeframe:

Baseline to end of treatment

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of subjects				
number (not applicable)				
Transfusion independent ≥20 g/L Hb increase (n=17)	5.9			
Transfusion dependent (n=4)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Glasdegib Plasma Concentration (Cmax), Minimum Glasdegib Plasma Concentration Observed Prior to the Next Dose (Cmin), and Average Observed Glasdegib Plasma Concentration (Cavg) in the Lead-in Cohort

End point title	Maximum Observed Glasdegib Plasma Concentration (Cmax), Minimum Glasdegib Plasma Concentration Observed Prior to the Next Dose (Cmin), and Average Observed Glasdegib Plasma Concentration (Cavg) in the Lead-in Cohort

End point description:

Cmax was the highest plasma concentration of glasdegib observed directly from the plasma concentration data. Cmin was the lowest plasma concentration of glasdegib observed directly from the plasma concentration data. Cavg was the average concentration at steady state estimated using non-compartmental pharmacokinetic (PK) analysis.

End point type	Secondary

End point timeframe:

Cycle 1, Day 15

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cmax (n=19)	996.8 (± 45)			

Cmin (n=19) Cav (n=17)	191.9 (± 68) 548.0 (± 50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Glasdegib Plasma Concentration versus Time Profile at the End of a Dosing Interval (AUCtau) in the Lead-in Cohort

End point title	Area Under the Glasdegib Plasma Concentration versus Time Profile at the End of a Dosing Interval (AUCtau) in the Lead-in Cohort

End point description:

AUCtau was the area under the glasdegib plasma concentration-time profile from time zero to the end of the dosing interval (24 hours) estimated by non-compartmental PK analysis using the linear/log trapezoidal method.

End point type	Secondary

End point timeframe:

Cycle 1, Day 15

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: ng·hr/mL				
geometric mean (geometric coefficient of variation)	13150 (± 50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach Cmax (Tmax) in the Lead-in Cohort

End point title	Time to reach Cmax (Tmax) in the Lead-in Cohort

End point description:

Tmax was the time of the first occurrence of Cmax observed directly from the plasma concentration data.

End point type	Secondary

End point timeframe:

Cycle 1, Day 15

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Hours				
median (full range (min-max))	1.02 (0.483 to 4.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving SVR ≥50% as Measured by MRI/CT Scan at Week 24 in the Randomized Cohort

End point title	Percentage of Subjects Achieving SVR ≥50% as Measured by MRI/CT Scan at Week 24 in the Randomized Cohort

End point description:

The double blind, randomized, placebo controlled phase of the study was not enrolled after the study was terminated early so no data were collected to assess this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: percentage of subjects				

Notes:

[9] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Monthly Mean Change from Baseline in Overall TSS in the Randomized Cohort

End point title	Monthly Mean Change from Baseline in Overall TSS in the Randomized Cohort

End point description:

The double blind, randomized, placebo controlled phase of the study was not enrolled after the study was terminated early so no data were collected to assess this endpoint.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 36 and 48

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: months				

Notes:

[10] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Anemia Response (Transfusion Dependent versus Independent) in the Randomized Cohort

End point title	Percentage of Subjects Achieving Anemia Response (Transfusion Dependent versus Independent) in the Randomized Cohort

End point description:

The double blind, randomized, placebo controlled phase of the study was not enrolled after the study was terminated early so no data were collected to assess this endpoint.

End point type	Secondary

End point timeframe:

Baseline to end of treatment

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: percentage of subjects				

Notes:

[11] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Subject Reported Outcomes of Health Related Quality of Life and Health Status in the Randomised Cohort

End point title	Subject Reported Outcomes of Health Related Quality of Life and Health Status in the Randomised Cohort

End point description:

The double blind, randomized, placebo controlled phase of the study was not enrolled after the study was terminated early so no data were collected to assess this endpoint.

End point type	Secondary

End point timeframe:

Baseline to end of treatment

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[12]			
Units: subjects				

Notes:

[12] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Duration of SVR in the Randomized Cohort

End point title	Median Duration of SVR in the Randomized Cohort

End point description:

The double blind, randomized, placebo controlled phase of the study was not enrolled after the study was terminated early so no data were collected to assess this endpoint.

End point type	Secondary

End point timeframe:

Baseline to end of treatment

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[13]			
Units: days				
number (not applicable)				

Notes:

[13] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Overall Survival in the Randomized Cohort

End point title	Kaplan-Meier Estimate of Overall Survival in the Randomized Cohort

End point description:

The double blind, randomized, placebo controlled phase of the study was not enrolled after the study was terminated early so no data were collected to assess this endpoint.

