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GENERIC DRUG NAME AND/OR COMPOUND NUMBER:

Glasdegib / PF-04449913

PROTOCOL NO.:

B1371013

PROTOCOL TITLE:

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

Study Center(s):

Ten centers took part in the study: 3 in Japan and 7 in the United States (US).

Study Initiation Date and Primary Completion or Final Completion Dates:

Study Initiation Date: 06 October 2014

Primary Completion Date: 14 December 2016

Last Patient Last Visit (LPLV): 31 January 2018

This study was to consist of an open-label lead-in cohort to evaluate the safety and tolerability of glasdegib in patients with myelofibrosis (MF) previously treated with ≥1 Janus kinase inhibitor (JAKi), followed by a Phase 2, randomized portion. Although the drug was considered safe and tolerable in MF, the key secondary efficacy endpoint was not met; therefore, the double-blind, randomized phase was not initiated, with no patients enrolled. As of the primary completion date, 3 patients from the lead-in cohort who continued to derive clinical benefit from treatment remained in the study. All 3 patients discontinued from study or completed the protocol-specified follow-up period as of LPLV.

Phase of Development:

Phase 2

Study Objectives:

Lead-In Cohort Objectives

The primary objective in the glasdegib lead-in cohort was to assess the safety and tolerability of glasdegib in patients with primary or secondary MF who had been previously treated with ≥1 JAKi.

The secondary objectives in the glasdegib lead-in cohort were as follows:

- To assess the effect of glasdegib on spleen volume reduction (SVR) in patients with primary or secondary MF who had been previously treated with ≥1 JAKi;
- To assess the effect of glasdegib on patient-reported MF symptoms in patients with primary or secondary MF who had been previously treated with ≥1 JAKi;
- To assess the effect of glasdegib on hematologic improvement (peripheral blood) in patients with primary or secondary MF who had been previously treated with ≥1 JAKi;
- To characterize the pharmacokinetics (PK) of glasdegib.

Randomized Cohort Objectives

The primary objective in the randomized cohort was to compare the effect of glasdegib versus placebo on SVR in patients with primary or secondary MF who had been previously treated with ruxolitinib.

The secondary objectives in the randomized cohort were as follows:

- To compare the effect of glasdegib versus placebo on patient-reported MF symptoms in patients with primary or secondary MF who had been previously treated with ruxolitinib;
- To compare the effect of glasdegib versus placebo on hematologic improvement (peripheral blood) in patients with primary or secondary MF who had been previously treated with ruxolitinib;
- To compare changes in patient-reported outcomes (PROs) of health-related quality of life (HRQoL) and health status between treatment arms;
- To evaluate duration of SVR within each treatment arm;
- To compare overall survival (OS) between treatment arms;
- To evaluate the overall safety profile in each treatment arm;
- To characterize the PK of glasdegib;

- To psychometrically validate and analyze interpretability of scores for the Myeloproliferative Neoplasm Symptom Assessment Diary (MPN-SAD).

METHODS

Study Design:

An open-label lead-in cohort of ≥20 MF patients previously treated with ≥1 licensed or experimental JAKi was planned to evaluate the safety and tolerability of 100 mg glasdegib once daily (QD). Following this, a Phase 2, randomized, double-blind, 2-arm study of oral single-agent glasdegib 100 mg QD versus placebo on a continuous regimen of 28-day cycles in primary or secondary symptomatic MF was to be initiated if the key secondary endpoint (≥50% reduction in MPN-SAD Total Symptom Score [TSS]) was met.

Patients were screened at 1 visit or over multiple visits across a 4-week period. Following this, patients entered the treatment phase of the study. Duration was up to 24 weeks and patients were eligible to remain on treatment after this for as long as they tolerated and derived clinical benefit from the treatment.

For the randomized cohort, all treatments were to be unblinded at 24 weeks; patients receiving placebo treatment were eligible to cross over to open-label glasdegib at this point or at any point prior to this if disease progression occurred.

The planned schedule of assessments for both the glasdegib lead-in and randomized cohorts is presented in Table 1. The PK and electrocardiogram (ECG) schedule of assessments for the glasdegib lead-in cohort is presented in Table 2. For the randomized cohort, the planned PK and ECG schedule of assessments for the majority of patients is presented in Table 3; in addition to this, approximately 30 patients were planned to be evaluated at additional time points, and patients in Japan were to follow a different schedule. The planned schedule of assessments for the crossover cohort (which would have consisted of the patients who crossed over to open-label glasdegib from previous placebo treatment) is presented in Table 4; the PK and ECG schedule for this cohort is provided in Table 5.

Table 1. Schedule of Activities for the Glasdegib Lead-In and Randomized Cohorts

Protocol Activity	Screening		28-Day Cycles						
			C1				C2, 3, 5 and 6	C4 and C7	After C7 Q3M (C10, C13, etc.
		D-7	D1 (predose)	D8	D15	D21	D1	D1	D1
Visit Window	**Up to 28 days before registration/ randomization**	-	-	**±1 day**	-	**±1 day**	**±2 days**	**±5 days (±7 days for imaging)**	**±7 days**
Informed consent[c]	X								
Medical history	X								
Cancer history[d]	X								
Baseline signs and symptoms[e]			X						
Physical examination[f]	X		X		X		X	X	X
Vital signs[g]	X		X		X		X	X	X
Performance status[h]	X		X				X	X	X
Contraception check[i]	X		X				X	X	X
Laboratory									
Hematology[j]	X		X	X	X	X	X	X	X
Blood chemistry[k]	X		X	X	X	X	X	X	X
Coagulation[l]	X		X				X	X	X
Urinalysis[m]	X		X				X	X	X
Pregnancy test[n]	X		X				X	X	X
Triplicate 12-lead ECG[o]	X		Refer to Table 2 and Table 3						
Randomization and treatment									
Registration (lead-in)/ randomization[p]			X						
Study treatment[q]			QD, orally, on a continuous basis						
Study drug compliance[r]			X				X	X	X
Disease response assessments									
Spleen and liver palpation[s]	X		X		X		X	X	X

Table 1. Schedule of Activities for the Glasdegib Lead-In and Randomized Cohorts

Protocol Activity	Screening		28-Day Cycles						
			C1				C2, 3, 5 and 6	C4 and C7	After C7 Q3M (C10, C13, etc.
		D-7	D1 (predose)	D8	D15	D21	D1	D1	D1
Visit Window	**Up to 28 days before registration/ randomization**	-	-	**±1 day**	-	**±1 day**	**±2 days**	**±5 days (±7 days for imaging)**	**±7 days**
Abdominal imaging[t]	X[t]							X	X
Response assessment (revised IWG-MRT)[u]								X	X
PROs[v]									

eDiary device set-up[w]		X							
Symptom score (MPN-SAD)[x]		X	X	X	X	X	X	X	X (weekly)
PGIC							X	X	X
EQ-5D-5L			X				X	X	X
EORTC QLQ-30			X				X	X	X
Other clinical assessments									
AEs[y]			X	X	X	X	X	X	X
Concomitant treatments			X	X	X	X	X	X	X
RBC and platelet transfusions[z]	X		X	X	X	X	X	X	X
Special laboratory assessments: blood samples									
PK			Refer to Table 2 and Table 3						
Survival follow-up[b]									