End point type	Secondary

End point timeframe:

Baseline to end of treatment

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[14]			
Units: weeks				
number (not applicable)				

Notes:

[14] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Glasdegib PK Parameters in the Randomized Cohort

End point title	Glasdegib PK Parameters in the Randomized Cohort

End point description:

The double blind, randomized, placebo controlled phase of the study was not enrolled after the study was terminated early so no data were collected to assess this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1, Day 15

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[15]			
Units: nanogram per mililiter				
number (not applicable)				

Notes:

[15] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Psychometric validation of the MPN-SAD in the Randomised Cohort

End point title	Psychometric validation of the MPN-SAD in the Randomised Cohort

End point description:

The double blind, randomized, placebo controlled phase of the study was not enrolled after the study was terminated early so no data were collected to assess this endpoint.

End point type	Secondary

End point timeframe:

Baseline to end of treatment

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[16]			
Units: scores on a scale				
number (not applicable)				

Notes:

[16] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment –Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs): Randomized Cohort

End point title	Number of Subjects With Treatment –Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs): Randomized Cohort

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. A treatment emergent AE was defined as an event that emerged during the treatment period that was absent before treatment, or worsened during the treatment period relative to the pretreatment state. The double blind, randomized, placebo controlled phase of the study was not enrolled as the study was terminated early so, no data were collected to assess this end point.

End point type	Secondary

End point timeframe:

Baseline up to Week 131

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[17]			
Units: subjects				

Notes:

[17] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Treatment –Related Adverse Events (AEs) and Serious Adverse Events (SAEs): Randomized Cohort

End point title	Number of Subjects With Treatment Emergent Treatment –Related Adverse Events (AEs) and Serious Adverse Events (SAEs): Randomized Cohort

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. A treatment emergent AE was defined as an event that emerged during the treatment period that was

absent before treatment, or worsened during the treatment period relative to the pretreatment state. Relatedness to study drug was assessed by the investigator. The double blind, randomized, placebo controlled phase of the study was not enrolled as the study was terminated early so, no data were collected to assess this end point.

End point type	Secondary

End point timeframe:

Baseline up to Week 131

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[18]			
Units: subjects				

Notes:

[18] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events (AEs) According to Maximum Severity: Randomized Cohort

End point title	Number of Subjects with Treatment Emergent Adverse Events (AEs) According to Maximum Severity: Randomized Cohort

End point description:

AE was untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship.SAE was AE resulting in any of following outcomes or deemed significant for any other reason:death; initial or prolonged inpatient hospitalization;life-threatening experience; persistent or significant disability/incapacity; congenital anomaly.A treatment emergent AE was defined as an event that emerged during the treatment period that was absent before treatment,or worsened during the treatment period relative to pretreatment state.AE were assessed according to maximum severity grading based on NCI CTCAE Version 4.03.G1=mild; G2=moderate; within normal limits.G3=severe or medically significant but not immediately life-threatening;G4=life-threatening or disabling; urgent intervention indicated; G5=death. Double blind, randomized, placebo controlled phase of study was not enrolled as study was terminated early so, no data were collected to assess this end point.

End point type	Secondary

End point timeframe:

Baseline up to Week 131

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[19]			
Units: subjects				

Notes:

[19] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Abnormalities in the Randomized Cohort

End point title	Number of Subjects With Laboratory Abnormalities in the Randomized Cohort

End point description:

Hematology:hemoglobin<0.8*LLN,platelets<0.5*LLN>1.75*ULN,WBC<0.6*LLN>1.5* ULN,lymphocytes,total neutrophils<0.8* LLN>1.2* ULN,band cells,basophils,eosinophils,monocytes >1.2*ULN, blast cells>1.0*ULN.Coagulation:activated partial thromboplastin time,prothrombin international ratio>1.1*ULN.Liver function:bilirubin>1.5*ULN, AST,ALT,lactate dehydrogenase,alkaline phosphatase>3.0*ULN,protein,albumin<0.8*LLN>1.2*ULN.Renal:blood urea nitrogen,creatinine >1.3* ULN,uric acid >1.2* ULN.Electrolytes:sodium<0.95*LLN>1.05*ULN, potassium,chloride,calcium, magnesium<0.9* LLN >1.1*ULN,phosphate<0.8* LLN >1.2*ULN.Chemistry: glucose<0.6*LLN >1.5*ULN,creatine kinase>2.0*ULN, amylase,lipase>1.5*ULN.Urinalysis:protein,blood>1.0*ULN,red blood cells,WBC>=20,epithelial cells>=6,casts,granular casts,hyaline >1,cellularcasts,crystals>=1,bacteria >20.The double blind,randomized,placebo controlled phase of study was not enrolled as study was terminated early so,no data were collected to assess this end point.

End point type	Secondary

End point timeframe:

Baseline up to Week 131

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[20]			
Units: subjects				

Notes:

[20] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Test Abnormalities By Maximum Severity: National Cancer Institute Common Terminology Criteria for Adverse Event (Version 4.0) Grade 3 and above Hematological Test Abnormalities: Randomized Cohort

End point title	Number of Subjects With Laboratory Test Abnormalities By Maximum Severity: National Cancer Institute Common Terminology Criteria for Adverse Event (Version 4.0) Grade 3 and above Hematological Test Abnormalities: Randomized Cohort

End point description:

Anemia g1:<LLN to10 g/dL, g2:<10 to 8g/dL,g3:<8g/dL,g4:lifethreatening);platelet (g1:<LLN to 75*10^3/mm^3, g2:<75*10^3/mm^3 to 50*10^3/mm^3,g3:<50*10^3/mm^3 to 25*10^3/mm^3,g4:<25*10^3/mm^3);lymphopenia (g1:<LLN to 8*10^2/mm^3, g2:<8*10^2 to 5*10^2/mm^3, g3:<5*10^2 to 2*10^2/mm^3, g4:<2*10^2/mm^3);neutrophil (absolute) (g1:<LLN to 15*10^2/mm^3, g2:<15*10^2 to 10*10^2/mm^3, g3:<10*10^2 to 5*10^2/mm^3, g4:<5*10^2/mm^3);white blood cell count (g1:<LLN to 3*10^3/mm^3,g2:<3*10^3 to 2*10^3/mm^3,g3: <2*10^3 to 1*10^3/mm^3, g4:<1*10^3/mm^3);hemoglobin(g1:increase in hemoglobin level>0 to 2 g/dL above ULN or above baseline if baseline is above ULN, g2: increase in hemoglobin level>2 to 4g/dL above ULN or above baseline if baseline is above ULN,g3:increase in hemoglobin level>4 g/dL above ULN or above baseline if baseline is above ULN). Double blind, randomized, placebo controlled phase of study was not enrolled as study was terminated early so,no

End point type	Secondary

End point timeframe:

Baseline up to Week 131

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[21]			
Units: subjects				

Notes:

[21] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Test Abnormalities By Maximum Severity: National Cancer Institute Common Terminology Criteria for Adverse Event (Version 4.0) Grade 3 and above Chemistry Test Abnormalities: Randomized Cohort

End point title	Number of Subjects With Laboratory Test Abnormalities By Maximum Severity: National Cancer Institute Common Terminology Criteria for Adverse Event (Version 4.0) Grade 3 and above Chemistry Test Abnormalities: Randomized Cohort

End point description:

ALT/AST g1:>ULN 3*ULN, g2:>3-5*ULN, g3:>5 20*ULN,g4:>20*ULN);Alkaline Phosphatase (g1:>ULN 2.5*ULN, g2:>2.5-5*ULN, g3:>5 20*ULN,g4:>20*ULN);Creatinine (g1:>ULN-1.5*ULN, g2:>1.5-3*ULN, g3:>3 6*ULN, g4:>6*ULN);hyperglycemia (g1:>ULN-160,g2:>160 250, g3:>250 500,g4:>500mg/dL); bilirubin(total) (g1:>ULN-1.5*ULN, g2:>1.5-3*ULN, g3:>3 10*ULN,g4:>10*ULN); hypoglycaemia (g1:<LLN-55,g2:<55-40, g3:<40 30, g4:<30mg/dL);hyperkalemia (g1:>ULN-5.5,g2:>5.5-6, g3:>6 7,g4:>7mmol/L);hypokalemia (g1:<LLN-3,g2:<LLN-3,g3:<3 2.5, g4:<2.5mmol/L);hypermagnesemia (g1:>ULN-3,g3:>3 8,g4:>8mg/dL);hypocalcemia (g1:<LLN-8,g2:<8-7, g3:<7-6, g4:<6mg/dL);hypercalcemia (g1:>ULN-11.5,g2:>11.5-12.5, g3:>12.5-13.5, g4:>13.5mg/dL);hypomagnesemia (g1:<LLN-1.2,g2:<1.2-0.9, g3:<0.9-0.7,g4:<0.7mg/dL);hyponatremia (g1:<LLN-130,g3:<130-120, g4:<120mmol/L);hypoalbuminemia (g1:<LLN-3,g2:<3-2, g3:<2, g4:lifethreatening);hypophosphatemia (g1:<LLN-2.5,g2:<2.5-2,g3:<2-1,g4:<1mg/dL). Study was