Abbreviations: AE=adverse event; BICR=blinded independent central review; C=cycle; CRF=case report form; CT=computed ton DIPSS=dynamic international prognosis scoring system; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end of treatmer patient-reported outcomes; EQ-5D-5L=EuroQol 5 Dimensions Questionnaire 5-level version; IEC=Independent Ethics Committee Board; IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; JAKi=Janus kinase inhibitor; MF=m MPN-SAD=Myeloproliferative Neoplasm Symptom Assessment Diary; MRI=magnetic resonance imaging; NCI CTCAE=Nationa Terminology Criteria for Adverse Events; PGIC=Patient Global Impression of Change; PK=pharmacokinetics; PRO=patient-repor control; QD=once daily; Q[X]M=every [X] months; QTc=corrected QT interval; QTcF= QT interval corrected by the Fridericia co blood cell; SAE=serious adverse event; SVR=spleen volume reduction; WBC=white blood cell.

a. **EOT visit:** Patients should have completed all assessments within 28 days of receiving last dose, unless otherwise specified. experience toxicity following discontinuation of treatment were to be followed by the investigator at least every 4 weeks until reso further improvement was expected in the clinical judgment of the investigator.

b. **Survival follow-up:** Survival follow-up was not collected for patients enrolled to the glasdegib lead-in cohort. Following disc for patients enrolled to the randomized cohort, survival status was to be collected every 3 months until death or up to 20 months af patient, whichever occurred first. Subsequent anticancer therapy(s) and relevant transplant information were also to be collected. been acceptable for follow-up monitoring.

c. **Informed consent:** Had to be obtained prior to undergoing any study-specific procedure.

d. **Cancer history:** Date of initial diagnosis, risk category at time of enrollment (per DIPSS), a complete history of MF prior the duration of therapy), best response and reason for discontinuation. Events leading to intolerance of a prior JAKi therapy, including events, were also collected.

e. **Baseline signs and symptoms:** Patients were asked about any signs and symptoms experienced within the 14 days prior to sta signs and symptoms were recorded on the AE page of the CRF.

f. **Physical examination:** Included examination of all the major body systems. If a physical examination was obtained within 4 evaluation did not need to be repeated. Weight had to be recorded at Screening and on Day 1 of each cycle. Height did not need t measurement.

g. **Vital signs:** Blood pressure and heart rate were recorded in the sitting position. If an assessment had been obtained within 48 collection, it did not need to be repeated.

h. **Performance status:** ECOG scale.

i. **Contraception check:** Male patients who were able to father children and female patients who were of childbearing potential criteria for correct use of 2 of the selected methods of contraception. The investigator or designee discussed with the patient the ne contraception methods consistently and correctly and documented such conversation in the patient's chart. In addition, the investig patient to call immediately if one or both selected contraception methods were discontinued, or if pregnancy was known or suspect patient's partner.

j. **Hematology:** Assessed locally by the site; laboratory certifications and normal ranges with units had to be provided to the spo also be repeated as clinically indicated. All platelet, absolute neutrophils, WBC and hemoglobin values observed during the screen the CRF.

k. **Blood chemistry:** Assessed locally by the site; laboratory certifications and normal ranges with units had to be provided to the tests could also be repeated as clinically indicated.

l. **Coagulation:** Assessed locally by the site. Coagulation tests could also be repeated as clinically indicated.

m. **Urinalysis:** Assessed locally by the site. Dipstick was acceptable. Microscopic analyses should have been performed if abno
protein or blood). If a urinalysis was obtained within 7 days of the scheduled collection, it did not need to be repeated at C1D1.
n. **Pregnancy test:** For female patients of childbearing potential, a urine or serum pregnancy test, with sensitivity of at least 25 m
certified laboratory, was performed on 2 occasions prior to starting study therapy: once at the start of screening and once at the C1
study treatment administration. Pregnancy tests were also routinely repeated at the beginning of every treatment cycle during the a
end of study treatment, and additionally whenever one menstrual cycle was missed or when potential pregnancy was suspected. A
also have been undertaken if requested by IRB/IECs or if required by local regulations.
o. **Triplicate 12-lead ECGs:** At Screening, 3 consecutive 12-lead ECGs were performed approximately 2 minutes apart to deter
(and derived QTcF). ECGs should have been assessed locally and were also submitted to a central vendor.
p. **Registration/randomization:** Patients had to meet all eligibility criteria prior to registration (glasdegib lead-in cohort) or rand
cohort).
q. **Study treatment (glasdegib or placebo):** Patients should have been reminded at each visit that the study treatment was to be
8 ounces (240 mL) of water at the same time each day. On protocol visit days, the patient was reminded that the study treatment sh
site staff, to support specific time point assessments (ie, PK sampling).
r. **Study drug compliance:** All study treatment bottle(s) including any unused tablets and patient dosing diaries should have bee
compliance assessment and drug accountability.
s. **Spleen and liver palpation:** Spleen and liver measurement should ideally have been performed by the same medical professio
provide consistency for each patient assessment. Palpable spleen length below left costal margin was measured in centimeters.
t. **Abdominal imaging:** MRI of the spleen and the liver was collected at baseline, then every 12 weeks (ie, C4D1 and C7D1) wh
treatment. In exceptional circumstances, patients unable to undergo an MRI could be assessed by CT scan, following consultation
method of assessment used at baseline should have been used for the duration of the trial to ensure consistency. Additional scans c
investigator's discretion. Patients should have refrained from eating or drinking and from exercise for at least 2 hours (preferably 4
exam. All scans were assessed by a BICR through a central imaging vendor. Baseline imaging should have been obtained at least
Phase 1b) or randomization (for Phase 2), to ensure acceptability of the scan by the central imaging vendor. Suspected disease pro
spleen size increase or symptomatic deterioration, was confirmed via imaging assessment, by the BICR. Scans that did not pass th
process were repeated within 2 weeks and resubmitted to ensure readability. At the time of permanent study treatment discontinua
been collected within 2 weeks after last dose of study treatment was administered. Patients discontinuing treatment with documen
need a repeat MRI/CT at the final visit.
u. **Response assessment (revised IWG-MRT):** At a minimum, evaluation of SVR, peripheral blood, and physical symptoms we
assessment. Where available, bone marrow samples were also evaluated for response.
v. **PROs:** All PROs were collected electronically. An eDiary device (similar to a smart phone) was used to capture MPN-SAD.
capture all other PRO data (eg, EORTC QLQ-30, EQ-5D-5L and PGIC) at the study visits. Site staff provided patient training on t
only used at the site.
w. **eDiary:** Site staff provided patient training on use of eDiary device, logged patients onto the device, and dispensed the device
enrollment. An eDiary device is physical hardware used by the patient to enter eDiary data from the MPN-SAD. Patients had to b
clinic visit to verify that the device was charging properly and to download accumulated data. The device was returned to the patie
study completion or discontinuation.
x. **Daily symptom score:** The total symptom score from the MPN-SAD was recorded daily each night beginning at least 7 days
through C7D1 (Week 24, for a total of 25 weeks). Thereafter, patients recorded their symptoms weekly until the time of treatment
treatment discontinuation, symptoms were to be recorded monthly by all patients participating in survival follow-up, through comp
study.
y. **AE assessments:** AEs should have been documented and recorded at each visit using the NCI CTCAE version 4.03. Patients
28 days after the last treatment administration or until all drug related toxicities had resolved, whichever was later, or earlier than 2
commenced another anticancer therapy in the meantime. For SAEs, the active reporting period to Pfizer or its designated represen
the patient provided informed consent, which was obtained prior to the patient's participation in the study, ie, prior to undergoing a
and/or receiving study treatment, through and including 28 calendar days after the last administration of the study treatment. SAEs
reporting period had ended should have been reported to the sponsor if the investigator became aware of them. At a minimum, all
believed had at least a reasonable possibility of being related to the study drug were to be reported to the sponsor.
z. **Transfusions:** All RBC and platelet transfusions, including the date of each transfusion and number of RBC or platelet units t
the patient was on treatment. Transfusion histories for the 3 months prior to C1D1 were also recorded in the CRF. The number of
was recorded.

Table 2. Pharmacokinetics and Electrocardiogram – Glasdegib Lead-In Cohort

Dose Day	**C1D1**					**C1D15**							**C1D16**	**C2 and C3,**	
Hour Postdose	**0**[a]	**0.25**	**1**	**2**	**4**	**0**[a]	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**24**	**0**[a]	**1**
PK plasma sample	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate 12-lead ECG[b]	X	-	X	X	X	X	-	-	X	X	X	-	-	-	X

Abbreviations: C=cycle; D=day; ECG=electrocardiogram; EOT=end of treatment; PK=pharmacokinetics; Q3M=every 3 months; C
QTcF= QT interval corrected by the Fridericia correction formula.

a. In all instances, "0 hour" represents a predose collection. The PK sample should have been collected within 30 minutes prior
Patients should have been reminded not to take their study medication prior to arriving at the clinic on protocol scheduled visits.

b. At each time point, 3 consecutive 12-lead ECGs were performed approximately 2 minutes apart to determine the mean QTc in
ECGs should have been assessed locally and were also submitted to a central vendor. When coinciding with blood sample draws f
have been performed prior to blood sample collection, such that the blood sample was collected at the nominal time. Additional tr
performed as clinically indicated.

Table 3. Pharmacokinetics and Electrocardiogram – Randomized Cohort (General)

Dose Day	**C1D1**			**C1D15**			**C2 and C3, D1**		
Hour Postdose	**0**[a]	**1**	**4**	**0**[a]	**1**	**4**	**0**[a]	**1**	**4**
PK plasma sample	-	X	X	X	X	X	X	X	X
Triplicate 12-lead ECG[b]	X	X	X	X	X	X	X	X	X

Abbreviations: C=cycle; D=day; ECG=electrocardiogram; EOT=end of treatment; PK=pharmacokinetics; Q3M=every 3 months; QTcF= QT interval corrected by the Fridericia correction formula.

a. In all instances, "0 hour" represents a predose collection. The PK sample should have been collected within 30 minutes prior Patients should have been reminded not to take their study medication prior to arriving at the clinic on protocol scheduled visits.

b. At each time point, 3 consecutive 12-lead ECGs were performed approximately 2 minutes apart to determine the mean QTc in ECGs should have been assessed locally and were also submitted to a central vendor. When coinciding with blood sample draws f have been performed prior to blood sample collection, such that the blood sample was collected at the nominal time. Additional tr performed as clinically indicated.

Table 4. Schedule of Activities for the Crossover Cohort

Protocol Activity	Baseline	28-Day Cycles							End of Treatment[a]	Survival Follow-Up[b]
		C1				C2, 3, 5 and 6	C4, C7	After C7, Q3M (C10, C13)		
	Up to 14 days prior to C1D1[c]	D1 Predose	D8	D15	D21	D1	D1	D1		
Visit Window	-	-	±1 day	-	±1 day	±2 days	±5 days ±7 days for imaging	±7 days		±14 days
Physical examination[d]	X	X		X		X	X	X	X	
Vital signs[e]	X	X		X		X	X	X	X	
Performance status[f]		X				X	X	X	X	
Contraception check[g]	X	X				X	X	X	X	
Laboratory assessments										
Hematology[h]	X	X	X	X	X	X	X	X	X	
Blood chemistry[i]	X	X	X	X	X	X	X	X	X	
Coagulation[j]	X					X	X	X	X	
Urinalysis[k]		X				X	X	X	X	
Pregnancy test[l]	X	X				X	X	X	X	
Triplicate 12-lead ECG[m]	X	Refer to Table 5								
Registration and study treatment										
IRT registration[n]	X									
Glasdegib administration[o]		QD orally on a continuous basis								
Drug compliance[p]		X				X	X	X	X	
Spleen and liver palpation[q]		X		X		X	X	X	X	
Efficacy assessments										
Abdominal MRI/CT[r]	X[r]						X	X	X	
Response assessment (revised IWG-MRT)[s]							X	X	X	
Patient-Reported Outcomes										
Daily symptom score (MPN-SAD)[t]	X	X	X	X	X	X	X	X (weekly)	X (weekly through	X (monthly)

									final visit)	

Table 4. Schedule of Activities for the Crossover Cohort

Protocol Activity		28-Day Cycles							End of Treatment[a]	Survival Follow-Up[b]
	Baseline	C1				C2, 3, 5 and 6	C4, C7	After C7, Q3M (C10, C13)		
	Up to 14 days prior to C1D1[c]	D1 Predose	D8	D15	D21	D1	D1	D1		
Visit Window	-	-	±1 day	-	±1 day	±2 days	±5 days ±7 days for imaging	±7 days		±14 days
PGIC						X	X	X	X	
EQ-5D-5L		X				X	X	X	X	
EORTC QLQ-30		X				X	X	X	X	
Other clinical assessments										
AEs[u]		X	X	X	X	X	X	X	X	
Concomitant treatments		X	X	X	X	X	X	X	X	
Transfusions[v]		X	X	X	X	X	X	X	X	
Blood and plasma samples										
PK		Refer to Table 5								
Post-treatment										
Survival follow-up[b]										X

Abbreviations: AE=adverse event; BICR= blinded independent central review; C=cycle; CT=computed tomography; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eDiary=electronic diary; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=EuroQol 5 Dimensions Questionnaire 5-level version; IEC=Independent Ethics Committee; IRB=Institutional Review Board; IRT=Interactive Response Technology; IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; MPN-SAD=Myeloproliferative Neoplasm Symptom Assessment Diary; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PGIC=Patient Global Impression of Change; PK=pharmacokinetics; QD=once daily; Q[X]M=every [X] months; RBC=red blood cell; SAE=serious adverse event.

a. **End of treatment visit:** Patients were to have completed all assessments within 28 days of receiving last dose, unless otherwise specified. Patients continuing to experience toxicity following discontinuation of treatment were to be followed by the investigator at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement was expected.

b. **Survival follow-up:** Following discontinuation of glasdegib, follow-up survival status was to be collected every 3 months until death or at least 20 months after randomization of the last patient. Subsequent anticancer therapy(ies) and transplant information were also to be collected. Telephone contact would have been acceptable for follow-up visits.

c. Assessments collected prior to crossover that fell within 2 weeks of crossover C1D1 would not have needed to be repeated, unless specifically indicated.

d. **Physical examination:** Was to include examination of all the major body systems. If physical examination had been obtained within 48 hours of crossover C1D1, the evaluation would not have needed to be repeated. Weight was to be recorded at crossover baseline and on D1 of each cycle. Height would not

have needed to be recorded after the first measurement.

e. **Vital signs:** Blood pressure and pulse rate were to be recorded in the sitting position. If an assessment had been obtained within 48 hours of crossover C1D1 scheduled collection, it would not have needed to be repeated.

f. **Performance status:** ECOG scale.

g. **Contraceptive check:** Male patients who were able to father children and female patients of childbearing potential were to affirm that they met the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee was to discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly, and document such conversation in the patient's chart. In addition, the investigator or his or her designee was to instruct the patient to call immediately if 1 or both selected contraception methods were discontinued, or if pregnancy was known or suspected in the patient or the patient's partner.

h. **Hematology:** Assessed locally by the site; laboratory certifications and normal ranges with units were to be provided to the sponsor. Hematology tests were to be repeated as clinically indicated.

i. **Blood chemistry:** Assessed locally by the site; laboratory certifications and normal ranges with units were to be provided to the sponsor. Blood chemistry tests were to be repeated as clinically indicated.

j. **Coagulation tests:** Assessed locally by the site. Coagulation tests were to be repeated as clinically indicated.

k. **Urinalysis:** Assessed locally by the site. Dipstick was to be acceptable. Microscopic analyses were to be done if results were abnormal (ie, presence of protein or blood). If urinalysis had been obtained within 7 days of the scheduled collection, it would not have needed to be repeated at crossover C1D1.

l. **Pregnancy test:** For female patients of childbearing potential, a urine or serum pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, were to be performed on 2 occasions prior to starting study therapy, once at the start of screening and once at the crossover C1D1 visit, immediately before glasdegib administration. Pregnancy tests were also to be routinely repeated at the beginning of every treatment cycle during the active treatment period, at the end of study therapy, and additionally whenever a menstrual cycle was missed or when potential pregnancy was suspected. Additional pregnancy tests were also to be undertaken if requested by IRB/IECs, or if required by local regulations.

m. **Triplicate 12-lead ECGs:** Refer to Table 5 for additional details.

n. **IRT registration:** Patients were to be reassigned from blinded treatment to open-label glasdegib via IRT prior to crossover C1D1.

o. **Glasdegib:** Patients were to be reminded at each visit that glasdegib was to be taken at the same time each day, with approximately 8 oz (240 mL) of water. On protocol visit days, the patient was to be reminded that glasdegib will be administered by the site staff, to support specific time point assessments (ie, PK sampling).

p. **Drug compliance:** All glasdegib bottles including any unused tablets and patient dosing diaries were to be returned to the clinic for compliance assessment and drug accountability.

q. **Spleen and liver palpation:** Spleen and liver size measurement by manual palpation were ideally to be performed by the same medical professional at each assessment to provide consistency. Palpable spleen length below the LCM was to be measured in centimeters.

r. **Abdominal imaging:** MRI (or CT if applicable) of the spleen and liver was to be collected and submitted to a central imaging vendor where a blinded independent central reader was to make volume assessments. The last imaging scan collected during the randomized portion of the trial was to be used for crossover baseline, after which an MRI/CT was to be collected every 12 weeks (eg, crossover C4D1, crossover C7D1, etc) while the patient was on treatment. The same method of assessment used to establish crossover baseline was to be used for the duration of the trial to ensure consistency. Patients were to refrain from eating or drinking and from exercise for at least 2 hours preferably 4 hours, prior to the MRI/CT exam. Additional scans were to be performed at the investigator's discretion. Suspected disease progression identified by palpable spleen size increase or symptomatic deterioration was to be confirmed via imaging assessment, by the BICR. Scans that were not accepted by the vendor were to be repeated within 2 weeks and resubmitted to ensure readability. At the time of permanent study treatment discontinuation, MRI/CT was to be collected within 2 weeks after last dose was administered. Patients discontinuing treatment with documented disease progression would not have needed a repeat MRI/CT at the final visit.

s. **Response assessment (Revised IWG-MRT):** Evaluation of spleen volume, peripheral blood and physical symptoms were to be required for response assessment.

t. **Daily symptom score:** The total symptom score from the MPN-SAD was to be recorded daily each night, without interruption during transition from blinded treatment to open-label glasdegib, and continuing through crossover C7D1. Thereafter, patients were to record their symptoms weekly until the time of treatment discontinuation. Following treatment discontinuation, symptoms were to be recorded monthly by all patients participating in survival follow-up, through completion or discontinuation of study. Patients were to bring the eDiary device to each clinic visit to verify that the device was charging properly, and to download accumulated data. The device was to be returned to the patients for continued use until study completion or discontinuation.

u. **AE assessments:** AEs were to be documented and recorded at each visit using the NCI CTCAE version 4.03. Patients were to be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities had resolved, whichever was later; or earlier than 28 days should the patient have commenced another anticancer therapy in the meantime. For SAEs, the active reporting period to Pfizer or its designated representative was to begin from the time that the patient provided informed consent, which was obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving any investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period had ended were to be reported to the sponsor if the investigator became aware of them. At a minimum, all SAEs that the investigator believed had at least a reasonable possibility of being related to the investigational product were to be reported to the sponsor.

v. **Transfusions:** All RBC and platelet transfusions, including the date of each transfusion and the number of red cell or platelet units transfused were to be recorded while the patient was on treatment. Note that the number of units, not the number of bags, was to be recorded.

Table 5. Pharmacokinetics and Electrocardiogram - Crossover Cohort (Placebo to Glasdegib)

Dose Day	**Cycle 1 Day 1**			**Cycle 1 Day 15**			**Cycle 2 Day 1**			**Cycles 3, 5 and 6 Day 1**	**Cycles 4, 7, then Q3M**	**EOT**
Hour Postdose	**0**[a]	**1**	**4**	**0**[a]	**1**	**4**	**0**[a]	**1**	**4**	**1**	**1**	**-**
PK plasma sample		X	X	X	X	X	X	X	X	-	-	-
Triplicate 12-lead ECG[b]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ECG=electrocardiogram; EOT=end of treatment; PK=pharmacokinetics; Q3M=every 3 months; QTc=corrected QT interval; QTcF=QT interval corrected by the Fridericia formula.

a. In all instances, "0 hour" represents a predose collection. The PK sample was to be collected within 30 minutes prior to dose administration. Patients were to be reminded not to take their study medication prior to arriving at the clinic on protocol scheduled visits.

b. At each time point, 3 consecutive 12-lead ECGs were to be performed approximately 2 minutes apart to determine the mean QTc interval (and derived QTcF). ECGs were to be assessed locally and would also have been submitted to a central vendor. When coinciding with blood sample draws for PK, ECG assessment were to be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. Additional triplicate ECGs could have been performed as clinically indicated.

Number of Patients (Planned and Analyzed):

The glasdegib lead-in cohort was planned to consist of ≥20 patients. A total of 21 patients enrolled, of whom 16 patients were in the US and 5 patients were in Japan.

The randomized cohort, which was not initiated, was planned to consist of approximately 202 patients.

Diagnosis and Main Criteria for Inclusion and Exclusion:

MF patients, who had a spleen palpable ≥5 cm below the left costal margin and who had previously been treated with ruxolitinib.

Study Treatment:

In the glasdegib lead-in cohort, open-label oral glasdegib tablets (25 mg and 100 mg) were supplied in bottles by the sponsor and administered 100 mg QD. Each bottle contained enough medication for a 28-day cycle of dosing, plus an additional amount to cover potential delays in visiting the study site. Treatment duration in the glasdegib lead-in cohort was planned to be at least 12 weeks followed by enrollment of the randomized cohort, where patients planned to be assigned to double-blind glasdegib or matching placebo in a 2:1 ratio. Patients were permitted to remain on glasdegib for as long as they continued to experience clinical benefit.

Efficacy, Pharmacokinetic, and Outcomes Research Endpoints:

The primary efficacy endpoint was achieving ≥35% SVR at Week 24 from baseline in the randomized cohort as assessed by magnetic resonance imaging (MRI), or computed tomography (CT) when applicable, by a central, independent, blinded reader.

The key secondary efficacy endpoint for the randomized cohort was symptom improvement, defined as achieving ≥50% reduction in TSS at Week 24 (Cycle 7 Day 1), as measured by the MPN-SAD.

Additional secondary endpoints were as follows:

- Achieving ≥35% SVR at Week 24 from baseline in the glasdegib lead-in cohort as assessed by MRI, or CT when applicable, by a central, independent, blinded reader;
- Peripheral blood count improvement;
- Duration of SVR in the randomized cohort;
- OS in the randomized cohort;
- PK parameters of glasdegib;
- Overall TSS at Week 24 as measured by MPN-SAD;
- PROs of HRQoL and health status in the randomized cohort;

- Psychometric validation of the MPN-SAD in the randomized cohort.

Safety Evaluations:

The primary endpoint for the glasdegib lead-in cohort was safety: Adverse Events (AEs) as characterized by type, frequency, severity (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] grades), timing, seriousness, and relationship to study therapy, and laboratory abnormalities as characterized by type, frequency, severity (CTCAE grades, or categorized as normal, abnormal or not done for tests without CTCAE definitions), and timing.

The timing of safety evaluations is provided in Table 1 through Table 5.

Adverse Events

An AE was defined as any untoward medical occurrence in a clinical investigation patient administered a product or medical device. The event need not necessarily have had a causal relationship with the treatment or usage. AEs were graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 for tables produced based upon the primary completion date for the study, and version 20.1 for data to LPLV. All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product were reported.

AEs should have been recorded from the time the patient had taken at least 1 dose of investigational product through the patient's last visit. The serious AE (SAE) reporting period began when a patient provided informed consent (ie, prior to undergoing any study-related procedure and/or receiving study treatment), through and including 28 calendar days after the last dose of study treatment. If the investigator became aware of SAEs occurring after the active reporting period had ended, the events should have been reported to the sponsor; at a minimum, SAEs believed by the investigator to have at least a reasonable possibility of being treatment-related were to be reported. If a patient began a new anticancer therapy, the AE reporting period for non-serious AEs ended at the time the new treatment was commenced. Death was reported if it occurred during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

Serious Adverse Events

An SAE was defined as any untoward medical occurrence at any dose that:

- Resulted in death;
- Was life-threatening (immediate risk of death);
- Required inpatient hospitalization or prolongation of existing hospitalization;
- Resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Resulted in congenital anomaly/birth defect.

Medical and scientific judgment was exercised in determining whether an event was an important medical event. An important medical event may not have been immediately life-threatening and/or have resulted in death or hospitalization. However, if it was determined that the event may have jeopardized the patient or have required intervention to prevent one of the other AE outcomes, then the important medical event should have been reported as serious.

Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAEs) were defined as follows:

- All deaths from start of treatment until 28 days after the final dose;
- All treatment-related SAEs even if occurring after 28 days after the final dose or after end of treatment;
- All treatment-unrelated SAEs from treatment start until 28 days after final dose of treatment;
- All nonfatal AEs occurring after treatment start up until 28 days after final dose of treatment or until start of new anticancer treatment, whichever was first.

Disease progression was not considered a TEAE unless the patient died of disease prior to 28 days after discontinuation of treatment. Events that were continuations of baseline abnormalities were considered TEAEs only if there was an increase in grade over baseline.

Laboratory Evaluations

The following laboratory assessments were analyzed at local laboratories:

- Hematology (bands, basophils, blast count, eosinophils, lymphocytes, monocytes, neutrophils, platelets, white blood cells, and hemoglobin);
- Blood chemistry (albumin, alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase, blood urea nitrate or urea, calcium, chloride, creatinine, creatine kinase/creatine phosphokinase, nonfasting glucose, lactate dehydrogenase, lipase, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, uric acid, and vitamin D);
- Urinalysis (dipsticks for urine protein and urine blood);
- Coagulation tests (activated partial thromboplastin time and international normalized ratio).

Vital Signs and Physical Examination

Vital signs included blood pressure (sitting) and heart rate. Patients also underwent a physical examination which included examination of major body systems, measurement of spleen and liver by palpation, weight, and assessment of Eastern Cooperative Oncology Group status.

Electrocardiogram

Triplicate 12-lead (with a 10-second rhythm strip) tracing was performed for ECGs at every time point and submitted to a central vendor for assessment. At each time point, 3 consecutive ECGs were performed approximately 2 minutes apart (but no longer than 5 minutes) to determine the mean QTcF intervals. Sites were provided with a simple calculation tool which allowed for real-time assessment of mean QTcF values from the triplicate QT interval and heart rate measurements.

Transfusions

All red blood cell (RBC) and platelet transfusions while the patient was on treatment were recorded, including the date and the number of RBC or platelet units transfused (as opposed to the number of bags).

Statistical Methods:

Only the statistical methodology for the glasdegib lead-in cohort is discussed below, as the other analyses were not performed. Summaries and statistical analyses were provided for data up to the primary completion date. All data collected after the primary completion date were provided as listings only.

The rates of binary endpoints were provided along with the corresponding two-sided 95% confidence intervals (CIs) using normal approximation unless otherwise stated. Descriptive statistics, such as the mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum values, were provided for continuous endpoints.

Efficacy Endpoints

The proportion of patients with ≥35% reduction in spleen volume at Week 24, the proportion of patients with ≥50% reduction in TSS at Week 24, and the proportion of patients ever achieving peripheral blood count improvement (anemia response) were estimated with two-sided 95% CI (using exact method).

The number and percentage of patients who completed the MPN-SAD were summarized. MPN-SAD TSS was summarized using means, medians, SDs, and 95% CIs at each assessment point based on the observed values as well as changes from baseline. The number of patients with symptom improvement (≥50% TSS improvement) together with the estimated percentage and 95% CI was presented.

Pharmacokinetic Endpoints

Standard plasma PK parameters including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC) for glasdegib were estimated using noncompartmental analysis. If data permitted, or if considered appropriate, minimum plasma concentration (C_{min}) and average plasma concentration (C_{avg}) were to be estimated. Descriptive statistics were provided for these PK parameters in tabular form (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle and day.

For glasdegib concentrations, individual values and descriptive statistics (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) were presented by dose, cycle, day of assessment, and nominal time in tabular form.

Outcomes Research Endpoints

MPN-SAD is discussed under Efficacy Endpoints.

Safety Endpoints

AEs were summarized by the frequency of patients experiencing TEAEs corresponding to MedDRA System Organ Class (SOC) and preferred term, and by worst NCI CTCAE (version 4.03) grade. Summaries of treatment-related TEAEs (TRAEs) were also provided. The number and percentage of patients who experienced laboratory test abnormalities were summarized according to worst toxicity grade observed for each assay, graded according to NCI CTCAE version 4.03. The analyses summarized laboratory tests both on the entire study period and by treatment cycle. Shift tables were provided to examine the distribution of laboratory toxicities. For laboratory tests without CTCAE grade definitions, results were categorized as normal, abnormal, or not done.

The analysis of ECG results was based on patients with both baseline and on-treatment ECG data. All ECGs obtained during the study were evaluated for safety. ECGs collected prior to the first day of dosing were considered the baseline ECGs. The triplicate data were averaged and all summary statistics and data presentations used the triplicate averaged data. Data were summarized and listed for QT, heart rate, RR interval, PR interval, QRS, QTcF and QT interval corrected by the Bazett formula; individual corrected QT intervals (all evaluated corrections) were listed by time.

Analysis Sets

The lead-in analysis set consisted of all patients treated in the lead-in portion of the study and was used for all analyses conducted on the lead-in portion of the study.

Additional analysis sets were planned for the randomized cohort, which was not initiated.

RESULTS

Patient Disposition and Demography:

A total of 21 patients were screened, all of whom were assigned to study treatment.

Discontinuation from treatment signified that a patient had permanently stopped taking the study treatment. Up to the primary completion date, a total of 18 patients (85.7%) discontinued from treatment. The most common reasons for discontinuing glasdegib treatment were AEs considered related to glasdegib (10 patients; 47.6%), and insufficient clinical response (3 patients; 14.3%). Of the 3 patients who remained in the study up to LPLV, 1 patient each discontinued glasdegib treatment due to an AE, due to starting a new treatment for the disease under study, and due to study termination by sponsor.

Discontinuation from the study signified that a patient had not only discontinued from treatment but had also discontinued from any follow-up. Ten (47.6%) patients discontinued from the study by the primary completion date. In these 10 patients, the most common reasons for discontinuing participation in the study were patient refused further follow-up (5 patients; 23.8%) and other reasons (4 patients; 19.0%). The "other reasons" were reported as follows: 1 patient was unable to return to the treatment center due to poor condition (considered possibly related to glasdegib), and 3 patients terminated early (survival follow-up was not required for the glasdegib lead-in cohort).

After the primary completion date, an additional 7 patients discontinued from the study: 5 patients due to AEs, and 1 patient each due to study termination by sponsor and starting new treatment for disease under study. In addition, 1 patient previously classified as having refused further follow-up was reclassified as having discontinued due to AE.

A total of 4 patients completed the protocol-specified follow-up period and, therefore, were not classified as having discontinued from the study (Table 15).

Of 21 patients, 13 were male (Table 6); the majority of patients were white (66.7%) and the mean (SD) age was 69.3 (7.0) years.

Table 6. Demographic Characteristics

	Glasdegib Lead-In		
	Male	**Female**	**Total**
Number (%) of patients	13	8	21
Age (years)			
Mean (SD)	68.2 (7.6)	71.0 (6.1)	69.3 (7.0)
Range	58-81	65-83	58-83
Race			
White	10 (76.9)	4 (50.0)	14 (66.7)
Asian	3 (23.1)	4 (50.0)	7 (33.3)

Efficacy, Pharmacokinetic, and Outcomes Research Results:

Efficacy: Primary

The primary efficacy endpoint (achieving ≥35% SVR at Week 24 from baseline in the randomized cohort as assessed by MRI, or CT when applicable, by a central, independent, blinded reader) was not analyzed, as the randomized cohort was not initiated.

Efficacy: Secondary

The following secondary efficacy endpoints were not analyzed: duration of SVR in the randomized cohort and OS in the randomized cohort. Symptom improvement (defined as achieving ≥50% reduction in TSS at Week 24 as measured by the MPN-SAD), peripheral blood count improvement, and overall TSS at Week 24 as measured by MPN-SAD were analyzed only in the glasdegib lead-in cohort, as the randomized cohort was not initiated.

For the secondary endpoint of achieving ≥35% SVR at Week 24 from baseline in the glasdegib lead-in cohort as assessed by MRI, or CT when applicable, by a central, independent, blinded reader, there were no responders (Table 7). Mean spleen volume at Week 24 was increased from baseline for the 6 patients evaluated: mean (SD) absolute change from baseline was 116712.14 (148671.45) mm^3; mean (SD) percentage change from baseline was 8.79% (9.01%).

Table 7. Responders: Percent Change from Baseline in Spleen Volume Reduction ≥35% at Week 24

	Glasdegib Lead-In (N = 21)		
		Change from Baseline	
	Result (mm^3)	mm^3	%
n (%)	6 (28.57)		
Number of responders at Week 24	0		
Mean (SD)	1542870.340 (719261.9024)	116712.137 (148671.4471)	8.793 (9.0111)
1st quartile	1012712.520	-31031.960	-1.993
Median	1402613.570	95869.740	12.337
3rd quartile	2123824.340	273661.900	13.564
Minimum, Maximum	727734.38, 2587723.66	-43179.41, 309082.81	-2.72, 19.24

Patients who were not known to have achieved ≥35% reduction of spleen volume at Week 24 were counted as nonresponders.
The window for Weeks 12 and 24 was -1/+2 weeks.
Overall represents the maximum change from baseline at any postbaseline visit (prior to any further anticancer therapy).
Patients were censored after starting anticancer therapy on another treatment as indicated on the follow-up therapy case report form page - further systemic therapy.
Abbreviations: N=number of patients in the population; n=number of patients in the analysis; SD=standard deviation.

There were no patients who achieved ≥35% SVR during the study.

For the secondary endpoint of reduction from baseline of ≥50% in TSS at Week 24, there was 1 (4.8%) MPN-SAD TSS responder who had a mean change from baseline of -55.0% (Table 8).

Table 8. Percentage of MPN-SAD TSS Responders – 28-Day Average at Week 24

	Glasdegib Lead-In (N = 21)		
	Result	**Change from Baseline**	**% Reduction from Baseline**
n	6		
Number of responders with TSS reduction from baseline ≥50%	1		
% (CI) of responders with TSS reduction from baseline ≥50%	4.8 (0.1, 23.8)		
Overall mean of responders	11.3	-13.6	-55.0

Responders were those patients with change from baseline in TSS ≤-50% (reduction of ≥50%).
Patients were censored after starting anticancer therapy on another treatment as indicated on the follow-up therapy case report form page - further systemic therapy.
Abbreviations: CI=confidence interval; MPN-SAD=Myeloproliferative Neoplasm Symptom Assessment Diary; N=number of patients in the population; n=number of patients in the analysis; TSS=Total Symptom Score.

Peripheral blood count was measured by anemia response, which was defined as transfusion-independent patients with a ≥20 g/L increase in hemoglobin level where baseline hemoglobin level was <100 g/L, or transfusion-dependent patients becoming transfusion-independent). Up to the primary completion date, anemia response was observed in 1 (5.9%) patient (Table 9). The data were not updated after the primary completion date.

Table 9. Anemia Response (Transfusion-Dependent versus Independent)

Postbaseline	Glasdegib Lead-In (N = 21)	
	Transfusion-Dependent at Baseline (N2 = 4)	Transfusion-Independent at Baseline (N2 = 17)
≥20 g/L increase in hemoglobin		
n (%)	-	1 (5.9)
95% CI	-	0.1, 28.7
Duration of ≥20 g/L increase in hemoglobin from baseline (days)		
Mean (SD)	-	92.0 (-)
Minimum, Maximum	-	92, 92
Number of patients transfusion-independent postbaseline among patients dependent at baseline		
n (%)	0	-
95% CI	-	-

Transfusion dependency before start of study treatment was defined as transfusions of ≥6 units of PRBC in the 12 weeks prior to start of study treatment, for a final pretreatment hemoglobin 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 PRBC transfusions during any consecutive rolling 12-week interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L.
Denominator for percentages was the number of patients in the lead-in analysis set. Exact CIs for percentages were calculated using the Clopper-Pearson method.
Abbreviations: CI=confidence interval; N=number of patients in the analysis set; N2=number of patients in the subset; n=number of patients with the characteristic; PRBC=packed red blood cells; SD=standard deviation.

For overall TSS at Week 24 as measured by MPN-SAD (Table 10), the monthly mean change from baseline was -4.95 (5.78) in the lead-in cohort.

Table 10. Overall MPN-SAD TSS

	Glasdegib Lead-In (N = 21)	
	n	Mean (SD) Change from Baseline
Monthly mean at Week 12 (Days 57 – 84)	13	-2.74 (14.07)
Monthly mean at Week 24 (Days 141 – 168)	6	-4.95 (5.78)
Monthly mean at Week 36 (Days 225 - 252)	1	-4.11 (-)
Monthly mean at Week 48 (Days 309 – 336)	2	-8.39 (11.52)

Patients were censored after starting anticancer therapy on another treatment as indicated on the follow-up therapy case report form page - further systemic therapy.
Abbreviations: CI=confidence interval; MPN-SAD=myeloproliferative neoplasm symptom assessment diary; N=number of patients in the population; n=number of patients in the analysis; TSS=Total Symptom Score.

Pharmacokinetics

As the randomized cohort was not initiated, PK was only analyzed in the glasdegib lead-in cohort.

Following administration of 100 mg QD oral dose of glasdegib for 15 days in the glasdegib lead-in cohort, C_{max} generally occurred at 1 hour postdose (T_{max}; Table 11). The geometric mean area under the concentration-time profile from time zero to time τ, the dosing interval, where tau = 24 hours for QD dosing (AUC_{tau}) and C_{max} values were 13150 ng.hr/mL and 996.8 ng/mL, respectively. Interpatient variability for glasdegib exposure (based on %CV of geometric means) in this study was 50% for AUC_{tau} and 45% for C_{max}. The glasdegib predose concentrations (C_{trough}) for the dose-compliant group were consistent over multiple cycles. At Cycle 1 Day 15 (number of patients = 19), Cycle 2 Day 1 (number of patients = 17), and Cycle 3 Day 1 (number of patients = 15), the geometric mean (%CV geometric mean) C_{trough} values were 204.1 ng/mL (61%), 201.0 ng/mL (63%), and 189.5 ng/mL (57%), respectively; 2 patients were dose reduced to 75 mg prior to the Cycle 3 Day 1 PK collection.

Table 11. Summary of Steady State Plasma Glasdegib Pharmacokinetic Parameter Values Following 100 mg QD Oral Dose of Glasdegib for 15 Days (Dose-Compliant Patients)

Parameter, Unit	Parameter Summary Statistics[a] by Treatment
	Glasdegib Lead-In Cohort
N, n	19, 17
AUC_{tau}, ng.hr/mL[*]	13150 (50)
C_{av}, ng/mL[*]	548.0 (50)
C_{max}, ng/mL	996.8 (45)
C_{trough}, ng/mL	204.1 (61)
C_{min}, ng/mL	191.9 (68)
T_{max}, hr	1.02 (0.483-4.00)

[*]Two patients were excluded from AUC_{tau} and C_{av} calculation due to truncated pharmacokinetic profiles up to 6 hours.
Abbreviations: %CV=percent coefficient of variation; AUC_{tau}=area under the concentration-time profile from time zero to time τ, the dosing interval, where tau = 24 hours for once daily dosing; C_{av}=average concentration at steady state; C_{max}=maximum plasma concentration; C_{min}=lowest concentration observed during dosing interval τ; if measured at end of dosing interval; C_{trough}=minimum plasma concentration before next dose; N=number of patients in the treatment group and contributing to the statistical summary; n=number of patients with reportable AUC_{tau} and C_{av}; QD=once daily; T_{max}=time to C_{max}.
a. Geometric mean (%CV) for all except: median (range) for T_{max}.

Outcomes Research

The secondary outcomes research endpoints (PROs of HRQoL and health status, and psychometric validation of the MPN-SAD) were not analyzed, as the randomized cohort was not initiated.

Safety Results:

The primary endpoint in the glasdegib lead-in cohort was safety. Up to the primary completion date, all 21 (100%) patients experienced at least 1 TEAE (Table 12). Of these, 4 (19.0%) patients experienced treatment-emergent SAEs; 1 (4.8%) experienced a Grade 5 TEAE, and 14 (66.7%) patients experienced Grade 3 or 4 TEAEs. Over the entire study duration up to LPLV, a total of 5 (23.8%) patients experienced SAEs.

Up to the primary completion date, 12 (57.1%) patients permanently discontinued from study treatment due to TEAEs (there is a discrepancy in the results in terms of 1 patient who discontinued treatment due to Grade 1 pyrexia; however, the reason for discontinuation was recorded as progressive disease). After the primary completion date, 1 additional patient discontinued from treatment due to AEs.

Table 12. Treatment-Emergent Adverse Events up to the Primary Completion Date (All Causalities)

	Glasdegib Lead-In (N = 21)
Number (%) of patients	
Patients evaluable for AEs	21
Number of AEs	190
Patients with AEs	21 (100.0)
Patients with SAEs	4 (19.0)
Patients with Grade 3 or 4 AEs	14 (66.7)
Patients with Grade 5 AEs	1 (4.8)
Patients discontinued due to AEs	12 (57.1)
Patients with dose reduced due to AEs	1 (4.8)
Patients with temporary discontinuations due to AEs	4 (19.0)
Patients with dose reduced and temporary discontinuation due to AEs	4 (19.0)

Includes 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.
SAEs - according to the investigator's assessment.
Severity counts were based on the maximum severity or grade of events.
MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in the population; SAE=serious adverse event.

There was 1 study-emergent death reported. The death was due to disease progression.

Table 13 summarizes the SAEs reported during the study. Five patients experienced a total of 15 SAEs, of which 8 were TRAEs.

By SOC, the most commonly reported SAEs were: Respiratory, thoracic and mediastinal disorders (2 patients [9.52%] who experienced 3 SAEs, 1 of which [Hypoxia] was a TRAE), General disorders and administration site conditions (2 patients [9.52%] who experienced 2 SAEs, 1 of which [Fatigue] was a TRAE), and Psychiatric disorders (2 patients [9.52%] who experienced 2 SAEs, both of which [Confusional state and Mental status changes] were TRAEs).

By preferred term, no SAE was reported in >1 patient; 1 patient experienced 2 SAEs of Respiratory failure.

Table 13. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All-Causality and Treatment-Related)

System Organ Class Preferred Term	Glasdegib Lead-In Cohort (N = 21) n	 %	 n1	 n2
Number (%) of Patients:				
Evaluable for AEs	**21**			
With AEs	**5**	**23.81**		
Cardiac disorders	**1**	**4.76**	**1**	**1**
Sinus tachycardia	1	4.76	1	1
Gastrointestinal disorders	**1**	**4.76**	**2**	**0**
Gastric varices haemorrhage	1	4.76	1	0
Varices oesophageal	1	4.76	1	0
General disorders and administration site conditions	**2**	**9.52**	**2**	**1**
Disease progression	1	4.76	1	0
Fatigue	1	4.76	1	1
Hepatobiliary disorders	**1**	**4.76**	**1**	**0**
Portal hypertension	1	4.76	1	0
Infections and infestations	**1**	**4.76**	**1**	**1**
Bronchitis	1	4.76	1	1
Injury, poisoning and procedural complications	**1**	**4.76**	**1**	**1**
Postoperative ileus	1	4.76	1	1
Metabolism and nutrition disorders	**1**	**4.76**	**1**	**0**
Failure to thrive	1	4.76	1	0
Nervous system disorders	**1**	**4.76**	**1**	**1**
Memory impairment	1	4.76	1	1
Psychiatric disorders	**2**	**9.52**	**2**	**2**
Confusional state	1	4.76	1	1
Mental status changes	1	4.76	1	1
Respiratory, thoracic and mediastinal disorders	**2**	**9.52**	**3**	**1**
Hypoxia	1	4.76	1	1
Respiratory failure	1	4.76	2	0

Except for 'n1' and 'n2', patients are only counted once per treatment for each row.
MedDRA (version 20.1) coding dictionary applied.
Includes data up to 28 days after last dose of study drug.
Abbreviations: AE=adverse event; N=number of patients in the analysis set; n=number of patients with the characteristic; n1=the number of occurrences of treatment-emergent all-causality AEs; n2=the number of occurrences of treatment-emergent causally related to treatment AEs.

Table 14 summarizes non-serious TEAEs reported in >5% of patients in the glasdegib lead-in cohort.

The most common all-causality TEAEs by SOC were Musculoskeletal and connective tissue disorders (reported in 15 patients [71.43%] who experienced 40 TEAEs, of which 28 were considered TRAEs) and Skin and subcutaneous tissue disorders (reported in 15 patients [71.43%] who experienced 25 TEAEs, of which 12 were considered TRAEs). The third most common SOC was Nervous system disorders (reported in 14 patients [66.67%] who experienced 26 TEAEs, of which 21 were considered TRAEs).

By preferred term, the most common all-causality TEAEs were Dysgeusia (reported in 13 patients [61.90%] who experienced 17 TEAEs, all of which were considered TRAEs), Muscle spasms (reported in 12 patients [57.14%] who experienced 20 TEAEs, of which

18 were considered TRAEs), and Alopecia (8 patients [38.10%] who experienced 10 TEAEs, all of which were considered TRAEs).

Table 14. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All-Causality and Treatment-Related) Reported in >5% of Patients

System Organ Class	Glasdegib Lead-In Cohort (N = 21)			
Preferred Term	**n**	**%**	**n1**	**n2**
Number (%) of Patients:				
Evaluable for AEs	21			
With AEs	21	100.00		
Blood and lymphatic system disorders	**9**	**42.86**	**16**	**8**
Anaemia	5	23.81	6	3
Neutropenia	2	9.52	3	2
Thrombocytopenia	3	14.29	4	1
Gastrointestinal disorders	**12**	**57.14**	**24**	**12**
Abdominal pain	2	9.52	2	0
Abdominal pain upper	2	9.52	2	1
Constipation	3	14.29	3	2
Diarrhoea	2	9.52	2	2
Dry mouth	2	9.52	2	2
Nausea	4	19.05	4	2
General disorders and administration site conditions	**11**	**52.38**	**27**	**9**
Asthenia	3	14.29	5	3
Fatigue	7	33.33	9	5
Pyrexia	4	19.05	6	0
Infections and infestations	**6**	**28.57**	**11**	**3**
Upper respiratory tract infection	3	14.29	5	0
Injury, poisoning and procedural complications	**4**	**19.05**	**6**	**2**
Fall	2	9.52	3	2
Investigations	**13**	**61.90**	**26**	**20**
Electrocardiogram QT prolonged	3	14.29	5	5
Lipase increased	5	23.81	10	8
Lymphocyte count decreased	3	14.29	3	0
Weight decreased	6	28.57	8	7
Metabolism and nutrition disorders	**12**	**57.14**	**21**	**11**
Decreased appetite	7	33.3	7	7
Dehydration	3	14.29	3	0
Hyperglycaemia	2	9.52	2	0
Hyperuricemia	4	19.05	4	1
Musculoskeletal and connective tissue disorders	**15**	**71.43**	**40**	**28**
Back pain	2	9.52	2	1
Muscle spasms	12	57.14	20	18
Myalgia	3	14.29	3	3
Pain in extremity	3	14.29	3	2
Nervous system disorders	**14**	**66.67**	**26**	**21**
Dizziness	3	14.29	4	3
Dysgeusia	13	61.90	17	17
Respiratory, thoracic and mediastinal disorders	**7**	**33.33**	**12**	**4**
Cough	3	14.29	3	0
Dyspnoea exertional	2	9.52	3	1
Skin and subcutaneous tissue disorders	**15**	**71.43**	**25**	**12**
Alopecia	8	38.10	10	10

Table 14. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All-Causality and Treatment-Related) Reported in >5% of Patients

System Organ Class	Glasdegib Lead-In Cohort (N = 21)			
Preferred Term	**n**	**%**	**n1**	**n2**
Night sweats	2	9.52	2	0
Pruritus	2	9.52	3	1
Pruritus generalised	2	9.52	2	0
Rash	3	14.29	3	1

Except for 'n1' and 'n2', patients are only counted once per treatment for each row.
MedDRA (version 20.1) coding dictionary applied.
Includes data up to 28 days after last dose of study drug.
Abbreviations: AE=adverse event; N=number of patients in the analysis set; n=number of patients with the characteristic; n1=the number of occurrences of treatment-emergent all-causality AEs; n2=the number of occurrences of treatment-emergent causally related to treatment AEs.

Table 15 summarizes discontinuations from the study. In total, 17 patients discontinued from the study. The most common reason for discontinuation was other (11 patients [52.4%]).

Table 15. Discontinuations from Study

	Glasdegib Lead-In Cohort (N = 21)	
	n	**%**
Patient died	1	4.8
Relationship to glasdegib not defined	16	76.2
Other	11	52.4
Study terminated by sponsor	1	4.8
Patient refused further follow-up	4	19.0
Completed	4	19.0
Total	**21**	**100.0**

Abbreviations: N=number of patients in the analysis set; n=number of patients with the characteristic.

CONCLUSION(S):

- There was 1 study-emergent death due to disease progression. A total of 5 patients experienced SAEs. By preferred term, no SAE was reported in >1 patient; 1 patient experienced 2 SAEs of Respiratory failure.

- The safety profile of glasdegib is manageable in this population. No new safety concerns have arisen during this study.

- Extended exposure to glasdegib in this population was not accompanied by any observed increase in toxicity and there have been no consistent patterns of AEs or abnormal laboratory results.

- Although the key secondary efficacy endpoint of SVR was not met, glasdegib may improve MF symptoms in this population of pretreated patients based upon PRO measures.

- In conclusion, further study of glasdegib in MF patients may be warranted.