End point type	Secondary

End point timeframe:

Baseline up to Week 131

End point values	Glasdegib Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	0[22]			
Units: subjects				

Notes:

[22] - The randomized part of the study was not enrolled so no data were collected to assess this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 131

Adverse event reporting additional description:

Event appear as both an AE and SAE.However,what is presented are distinct events.Event may categorized as serious in 1 subject and non-serious in another subject,or 1 subject may have experienced both a serious and non-serious event.All subjects treated in lead-in portion of study.It was analysis population for analyses on lead-in portion of study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Glasdegib Lead-in

Reporting group description:

Glasdegib administered orally at a daily starting dose of 100 mg on a continuous regimen of 28-day cycles.

Serious adverse events	Glasdegib Lead-in		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 21 (23.81%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Postoperative ileus			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Memory impairment			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fatigue			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric varices haemorrhage			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Varices oesophageal			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Portal hypertension			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Glasdegib Lead-in		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 21 (95.24%)		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	5		
Lipase increased			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	10		
Lymphocyte count decreased			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Weight decreased			

subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	13 / 21 (61.90%)		
occurrences (all)	17		
Dizziness			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	5		
Neutropenia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	4		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	7 / 21 (33.33%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2 3 / 21 (14.29%) 3 2 / 21 (9.52%) 2 2 / 21 (9.52%) 2 2 / 21 (9.52%) 2 4 / 21 (19.05%) 4		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea exertional subjects affected / exposed occurrences (all)	 3 / 21 (14.29%) 3 2 / 21 (9.52%) 3		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Night sweats subjects affected / exposed occurrences (all) Pruritus generalised subjects affected / exposed occurrences (all) Pruritus	 8 / 21 (38.10%) 10 2 / 21 (9.52%) 2 2 / 21 (9.52%) 2		

subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	12 / 21 (57.14%)		
occurrences (all)	20		
Myalgia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 21 (33.33%)		
occurrences (all)	7		
Dehydration			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Hyperuricaemia			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	4		
Hyperglycaemia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2014	The requirement for 1 form of highly effective contraception was amended to 2 forms. The inclusion criterion concerning creatinine clearance and the exclusion criterion concerning corrected QT interval were clarified. A precaution was added for phototoxicity. The schedule of assessments was corrected to indicate ongoing collection of AEs during the study treatment period.
19 February 2015	The schedule of assessments was amended to clarify PK, electrocardiogram and bone marrow aspirate collection time points. The threshold for prolongation of QT interval corrected by the Fridericia formula (QTcF) was clarified in the exclusion criteria. Dosing modification guidelines for treatment related QTcF were revised. An administrative update to the AE reporting section was made. Communication of results by Pfizer was updated in line with Pfizer policy.
26 May 2015	Background information was updated, including estimated overall survival and preliminary data from B1371013 lead-in cohort. Pharmacodynamic data were added for the 50 mg glasdegib dose and details of the clinical development program were updated. Subject enrolment in the lead in cohort was revised; the potential to evaluate lower starting doses or intermittent dosing schedules for glasdegib was added, and overall survival was removed as an objective/endpoint for the lead in cohort. An inclusion criterion requiring documentation by the investigator that the subject had exhausted available therapies was added, and the exclusion criterion for prior anticancer therapy washout was revised. The inclusion criterion for MF symptom assessment to be based upon patient reported symptoms on the MPN-SAD screening form was revised. The inclusion criterion for pregnancy and contraception was updated to align with current guidelines, lifestyle guidelines were updated and a contraception check was added. The exclusion criteria for prior malignancies were revised. Protocol defined best supportive therapy was removed from the prohibited/permitted treatments section. Drug storage requirements were updated. Text emphasizing dosing compliance was added. Recommended dose modifications for muscle spasms/myalgia were added. The magnetic resonance imaging/computed tomography scan process was clarified and the requirement for a 5 day window for repeated imaging scans was removed. MPN-SAD collection was expanded. The follow up period was adjusted. Immunophenotyping and cytogenetics were removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported