Official Title: A PHASE II, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF IDASANUTLIN MONOTHERAPY IN PATIENTS WITH HYDROXYUREA-RESISTANT/INTOLERANT POLYCYTHEMIA VERA

NCT Number: NCT03287245

Document Date: Protocol Version 3: 01-July-2019

PROTOCOL

TITLE:	**A PHASE II, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF IDASANUTLIN MONOTHERAPY IN PATIENTS WITH HYDROXYUREA-RESISTANT/INTOLERANT POLYCYTHEMIA VERA**
PROTOCOL NUMBER:	NP39761
VERSION NUMBER:	3
EUDRACT NUMBER:	2017-000861-58
IND NUMBER:	117005
TEST PRODUCT:	Idasanutlin (RO5503781)
MEDICAL MONITOR:	[redacted], *M.D., DMSc*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 10 May 2017
DATES AMENDED:	Version 2: 15 February 2018 Version 3: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
01-Jul-2019 15:52:40	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol NP39761 has been amended to clarify and provide additional detail to allow for logistical or pragmatic concerns with implementation. Changes to the protocol, along with a rationale for each change, are summarized below:

- The definition of ruxolitinib resistance or intolerance has been introduced to formally assess the efficacy of idasanutlin in this patient population, based on protocol-defined criteria. Accordingly, Table 3 has been updated to distinguish between ruxolitinib-naive and ruxolitinib-exposed patients for response assessment.
- The study design (Section 4) has been updated to include details on enrollment of ruxolitinib resistant or intolerant patients. An expansion cohort has been added as an option in this patient population if initial results warrant further evaluations of the safety and activity of idasanutlin monotherapy in this subpopulation. In addition, the study schema (Figure 1) and the statistical analysis section (Section 9.2) have also been updated.
- Mandatory anti-emetic prophylaxis and management of gastrointestinal toxicity has been updated in Sections 6.1.1 and 8.3.9.1, respectively, for better mitigation of gastrointestinal toxicity.
- The dosage has been updated with the 150-mg strength tablet, as this is now available (Table 4).
- The dose-escalation decision criteria after Cycle 3 have been updated in Sections 4.1 and 6.6 to allow flexibility and accommodate individual patient needs on case of inadequately controlled leukocytosis and/or thrombocytosis in addition to the previously used hematocrit control/composite response.
- Language has been updated to indicate that therapeutic or elective abortions are not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a serious adverse event. Language has also been added to clarify that all abortions are to be reported on the paper Clinical Trial Pregnancy Reporting Form (Section 5 of Appendix 6). As a result of this change, minor clarifications have also been made in Section 8.3.6.
- The guidelines for managing hematologic toxicity (Section 8.3.9.2, Table 8) have been updated to enhance clarity and allow patients to benefit from idasanutlin treatment in case of clinically insignificant thrombocytopenia. Furthermore, the guideline provides detailed recommendations on management of cytopenias.
- Time window for bone marrow examinations at screening is extended from –28 days to –35 days to avoid unnecessary repeat of an invasive procedure (Section 1.3, Table 1).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Appendix 7).

- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Appendix 7).
- Language has been added to clarify that, after withdrawal of consent for participation in the Research Biosample Repository (RBR), remaining RBR samples will be destroyed or will no longer linked to the patient. In addition, instructions about patient withdrawal from the RBR after site closure have been modified to indicate that the investigator must inform the Sponsor of patient withdrawal by emailing the study number and patient number to global_rcr-withdrawal@roche.com (Appendix 7).
- Samples for health-related questionnaires are added (Appendices 14–16).
- A clarification has been made to the Schedule of Activities to state that patients without baseline splenomegaly according to protocol definition will not need re-assessment with imaging of spleen except for Week 32 for European Leukemia Net (ELN) response assessment (Table 1, footnote 16). Furthermore, the definition of splenomegaly in an inclusion criterion has been updated to avoid contradiction between palpation findings and imaging (Section 5.1).
- Complete hematologic remission at Cycle 11 Day 28 and the definition for duration of response has been included as secondary endpoints for all populations (Table 3).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF IDASANUTLIN MONOTHERAPY IN PATIENTS WITH HYDROXYUREA-RESISTANT/INTOLERANT POLYCYTHEMIA VERA**
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MEDICAL MONITOR:	[redacted], *M.D., DMSc*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please keep the signed original form in your study files, and return a copy to your local Study Monitor.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
CHR	Complete hematologic response
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
C_{max}	Maximum concentration
CNS	Central nervous system
COA	Clinical outcome assessment
CR	*Complete response*
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLT	Dose-limiting toxicities
DNA	Deoxyribonucleic acid
DRE	disease-related event
EC	Ethics Committee
ECG	Electrocardiograms
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
ELN	European Leukemia Net
EORTC QLQ-C30	*European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30*
EOS	End of study
ESF	Eligibility screening form
ET	Essential thrombocythemia
EU	European Commission
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone

Abbreviation	Definition
GI	Gastrointestinal
HBsAG	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
Hct	Hematocrit
HCV	Hepatitis C
HDL	High-density lipoproteins
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	*Health-related quality of life*
HU	Hydroxyurea
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IRF	Independent review facility
IUD	Intrauterine device
IV	Intravenous*(ly)*
IxRS	*Interactive voice or web-based response system*
JAK-STAT	Janus kinase-signal transducer and activator of transcription
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LH	Luteinizing hormone
LPLV	Last patient, last visit
MAD	Multiple-ascending doses
MD	Multiple doses
MDM2	Murine double minute 2
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MPN	Myeloproliferative neoplasm
MPN-SAF TSS	*MPN symptom assessment form total symptom score*
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect level

Abbreviation	Definition
NR	No response
OATP1B1	Organic anion transporting polypeptide 1B1
OTC	Over-the-counter
PD	Progressive disease
PHR	Partial hematologic response
PK	Pharmacokinetic
PLT	Platelet
PMF	Primary myelofibrosis
PR	Partial response
PRN	*pro re nata (a*s needed*)*
PT	Prothrombin time
PV	Polycythemia vera
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia correction factor
RA	*Receptor antagonist*
RBC	Red blood cell
RBR	Research Biosample Repository
RNA	Ribonucleic acid
RR	RR interval
SAD	Single-ascending dose
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SD	Single dose
SDP	Spray-dried powder
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Elimination half-life
t_{max}	Time of maximum concentration observed
TQT	Thorough QT
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UGT	Uridine diphosphate (UDP)-glucuronosyltransferase
US	United States
V_d	Volume of distribution
VAS	Visual analogue scale
V_d/F	Apparent volume of distribution
WBC	White blood cell

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE II, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF IDASANUTLIN MONOTHERAPY IN PATIENTS WITH HYDROXYUREA-RESISTANT/INTOLERANT POLYCYTHEMIA VERA**
SHORT TITLE	Idasanutlin monotherapy in patients with hydroxyurea-resistant/intolerant polycythemia vera
PROTOCOL NUMBER:	NP39761
VERSION NUMBER:	3
EUDRACT NUMBER:	2017-000861-58
IND NUMBER:	117005
TEST PRODUCT:	Idasanutlin (RO5503781)
PHASE:	II
INDICATION:	Polycythemia vera
SPONSOR:	F. Hoffmann-La Roche Ltd

RATIONALE

The tumor suppressor p53 is a powerful growth suppressive and pro-apoptotic protein that plays a central role in protection from tumor development and is frequently inactivated in human cancer. Murine double minute homolog 2 (MDM2) regulates p53 through a negative feedback loop.

More than 95% of patients with the hematopoietic stem cell malignancy polycythemia vera (PV) have been found to have the constitutively-activated JAK2 mutant V617F allele which dysregulates MDM2, leading to a decrease in p53 activation.

Idasanutlin (RO5503781) is a selective inhibitor of the p53-MDM2 binding which frees p53 from negative control and activates the p53 pathway. Therefore, it may allow for an increase in p53 activity and decrease of the malignant proliferation seen in PV.

An Investigator-led, open label Phase I study of single agent oral idasanutlin in patients with PV and essential thrombocythemia (ET) is currently ongoing, with 12 patients in total having received idasanutlin at 100 mg (n=6) and 150 mg (n=6) given once daily for five consecutive days. Preliminary observations indicate that treatment with 5 days of idasanutlin, at doses lower than the maximum tolerated dose (MTD) identified in previous studies in solid tumor and acute myeloid leukemia (AML) patients, shows promising efficacy and can control hematocrit (Hct) levels in PV patients. These early results support the inhibition of the MDM2-p53 interaction as an important pathway in treatment of this disease.

OBJECTIVES AND ENDPOINTS

Ruxolitinib-Naive Patients:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of idasanutlin monotherapy in patients with HU resistant/intolerant PV *and **without prior ruxolitinib** exposure*: – For patients **with splenomegaly at baseline** using composite response criteria – For patients **without splenomegaly at baseline** by Hct control without phlebotomy – For all patients (with and without splenomegaly) by Hct control without phlebotomy	• Composite response at Week 32 for patients **with splenomegaly at baseline** (per inclusion criteria) defined as: – Hct control defined as protocol-specified ineligibility for phlebotomy between Week 8-Week 32 and ≤1 instance of phlebotomy eligibility between first dose and Week 8 – ≥35% reduction in spleen volume at Week 32 • Hct control in patients **without splenomegaly at baseline** and in all patients (with and without splenomegaly); defined as protocol-specified ineligibility for phlebotomy between Week 8–Week 32 and ≤ 1 instance of phlebotomy eligibility between first dose and Week 8 Definition of eligibility for phlebotomy: a Hct of ≥45% that was ≥3% higher than baseline level or a Hct of > 48%
Secondary	
• *To evaluate the efficacy of idasanutlin monotherapy in all patients (with and without splenomegaly) by complete hematologic response*	• *Complete hematologic response at Week 32* *Complete hematologic response requires **all** of the following:* – *Hct control (protocol-specified ineligibility for phlebotomy between Weeks 8–32 and ≤1 instance of phlebotomy eligibility between first dose and Week 8);* – *White blood cell count ≤10 ×10⁹/L at Week 32 assessment; AND* – *Platelet count ≤400 ×10⁹/L at Week 32 assessment* • *Complete hematologic remission at response Cycle 11 Day 28 defined as patients with all of the following:* – *Hct control defined as protocol specified ineligibility for phlebotomy between Week 32 assessment and Cycle 11 Day 28* – *White blood cell count ≤10 ×10⁹/L at Cycle 11 Day 28 assessment; AND* – *Platelet count ≤400 ×10⁹/L at Week 32 assessment* • *Duration of complete hematologic remission response with a durable responder defined as a subject in remission at Week 32 and Cycle 11 Day 28, as defined above*

Objectives	Endpoints
• To evaluate the efficacy of idasanutlin monotherapy by using modified ELN hematologic response criteria (complete and partial response) in patients with baseline splenomegaly, patients without baseline splenomegaly and in *all* patient*s irrespective of spleen size*	• Response by using modified ELN hematologic response criteria: – Complete response – Partial response – NR – Progressive disease - as defined by increased bone marrow fibrosis from baseline, and/or transformation to MF, MDS or acute leukemia • Duration of response, including proportion of patients with durable response lasting at least 12 weeks *(Cycle 11 Day 28) from Week 32 (Cycle 8 Day 28) (Hct control, CHR, ELN 2009 response and composite response, if applicable)*
• To evaluate the safety of idasanutlin monotherapy in patients with HU resistant/intolerant PV *and without prior ruxolitinib exposure*	• Clinical safety laboratory tests (hematology, clinical chemistry, urinalysis, pregnancy testing) • Incidence, nature and severity of AEs graded according to the NCI CTCAE v4.0 • Incidence and severity of AEs, including targeted AEs • ECOG PS, ECG, vital signs • Concomitant medication
• To characterize the pharmacokinetic (PK) parameters of idasanutlin and M4 metabolite in patients with HU resistant/intolerant PV.	• C_{max}, C_{trough}, t_{max}, CL, CL/F, Vd_{ss}, AUC, $t_{1/2}$, and potentially other parameters derived.
• To evaluate the effect of treatment with idasanutlin on the symptoms of PV, physical functioning, general health status/*HR*QoL, and change in condition in all enrolled patients, as well as in those with and without baseline splenomegaly	• Mean and mean change from baseline to each assessment: – MPN symptom assessment form total symptom score (MPN-SAF TSS) – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) • *D*istribution of responses at each assessment *and across time*: – Patient Global Impression of Change scale

Ruxolitinib-Resistant or Intolerant Patients:

Objectives	*Endpoints*
Primary	
• *To evaluate the efficacy of idasanutlin monotherapy:* – *by Hct control without phlebotomy*	• *Hct control is defined as protocol-specified ineligibility for phlebotomy between Week 8-Week 32 and ≤1 instance of phlebotomy eligibility between first dose and Week 8* *Definition of eligibility for phlebotomy: a Hct of ≥45% that was ≥ 3% higher than baseline level or a Hct of >48%*
Secondary	
• *To evaluate the efficacy of idasanutlin monotherapy by complete hematologic response*	• *Complete hematologic response at Week 32* *Complete hematologic response requires **all** of the following:* – *Hct control (protocol-specified ineligibility for phlebotomy between Weeks 8–32 and ≤1 instance of phlebotomy eligibility between first dose and Week 8);* – *White blood cell count ≤10 ×10⁹/L at Week 32 assessment; AND* – *Platelet count ≤400 ×10⁹/L at Week 32 assessment* • *Complete hematologic remission at response Cycle 11 Day 28 defined as patients with all of the following:* – *Hct control defined as protocol specified ineligibility for phlebotomy between Week 32 assessment and Cycle 11 Day 28* – *White blood cell count ≤10 ×10⁹/L at Cycle 11 Day 28 assessment; AND* – *Platelet count ≤400 ×10⁹/L at Week 32 assessment* • *Duration of complete hematologic remission response with a durable responder defined as a subject in complete hematologic remission at Week 32 and Cycle 11 Day 28, as defined above*
• *To evaluate the efficacy of idasanutlin monotherapy by using modified ELN hematologic response criteria (complete and partial response) in patients with baseline splenomegaly, patients without baseline splenomegaly and in all patients irrespective of spleen size*	• *Response by using modified ELN hematologic response criteria:* – *Complete response* – *Partial response* – *NR* – *Progressive disease, as defined by increased bone marrow fibrosis from baseline, and/or transformation to MF, MDS or acute leukemia* • *Duration of response, including proportion of patients with durable response lasting at least 12 weeks from Week 32 (Hct control, CHR, ELN 2009 response and composite response, if applicable)*

Objectives	*Endpoints*
• *To evaluate the safety of idasanutlin monotherapy in patients with HU resistant/intolerant PV and ruxolitinib resistant/intolerant patients*	• *Clinical safety laboratory tests (hematology, clinical chemistry, urinalysis, pregnancy testing)* • *Incidence, nature and severity of AEs graded according to the NCI CTCAE v4.0* • *Incidence and severity of AEs, including targeted AEs.* • *ECOG PS, ECG, vital signs* • *Concomitant medication*
• *To characterize the pharmacokinetic (PK) parameters of idasanutlin and M4 metabolite in patients with HU resistant/intolerant PV*	• *C_{max}, C_{trough}, t_{max}, CL, CL/F, Vd_{ss}, AUC, $t_{1/2}$, and potentially other parameters derived.*
• *To evaluate the effect of treatment with idasanutlin on the symptoms of PV, physical functioning, general health status/HRQoL, and change in condition in all enrolled patients, as well as in those with and without baseline splenomegaly*	• *Mean and mean change from baseline to each assessment:* – *MPN symptom assessment form total symptom score (MPN-SAF TSS)* – *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30)* • *Distribution of responses at each assessment and across time:* – *Patient Global Impression of Change scale*

All Patients, Irrespective of Prior Ruxolitinib Exposure:

Objectives	*Endpoints*
Secondary	
• *To evaluate the safety of idasanutlin monotherapy in patients with HU resistant/intolerant PV irrespective of ruxolitinib exposure (all patients)*	• *Clinical safety laboratory tests (hematology, clinical chemistry, urinalysis, pregnancy testing)* • *Incidence, nature and severity of AEs graded according to the NCI CTCAE v4.0* • *Incidence and severity of AEs, including targeted AEs.* • *ECOG PS, ECG, vital signs* • *Concomitant medication*
Tertiary/Exploratory	
• To assess the relationship between PK exposure and clinical responses, including AEs	• Concentration-time profiles following administration of idasanutlin or derived (or modeled/simulated) parameters will be correlated with clinical endpoints including PD and AEs
• To assess the pharmacodynamic effects of idasanutlin by serum MIC-1 levels	• Serum MIC-1 profile (raw and/or adjusted from baseline as percentage of change)
• To explore the molecular response to idasanutlin	• Molecular response by percent reduction from baseline in JAK2V617F or JAK exon 12 allele

	burden after treatment with idasanutlin
Objectives	**Endpoints**
• To measure the histologic response (via bone marrow histology)	• Histologic response changes in bone marrow including histopathologic abnormalities and reduction in baseline reticulin/collagen fibrosis (with fibrosis grading per European consensus on grading bone marrow fibrosis and degree of cellularity at Week 32 • Number of patients with transformation to myelofibrosis, MDS, or acute leukemia
• To explore the cytogenic response (cytogenetics) to idasanutlin compared to baseline	• Loss or gain of karyotypic abnormalities in response to treatment with idasanutlin
• To evaluate potential predictive, pharmacodynamic and response assessment biomarkers for idasanutlin in PV	• Characterization of protein, nucleic acid, and other tissue derived biomarkers relating to the proposed mechanism of action of idasanutlin and response to treatment which may include, but are not limited to, nucleic acid-based analysis of JAK2 and TP53 mutation status (via gene sequencing) and gene expression signatures • Flow cytometry of MDM2 expression in CD34+ cells • Determination of absolute counts and percentages of mature T, B, and NK lymphocyte populations as well as CD4+ and CD8+ T-cell subset ratios

AE=adverse event; AUC=area under the curve; CL=clearance; CL/F=apparent clearance; C_{max}=maximum concentration; C_{trough}=trough concentration; ECOG PS=Eastern Cooperative Oncology Group performance status; *EORTC QLQ-C30 =European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30;* Hct=hematocrit; HU=hydroxyurea; MDM2=murine double minute 2; MDS=myelodysplastic syndrome; MF=myelofibrosis; MPN=myeloproliferative neoplasm; *MPN-SAF TSS =MPN symptom assessment form total symptom score;* NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PD=progressive disease; PGIC=Patient Global Impression of Change ; PK=pharmacokinetic; PV=polycythemia vera; *HR*QoL=*health-related* quality of life; $t_{1/2}$=elimination half-life; t_{max}=time of maximum concentration observed; Vd_{ss}=volume of distribution at steady state.

OVERALL DESIGN

Study Design

This is an open-label, single-arm, study of idasanutlin monotherapy in patients with hydroxyurea (HU)-resistant/intolerant PV.

The study will include two phases: initial phase and expansion phase. The initial phase will assess the safety and efficacy of idasanutlin monotherapy in ruxolitinib naive and ruxolitinib-resistant or intolerant patients, respectively. If the initial phase shows promising results for ruxolitinib-resistant or intolerant patients, an expansion phase with the purpose of registration will be opened to further characterize the efficacy of idasanutlin.

Initial Phase of the Study for Both Ruxolitinib-Naïve and Ruxolitinib-Resistant or Intolerant Patients

*For ruxolitinib-naïve patients, t*he primary endpoint is efficacy , defined as response at Week 32:

- Hct control and ≥35% reduction in spleen volume in patients with splenomegaly
- Hct control in patients without splenomegaly
- Hct control in all patients (with and without splenomegaly)

For ruxolitinib-resistant or intolerant patients, the primary endpoint is efficacy, defined as response at Week 32:

- *Hct control*

Assessments earlier than Week 32, i.e., after Cycles 3 and 5, may enable understanding of whether idasanutlin-driven efficacy is apparent earlier.

All patients will be treated and assessed according to the Schedule of Activities (SoA) for up to 2 years after the first dose.

Expansion Phase for Ruxolitinib-Resistant or Intolerant Patients

For ruxolitinib-resistant or intolerant patients, an expansion phase with identical treatment schedule as the initial phase will be opened at the Sponsor's discretion if data from the initial phase of the study indicate a clear signal of a positive benefit/risk profile, as described in the protocol. This expansion cohort will include approximately 40 additional patients to further characterize the efficacy and safety of idasanutlin in PV patients who are ruxolitinib-resistant or intolerant.

Treatment Groups and Duration

The investigational medicinal product (IMP) in this study is idasanutlin (RO5503781) 50 mg and 200 mg film-coated tablets for oral administration.

All patients will receive 150 mg idasanutlin orally, once daily for five consecutive days every 28 days. Intra-patient dose-escalation to 200 mg daily for 5 days may be permitted after Cycle 3 for patients who *demonstrate no* Hct control *and/or for patients with inadequately controlled leukocytosis and/or thrombocytosis in which the investigator judges that better control is important.*

Length of Study

The total duration of the study for each patient will be up to 112 weeks divided as follows:

- Screening Period: up to 28 days (4 weeks)
- Treatment Period: begins with Cycle 1 Day 1 and continues with repeating treatment cycles until patients discontinue study treatment or at end of study (EOS; defined as 2 years [104 weeks] post initial dose)
- Safety follow-up: until at least 28 days (4 weeks) after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first

End of Study

The EOS is defined as the date when the last data point from the last patient is received, which is expected to be up to 28 days post final dose.

EOS for each patient is defined as 2 years post initial dose.

PATIENT POPULATION

All patients must be diagnosed with PV and resistant or intolerant to HU.

NUMBER OF PATIENTS

Approximately 20 *efficacy-evaluable* patients without prior ruxolitinib therapy *and approximately 20 efficacy-evaluable patients who are resistant or intolerant to ruxolitinib* will be enrolled *in the initial phase of the study. Up to 20 a*dditional *efficacy-evaluable ruxolitinib-naïve* patients may be enrolled *in the initial phase of the study* for confirmation of response,

safety, and/or pharmacokinetic (PK) *at the discretion of the Sponsor (maximum overall 40 efficacy-evaluable ruxolitinib-naïve patients).*

INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA

Patients are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Ability to understand and willingness to sign a written informed consent form and comply with the study protocol according to ICH and local regulations.

Age

2. Adults > 18 years of age

Type of Patients and Disease Characteristics

3. Documentation that the patient meets the revised 2016 WHO criteria for the diagnosis of polycythemia vera. Diagnosis requires the presence of all three major criteria, or the first two major criteria and the minor criterion. To verify that the criteria have been met, appropriate laboratory or pathology reports must be submitted during screening demonstrating that the patient has documentation of these diagnostic criteria. These reports do not have to exactly coincide with the original date of diagnosis.
   - Major Criteria:
     a) Hemoglobin > 16.5 g/dL in men, > 16.0 g/dL in women OR Hct > 49% in men, > 48% in women, OR other evidence of increased red cell mass.
     b) Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size).
     c) Presence of JAK2V617F or JAK2 exon 12 mutation.
   - Minor Criteria:
     - Serum erythropoietin level below the reference range for normal.

     NOTE: Major criterion number b) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels > 18.5 g/dL in men (Hct, 55.5%) or > 16.5 g/dL in women (Hct, 49.5%) if major criterion c) and the minor criterion are present.
4. Hct at screening and initiation of idasanutlin > 40%.
5. Phlebotomy-dependent patients with splenomegaly by magnetic resonance imaging (MRI) or computerized tomography (CT) imaging (≥ 450 cm^3) or without splenomegaly (< 450 cm^3 or prior splenectomy).

   Phlebotomy dependence is defined as at least one phlebotomy within 16 weeks before screening.
6. Resistance to/intolerance to hydroxyurea according to modified *European Leukemia Net* (ELN) criteria:
   - Resistance to HU is defined at a dose ≥ 2 g/day or a maximum tolerated dose < 2 g/day resulting in at least one of the following:
     - Need for phlebotomy to maintain Hct < 45% after 3 months of HU.
     - Platelet (PLT) count > 400×10^9/L and white blood cell (WBC) count > 10×10^9/L after 3 months of HU.
     - Failure to reduce splenomegaly extending > 10 cm below the costal margin by > 50%, as measured by palpation after 3 months of HU.
   - Intolerance to HU is defined as at least one of the following:
     - Absolute neutrophil count (ANC) < 1.0×10^9/L.

- PLT count $< 100 \times 10^9$/L or hemoglobin < 100 g/L (i.e., 10 g/dL) at the lowest dose of HU required to achieve a response.
- Presence of leg ulcers or other unacceptable HU-related non-hematologic toxicities (such as mucocutaneous manifestations, gastrointestinal [GI] symptoms, pneumonitis, or fever at any dose of HU).

For patients previously exposed to ruxolitinib, inclusion requires the following in addition to previous treatment for myeloproliferative disorder with HU:

- *Therapy resistant PV after at least 6 months of treatment with ruxolitinib, defined by at least one of following:*
  - *Need for phlebotomy to achieve Hct <45%, at least two over 6 months*
  - *Uncontrolled leukocytosis (WBC count $>10 \times 10^9$/L)*
  - *Uncontrolled thrombocytosis (PLT count $>400 \times 10^9$/L)*
  - *Failure to achieve a >50% reduction in palpable splenomegaly measuring >5 cm from the left costal margin or failure to become non-palpable in palpable splenomegaly measuring 0–5 cm*
  - *Inadequately controlled disease-related symptoms (e.g., pruritus, headache, night sweats, excluding fatigue) after excluding other causes*
- *Ruxolitinib intolerance defined as at least one of following at lowest dose of ruxolitinib to achieve adequate response:*
  - *Cytopenia defined as one or more of the following:*

    Neutropenia, ANC $<1.0 \times 10^9$/L

    Thrombocytopenia, PLT count $<100 \times 10^9$/L

    Anemia, hemoglobin <10 g/dL
  - *Life threatening infections deemed associated with ruxolitinib or other infections complications possibly associated with ruxolitinib (shingles, TB, hepatitis reactivation) at any time during study treatment*
  - *Non-melanoma skin cancer (recurrence of or multiple) at any time during study treatment*

7. *Adverse events likely caused by ruxolitinib (assessment of attending physician) and that is of a severity that precludes further treatment with ruxolitinib (as per judgment of the attending physician and the patient)*
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
9. Patients must be willing to submit the blood sampling and bone marrow sampling for the PK and pharmacodynamic analyses and exploratory biomarkers.
10. Adequate hepatic function assessed by:
    - Serum total bilirubin < 2 mg/dL, unless resulting from hemolysis or known Gilbert's disease.
    - AST/ALT $< 2.5 \times$ institutional ULN.
11. Adequate renal function assessed by serum creatinine within reference lab normal limits OR creatinine clearance ≥ 50 mL/min calculated by the Cockcroft Gault formula.
12. Patients must meet all of the general inclusion criteria listed above prior to dosing on Cycle 1, Day 1 (including ECOG and labs checked following initial screening eligibility verification) when screening performed > 72 hours from start of treatment.
13. Ability and willingness to comply with the study protocol procedures, including clinical outcome assessment (COA) measures.

Contraception

14. Male and/or female patients:
    a) Male Patients:

       Agreement to use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

       With female partners of childbearing potential or pregnant female partners, men must use a condom during the treatment period and for at least 90 days after the last dose of idasanutlin. Men must refrain from donating sperm during this same period.

    b) Female Patients:

       For women of childbearing potential: agreement to use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 6 weeks after the last dose of idasanutlin.

       A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (at least 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

       Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation; male sterilization; established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices; and copper intrauterine devices.

EXCLUSION CRITERIA

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Patient meets the criteria for post-PV myelofibrosis (MF) as defined by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT).
2. Blast phase disease ($>20\%$ blasts in the marrow or peripheral blood).
3. Clinically-significant thrombosis within 3 months of screening.

Prior/Concomitant Therapy

4. Patients who must receive CYP2C8 inhibitors, substrates and inducers, strong CYP3A4 inducers, or OATP1B1/3 substrates while on study. These must be discontinued 7 days (inhibitors and substrates) or 14 days (inducers) prior to start of study medication.

   Treatment with the following agents within 7 days prior to the first dose of idasanutlin:

   - CYP2C8 inhibitors such as gemfibrozil (also a UGT1A3 inhibitor)
   - CYP2C8 substrates such as repaglinide
   - OATP1B1/3 substrates such as statin drugs

   Treatment with the following agents within 14 days prior to the first dose of idasanutlin:

   - Strong CYP3A inducers such as rifampin (also a CYP2C8 inducer) and carbamazepine

   Chronic use of CYP2C8 or OATP1B1/3 substrates during treatment with idasanutlin is prohibited.
5. Patients previously treated with MDM2 antagonist therapies or patients receiving interferon-alpha, anagrelide, or ruxolitinib within 28 days or 5 half-lives (whichever is shorter), or HU within 1 day, or patients receiving any other cytoreductive or investigational agents within 28 days or 5 half-lives (whichever is shorter) of initial dose. Aspirin is permitted per treatment guidelines for PV unless medically contraindicated.

Other Exclusions

6. Patients with evidence of electrolyte imbalance such as hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypermagnesemia of Grade >1 intensity, as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 prior to dosing on Cycle 1 Day 1. Treatment for correction of electrolyte imbalances is permitted to meet eligibility.
7. Neutrophil count $<1.5\times10^9$/L prior to dosing on Cycle 1 Day 1.
8. PLT count $\leq150\times10^9$/L prior to dosing on Cycle 1 Day 1.
9. Women who are pregnant or breastfeeding.
10. Ongoing serious non-healing wound, ulcer, or bone fracture.
11. History of major organ transplant.
12. Uncontrolled intercurrent illness including, but not limited to, concurrent malignancy that could affect compliance with the protocol or interpretation of results, hepatitis A, B, and C, human immunodeficiency virus (HIV)-positive, ongoing or active infection, clinically significant cardiac disease (New York Heart Association Class III or IV), symptomatic congestive heart failure, unstable angina pectoris, ventricular arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

    Concurrent malignancy exceptions include: Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer. Any previously treated early-stage non-hematological malignancy that has been in remission for at least 2 years is also permitted.
13. Patients with active GI conditions (Crohn's disease, ulcerative colitis, diverticulosis associated colitis, and Behçet's disease).
14. Clinically significant toxicity (other than alopecia) from prior therapy that has not resolved to Grade ≤1 (according to the NCI CTCAE, v4.0) prior to Day 1 Cycle 1

CONCOMITANT MEDICATIONS

Permitted Medication

- Megestrol administered as an appetite stimulant is acceptable when the patient is enrolled in the study.
- Since nausea is a commonly reported adverse event in previous studies, *anti-emetic* prophylaxis is mandatory *prior to each cycle, unless otherwise agreed upon between the investigator and the Medical Monitor*.
- Phlebotomy can occur anytime if clinically warranted per institutional guidelines.
- Institutional guidelines for use of growth factor support, transfusions, and antibiotics should be followed with consideration for prohibited medications.

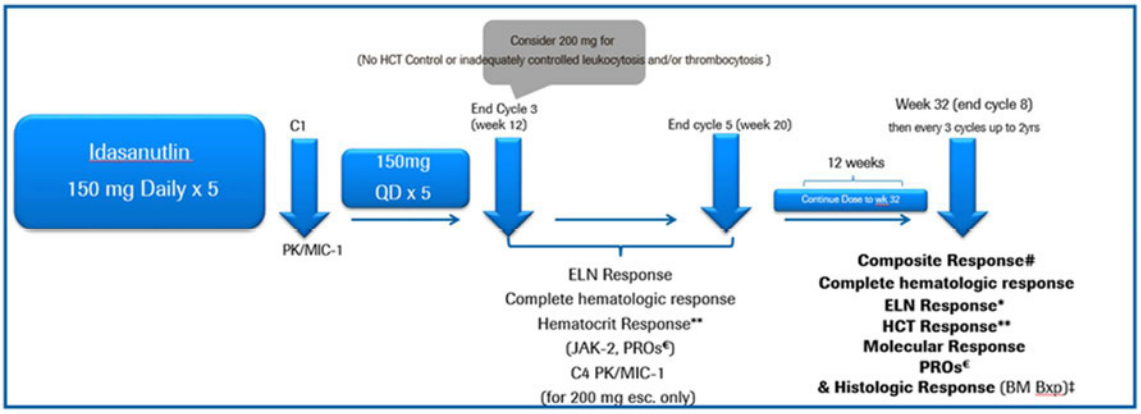
Prohibited Medication

- The use of HU or other therapy intended to treat PV (other than phlebotomy, aspirin and other supportive therapies) is not permitted while the patient is on study.
- The use of CYP2C8 substrates, inhibitors, or inducers; OATP1B1/3 substrates; or CYP3A4 inducers is prohibited during the study and for at least 7 days (for inhibitors and substrates) and 14 days (for inducers), respectively, prior to initiation of study treatment, unless otherwise specified. Note that CYP3A4 inhibitors are not excluded and OATP1B1/3 substrates with $t_{1/2}$ shorter than 1 day are allowed except during idasanutlin treatment and for 72 hours after the last dose of idasanutlin.

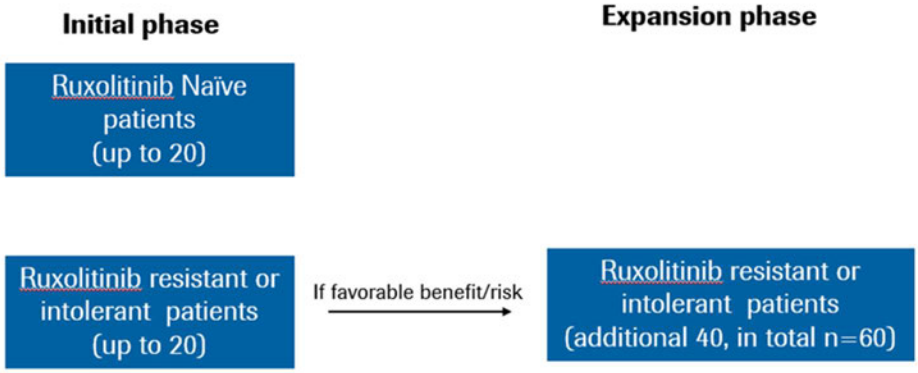
1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is shown in Figure 1.

Figure 1 Overview of Study Design



**Patients without measurable splenomegaly at baseline ^spleen imaging at end C5 only if <35% reduction at end C3 €MPN-SAF-TSS, EORTC QLQ-C30 , PGIC ‡Bone Marrow biopsy every 6 cycles post week 32 per PI discretion in context of ELN CHR response *to be evaluated in ruxolitinib naive patients



1.3 SCHEDULE OF ACTIVITIES

The Schedule of Activities (SoA) is provided in Table 1 and Table 2.

All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly. If this deviates more than ±2 days from the planned visit, it must be agreed upon with the Medical Monitor.

Table 1 Overall Schedule of Activities

Cycle	Screening	Cycle 1							Cycle 2 and Cycle 3		Cycle 3	Cycle 4 and Beyond	Cycle 5	End of Cycle 8 (32 Weeks) and beyond [17,19]	Final Visit [14]
Day	Up to 28 Days	Day 1	Day 2	Day 3	Day 4	Day 5	Day 15	Day 22	Day 1	Day 15	Day 28[19]	Day 1	Day 28[19]		EOS or 28 days post last dose
Assessments															
Informed Consent [1]	x														
Review Inclusion/Exclusion Criteria	x														
Demography	x														
Medical History	x														
Previous and Concomitant Treatments	x														
Cancer (PV) History	x														
Height	x														
Weight	x								x			x			x
Vital Signs [2]	x	x					x	x	x	x		x			x
ECOG Performance Status [2]	x	x					x	x	x	x		x			x
ECG 12-Lead [3]	x	x	x			x			(x)						
Complete Physical Examination [2,4]	x	x					x	x	x	x		x			x
Adverse Events [5]	x														
Rx Administration															
Idasanutlin administration [6]		x	x	x	x	x			x			x			
Disease Assessment [7]															
CT or MRI of Spleen [16]	x										x		x	x	x

Table 1 Overall Schedule of Activities (cont.)

Cycle	Screening	Cycle 1							Cycle 2 and Cycle 3		Cycle 3	Cycle 4 and Beyond	Cycle 5	End of Cycle 8 (32 Weeks) and beyond [17,19]	Final Visit [14]
Day	Up to 28 Days	Day 1	Day 2	Day 3	Day 4	Day 5	Day 15	Day 22	Day 1	Day 15	Day 28[19]	Day 1	Day 28[19]		EOS or 28 days post last dose
Symptom Assessment Form (MPN-SAF TSS) [19, 21]		x							x[23]		x		x	x	x
EORTC QLQ -C30 [19, 21]		x							x[23]		x		x	x	x
Patient Global Impression of Change (PGIC) [19, 21]									x[23]		x		x	x	x
Bone Marrow Biopsy	x													x	x
Bone Marrow Aspirate	x													x	x
ELN Response/Hct Response [20]											x		x	x	x
Composite Response [16,17]											x		x	x	x
Histologic Response [17]														x	x
Local Laboratory Assessments															
HBV, HCV, and HIV screening [9]	x														
Hematology with differential [2,10]	x	x				x	x	x	x	x	x[22]	x	x[22]	x[22]	x
Serum chemistry, Liver function tests, and creatinine [2,11]	x	x				x	x	x	x	x	x[22]	x	x[22]		x
Erythropoietin (EPO) level [2]	x	x												x	x
Iron [2]	x	x												x	x
Urinalysis [2]	x	x							x		x	x			x
Pregnancy Test [12]	x								x			x			x
Bone marrow histology [8,17]	x													x	x
Cytogenetics [17,18,19]	x													x	x
Molecular Markers	x														

Table 1 Overall Schedule of Activities (cont.)

Cycle	Screening	Cycle 1							Cycle 2 and Cycle 3		Cycle 3	Cycle 4 and Beyond	Cycle 5	End of Cycle 8 (32 Weeks) and beyond [17,19]	Final Visit [14]
Day	Up to 28 Days	Day 1	Day 2	Day 3	Day 4	Day 5	Day 15	Day 22	Day 1	Day 15	Day 28[19]	Day 1	Day 28[19]		EOS or 28 days post last dose
Central Laboratory Assessments															
PK idasanutlin [13]	Refer to Additional Schedule of Assessments for specific Sample Collection Timepoint Details														
Serum MIC-1															
Nucleic Acid Whole Blood [15]															
Paxgene Whole Blood															
Exploratory Biomarker pharmacodynamic Flow Blood															
Blood Flow Cytometry TBNK Panel															
Cytokine Assay															
RBR DNA															
RBR Serum															

AE=adverse event; COA=Clinical Outcome Assessment; CT=computed tomography; eCRF=electronic case report form; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EOS=end of study; HBsAg=Hepatitis B surface antigen; HBV=hepatitis B; Hct=hematocrit; HCV=hepatitis C; MPN-SAF TSS=myeloproliferative neoplasm symptom assessment form total symptom score; MRI=magnetic resonance imaging; PGIC=Patient Global Impression of Change; PI=principal investigator; PK=pharmacokinetic; PV=polycythemia vera; RBR=Research Biosample Repository; SAE=serious adverse event; TBNK=T, B, and NK.

1 Informed consent must be obtained before any study-specific procedures. (Note: A separate consent form is required for RBR testing).

2 If indicated assessments are performed within 72 hours before the first/next dose administration, the assessments do not have to be repeated on the first day of Cycle 1. If performed on the day of study drug administration they must be done PRIOR to study drug administration.

Table 1 Overall Schedule of Activities (cont.)

[3] Single interpretable ECG QT interval (using QTcF) should be used to determine eligibility. Obtain post screening 12-lead digital ECG measurement as close as possible to scheduled serum and plasma PK samples (see Section 8.2.3). For Cycle 3 and beyond, ECGs must be performed on Days 1 and 2 (24-hour timepoint, prior to the dose when applicable) and 4, 6, and 24 hours post dose only if there is evidence of QTc prolongation > 30 ms during Cycle 1 and Cycle 2 once the patient has received study medication as compared with the QTcF interval of the screening ECG. Otherwise, ECGs will NOT be required for Cycle 3 and beyond unless the Investigator considers it necessary on behalf of the patient's safety. An unscheduled ECG can be performed at any time as clinically indicated.

[4] Complete physical examinations must be performed during screening, Day 1 of each treatment cycle, and at study treatment discontinuation and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[5] Adverse Events: After initiation of study drug, all AEs and SAEs, regardless of attribution, must be reported until 28 days following the last administration of study drug or until study completion or patient discontinuation, whichever is later. After this period, investigators should report only SAEs that are believed to be related to prior treatment with study drug.

[6] Day 1 of each cycle of idasanutlin will be taken in clinic, remaining days (Day 2 to Day 5) may be taken at home.

[7] After Week 32, these disease assessments will occur every 3 cycles, except where noted (i.e., bone marrow evaluation every 6 cycles per PI discretion).

[8] Bone marrow examinations should include biopsy and aspirate for morphology, cellularity, blast percentage and reticulin fibrosis grade. Unsuccessful attempts at marrow aspiration or biopsy will not be considered a protocol violation. *Bone marrow examination within 7 days of screening does not need to be repeated (i.e., Day –35 to –1).*

[9] HBsAg, Hep C Ab, and HIV Ab serology (see details in Inclusion Criteria [Section 5.1]).

[10] Complete blood count (see Appendix 9 for details). Differential counts may be manual or automated, but must occur with each hematology assessment, with emphasis on determination of the presence of peripheral blasts.

[11] See Appendix 9 for details.

[12] Serum pregnancy testing is required for females of childbearing potential during the Screening Period (within 7 days of Cycle 1 Day 1). Cycle 2 and beyond, urine or serum pregnancy test should occur prior to every cycle. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test. Pregnancy test (urine or serum) can be done anytime during the study if clinically indicated.

[13] PK samples collected Cycle 4 only if dose escalation to 200 mg takes place in a patient with no response/no Hct control after first 3 cycles following discussion with Sponsor.

[14] Final Visit (±7days): Patients who discontinue will be asked to return to the clinic for a final visit within 28 days after the last dose. In some instances, the visit at which a response assessment shows progressive disease may be used as the final visit. Alternatively, final visit may be the EOS, defined as 2 years post initial dose.

[15] For JAK2V617, JAK2 exon 12 and p53 mutational analysis (DNA). See Appendix 2.

Table 1 Overall Schedule of Activities (cont.)

[16] Routine MRI (or CT) within 7 days of screening does not need to be repeated if it meets the study specifications (i.e., Day –35 to –1). Splenic imaging required at Cycle 5 Day 28 only if reduction in spleen volume is <35% at Cycle 3 Day 28. Composite response captured only if splenic imaging is completed Cycle 5 Day 28. Patients without protocol-defined splenomegaly at baseline (i.e. spleen $<$450 cm^3 on MRI or CT at baseline) *do not need to undergo further spleen imaging.*.

[17] On Day 28 of every 3 cycles after Week 32 up to two years after first dose (i.e., timing if no dose delays occur Cycle 11 Day 28, Cycle 14 Day 28, Cycle 17 Day 28, Cycle 20 Day 28, Cycle 23 Day 28, etc.). Note, bone marrow histology and cytogenetics Day 28 every 6 cycles post Week 32 (i.e., timing if no dose delays occur Cycle 14 Day 28, Cycle 20 Day 28, etc.) *for* up to 2 years per PI discretion in context of complete hematologic response.

[18] Cytogenetics preferentially on bone marrow aspirate sample. Blood sample will be utilized if bone marrow result is inconclusive.

[19] (-)3/(+)1 day window for Cycle 3 Day 28, Cycle 5 Day 28 and End of Cycle 8 (Week 32) and for every 3 cycles beyond. Must be prior to start of subsequent cycle. For the timepoint "End of Cycle 8" (Week 32), a patient experiencing a Dose Delay would perform the critical efficacy assessment(s) at whichever timepoint came first (Week 32 or End of Cycle 8) and performed assessment(s) would be recorded within the appropriate folder. In cases of dose delay where Week 32 occurs prior to the End of Cycle 8, any assessments performed at Week 32 would not need to be repeated at the End of Cycle 8.

[20] Per modified 2009 ELN Criteria (see Appendix 1) for patients with splenomegaly at baseline. Solely Hct control for patients without splenomegaly at Baseline.

[21] (-3) day window for COA; the questionnaires must be completed before the patient receives any information on disease status, prior to the performance of non-COA assessments, and prior to the administration of study treatment.

[22] Hematology and Serum Chemistry need only be obtained once end of Cycles 3, 5, and 8, but pre-dose Cycles 4, 6, and 9 based on window in footnote 19. Ideally these Hematology and Serum Chemistry assessments will be done at the same time as all other Response assessments required at end of Cycles 3, 5, and 8.

[23] COA questionnaires are only to be completed at Cycle 2 Day 1, not at Cycle 3 Day 1.

Table 2 Detailed Schedule of Activities

Cycle	Day	Hours Post Dose	ECG - 12 Lead	PK Sample [a]	PDy Serum MIC-1 [a]	Nucleic Acid Whole Blood [b, c]	Paxgene Whole Blood	Exploratory Biomarker PDy Flow Blood	TBNK Panel Flow Cytometry Blood	Cytokine Assay Plasma [c]	RBR DNA Optional [d]	RBR Serum Optional
Cycle 1	Day 1	0 PreDose	x	x	x	x	x	x	x	x	x	x
		1		x								
		2		x								
		4	x	x								
		6	x	x								
		10 [e]		x								
	Day 2	0/PreDose	x	x	x		x					
	Day 5	0 PreDose	x	x	x		x					
		1		x								
		2		x								
		4	x	x	x							
		6	x	x	x							
		10 [e]		x	x		x		x	x		
Cycle 2	Day 1	0 PreDose	x			x	x		x	x		
Cycle 3	Day 1	0 PreDose	x [f]			x						
		4	x [f]									
		6	x [f]									
	Day 2	24/PreDose	x [f]									
	Day 28 [g]	N/A				x				x		

Table 2 Detailed Schedule of Activities (cont.)

Cycle	Day	Hours Post Dose	ECG - 12 Lead	PK Sample [a]	PDy Serum MIC-1 [a]	Nucleic Acid Whole Blood [b, c]	Paxgene Whole Blood	Exploratory Biomarker PDy Flow Blood	TBNK Panel Flow Cytometry Blood	Cytokine Assay Plasma [c]	RBR DNA Optional [d]	RBR Serum Optional
Cycle 4	Day 1	0 PreDose		x	x							
		1		x								
		2		x								
		4		x								
		6		x								
		10 [e]		x								
	Day 2	PreDose		x	x							
	Day 5	0 PreDose		x	x							
		1		x								
		2		x								
		4		x	x							
		6		x	x							
		10 [e]		x	x							
Cycle 5	Day 28 [g]	N/A				x				x		
End of Cycle 8 (32 weeks) and Beyond [h, g]		N/A				x				x		
No Response or Disease Progression [i]		N/A				x				x		

N/A=not applicable; NR=no response; PD=Disease Progression; PDy=pharmacodynamic; PK=pharmacokinetic; RBR=Research Biosample Repository; TBNK=T, B, and NK.

[a] Cycle 4 PK and MIC-1 only for patients with incomplete response and dose escalation to 200 mg after Cycle 3.

[b] For JAK2 V617 and JAK2 exon 12 mutational analysis (DNA) all timepoints, p53 mutational analysis (DNA) only Cycle 1 Day 1 0 predose and at NR/PD.

Table 2 Detailed Schedule of Activities (cont.)

[c] In cases of Dose Delay where Week 32 occurs prior to the End of Cycle 8 any assessments performed at Week 32 would not need to be repeated at the End of Cycle 8.

[d] Samples for RBR DNA will be collected on Day 1 from all patients who signed RBR Informed Consent. If, however, the RBR DNA blood sample is not collected during the scheduled visit, it may be collected at any time during the conduct of the clinical study.

[e] (-)2 hour window for 10-hour timepoints.

[f] For Cycle 3 and beyond, ECGs must be performed on Days 1 and 2 (24-hour timepoint, prior to the dose when applicable) and 4, 6, and 24 hours post dose only if there is evidence of QTc prolongation >30 ms during Cycle 1 and Cycle 2 once the patient has received study medication as compared with the QTcF interval of the screening ECG. Otherwise, ECGs will NOT be required for Cycle 3 and beyond unless the investigator considers it necessary on behalf of the patient's safety. An unscheduled ECG can be performed at any time as clinically indicated. See Section 8.2.3 (Electrocardiograms) for ECG requirement for Cycle 3 and beyond.

[g] (-)3/(+)1 day window for C3D28, C5D28 and end of Cycle 8 (Week 32). Must be prior to start of subsequent cycle.

[h] On Day 28 of every 3 cycles after Week 32 up to two years after first dose (i.e., Cycle 11 Day 28, Cycle 14 Day 28, Cycle 17 Day 28, Cycle 20 Day 28, Cycle 23 Day 28, etc.), including the end of study visit.

[i] No response by ELN 2009 or Progressive Disease (Appendix 1).

2. INTRODUCTION

2.1 STUDY RATIONALE

The tumor suppressor p53 is a powerful growth suppressive and pro-apoptotic protein that plays a central role in protection from tumor development and is frequently inactivated in human cancer. Murine double minute homolog 2 (MDM2) protein regulates p53 through a negative feedback loop (Harris and Levine 2005).

More than 95% of patients with the hematopoietic stem cell malignancy polycythemia vera (PV) have been found to have the constitutively-activated JAK2 mutant V617F allele which dysregulates MDM2, leading to a decrease in p53 activation (James et al. 2005, Nakatake et al. 2012).

Idasanutlin (RO5503781) is a selective inhibitor of the p53-MDM2 binding which frees p53 from negative control and activates the p53 pathway. Therefore, it may allow for an increase in p53 activity and decrease of the malignant proliferation seen in PV.

An Investigator-led, open label Phase I study of single agent oral idasanutlin in patients with PV and essential thrombocythemia (ET) is currently ongoing, with 12 patients in total having received idasanutlin at 100 mg (n = 6) and 150 mg (n = 6) given once daily for five consecutive days. Preliminary observations indicate that treatment with 5 days of idasanutlin, at doses lower than the maximum tolerated dose (MTD) identified in previous studies in solid tumor and acute myeloid leukemia (AML) patients, shows promising efficacy and can control hematocrit (Hct) levels in PV patients. These early results support the inhibition of the MDM2-p53 interaction as an important pathway in treatment of this disease.

The rationale for the study design is provided in Section 4.2.

2.2 BACKGROUND

2.2.1 Background on Disease

PV belongs to a group of hematopoietic stem cell malignancies called the Philadelphia chromosome-negative chronic myeloproliferative neoplasms (MPNs), which also includes essential thrombocythemia (ET), and primary myelofibrosis (MF). Both PV and ET can evolve into myelofibrosis, termed post PV/ET MF (Mesa et al. 2007). ET, PV and primary MF have variable tendencies to transform to blast phase disease with a dismal prognosis (Mesa et al. 2005).

PV is characterized by trilineage hyperproliferation of red cells, platelets and white cells, with erythrocytosis or an absolute increase in red cell mass being the predominant characteristic of the disease (Kremyanskaya et al. 2012). Patients with PV have a median survival of approximately 18 months from diagnosis if untreated and of approximately 18 years if treated (Berk et al. 1986). PV-related signs include hypertension, gout, left upper abdominal quadrant pain, high Hct, leukocytosis, and

thrombocytosis. Major causes of reduced survival include thrombosis (29%), bleeding (7%), evolution to myelofibrosis (3%), transformation to acute leukemia (23%), and secondary malignancy (16%) (Berk 1995). PV also has a significant impact on quality of life, with symptoms including headache, weakness, dizziness, epigastric distress, and pruritus and splenomegaly developing as disease progresses (Geyer and Mesa 2014).

With regards to patient outcomes, approximately 7% of patients with PV will develop acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and 12%–20% of patients will develop myelofibrosis. This progression to other hematologic malignancies and heightened potential for thrombosis (cardiovascular events) comprise the two most common causes of mortality (Trefferi 2016). Therefore, prevention of thrombotic events is clearly an important goal of treatment. This is accomplished by maintaining Hct (<45%) and is associated with a dramatically decreased cardiovascular risk and decreased risk of death (Vannuchi et al. 2015). Phlebotomy is the primary treatment for low risk PV along with low dose aspirin (Landolfi et al. 2004). A significant proportion of patients with PV (high risk, symptomatic or intolerant to phlebotomy) require cytoreductive therapy to achieve target Hct levels and to normalize white blood cells (WBC) and platelet counts per European Leukemia Net (ELN) response criteria (Cervantes et al. 2008).

The predominant first-line treatment for PV is hydroxyurea (HU), which serves as a cytoreductive agent to manage elevated blood counts and to decrease frequency of phlebotomy for patients with PV. However, HU does not appear to affect the underlying disease biology, and many patients have inadequate response or intolerable side-effects. Resistance or intolerance to HU, as defined by the modified ELN criteria (Barosi et al. 2010) was found to occur in 11% and 13% of patients, respectively, and is associated with higher risk of death. Alternatives to HU in the first-line include interferon alpha, which, although able to induce an antiproliferative effect on hematopoietic precursors and reduce the JAK2V617F allele burden, has side-effects which limit its use, including flu-like symptoms, fatigue, and neuropsychiatric symptoms (Sever et al. 2014).

For PV patients resistant or intolerant to HU, ruxolitinib, a JAK2 kinase inhibitor, was approved as Jakafi in December 2014 in US and as Jakavi in March 2015 in EU. In a pivotal Phase III trial (RESPONSE), ruxolitinib met its primary endpoint of improved composite response, defined as Hct control along with at least 35% reduction in spleen volume at 32 weeks compared to best available therapy (BAT) (Vannucchi et al. 2015). This trial only included PV patients with splenomegaly amenable to imaging. The RESPONSE-2 trial (Passamonti et al. 2017) enrolled patients without splenomegaly and met the primary endpoint of Hct control by Week 28 (62% vs 19% for BAT), and had a complete hematologic response (CHR) of 23% in this population by revised ELN response criteria (Barosi et al. 2009; Appendix 1).

Ruxolitinib as a second-line agent in PV requires continuous daily treatment and following interruption/discontinuation, symptoms and blood counts return to pretreatment

levels. The JAK/STAT pathway is associated with immune function and targeting it with ruxolitinib has been associated with increased risk of developing serious bacterial, fungal, and viral infections (Jakavi SmPC, Jakafi USPI). Slow and infrequent effects are seen on the JAK2V617F allele burden. *Overall, 34% of patients discontinued ruxolitinib over a 5-year follow-up period (Kiladjian et al. 2018). For this subgroup of patients, there is no standard of care, leaving a high unmet medical need.*

2.2.2 Background on Idasanutlin

The JAK-STAT pathway is important for functional hematopoiesis and several activating mutations in JAK proteins have recently been described as underlying cause of blood disorders. One of the best studied examples is the JAK2 V617F mutant which is found in 95% of PV patients and 50% of patients suffering from essential thrombocythemia and primary myelofibrosis.

The tumor suppressor p53 plays an integral role in the regulation of the cell cycle, apoptosis, DNA repair, and senescence. A significant proportion of cancers have inactivating mutations of p53, but mutations in p53 are rare in PV (2.8%) (Harutyunyan et al. 2011). However, the enhanced JAK2V617F signaling via the PI3K/mTOR pathway upregulates LA autoantigen which increases MDM2 and thus, decreases p53 activation (Nakatake et al. 2012), thereby making PV CD34+ cells addicted to MDM2 activation. In JAK2V617F-positive PV CD34+ cells, this phenomenon was shown to lead to a concomitant increase in MDM2 expression with reduced p53 levels (Lu et al. 2012). Therefore, there is a clear rationale for targeting MDM2-addicted PV CD34+ cells to decrease p53 degradation and induce p53 activation in treating PV (Plo 2014).

Inhibition of MDM2 via an MDM2 antagonist would be expected to release the negative regulation of p53 and ultimately promote its tumor suppressor function. The physical structure and interaction of p53 and MDM2 is known and has allowed for the development of small molecule inhibitors of MDM2-p53 interaction.
Previously-investigated small molecule antagonists of MDM2, were shown to inhibit the proliferation of PV CD34+ cells through increased p53-mediated apoptosis (Lu et al. 2012; Lu et al. 2014). Thus, MDM2 appears to be a novel therapeutic target in JAK2V617F-positive PV.

Idasanutlin is a potent and selective inhibitor of the p53-MDM2 interaction which activates the p53 pathway and induces cell cycle arrest and/or apoptosis in tumor cells expressing functional p53 in vitro and in vivo. In cell-free assays, idasanutlin binds to MDM2 protein with high affinity and inhibits MDM2-p53 binding. Exposure of cancer cells to idasanutlin results in a dose-dependent accumulation of p53 protein and activation of its transcriptional targets and the p53 pathway, which in turn leads to a cell cycle block in the G1 and G2 phases and apoptosis in cancer cells.

In vivo, idasanutlin has demonstrated anti-tumor activity against an established osteosarcoma xenograft model, increased efficacy and survival when given in combination with cytarabine in an AML model in immunodeficient mice, and increased efficacy when given in combination with obinutuzumab in a non-Hodgkin lymphoma (NHL) model in immunodeficient mice.

Idasanutlin has been evaluated in two completed Phase I studies in patients with solid tumors: Studies NP27872 (99 patients) and NP28902 (61 patients) and in another Phase I study in 122 patients with AML (NP28679). A Phase III, 2:1 randomized, placebo-controlled blinded study (WO29519) is being conducted in combination with cytarabine in patients with AML and a Phase Ib/II study (GH29914) in combination with venetoclax is ongoing in patients with AML. In addition, two Phase Ib/II studies are being conducted in combination with obinutuzumab or rituximab (Study BH29812) and in combination with obinutuzumab or rituximab and venetoclax (Study BH39174) in patients with follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL).

Identified risks for idasanutlin in the targeted dose-range are gastrointestinal (nausea, vomiting, diarrhea, decreased appetite), hematological (neutropenia, thrombocytopenia with increased hemorrhagic risk and anemia) and electrolyte disorders.

Clinical pharmacokinetic (PK) data showed approximate dose-proportionality in exposure parameter AUC_{24h} on Day 5 of the daily × 5 days schedule for the test range of 100-2400 mg/day with inter-patient variability of approximately 40%–50%. The $t_{1/2}$ of idasanutlin is approximately one day and there was no major effect of high-fat or low-fat food on PK exposure. Although it is a substrate for cytochrome P450 isoenzymes CYP2C8 and CYP3A, and uridine 5'-diphospho-glucuronosyltransferase (UGT), a single dose of idasanutlin administered with a strong CYP3A inhibitor, posaconazole, showed no change in C_{max} and only a 32% increase in area under the curve (AUC) for idasanutlin. Metabolite M4 (RO6802287) was the only major metabolite in human plasma samples (at steady-state on Day 5) and, in contrast to idasanutlin, it inhibits OATP1B1 (IC50 2.8 µM) and OATP1B3 (IC50 1.6 µM) at the dose level to be applied in this study.

A detailed description of the chemistry, pharmacology, efficacy and safety of idasanutlin is provided in the Idasanutlin Investigator's Brochure (IB).

2.3 BENEFIT/RISK ASSESSMENT

Patients with PV who are resistant or intolerant to HU have few therapeutic options. There is still an unmet medical need for additional agents as second-line treatments and beyond with potentially better attributes than ruxolitinib, particularly for the subgroup of patients who *are intolerant or respond insufficiently* to ruxolitinib treatment. These novel agents should be capable of extending the clinical benefit with a higher composite response or increasing CHR rates/Hct control. Idasanutlin represents a first-in-class MDM2-antagonist therapy with a unique mechanism of action.

In an ongoing, Investigator-led, open label Phase I study of single agent oral idasanutlin in patients with PV and ET (Study NP29207, "Open Label Phase I Study of Single Agent Oral RG7388 in Patients With Polycythemia Vera and Essential Thrombocythemia [With Pilot Feasibility Study in Combination With Pegylated Interferon Alfa 2a for Patients Who do Not Respond to the Single Agent at Each Dose Level]"), 12 patients in total have received idasanutlin at 100 mg (n = 6) and 150 mg (n = 6) once daily for five consecutive days. So far, these doses, which are lower than the maximum tolerated dose (MTD) identified in both solid tumor and AML patients, have been shown to be tolerable in the PV patient population. Patients have received up to 10 cycles of idasanutlin with no dose-limiting toxicities reported. The most commonly reported side effects have been GI: nausea (7 patients, 21 events) which have all been Grade 1 except for 2 Grade 2 events and diarrhea (7 patients, 22 events), also all Grade 1 except for 3 Grade 2 events. Preliminary assessments suggest promising efficacy, with most patients achieving decreased phlebotomy needs. By ELN criteria, 4 patients have achieved a CHR or PHR, and 4 patients have not yet reached the evaluation time at 6 cycles, 2 patients ELN responses are not available and one patient did not achieve a CHR or PHR. Based on the criteria for re-treatment in this study, some patients have had treatment breaks until hematologic parameters indicated the need to resume treatment (personal communication from investigator).

The observation that treatment with 5 days of idasanutlin at doses lower than the MTD identified in solid tumor patients is able to control Hct levels in PV patients suggests that inhibition of the MDM2-p53 interaction may be an important pathway in treatment of this disease. New mechanisms such as MDM2 inhibition may affect the underlying PV biology in a positive manner, where current standard of care options have not been shown to do so in the majority of the patients.

The majority of the adverse events (AEs) recorded for idasanutlin treatment are transient in nature and reversible. Clinical experience to date suggests a dose-relationship for idasanutlin and GI AEs, with increased incidence of nausea, vomiting, and diarrhea at higher dose levels. Prophylaxis with anti-emetics is therefore *mandatory* for patients in this study. Cytopenias, manifesting as thrombocytopenia and neutropenia, are expected to occur at higher dose/exposure levels and appears to be related to toxicity on normal (non-PV) early hematopoietic progenitors. Frequent monitoring of hematologic values (count of blood cells, including differential) is required. The doses planned to be administered in this study are lower than the MTD in solid tumor patients.

Based on the non-clinical and clinical evidence supporting a potential clinical benefit of MDM2 inhibition in PV, the unmet medical need, and the observed safety profile of MDM2 inhibition to date, further clinical development of idasanutlin in this patient population is supported.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 3.

Table 3 Objectives and Endpoints

Ruxolitinib Naive Patients:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of idasanutlin monotherapy in patients with HU resistant/intolerant PV *and without prior ruxolitinib exposure*: – For patients **with splenomegaly at baseline** using composite response criteria – For patients **without splenomegaly at baseline** by Hct control without phlebotomy – For all patients (with and without splenomegaly) by Hct control without phlebotomy	• Composite response at Week 32 for patients **with splenomegaly at baseline** (per inclusion criteria) defined as: – Hct control defined as protocol-specified ineligibility for phlebotomy between Week 8-Week 32 and ≤1 instance of phlebotomy eligibility between first dose and Week 8 – ≥35% reduction in spleen volume at Week 32 • Hct control in patients **without splenomegaly at baseline** and in all patients (with and without splenomegaly); defined as protocol-specified ineligibility for phlebotomy between Week 8–Week 32 and ≤ 1 instance of phlebotomy eligibility between first dose and Week 8 Definition of eligibility for phlebotomy: a Hct of ≥45% that was ≥3% higher than baseline level or a Hct of >48%
Secondary	
• *To evaluate the efficacy of idasanutlin monotherapy in all patients (with and without splenomegaly) by complete hematologic response*	• Complete hematologic response at Week 32 Complete hematologic response requires **<u>all</u>** of the following: – Hct control (protocol-specified ineligibility for phlebotomy between Weeks 8–32 and ≤1 instance of phlebotomy eligibility between first dose and Week 8); – *WBC count ≤10 ×10⁹/L at Week 32 assessment; AND* – *PLT count ≤400 ×10⁹/L at Week 32 assessment* • *Complete hematologic remission at response Cycle 11 Day 28 defined as patients with all of the following:* – *Hct control defined as protocol specified ineligibility for phlebotomy between Week 32 assessment and Cycle 11 Day 28* – *WBC count ≤10 ×10⁹/L at Cycle 11 Day 28 assessment; AND* – *PLT count ≤400 × 10⁹/L at Week 32 assessment* – *Duration of complete hematologic remission response with a durable*

Objectives	Endpoints
	responder defined as a subject in remission at Week 32 and Cycle 11 Day 28, as defined above
• To evaluate the efficacy of idasanutlin monotherapy by using modified ELN hematologic response criteria (complete and partial response) in patients with baseline splenomegaly, patients without baseline splenomegaly and in *all* patient*s irrespective of spleen size*	• Response by using modified ELN hematologic response criteria: – Complete response – Partial response – NR – Progressive disease - as defined by increased bone marrow fibrosis from baseline, and/or transformation to MF, MDS or acute leukemia • Duration of response, including proportion of patients with durable response lasting at least 12 weeks *(Cycle 11 Day 28) from Week 32 (Cycle 8 Day 28) (Hct control, CHR, ELN 2009 response and composite response, if applicable)*
• To evaluate the safety of idasanutlin monotherapy in patients with HU resistant/intolerant PV *and without prior ruxolitinib exposure*	• Clinical safety laboratory tests (hematology, clinical chemistry, urinalysis, pregnancy testing) • Incidence, nature and severity of AEs graded according to the NCI CTCAE v4.0 • Incidence and severity of AEs, including targeted AEs. • ECOG PS, ECG, vital signs • Concomitant medication
• To characterize the pharmacokinetic (PK) parameters of idasanutlin and M4 metabolite in patients with HU resistant/intolerant PV	• C_{max}, C_{trough}, t_{max}, CL, CL/F, Vd_{ss}, AUC, $t_{1/2}$, and potentially other parameters derived.
• To evaluate the effect of treatment with idasanutlin on the symptoms of PV, physical functioning, general health status/*HR*QoL, and change in condition in all enrolled patients, as well as in those with and without baseline splenomegaly	• Mean and mean change from baseline to each assessment: – MPN symptom assessment form total symptom score (MPN-SAF TSS) – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) • *D*istribution of responses at each assessment *and across time*: – Patient Global Impression of Change scale

Ruxolitinib-Resistant or Intolerant Patients:

Objectives	*Endpoints*
Primary	
• *To evaluate the efficacy of idasanutlin monotherapy:* – *by Hct control without phlebotomy*	• *Hct control is defined as protocol-specified ineligibility for phlebotomy between Week 8-Week 32 and ≤1 instance of phlebotomy eligibility between first dose and Week 8* *Definition of eligibility for phlebotomy: a Hct of ≥45% that was ≥3% higher than baseline level or a Hct of > 48%*
Secondary	
• *To evaluate the efficacy of idasanutlin monotherapy by complete hematologic response*	• *Complete hematologic response at Week 32* *Complete hematologic response requires **all** of the following:* – *Hct control (protocol-specified ineligibility for phlebotomy between Weeks 8–32 and ≤1 instance of phlebotomy eligibility between first dose and Week 8);* – *WBC count ≤10 ×10⁹/L at Week 32 assessment; AND* – *PLT count ≤400 ×10⁹/L at Week 32 assessment* • *Complete hematologic remission at response Cycle 11 Day 28 defined as patients with all of the following:* – *Hct control defined as protocol specified ineligibility for phlebotomy between Week 32 assessment and Cycle 11 Day 28* – *WBC count ≤10 ×10⁹/L at Cycle 11 Day 28 assessment; AND* – *PLT count ≤400 ×10⁹/L at Week 32 assessment* • *Duration of complete hematologic remission response with a durable responder defined as a subject in complete hematologic remission at Week 32 and Cycle 11 Day 28, as defined above*
• *To evaluate the efficacy of idasanutlin monotherapy by using modified ELN hematologic response criteria (complete and partial response) in patients with baseline splenomegaly, patients without baseline splenomegaly and in all patients irrespective of spleen size*	• *Response by using modified ELN hematologic response criteria:* – *Complete response* – *Partial response* – *NR* – *Progressive disease, as defined by increased bone marrow fibrosis from baseline, and/or transformation to MF, MDS or acute leukemia* • *Duration of response, including proportion of patients with durable response lasting at least 12 weeks from Week 32 (Hct control, CHR, ELN 2009 response and composite response, if applicable)*

Objectives	*Endpoints*
• *To evaluate the safety of idasanutlin monotherapy in patients with HU resistant/intolerant PV and ruxolitinib resistant/intolerant patients*	• *Clinical safety laboratory tests (hematology, clinical chemistry, urinalysis, pregnancy testing)* • *Incidence, nature and severity of AEs graded according to the NCI CTCAE v4.0* • *Incidence and severity of AEs, including targeted AEs.* • *ECOG PS, ECG, vital signs* • *Concomitant medication*
• *To characterize the pharmacokinetic (PK) parameters of idasanutlin and M4 metabolite in patients with HU resistant/intolerant PV*	• C_{max}, C_{trough}, t_{max}, CL, CL/F, Vd_{ss}, AUC, $t_{1/2}$, *and potentially other parameters derived.*
• *To evaluate the effect of treatment with idasanutlin on the symptoms of PV, physical functioning, general health status/HRQoL, and change in condition in all enrolled patients, as well as in those with and without baseline splenomegaly*	• *Mean and mean change from baseline to each assessment:* – *MPN symptom assessment form total symptom score (MPN-SAF TSS)* – *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30)* • *Distribution of responses at each assessment and across time:* – *Patient Global Impression of Change scale*

All Patients, Irrespective of Prior Ruxolitinib Exposure:

Objectives	*Endpoints*
Secondary	
To evaluate the safety of idasanutlin monotherapy in patients with HU resistant/intolerant PV irrespective of ruxolitinib exposure (all patients)	• *Clinical safety laboratory tests (hematology, clinical chemistry, urinalysis, pregnancy testing)* • *Incidence, nature and severity of AEs graded according to the NCI CTCAE v4.0* • *Incidence and severity of AEs, including targeted AEs* • *ECOG PS, ECG, vital signs* *Concomitant medication*
Tertiary/Exploratory	
• To assess the relationship between PK exposure and clinical responses, including AEs	• Concentration-time profiles following administration of idasanutlin or derived (or modeled/simulated) parameters will be correlated with clinical endpoints including PD and AEs
• To assess the pharmacodynamic effects of idasanutlin by serum MIC-1 levels	• Serum MIC-1 profile (raw and/or adjusted from baseline as percentage of change)
• To explore the molecular response to idasanutlin	• Molecular response by percent reduction from baseline in JAK2V617F or JAK exon 12 allele burden after treatment with idasanutlin (Appendix 2)

Objectives	*Endpoints*
• To measure the histologic response (via bone marrow histology)	• Histologic response changes in bone marrow including histopathologic abnormalities and reduction in baseline reticulin/collagen fibrosis (with fibrosis grading per European consensus on grading bone marrow fibrosis and degree of cellularity at Week 32 [Appendix 3]) • Number of patients with transformation to myelofibrosis, MDS, or acute leukemia
• To explore the cytogenic response (cytogenetics) to idasanutlin compared to baseline	• Loss or gain of karyotypic abnormalities in response to treatment with idasanutlin
• To evaluate potential predictive, pharmacodynamic and response assessment biomarkers for idasanutlin in PV	• Characterization of protein, nucleic acid, and other tissue derived biomarkers relating to the proposed mechanism of action of idasanutlin and response to treatment which may include, but are not limited to, nucleic acid-based analysis of JAK2 and TP53 mutation status (via gene sequencing) and gene expression signatures • Flow cytometry of MDM2 expression in CD34+ cells • Determination of absolute counts and percentages of mature T, B, and NK lymphocyte populations as well as CD4+ and CD8+ T-cell subset ratios

AE=adverse event; AUC=area under the curve; CL=clearance; CL/F=apparent clearance; C_{max}=maximum concentration; C_{trough}=trough concentration; ECOG PS=Eastern Cooperative Oncology Group performance status; *EORTC QLQ-C30 =European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30;* Hct=hematocrit; HU=hydroxyurea; MDM2=murine double minute 2; MDS=myelodysplastic syndrome; MF=myelofibrosis; MPN=myleloproliferative neoplasm; *MPN-SAF TSS =MPN symptom assessment form total symptom score;* NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PD=progressive disease; PGIC=Patient Global Impression of Change ; PK=pharmacokinetic; PV=polycythemia vera; *HR*QoL=*health-related* quality of life; $t_{1/2}$=elimination half-life; t_{max}=time of maximum concentration observed; Vd_{ss}=volume of distribution at steady state*; WBC =white blood cell.*

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label, single-arm study of idasanutlin monotherapy. All patients must be diagnosed with PV according to the revised 2016 WHO criteria (Arber et al. 2016; Appendix 4) and resistant or intolerant to HU.

The study will include two phases: initial phase and expansion phase. The initial phase will assess the safety and efficacy of idasanutlin monotherapy in ruxolitinib naive and ruxolitinib-resistant or intolerant patients, respectively. If the initial phase shows promising results for ruxolitinib-resistant or intolerant patients, an expansion phase with the purpose of registration will be opened to further characterize the efficacy of idasanutlin.

Initial Phase of the Study for Both Ruxolitinib-Naïve and Ruxolitinib-Resistant or Intolerant Patients

Approximately 20 *efficacy-evaluable* patients without prior ruxolitinib therapy *and approximately 20 efficacy-evaluable patients who are resistant or intolerant to ruxolitinib* are expected to be enrolled *in the initial phase of the study. Up to 20 a*dditional *efficacy-evaluable ruxolitinib-naïve* patients may be enrolled *in the initial phase of the study* for confirmation of response, safety, and/or PK *at the discretion of the Sponsor (maximum overall 40 efficacy-evaluable ruxolitinib-naïve patients).*

All patients will receive 150 mg idasanutlin orally, once daily for five consecutive days every 28 days (see Section 4.3: Dose Justification). Intra-patient dose-escalation to 200 mg daily for 5 days may be permitted after Cycle 3 for patients who demonstrate no Hct control *and/or for patients with inadequately controlled leukocytosis and/or thrombocytosis in which the investigator judges that better control is important.* See Section 4.1.2 for details regarding review process which also includes review of individual patient safety and laboratory data prior to any intra-patient dose escalation.

*For ruxolitinib-naïve patients, t*he primary endpoint is efficacy, defined as response at Week 32:

- Hct control and ≥35% reduction in spleen volume in patients with splenomegaly
- Hct control in patients without splenomegaly
- Hct control in all patients (with and without splenomegaly)

These endpoint*s (Hct control and composite response at Week 32) have been* chosen to allow *cross-study* comparison to the Composite Response (*including* Hct control) *used* in the RESPONSE*-1* study *of patients with splenomegaly* and to Hct control *used* in the RESPONSE-2 study *of patients without splenomegaly* (Vannucchi et al. 2015; Passamonti et al. 2017).

For ruxolitinib-resistant or intolerant patients, the primary endpoint is efficacy, defined as response at Week 32:

- *Hct control*

There is no available standard therapy for this population. Hct control is a broadly established endpoint in PV, as maintaining Hct control is important for reducing thrombosis risk (Marchioli et al. 2013). Therefore, Hct control has been selected for primary endpoint in this population. Spleen volume reduction has not been established as an endpoint for relevant disease-related events such as thrombosis or transformation, and therefore, this is not considered in the primary endpoint definition in this patient group.

Note that assessments earlier than Week 32, i.e., after Cycles 3 and 5, may enable understanding of whether idasanutlin-driven efficacy is apparent earlier.

Patients will be treated and assessed according to the SoA (Section 1.2) for up to 2 years after the first dose.

An overview of the study design is provided in Section 1.1.

Expansion Phase for Ruxolitinib-Resistant or Intolerant Patients

For ruxolitinib-resistant or intolerant patients, an expansion phase with identical treatment schedule as the initial phase will be opened at the Sponsor's discretion if data from the initial phase of the study indicate a clear signal of a positive benefit/risk profile, as described in Section 9.2.2. This expansion cohort will include approximately 40 additional patients to further characterize the efficacy and safety of idasanutlin in PV patients who are ruxolitinib-resistant or intolerant.

4.1.1 Length of the Study

The total duration of the study for each patient will be up to 112 weeks divided as follows:

- Screening Period: up to 28 days (4 weeks)
- Treatment Period: Day 1 Cycle 1 continues with repeating treatment cycles of 28 days until patients discontinue study treatment or at end of study (EOS; defined as 2 years [104 weeks] post initial dose).
- Safety follow-up: until 28 days (4 weeks) after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first (see Section 1.2 for safety assessments at follow up).

Patients will be asked to return to the clinic 28 days (±7-day window) after the last dose of study medication to complete Final Visit assessments. In the event that the decision to withdraw from the study occurs after 28 days from the last dose of idasanutlin, e.g., due to interruption of intended cycle continuation due to an AE, then the Final Visit should occur on or as close as possible to the date of withdrawal. The visit at which a response assessment shows *no response* (NR) or PD may be used as the Final Visit if treatment is discontinued.

4.1.2 Dose-Escalation Decision Criteria

Intra-patient dose-escalation from 150 mg to 200 mg may be allowed *at Cycle 4 or 5* for patients who have demonstrated adequate tolerability *but have* a lack of Hct control *or inadequately controlled leukocytosis and/or thrombocytosis at the end of Cycle 3*. The goal is to bring these patients to a *better* hematologic response by end of Cycle 5 to allow for assessment for durability of response through Week 32. PK samples will be taken from these dose-escalated patients at the beginning of Cycle 4 to assess PK characteristics at the higher dose compared to Cycle 1.

Patients with progressive disease will not be permitted to dose-escalate and the patient should come off the study.

Consideration for dose-escalation will be based on a review of patient data, including but not limited to, response assessments, laboratory, and safety data. All intra-patient dose-escalation decisions will be made in consultation with the Investigator and Sponsor, including the Medical Monitor and Safety Science Leader.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

4.2.1 Rationale for Study Population

It has previously been shown that in primary hematopoietic cells from PV patients with JAK2V617F mutation that reduced expression of p53 occurs as a result of increased LA autoantigen expression leading to increased translation of MDM2 (Nakatake et al. 2012). It would appear that JAK2V617F induces this ribonucleoprotein and furthermore, LA protein expression can be down-regulated by in vitro JAK2 inhibitor treatment. Lu et al. demonstrated increased MDM2 expression and reduced p53 levels in PV patients' JAK2V617F-positive CD34+ cells (Lu et al. 2012). Nutlin-3, a small molecule antagonist of MDM2, was shown to inhibit the proliferation of PV CD34+ cells through increased p53-mediated apoptosis (Lu et al. 2012, Lu et al. 2014). Thus, the use of idasanutlin would be anticipated to enhance p53 activity by different mechanisms and presents a novel approach to the treatment of PV.

Patients with PV who require cytoreductive therapy because of risk features or increasing phlebotomy needs have poorer survival. As previously noted, PV patients can experience symptoms such as fatigue, pruritus, thrombotic complications (stroke, myocardial infarction, etc.) and some patients will have transformation of their disease to MF, MDS or AML.

Resistance or intolerance to HU, as defined by the modified ELN criteria (Barosi et al. 2010) was found to occur in 11% and 13% of patients with PV, respectively. Resistance to HU was associated with higher risk of death (hazard ratio [HR] 5.6; 95% confidence interval [CI] 2.7%–11.9%; $p<0.001$) and transformation (HR 6.8; 95% CI 3.0%–15.4%; $p<0.001$).

As described in Section 2.2.1, patients with PV who are resistant or intolerant to HU have few therapeutic options and there is a need for improved second-line treatments for this patient population.

Therefore, the HU-resistant or intolerant population is an appropriate population for the clinical testing of MDM2 antagonists.

Patients who are resistant or intolerant to second-line ruxolitinib treatment have limited treatment options and represent a high unmet medical need. About one-third of patients discontinued ruxolitinib treatment over 5 years in the ruxolitinib RESPONSE trial (Kiladjian et al. 2018). In this situation, there is no standard of care available for

these patients to maintain Hct control and/or hematologic remission, which exposes this subgroup to risk of PV complications such as thrombosis. Based on the known mechanism of action of idasanutlin, patients who are resistant or intolerant to ruxolitinib may derive clinical benefit from idasanutlin treatment.

4.2.2 Rationale for Biomarker Assessments

MIC-1 (macrophage inhibitory cytokine 1) is a secretory protein that is strongly upregulated by activated p53, and can be detected in the blood of patients treated with idasanutlin as demonstrated in the solid tumor study, NP27872, and the AML study, NP28679 (see Idasanutlin IB). MIC-1 levels can be determined by a sensitive ELISA test and serve as a serum biomarker for p53 activation, the intended mechanism of action.

Blood samples will be tested for the molecular status of JAK2. Nucleic acid-based monitoring of JAK2 mutation status will be performed as a means of examining changes in disease burden by mutational allele monitoring. Monitoring of JAK2 mutational allelic burden is an important component to measure pharmacodynamic response in PV patients. The expected prevalence of TP53 mutation is low in PV patients (2%–3%) and will be tested at baseline. Additional assessment of TP53 mutation status may be performed at progression to investigate whether extended administration of idasanutlin drives an emergence of TP53 mutation.

MDM2 protein expression in myeloid cells will be assessed as an exploratory biomarker predictive of response. Understanding whether elevated MDM2 protein is a predictive biomarker of idasanutlin activity may also have diagnostic utility.

Understanding the effects of idasanutlin on PV patient immune cell context will be assessed by TBNK panel testing. Towards this understanding, absolute counts and percentages of mature T, B, and NK lymphocyte populations as well as CD4+ and CD8+ T-cell subset ratios in human peripheral blood in response to treatment will be assessed.

4.2.3 Rationale for Clinical Outcome Assessments

Patients with PV often experience a variety of symptoms, most commonly including, but not limited to fatigue and itching (Stein et al. 2014), which can contribute to considerable burden on their health-related quality of life (HRQoL) (Abelsson et al. 2013), and ultimately impact functioning and daily living (Scherber et al. 2010). Since PV patients experience considerable burden, collecting information on the patient experience during treatment is important to be able to comprehensively quantify treatment benefit.

In order to better understand treatment characteristics and effects, information from the patient perspective on disease and treatment-related symptoms, functioning, and HRQoL will be collected through the inclusion of clinical outcome assessment (COA) measures, allowing a better understanding of the patient experience. In this study, the

following COAs will be administered: MPN-SAF TSS, EORTC QLQ-C30, and PGIC. Additional details about these COAs are provided in Section 8.1.2.

4.3 DOSE JUSTIFICATION

During Phase 1 development, two formulations were tested: microprecipitated bulk powder (MBP) and spray-dried powder (SDP); the relative bioavailability of SDP to MBP is approximately 2. For clarity, the doses of MBP tested have been re-designated to SDP equivalent (SDP eq) in this section.

Serum levels of macrophage inhibitory cytokine (MIC-1), a secreted protein that is strongly induced by activated p53, have been used to assess pharmacodynamic effects of idasanutlin in Phase 1 studies NP27872 and NP28679 (see Idasanutlin IB). Analysis of patients on 50 to 400 mg (SDP eq) daily × 5 days idasanutlin showed that the minimum level for p53 induction occurs at a dose of 50 mg (SDP eq)/day or a corresponding plasma level of 500 ng/mL of idasanutlin. In comparison, a weekly dosing schedule had a less pronounced effect on MIC-1.

A comparison of MIC-1 elevation between the idasanutlin dosing schedules demonstrated limited ability to activate p53 with the weekly schedule. The daily × 3 days dose regimen did not achieve steady-state exposure, displayed shorter duration for SD (median 57 and 103 days for daily × 3-day and daily × 5-day schedules, respectively), and did not alleviate thrombocytopenia. Therefore, the daily × 5-day schedule was chosen as optimal for future clinical trials.

In a study of idasanutlin-treated patients with solid tumors, NP27872, the 5-day schedule MTD was determined to be 250 mg (SDP eq) QD, in a 28-day cycle. Thrombocytopenia, neutropenia, febrile neutropenia and diarrhea were dose-limiting toxicities (DLTs). PK and safety data showed that there was an apparent pharmacokinetic/pharmacodynamic relationship between an AUC per cycle and Cycle 1 platelet nadir. In the AML study, NP28679, a protocol-defined MTD, with or without concomitant 1 g/m^2 cytarabine, was not achieved. Instead, 300 mg (SDP eq) BID for 5 days in a 28-day cycle was determined to be the maximum tolerable threshold based on GI tolerability.

It is important to note that the bone marrow of PV patients is more similar to solid tumor than AML patients; therefore the lower solid tumor MTD (250 mg SDP eq) daily × 5 days is considered more relevant as reference for PV patients. The desirable outcome for PV would be to utilize a tolerated dose (lower than the solid tumor MTD) needed for p53 induction as demonstrated by MIC-1 (i.e., 150 mg) utilizing the 5-day schedule with the goal of preferentially targeting MDM2-addicted CD34+ PV cells and while at the same time sparing patients the cytopenic side-effects associated with higher exposures. Idasanutlin monotherapy doses at a level equal to 150 mg daily × 5 days is projected to be associated with a tolerable safety profile and appears suitable for prolonged treatment of PV patients.

In an Investigator-led, open-label Phase I study of single agent oral idasanutlin in patients with PV and ET, idasanutlin has been tested at 100 mg and 150 mg SDP daily × 5 days. Thus far, these lower doses, which are lower than the MTD identified in solid tumor or AML patients, have shown clinical efficacy and are tolerated in the PV patient population.

In this Phase II study, intra-patient dose-escalation from 150 mg to 200 mg may be considered *at Cycle 4* for patients who have a lack of Hct control *or who have inadequately controlled leukocytosis and/or thrombocytosis* at end of Cycle 3. Note that due to the MTD at 250 mg, intra-patient dose escalation will be limited to 200 mg to balance the potential for improving a patient response with higher exposure with the potential for increased side effects. The goal is to optimize the response by the end of Cycle 5 in order to assess 12-week response duration by Week 32. PK and MIC-1 samples will be taken at the beginning of Cycle 4 from these dose-escalated patients to confirm increased exposure and p53 pathway induction with dose increase as compared to Cycle 1 (Section 4.1.2).

Further details are provided in the Idasanutlin IB.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date when the last data point from the last patient is received, up to 28 days post final dose.

The end of study for each patient is defined as 2 years post initial dose (see Section 4.1.1).

Due to the exploratory nature of this clinical study, the Sponsor may review the data at various timepoints during the course of the study and its conduct can be discontinued at any time at the discretion of the Sponsor (see Section 9.5).

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The patients in this study must be adults older than 18 years of age with PV as diagnosed by 2016 WHO criteria (Arber et al. 2016; Appendix 4). Additionally, the patients must be HU intolerant or resistant as defined by ELN criteria listed in Appendix 1.

Prospective approval of protocol deviations from recruitment and enrollment criteria, also known as protocol waivers or exemptions, *are* not permitted.

5.1 INCLUSION CRITERIA

Patients are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Ability to understand and willingness to sign a written informed consent form and comply with the study protocol according to ICH and local regulations.

Age

2. Adults > 18 years of age

Type of Patients and Disease Characteristics

3. There must be documentation that the patient has met the revised 2016 WHO criteria for the diagnosis of polycythemia vera (Arber et al. 2016; Appendix 4). Diagnosis requires the presence of all three major criteria, or the first two major criteria and the minor criterion. To verify that the criteria have been met, appropriate laboratory or pathology reports must be submitted during screening demonstrating that the patient has documentation of these diagnostic criteria. These reports do not have to exactly coincide with the original date of diagnosis.
   - Major Criteria:
     a) Hemoglobin > 16.5 g/dL in men, > 16.0 g/dL in women OR Hct > 49% in men, > 48% in women, OR other evidence of increased red cell mass.
     b) Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size).
     c) Presence of JAK2V617F or JAK2 exon 12 mutation.
   - Minor Criteria:
     – Serum erythropoietin level below the reference range for normal.

     NOTE: Major criterion number b) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels > 18.5 g/dL in men (Hct, 55.5%) or > 16.5 g/dL in women (Hct, 49.5%) if major criterion c) and the minor criterion are present.
4. Hct at screening and initiation of idasanutlin > 40%
5. Phlebotomy-dependent patients with splenomegaly by magnetic resonance imaging (MRI) or computerized tomography (CT) imaging (≥ 450 cm^3) or without splenomegaly (< 450 cm^3 or prior splenectomy).

   Phlebotomy dependence is defined as at least one phlebotomy within 16 weeks before screening.

6. Resistance to/intolerance to hydroxyurea according to modified ELN criteria (Barosi et al. 2010):

   - Resistance to HU is defined at a dose $\geq$ 2 g/day or a maximum tolerated dose $<$ 2 g/day resulting in at least one of the following:
     - Need for phlebotomy to maintain Hct $<$ 45% after 3 months of HU.
     - Platelet (PLT) count $>$ 400×10^9/L and white blood cell (WBC) count $>$ 10×10^9/L after 3 months of HU.
     - Failure to reduce splenomegaly extending $>$ 10 cm below the costal margin by $>$ 50%, as measured by palpation after 3 months of HU.
   - Intolerance to HU is defined as at least one of the following:
     - Absolute neutrophil count (ANC) $<$ 1.0×10^9/L.
     - PLT count $<$ 100×10^9/L or hemoglobin $<$ 100 g/L (i.e., 10 g/dL) at the lowest dose of HU required to achieve a response.
     - Presence of leg ulcers or other unacceptable HU-related non-hematologic toxicities (such as mucocutaneous manifestations, GI symptoms, pneumonitis, or fever at any dose of HU).

   For patients previously exposed to ruxolitinib, inclusion requires the following in addition to previous treatment for myeloproliferative disorder with HU:

   - *Therapy resistant PV after at least 6 months of treatment with ruxolitinib, defined by at least one of following:*
     - *Need for phlebotomy to achieve Hct <45%, at least two over 6 months*
     - *Uncontrolled leukocytosis (WBC count >10 ×10⁹/L)*
     - *Uncontrolled thrombocytosis (PLT count >400 ×10⁹/L)*
     - *Failure to achieve a >50% reduction in palpable splenomegaly measuring >5 cm from the left costal margin or failure to become non-palpable in palpable splenomegaly measuring 0–5 cm*
     - *Inadequately controlled disease-related symptoms (e.g., pruritus, headache, night sweats, excluding fatigue) after excluding other causes*
   - *Ruxolitinib intolerance defined as at least one of following at lowest dose of ruxolitinib to achieve adequate response:*
     - *Cytopenia defined as one or more of the following:*

       Neutropenia, ANC <1.0 ×10⁹/L

       Thrombocytopenia, PLT count <100 ×10⁹/L

       Anemia, hemoglobin <10 g/dL
     - *Life threatening infections deemed associated with ruxolitinib or other infections complications possibly associated with ruxolitinib (shingles, TB, hepatitis reactivation) at any time during study treatment*

– *Non-melanoma skin cancer (recurrence of or multiple) at any time during study treatment*

7. *Adverse events likely caused by ruxolitinib (assessment of attending physician) and that is of a severity that precludes further treatment with ruxolitinib (as per judgment of the attending physician and the patient)*
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
9. Patients must be willing to submit the blood sampling and bone marrow sampling for the PK and pharmacodynamic analyses and exploratory biomarkers.
10. Adequate hepatic function assessed by:
    - Serum total bilirubin <2 mg/dL, unless resulting from hemolysis or known Gilbert's disease.
    - AST/ALT $<2.5\times$ institutional ULN.
11. Adequate renal function assessed by serum creatinine within reference lab normal limits OR creatinine clearance ≥ 50 mL/min calculated by the Cockcroft Gault formula (Appendix 5).
12. Patients must meet all of the general inclusion criteria listed above prior to dosing on Cycle 1, Day 1 (including ECOG and labs checked following initial screening eligibility verification) when screening performed >72 hours from start of treatment.
13. Ability and willingness to comply with the study protocol procedures, including clinical outcome assessment (COA) measures.

Contraception

14. Male and/or female patients

    a) Male Patient:

    Agreement to use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

    With female partners of childbearing potential or pregnant female partners, men must use a condom during the treatment period and for at least 90 days after the last dose of idasanutlin. Men must refrain from donating sperm during this same period.

    b) Female Patients:

    For women of childbearing potential: agreement to use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 6 weeks after the last dose of idasanutlin.

    A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (at least 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

    Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation; male sterilization; established, proper use of hormonal

contraceptives that inhibit ovulation, hormone-releasing intrauterine devices; and copper intrauterine devices.

5.2 EXCLUSION CRITERIA

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Meets the criteria for post PV MF as defined by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT).
2. Blast phase disease (>20% blasts in the marrow or peripheral blood).
3. Clinically-significant thrombosis within 3 months of screening.

Prior/Concomitant Therapy

4. Patients who must receive CYP2C8 inhibitors, substrates and inducers, strong CYP3A4 inducers, or OATP1B1/3 substrates while on study. These must be discontinued 7 days (inhibitors and substrates) or 14 days (inducers) prior to start of study medication.
   - Treatment with the following agents within 7 days prior to the first dose of idasanutlin:
     - CYP2C8 inhibitors such as gemfibrozil (also a UGT1A3 inhibitor)
     - CYP2C8 substrates such as repaglinide
     - OATP1B1/3 substrates such as statin drugs
   - Treatment with the following agents within 14 days prior to the first dose of idasanutlin:
     - Strong CYP3A inducers such as rifampin (also a CYP2C8 inducer) and carbamazepine
   - Chronic use of CYP2C8 or OATP1B1/3 substrates during treatment with idasanutlin is prohibited.
5. Patients previously treated with MDM2 antagonist therapies or patients receiving interferon-alpha, anagrelide, or ruxolitinib within 28 days or 5 half-lives (whichever is shorter), or HU within 1 day, or patients receiving any other cytoreductive or investigational agents within 28 days or 5 half-lives (whichever is shorter) of initial dose. Aspirin is permitted per treatment guidelines for PV unless medically contraindicated.

Other Exclusions

6. Patients with evidence of electrolyte imbalance such as hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypermagnesemia of Grade >1 intensity, as per NCI CTCAE, version 4.0 prior to dosing on Cycle 1 Day 1. Treatment for correction of electrolyte imbalances is permitted to meet eligibility.
7. Neutrophil count $< 1.5 \times 10^9$/L prior to dosing on Cycle 1 Day 1.

8. PLT count $\leq 150 \times 10^9$/L prior to dosing on Cycle 1 Day 1.
9. Women who are pregnant or breastfeeding.
10. Ongoing serious non-healing wound, ulcer, or bone fracture.
11. History of major organ transplant.
12. Uncontrolled intercurrent illness including, but not limited to hepatitis, concurrent malignancy that could affect compliance with the protocol or interpretation of results, hepatitis A, B, and C, human immunodeficiency virus (HIV)-positive, ongoing or active infection, clinically significant cardiac disease (New York Heart Association Class III or IV), symptomatic congestive heart failure, unstable angina pectoris, ventricular arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

    Concurrent malignancy exceptions include: Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer. Any previously treated early-stage non-hematological malignancy that has been in remission for at least 2 years is also permitted.
13. Patients with active GI conditions (Crohn's disease, ulcerative colitis, diverticulosis associated colitis, and Behçet's disease)
14. Clinically significant toxicity (other than alopecia) from prior therapy that has not resolved to Grade ≤ 1 (according to the NCI CTCAE, v4.0) prior to Day 1 Cycle 1

5.3 LIFESTYLE CONSIDERATIONS

Patients will be expected to follow protocol requirements for contraception (see Appendix 6) and study center house rules during visits, but there are no other lifestyle restrictions during the study.

5.4 SCREEN FAILURES

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for re-screening at the discretion of the Investigator in consultation with the Sponsor.

5.5 RECRUITMENT PROCEDURES

Patients will be identified by direct referrals from Investigators and local networks. Patients may be identified for potential recruitment using pre-screening enrollment logs, clinical database and IEC/IRB approved newspaper/radio/social-media advertisements and mailing lists prior to consenting to take place on this study. *After initial written*

informed consent/assent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's unique identification number from an interactive voice or web-based response system (IxRS).

Under no circumstances are patients who enroll in this study permitted to withdraw and re-consent for a second course of treatment.

6. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

The investigational medicinal product (IMP) required for completion of this study (idasanutlin) will be provided by the Sponsor. *The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.*

6.1 TREATMENTS ADMINISTERED

Table 4 summarizes the treatments administered.

Table 4 Summary of Treatments Administered

Study Treatment Name:	Idasanutlin (RO5503781)
Dosage Formulation:	Film-coated tablets (containing spray-dried powder)
Unit Dose Strength(s)/Dosage Level(s):	50, *150,* and 200 mg
Dose:	150 mg (with possible intra-patient dose-escalation to 200 mg; *100 mg in case of dose reduction*)
Route of Administration:	Oral
Dosing Instructions:	Idasanutlin should be taken orally QD in the morning on Days 1–5 of each 28-day treatment cycle. On days that PK sampling is required, study treatment dose scheduled for that day should be taken in the clinic to ensure accurate timing of the PK sampling. Idasanutlin should be taken at approximately the same time each day. Idasanutlin is administered orally with or without food. Water may be taken as needed. If vomiting occurs within 15 minutes after taking idasanutlin and all expelled tablets are still intact, another dose should be given and the second dose should be noted in the drug diary. Otherwise no replacement dose should be given. Idasanutlin tablets should never be chewed, crushed, or broken before swallowing. For the QD regimen, if an idasanutlin dose is missed, it may be taken until noon. Otherwise, the dose should not be taken and dosing should be resumed with the next scheduled dose.
Packaging and Labeling:	Study treatment will be provided in high-density PE plastic bottles. Each bottle will be labeled as required per Roche standard and country requirement.

PK = pharmacokinetic; QD = once daily.

A drug diary will be provided to the patient to record oral administration of doses, including the date and time of dosing. Patients will be instructed to return empty bottles or unused tablets.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

Please see the Idasanutlin IB for more details.

6.1.1 Pre-medication and Prophylaxis

Nausea and vomiting have been commonly observed in idasanutlin studies. In some cases, they have led to treatment discontinuation.

- *Treatment to mitigate emesis must be given prophylactically prior to each cycle as follows: At least 30–60 minutes (timing depending on use of transdermal or oral 5-HT$_3$-receptor antagonist [RA]) before start of a treatment cycle and on each treatment day for dexamethasone administer:*
  - *Long-acting 5-HT$_3$-RA orally or intravenously (IV) on Day 1 (preferably palonosetron IV 0.25 mg or oral 0.5 mg) 30–60 minutes prior to idasanutlin administration or granisetron transdermal system ≥24 hours to a maximum of 48 hours prior to idasanutlin administration*

    If the above recommended 5-HT$_3$-RAs are not available, treatment with short-acting 5-HT$_3$-RAs (e.g., 8 mg ondansetron) is mandatory 30 minutes prior to intake of idasanutlin on all treatment days (an extra dose of 8 mg ondansetron can be taken if symptoms appear later on treatment days, with a minimum of 8 hours between ondansetron doses).

    AND

  - *Dexamethasone 12 mg orally/IV on Day 1 (30–60 minutes before idasanutlin), then 8 mg orally on Days 2–5*

  Investigators are to choose IV/oral/transdermal system administration at their discretion.
- *Anticipatory nausea: If the patient experiences nausea during the first cycle, consider adding anxiolytics, like lorazepam, from Cycle 2 onwards.*
- *Additional prophylaxis on top of the long-acting 5-HT$_3$-RA and dexamethasone is allowed per site local guideline and experience.*

Decrease in intensity of prophylaxis following Cycle 1 may be utilized based on investigator discretion, in agreement with the Medical Monitor, and patient tolerability.

All premedications for prophylaxis and on-study modifications should be captured on the patient's concomitant medications eCRF, indicating as intended for prophylaxis. The adverse GI events in the Phase I idasanutlin studies primarily included nausea, *diarrhea,* vomiting, abdominal pain, constipation, and anorexia. Supportive therapies for diarrhea and nausea are encouraged in this study.

See Section 8.3.9 for guidance for management of AEs and prophylaxis in subsequent cycles.

Re-dosing of study medication after emesis:

If vomiting occurs within 15 minutes of administering study medication and whole tablets are still intact, another dose may be administered, and the second dose must be

recorded in the drug log. Otherwise, no replacement dose is to be administered. Please refer to Section 8.3.9.1 for additional details.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication will be in accordance with Roche standard and local regulations.

Upon arrival of the IMP at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints *via the IxRS*.

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the dosing schedule.

The Investigator or delegate must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, Institution, or the Head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).

The IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used investigational medicinal product for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is an open-label study, blinding procedures are not applicable. The *assignment* of *a unique identification number for each* patient will be *completed by the IxRS*.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the planned dosing. This individual will write the date dispensed and patient number on the study treatment vial label and on the Drug Accountability Record. This individual will also record the study treatment number received by each patient during the study.

6.5 CONCOMITANT THERAPY

6.5.1 Permitted Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a patient from 28 days prior to screening until the final visit or EOS must be recorded along with reason for use, dates of administration (including start and end dates, or if ongoing).

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All concomitant medications should be recorded on the Previous and Concomitant Treatments eCRF.

All concomitant medications to treat PV related symptoms as defined in Section 8.3.8 should be recorded on the Previous and Concomitant Treatments (Targeted - Polycythemia Vera Associated) eCRF.

All therapy and/or medication administered to manage AE should be recorded on the AE eCRF.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

Megestrol administered as an appetite stimulant is acceptable when the patient is enrolled in the study.

Since nausea is a commonly reported AE in previous studies, *anti-emetic* prophylaxis is mandatory *prior to each cycle, unless otherwise agreed upon between the investigator and the Medical Monitor*. The use of anti-emetic agents should be documented in the eCRF (see Section 6.1.1).

Phlebotomy can occur anytime it is clinically warranted per institutional guidelines. Any phlebotomies prior to Study C1D1 (up to 1 year) and while on study will be individually entered on the Previous and Concomitant Treatments (Phlebotomy) eCRF.

Institutional guidelines for use of growth factor support, transfusions, and antibiotics should be followed with consideration for prohibited medications (Section 6.5.2).

6.5.2 Prohibited Therapy

The use of HU or other therapy intended to treat PV (other than phlebotomy, aspirin and other supportive therapies) is not permitted while the patient is on study.

As idasanutlin is metabolized mainly by CYP3A4, CYP2C8, and UGT (UDP glucuronosyltransferase) enzymes and it may inhibit CYP2C8 metabolism and OATP1B1/3 substrates, the use of any medication listed in Table 5 during the study and for at least 7 days (for inhibitors and substrates) and 14 days (for inducers), respectively, prior to initiation of study treatment, unless otherwise specified is prohibited in order to prevent undesirable drug-drug interactions.

Note that CYP3A4 inhibitors are not excluded: preliminary data suggests minimal (not clinically significant) drug-drug interaction (DDI) potential with posaconazole, a strong CYP3A4 inhibitor.

Metabolite M4 (RO6802287) was the only major metabolite in human plasma samples (at steady-state on Day 5) and, in contrast to idasanutlin, it inhibits OATP1B1 (IC50 2.8 μM) and OATP1B3 (IC50 1.6 μM) at the dose level to be applied in this study and the concomitant administration of OATP1B1/3 together with idasanutlin is therefore avoided.

Table 5 Prohibited Therapies

CYP2C8			OATP1B1/3*	CYP3A4
Substrates	**Inhibitors**	**Inducers (Moderate)**	**Substrates**	**Inducers (Moderate to Strong)**
amodiaquine	gemfibrozil	rifampicin	atorvastatin	carbamazepine
paclitaxel	montelukast		asunaprevir atrasentan	cyproterone enzalutamide
repaglinide	pioglitazone		danoprevir bosentan	efavirenz
rosiglitazone	rosiglitazone		ezetimibe	etravirine
torasemide	clopidogrel		fexofenadine fluvastatin	modafinil
amiodarone			glyburide	nevirapine mitotane
chloroquine			docetaxel irinotecan	oxcarbazepine
lovastatin			nateglinide olmesartan *paclitaxel*	phenobarbital
			pitavastatin	phenytoin
			pravastatin	rifampicin
			repaglinide	St John's Wort
			rifampin	
			rosuvastatin	
			simvastatin acid	
			telmisartan	
			Valsartan	

Note: Drugs with overlapping classes may appear only once for simplicity.

* Note that if $t_{1/2}$ is shorter than 1 day, use of the OATP1B1/3 substrate drug only needs to be temporarily interrupted during idasanutlin treatment and for 72 hours after the last dose of idasanutlin. In addition, resuming statins at lower doses after Week 32 may be considered if patients are treated with short-$t_{1/2}$ statins for a long duration.

6.6 DOSAGE MODIFICATION

Intra-patient dose-escalation from 150 mg to 200 mg is allowed after Cycle 3 *(preferable at Cycle 4, or latest, Cycle 5)* for patients who have demonstrated adequate tolerability and are showing a lack of Hct control *and/or inadequately controlled leukocytosis and/or thrombocytosis* at end of Cycle 3 (Section 4.1.2). Patients with PD will not be permitted to dose-escalate and should come off the study. Consideration for dose-increase will be based on a review of patient data, including but not limited to, safety data, response assessments and laboratory data. All intra-patient dose-escalation decisions will be

made in consultation with the Investigator and Sponsor, including the Medical Monitor and Safety Science Leader.

In case of hematologic toxicity (i.e., anemia, thrombocytopenia and/or neutropenia), patients may need treatment interruptions and/or dose reductions (see Table 8*).* Guidance for dose-reductions for AEs is described in Section 8.3.9. Furthermore, after one year of treatment (end of Cycle 13), a reduction of the idasanutlin dose to 100 mg for all subsequent cycles may occur for any patient that has not previously had a reduction to 100 mg for other reasons to generate data for longer term tolerability. This reduction will be based on communication between the Investigator and Sponsor. Treatment may be re-escalated back to the prior highest tolerated dose if Hct increases to $\geq$45% and/or CHR response is lost (WBC$\geq 10\times10^9$/L and PLT count $>450\times10^9$/L) *to achieve a hematologic response*. Treatment *must* not be re-escalated if the patient has progressive disease (see Appendix 1).

A treatment break may also be exercised if sufficient clinical response (CHR/Hct control) is ongoing at end of Cycle 13 or in subsequent cycles. For these patients, unscheduled hematologic response assessments should occur every 28 days and unscheduled full response assessment (as defined on SoA as for Week 32) should occur every 84 days, if treatment holiday is prolonged. Treatment may resume if Hct increases to $\geq$45% and/or CHR response is lost (WBC $\geq 10\times10^9$/L and PLT count$>450\times10^9$/L). Treatment will thereafter continue until 2 years post initial dose. Treatment should not be re-initiated if the patient has progressive disease. If subsequent scheduled efficacy assessment after re-escalation indicate a lack of Hct control ($\geq$45%) or NR by ELN 2009, treatment should be discontinued.

6.7 TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer post-trial access to idasanutlin free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product.

A patient will be eligible to receive study treatment after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study treatment for his/her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his/her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive study treatment after the end of the study if any of the following conditions are met:

- The study treatment is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the study treatment or data suggest that the study treatment is not effective for PV.
- The Sponsor has reasonable safety concerns regarding the study treatment as treatment for PV.
- Provision of study treatment is not permitted under the laws and regulations of the patient's country.

7. PATIENT DISCONTINUATION/WITHDRAWAL

Details on study and site closures are provided in Appendix 7.

7.1 DISCONTINUATION OF STUDY TREATMENT

Patient must discontinue study treatment if they experience any of the following:

- Pregnancy
- Unacceptable toxicity as determined by Investigator.
  - For cardiac changes:

    If a clinically significant finding is identified (including, but not limited to QTcF $\geq$500 ms and/or an increase of $\geq$60 ms in QTcF from screening), the Investigator or qualified designee will determine if the patient can continue in the study and if any change in clinical management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the patient.
- Disease progression at any point (Appendix 1).

Study treatment may be discontinued due to non-compliance (e.g., consistent failure to show up for scheduled visits) or if no evidence of clinical benefit in the form of lack of achieving a CR or PR per the ELN 2009 criteria, lack of achieving a Hct response or lack of decreased phlebotomy requirement at Week 32 assessment (see Appendix 1).

Patients who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 8.9.3) and may undergo follow-up assessments (see Section 8.9.4). The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Patients

who discontinue study treatment prematurely for reasons other than progression or NR (withdraw prior to Week 32) may be replaced.

7.1.1 Temporary Interruption and Discontinuation

Table 6 shows the general guidance for dosing delay due to AEs. For details of temporary interruption secondary to specific AEs, see Section 8.3.9.

Table 6 General Guidance for Dosing Delay

Clinical Event Grade	
1	No dose modification required. [a]
2	No dose modification necessary. [a]
3	Duration ≤ 2 weeks: Hold further dosing until resolution to Grade ≤ 1 and then, resume at original dose or 100 mg. [b, c, d] Duration > 2 weeks, but ≤ 4 weeks: dose reduce to 100 mg. [d] Duration > 4 weeks: discontinue treatment. [e]
4	Duration ≤ 4 weeks: Hold further dosing until resolution to Grade ≤ 1, resume at 100 mg. [d] Duration > 4 weeks: discontinue treatment. If the Grade 4 AE recurs (a second time), then idasanutlin should be discontinued.

AE = adverse event.

[a] Grade 1 or 2 AEs do not necessarily require dose holding or modification unless specifically noted in Table 8 (Guidelines for Managing Hematologic Toxicity). For Grade 2 events, idasanutlin can be resumed at the same dose when the event resolves to at least Grade 1.

[b] Dose-reduction is allowed to 100 mg idasanutlin if by collective Investigator and Sponsor judgment that such a change is warranted.

[c] Patients with Grade 3 AEs that are clearly unrelated to the study drug in the opinion of the Investigator and Sponsor and for which restarting/continuing idasanutlin does not pose a safety risk are allowed to continue receiving therapy without a necessary dose hold or modification.

[d] If the patient is on 200-mg dose level, idasanutlin will resume at 150 mg (i.e., 50 mg dose reduction).

[e] The decision to extend the dose delay will be made on the basis of the Investigator's assessment of ongoing clinical benefit and in consultation with the Medical Monitor.

7.2 WITHDRAWAL FROM THE STUDY

Patients have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he/she continues in the study.

- Investigator or Sponsor determines it is in the best interest of the patient.
- Patient non-compliance.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn.

When a patient voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the patient specifically requests for these to be discarded or local laws require their immediate destruction. A patient's withdrawal from this study does not, by itself, constitute withdrawal of specimens donated to the Research Biosample Repository (RBR).

Patients who withdraw from the study after Week 32 assessments will not be replaced. Patients who withdraw prior to Week 32 from the study for reasons other than NR or PD may be replaced.

7.3 LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timepoints are summarized in the SoA (Section 1.2).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time-frame defined in the SoA.

8.1 EFFICACY ASSESSMENTS

8.1.1 Response Assessments

Efficacy assessments will be performed at the timepoints specified in the SoA (Section 1.2) and must be conducted in accordance with the separate Laboratory Manual and the SoA (Section 1.2).

Response assessments will be at the end Cycle 3, Cycle 5, Week 32, or end of Cycle 8, then every 3 cycles after Week 32 up to 2 years and at the final visit. Week 32 response assessment is the critical efficacy timepoint and should occur regardless if it coincides with end of Cycle 8. Aspects of hematology will be used for response assessment, and hence will be highlighted as response assessments below at Week 32 and final visit.

If Week 32 occurs prior to the end of Cycle 8 (e.g., as a result of a dose delay) and there is a significant gap between Week 32 and Cycle 11 Day 28 (and Cycle 14 Day 28 for bone marrow assessment), an unscheduled visit may be requested by the Medical Monitor for completion of response assessments at the discretion of the investigator.

*For ruxolitinib-naïve patients, e*fficacy of idasanutlin will be assessed by composite response (Hct control and ≥35% reduction in spleen volume) in patients with splenomegaly *and* Hct control *alone* in patients without splenomegaly. *Efficacy in terms of Hct control, CHR, and the 2009 ELN hematologic response criteria for PV (see Appendix 2) will also be assessed in all ruxolitinib-naïve patients regardless of the presence of splenomegaly.*

For ruxolitinib-resistant or intolerant patients, efficacy will be assessed by Hct control, CHR, and the 2009 ELN hematologic response criteria.

Spleen volume and length should be measured by CT or MRI scans according to standard procedures. The same radiographic assessment modality must be used for all response evaluations to ensure consistency across different timepoints (including unscheduled assessments). Routine MRI (or CT) within 7 days of screening does not need to be repeated if it meets the study specifications (i.e., Day –35 to Day –1). Details regarding imaging procedures are provided in the Imaging Manual.

8.1.2 Clinical Outcome Assessments

In this study, COA data will be elicited from patients to fully characterize the clinical profile of the study treatment. Patient experience of disease-related symptoms over the course of treatment will be evaluated with the MPN-SAF TSS *(see Appendix 14,)*. In addition, the EORTC QLQ-C30 *(see Appendix 15)* will be used to evaluate the impact of

treatment on functioning and global health status/*HR*QoL, as well as monitor the experience of treatment-related symptoms. A PGIC *(see Appendix 16)* will be administered after baseline to assess the degree to which patients feel their experience of PV symptoms have improved since starting treatment. The COAs, translated as required in the local language, will be distributed by the Investigator staff and completed in their entirety by the patients at specified timepoints during the study. It is estimated that the assessment measures will take approximately 10–15 minutes to complete.

The COA questionnaires (MPN-SAF TSS, EORTC QLQ-C30, and PGIC) will be completed on paper at the site on C1D1 (MPN-SAF TSS and EORTC QLQ-C30 only), and at C2D1 and the end of Cycle 3, Cycle 5, Week 32 or end of Cycle 8, (whichever comes first), and on Day 28 of every 3 cycles after Cycle 8 up to two years after first dose, and/or at the end of treatment/discontinuation visit. *End of cycle assessments will ensure symptom assessments are aligned to efficacy assessments, which allows for the evaluation of improvement of symptoms at key time points when also looking at efficacy.*

Entries should be reviewed for completeness by the site staff during the visit and the patient should be requested to complete any blank items. Changes to the form should not be made once the patient has left the site visit.

8.1.2.1 *Myeloproliferative Neoplasm*-Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

The constitutional symptoms of PV significantly impact social and physical activities, impede on independence and disrupt overall quality of life. Experts in the field devised an assessment form to measure the severity of 17 key symptoms of PV known as the *Myeloproliferative Neoplasm*-Symptom Assessment Form (MPN-SAF) (Cervantes et al. 2009). More recently, a revised abbreviated version known as the MPN-SAF total symptom score (MPN-SAF TSS) was created focusing on the nine most clinically important PV symptoms from the MPN-SAF *(see Appendix 14)* (Emanuel et al. 2012; Scherber et al. 2011). These include: early satiety, abdominal discomfort, inactivity, concentration issues, night sweats, itching, bone pain, fever, and weight loss. A tenth symptom, fatigue, is assessed using the "worst" fatigue item from the Brief Fatigue Inventory (BFI). The patient provides a severity score for each additional symptom on a scale of 0 (none/absent) to 10 (worst imaginable).

8.1.2.2 European Organization for Research and Treatment of Cancer *Quality of Life-Core 30* (EORTC QLQ-C30) *Questionnaire*

The EORTC QLQ-C30 is a validated, reliable self-report measure *(see Appendix 15)* (Aaronson et al. 1993; Fitzsimmons et al. 1999). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health status/*HR*QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week.

8.1.2.3 Patient Global Impression of Change (PGIC)

The PGIC is a one-item measure that has been used in previous research in PV to assess perceived treatment benefit *(see Appendix 16)* (Mesa et al. 2016). Patients will be asked "Since the start of the treatment you've received in this study, your polycythemia vera (PV) symptoms are: 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse', and 'very much worse'.

8.2 SAFETY ASSESSMENTS

Safety assessments will consist of monitoring and recording AE, including serious adverse events and non-serious adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

ECG testing will be monitored at baseline and on treatment as outlined in Section 1.2 and in Section 8.2.3. ECG monitoring will be performed locally to mitigate the potential risk for idasanutlin of supraventricular arrhythmias. In case of emergence of supraventricular arrhythmias the Sponsor needs to be immediately notified as this represents an adverse event of special interest for this protocol Section 8.3.6.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 8.3.5.2. Planned timepoints for all safety assessments are provided in the SoA (Section 1.2).

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological, musculoskeletal systems in addition to head, eyes, ears, nose, throat, neck and lymph nodes. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

Height at baseline and weight at each cycle will also be measured and recorded.

Performance status will be measured using the ECOG Performance Status Scale Appendix 8).

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed as outlined in the SoA (see Section 1.2).

Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available. When possible, the same arm should be used for all blood pressure measurements.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will be measured in a supine position after 5-minute rest and will include temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The ECG should be confirmed as interpretable at site.

To minimize variability, it is important that patients be in a resting position for $\geq$5 minutes prior to the ECG evaluation. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the patient's permanent study file at the site. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

ECG characteristics, including heart rate, QRS duration, and PQ(PR), and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction), QTcF (Fridericia's correction) and RR will be recorded on the eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

For Cycle 3 and beyond, ECGs must be done on Day 1 pre-dose, 4, 6 hours, and prior to the dose on Day 2 (24 hours post Day 1 dose) if there is evidence of QTc prolongation >30 ms during Cycle 1 and Cycle 2 once the patient has received study medication as compared with the the QTcF interval of the screening ECG. Otherwise, ECGs will NOT be required for Cycle 3 and beyond unless the Investigator considers it necessary on behalf of the patient's safety. An unscheduled ECG can be performed as needed any time.

Allowed ECG sampling assessment windows are as follows:

- Pre-dose assessments: within 2 hours
- Assessments < 2 hours: ±5 minutes
- Assessments 2–24 hours: ±5% (equal to 3 mins/hr)
- Assessments > 24 hours: ±2 hours

8.2.4 Clinical Safety Laboratory Assessments

Reference ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. A list of clinical laboratory tests to be performed is provided in Appendix 9 and these assessments must be conducted in accordance with the separate Laboratory Manual and the SoA (Section 1.2).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

- In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the reference range and/or an adequate explanation of the abnormality is found.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- If laboratory values from non-protocol specified laboratory assessments performed at the local laboratory require a change in patient management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose-modification) then, the results must be recorded in the CRF.

Results of clinical laboratory testing will be recorded on the eCRF.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient safety.

Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before idasanutlin administration to confirm eligibility.

Based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

8.2.5 Suicidal Risk Monitoring

Not applicable.

8.2.6 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, PV history (including prior PV therapies, HU therapy, and phlebotomies), reproductive status and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to the screening visit.

PV has specific constitutional symptoms associated with the disease such as fever, night sweats, pruritus, microvascular disturbances, headaches, abdominal swelling and weight loss. Any specific PV symptoms should be clearly documented if present at baseline in the patients PV Medical History eCRF. Ongoing treatments specific to these conditions should be noted on the Targeted previous and concomitant medicines eCRF.

Demographic data will include age, sex, and self-reported race/ethnicity.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 10. The non-serious adverse events of special interest and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Sections 8.3.6 and 8.3.8.

The Investigator is responsible for ensuring that all adverse events (including assessment of seriousness, severity and causality; see Appendix 10) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 11.

Procedures used for recording AEs are provided in Appendix 11 and include:

- Diagnosis versus signs and symptoms
- AEs occurring secondary to other events
- Persistent or recurrent AEs
- Abnormal laboratory values
- Abnormal vital sign values

- Abnormal liver function tests
- Deaths
- Preexisting medical conditions
- Lack of efficacy or worsening of PV
- Hospitalization or prolonged hospitalization
- Clinical outcome assessment data

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

Investigators are not obligated to actively seek AE or SAE in post-study follow-up. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10 and Appendix 11.

Investigators will seek information on adverse events at each patient's contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record. Adverse events will then be reported on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., SAE related to invasive procedures such as bone marrow biopsies). Any other adverse event should not be reported.

After initiation of study treatment, all AE, regardless of relationship to study treatment, will be reported until 28 days after the last dose of study treatment.

After a period of 28 days from the last dose of study treatment, Investigators should report any deaths, SAE, or other AE of concern that are believed to be related to prior treatment with study treatment (see Section 8.3.2).

8.3.2 Post-Study Adverse Events and Serious Adverse Events

The Investigator is not required to actively monitor patients for AE after the end of the AE reporting period (defined as 28 days after the last dose of study drug).

8.3.3 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation timepoints.

8.3.4 Follow-Up of Adverse Events and Serious Adverse Events

8.3.4.1 Investigator Follow-Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAE considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AE (with dates) should be documented on the AE eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the AE eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 8.3.6.

8.3.4.2 Sponsor Follow-Up

For SAE, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

8.3.5 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies and will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators. Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
An investigator who receives an investigator safety report describing a SAE or other

specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical monitors is available 24 hours a day 7 days a week. Medical monitors contact details will be available on a separate list generated by the study management team.

8.3.5.2 Immediate Reporting Requirements from Investigator to Sponsor

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies (see Section 8.3.6)

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting SAE to the local Health Authority and IRB/EC.

8.3.6 Pregnancy

Details of all pregnancies in female patients of childbearing potential and female partners of male patients will be collected after the start of study treatment and for 28 days after the last dose of idasanutlin.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 6.

Abortions (spontaneous), underlying maternal or embryo fetal toxicities that led to therapeutic or elective abortion, and any congenital anomalies/birth defects are considered SAEs (Appendix 6).

8.3.7 Non-Serious Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 10 for reporting instructions).

Adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 11.
- Suspected transmission of an infectious agent by the study treatment, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- Thromboembolic events (Grade $\geq$ 2) are of particular interest for the PV population and should be reported to the Sponsor.
- Grade 3 or 4 (or any grade in presence of bleeding) thrombocytopenia (refer to Appendix 12 for a list of example Preferred Terms considered pertinent to thrombocytopenia)
- Grade $\geq$3 systemic infection;
- Grade $\geq$3 GI toxicity (refer to Appendix 12 for the list of PT considered pertinent to GI toxicity);
- Any grade supraventricular arrhythmias (MedDRA PT reported included in the Supraventricular tachyarrhythmias (refer to Appendix 12 for a list of example Preferred Terms considered pertinent to Supraventricular tachyarrhythmias).

8.3.8 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in patients with PV and can be serious/life-threatening:

- Fever, in the absence of neutropenia
- Abdominal swelling without known organomegaly
- Pruritus
- Fatigue
- Early satiety

- Night sweats
- Splenomegaly

If present at baseline and related to PV, the event should be added to the PV Medical History eCRF and marked as ongoing with or without treatment, indicating any ongoing treatments on the Previous and Concomitant Treatments (Targeted - Polycythemia Vera Associated) eCRF.

Because these events are typically associated with the disease under study, they will not be reported as AEs or according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual patient.

  OR

- The Investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product.

Events considered related to PV will instead be recorded on the PV Medical History eCRF with any treatments administered noted on the Previous and Concomitant Treatments (Targeted - Polycythemia Vera Associated) eCRF. In the event that a patient achieves a CHR at Week 32, then subsequent episodes of these events should be reported as AEs.

These DREs will be reviewed by the Medical Monitor.

8.3.9 Management of Specific Adverse Events

The safety profile of idasanutlin is currently available at higher dose regimens than those to be investigated in this study *and primarily based on patients with solid tumor or AML*. At such high*er* doses the following identified risks are present: diarrhea; nausea; vomiting; decreased appetite/anorexia; fatigue/asthenia; thrombocytopenia and increased hemorrhagic risk; neutropenia and febrile neutropenia; anemia; pyrexia; sepsis; pneumonia; fungal infections; electrolyte disorders; tumor lysis syndrome. Thrombocytopenia and GI toxicity are dose/exposure dependent but are not expected to occur as severe events at the dose levels investigated in this study. In case of occurrence of events different from those outlined below, guidelines to manage the risk can be found in the Idasanutlin IB.

8.3.9.1 Management of Gastrointestinal Toxicity (Diarrhea, Nausea and Vomiting)

GI toxicity has early onset and occurs frequently within hours from dosing. Nausea and vomiting are common events secondary to idasanutlin treatment. Appropriate

mandatory anti-emetic prophylaxis is described in Section 6.1.1. Rescue medication may include blockers of neurokinin 1 receptor (NK-1 RA*; aprepitant 125 mg orally on Day 1, then 80 mg orally daily, fosaprepitant 150 mg IV on Day 1 or switch to oral fixed-combination netupitant/palonosetron [dexamethasone dose should be adjusted if netupitant/palonosetron is administered]*). It is recommended to administer IV fluids and correct electrolytes as clinically required.

Diarrhea is also commonly reported in patients treated with idasanutlin. Specific guidelines to manage this risk are summarized in Table 7.

Table 7 Guidelines for Managing Diarrhea

Event	Action to Be Taken
Grade 1−2 diarrhea	Rule out other or concomitant causes, including medications (e.g., stool softeners, laxatives, antacids), malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber. Dietary modifications: – Stop all lactose-containing products and eat small meals. – The BRAT (banana, rice, apples, toast) diet may be helpful. – Encourage adequate hydration. Loperamide treatment – Suggested initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool; up to a maximum of 16 mg/day. – Recommend to continue loperamide treatment until diarrhea-free for 24 hours. – If Grade ≤2 diarrhea persists after 48 hours total treatment with loperamide, consider second-line agents (diphenoxylate and atropine, octreotide, budesonide, or tincture of opium). No change in study drug dosing will be implemented for Grade ≤2 diarrhea; patients should receive maximal supportive care as described above. If the event Grade ≥2 occurs, patients will be advised to undergo antidiarrheal prophylaxis for subsequent cycles.
Grade ≥3 diarrhea	If Grade ≥3 diarrhea occurs despite adequate supportive care, then all study drugs should be held until the diarrhea has improved to Grade ≤1. – If recovery occurs within 28 days, study drugs may be re-started with idasanutlin with a 50 mg dose reduction (lowest idasanutlin dose is 100 mg), with continued supportive care or prophylaxis. – If bowel movement characteristics have NOT improved to Grade ≤1 or baseline with maximal supportive care by 28 days, then idasanutlin should be permanently discontinued. If Grade ≥3 diarrhea recurs despite supportive care and idasanutlin dose-reduction, all study drug should be held until the diarrhea resolves to Grade ≤1. – If recovery occurs within 28 days, then the idasanutlin dose will be maintained at the previously reduced dose of 100 mg. If recovery is >28 days, idasanutlin should be permanently discontinued. If the diarrhea recurs at Grade ≥3, idasanutlin should be permanently discontinued.

In order to reduce the risk of developing diarrhea, patients should be carefully screened for active GI conditions including uncontrolled bowel disease (i.e., Crohn disease, ulcerative colitis, diverticulosis associated colitis, and Behçet's disease). Patients with active GI conditions at screening should be excluded from treatment with idasanutlin as per Section 5.2.

Prophylactic antidiarrheal regimen has shown efficacy in moderating symptoms in AML patients treated with higher doses of idasanutlin. Antidiarrheal therapy is recommended as prophylaxis for all patients who manifested Grade ≥ 2 diarrhea during a previous cycle. An oral loading dose of 4 mg loperamide 30 minutes before the administration of study medication has proven to be effective for managing the severity of diarrhea.

If diarrhea occurs, 2 mg loperamide should be administered orally every 4 hours or after every unformed stool to a maximum dose of 16 mg per 24 hours. It is recommended to monitor concomitant causes of GI toxicity, malabsorption/lactose intolerance, fecal impaction, dietary supplements high in fiber, and medications (e.g., stool softeners, laxatives, and antacids).

It is advised to discontinue all lactose-containing products, alcohol, and high osmolar supplements. Patients should be instructed to eat frequent small meals that include food with anti-diarrheal properties such as bananas, rice, apples, and toast. If Grade ≥ 2 diarrhea occurs, electrolytes need to be monitored at least daily and adequate hydration may be achieved if necessary through IV fluids for electrolyte correction.

8.3.9.2 Management of Hematologic Toxicity and Risk of Infections

Idasanutlin has exposure-dependent suppressive effects on bone marrow progenitors and thus a balance between the desired effects on PV progenitor cells and the normal cells must be targeted. At the dose levels used in this study, a significant reduction in the counts of normal blood cells is not expected to be observed. Specific guidelines to manage the risk of hematologic toxicity are provided in Table 8.

Frequent monitoring of hematologic values (count of blood cells, including differential) is recommended. See Table 8 for guidelines for the management of hematologic toxicity.

Increased hemorrhagic risk should be proactively managed following institutional guidelines in case of Grade ≥ 2 thrombocytopenic events.

In case of a patient showing ANC count $< 1.0 \times 10^9/L$ and concomitant fever, idasanutlin should be permanently discontinued, *unless AEs are clearly unrelated to the treatment*. Similarly, in case of a Grade ≥ 3 systemic infection associated with any grade leukopenia (refer to Appendix 12 for the list of PT considered pertinent to leukopenia) idasanutlin should be permanently discontinued, *unless AEs are clearly unrelated to the treatment*.

Table 8 Guidelines for Managing Hematologic Toxicity

Hgb level	*ANC / PLT level*	*Management*
*Hgb ≥12 g/dL(women), 13 g/dL (men) (>7.5mmol/L [women]; >8.1 mmol/L [men]) **AND***	*PLT ≥120 ×10⁹/L **AND** ANC ≥1.5 ×10⁹/L*	• *No dose modifications required.*
	*PLT 75 to <120 ×10⁹/L **AND** ANC ≥1.5x10⁹/L*	• *Interrupt dose until PLT ≥120 ×10⁹/L.* • *Resume with reduced idasanutlin dose with a 50-mg dose reduction (lowest idasanutlin dose is 100 mg; no dose modification required, if dose is already at 100 mg). If the event does not resolve within 28 days, discontinue treatment.* [a] • *Monitor labs at least every 2 weeks until PLT ≥120 ×10⁹/L.*
	*PLT 50 to <75 ×10⁹/L **AND/OR** ANC 0.5 to <1.5 ×10⁹/L*	• *Interrupt dose until PLT ≥120 ×10⁹/L and ANC ≥1.5 ×10⁹/L.* • *Resume with reduced idasanutlin dose with a 50-mg dose reduction (lowest idasanutlin dose is 100 mg).* • *If the event does not resolve within 28 days despite dose interruption, discontinue treatment.* • *No further treatment if recurrence at 100 mg (discontinue patient).* • *Monitor labs at least every week until PLT ≥120 ×10⁹/L or ANC ≥1.5 ×10⁹/L.*
	*PLT <50 ×10⁹/L **OR** ANC <0.5 ×10⁹/L **OR** ANC <1 ×10⁹/L **and** any episode of fever (38°C)*	• *No further treatment (discontinue patient).*
*Hgb 8 to <12 g/dL (women), 8 to <13 g/dL (men) (4.9 to <7.5 mmol/L [women]; 4.9 to <8.1 mmol/L [men]) **AND***	*PLT ≥120 ×10⁹/L **AND** ANC ≥1.5 ×10⁹/L*	• *Interrupt dose until Hgb ≥12g/dL (women), 13 g/dL (men).* • *First episode: Resume without dose modifications.* • *If recurrent, resume with reduced idasanutlin dose with a 50-mg dose reduction (lowest idasanutlin dose is 100 mg; no dose modification required, if dose is already at 100 mg).* • *If the event does not resolve within 28 days, discontinue treatment.* [a] • *If recurrence more than twice on lowest dose (100 mg) of*

Hgb level	*ANC / PLT level*	*Management*
		idasanutlin, discontinue treatment. [a] • *Monitor the labs at least every 2 weeks until and Hgb ≥12 g/dL (women), 13 g/dL (men).*
	*PLT 75 to <120 ×10⁹/L **AND** ANC ≥1.5 ×10⁹/L*	• *Interrupt dose until PLT ≥120 ×10⁹/L and Hgb ≥12 g/dL (women), 13 g/dL (men).* • *Resume with reduced idasanutlin dose with a 50-mg dose reduction (lowest idasanutlin dose is 100 mg; no dose modification required, if dose is already at 100 mg).* • *If the event does not resolve within 28 days or if recurrent, discontinue treatment.* • *Monitor labs at least every 2 weeks until PLT ≥120 ×10⁹/L and Hgb ≥12 g/dL (women), 13 g/dL (men).*
	*PLT 50 to <75 ×10⁹/L **AND/OR** ANC 0.5 to <1.5 ×10⁹/L **OR***	• *Interrupt dose until ANC ≥1.5 ×10⁹/L and Hgb ≥12 g/dL (women), 13 g/dL (men) and PLT ≥120 ×10⁹/L.* • *Idasanutlin may be resumed with a 50-mg dose reduction (lowest idasanutlin dose is 100 mg).* • *If the event does not resolve within 28 days or if recurrent, discontinue treatment.* • *Monitor labs at least every week until PLT ≥120 ×10⁹/L or ANC ≥1.5 ×10⁹/L or Hgb ≥12 g/dL (women), 13 g/dL (men).*
	*PLT <50 ×10⁹/L **OR** ANC <0.5 ×10⁹/L **OR** ANC <1 ×10⁹/L **and** any episode of fever (38°C)*	• *No further treatment.* • *Discontinue patient.*
*Hgb < 8g/dL (4.9 mmol/L) **OR***	*ANC <1 ×10⁹/L **and** any episode of fever (38°C) **OR** ANC <0.5 ×10⁹/L **OR** PLT <50 ×10⁹/L*	• *No further treatment.* • *Discontinue patient.*

ANC =absolute neutrophil count; Hgb =hemoglobin; PLT =platelet.

[a] *The decision to extend the dose delay or to continue treatment will be made on the basis of the investigator's assessment of ongoing clinical benefit and in consultation with the Medical Monitor.*

8.3.9.3 Management of Other Toxicities

Oral administration of idasanutlin was associated with body weight loss and/or reduced body weight gain associated with decreased food consumption in preclinical safety toxicology studies performed in cynomolgus monkeys. Decreased appetite and anorexia have been commonly reported during idasanutlin clinical development. It is recommended to investigators to monitor weight and intervene with nutritional support if required.

Fatigue and asthenia are common clinical signs associated with PV. During clinical development of idasanutlin, fatigue and asthenia were commonly observed and can be interrelated with GI toxicity and decreased appetite/anorexia. It is recommended to investigators to monitor root cause and intervene on underlying causes with nutritional support as clinically required.

Idasanutlin has hepatic toxicity as a potential risk. Accordingly, ALT, AST and bilirubin will be monitored throughout the trial as specified in Section 1.2 and will be captured as AESI as specified in Section 8.3.6. Patients at screening also need to have adequate hepatic function as described in the inclusion criteria (Section 5.1). Patients with active hepatitis will not be eligible for treatment as per Exclusion Criteria (Section 5.2). In the case of abnormal liver function test during the trial, patients will be managed as described in Table 6.

In previous clinical studies, electrolyte disorders (reported with the following PTs: hypercalcaemia, hyperkalaemia, hypernatraemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hyponatremia, hyperphosphataemia, hypophosphataemia) very commonly occurred in patients treated with idasanutlin. Patients with clinically significant electrolyte abnormalities as per exclusion criteria (Section 5.2) will not be allowed to start idasanutlin treatment. Treatment for correction of above electrolyte imbalances is permitted during screening to meet eligibility. On treatment, electrolytes need to be frequently monitored and any eventual imbalances promptly corrected as per local medical guidelines.

The management of toxicity not listed in Table 7 or Table 8 will be managed as described in Table 6.

8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an adverse event unless it results in untoward medical effects (see Appendix 11 for further details).

Decisions regarding dose-interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.5 PHARMACOKINETICS

Mandatory blood samples will be obtained for patients at the timepoints specified in the SoA (Section 1.2) for determination of plasma concentration of idasanutlin and M4 metabolite. Samples will be reserved for potential analysis of other metabolites. Additional unscheduled PK samples may be obtained if additional PK information is required to better characterize safety and PK profile (e.g., for safety observations, dosing delays, etc.). The date and time of each sample collection will be recorded in the eCRF. Idasanutlin levels will be analyzed by using validated assays.

Details on sampling procedures, sample storage and shipment are given in the lab manual. PK samples will be destroyed no later than five years after the final clinical study report.

Allowed PK sampling assessment windows are as follows:

- Pre-dose assessments: within 2 hours
- Assessments < 2 hours: ±5 minutes
- Assessments 2–24 hours: ±5% (equal to 3 mins/hr)
- Assessments > 24 hours: ±2 hours

8.6 PHARMACODYNAMICS

Samples will be collected for pharmacodynamic assessments at the times specified in the SoA (Section 1.2). These samples will be tested for protein, nucleic acid, or other biomarkers relating to the proposed mechanism of action of idasanutlin in PV or other disease-related markers or the improvement of diagnostic assays.

These include, but are not limited to, the molecular status of JAK2 (including V617F or exon 12 mutational status) and TP53 mutational analysis in samples.

Further, gene expression changes may be assessed, including p53 regulated genes may be assessed.

Protein expression may be additionally analyzed for predictive and/or prognostic association with patients benefitting from idasanutlin treatment.

Measurement of cytokines, inclusive of inflammatory cytokine signatures may also be utilized in this study (Pourcelot et al. 2014). These cytokine levels may then be compared to symptom data as generated by the MPN-SAF TSS.

The specimens may also be used for research purposes to identify biomarkers useful for predicting and monitoring response to idasanutlin treatment, identifying biomarkers useful for predicting and monitoring idasanutlin safety, assessing pharmacodynamics effects of idasanutlin treatment, and investigating mechanism of therapy resistance.

Additional markers may be measured in case a strong scientific rationale for these analyses develops. Based on continuous analysis of the data in other MDM2-antagonist studies and this study any sample timepoint or type may be stopped at any time if the data does not support a strong scientific justification to continue.

Whole blood samples will be collected for:

- **Exploratory Biomarker Pharmacodynamic** samples may be acquired before and after treatment to enable assessment of protein or other cellular markers of PV and markers related to the mechanism of action.
- **TBNK Panel Flow Cytometry Blood** for T- and B-cell quantitation by flow cytometry.

Plasma samples will be collected for:

- **Cytokine Assay** as measured utilizing a protein assay.

Serum samples for pharmacodynamic analyses will be obtained for patients as described in SoA (Section 1.2) for:

- **MIC-1** increase to be associated with steady-state exposure of idasanutlin as confirmation of intended mechanism of action engagement.

The following bone marrow samples will be collected:

- **Bone marrow biopsy** for histological assessment of cellularity (age-adjusted normocellularity), morphology on Hematoxylin and Eosin (H & E), blast percentage, and reticulin fibrosis grade. If screening bone marrow biopsy is unsuccessful, a biopsy within 3 months of first dose is required to establish baseline histology.
- **Bone marrow aspirate** for cytogenetics by local routine karyotypic analysis. If bone marrow aspirate sample insufficient/inconclusive, backup whole blood sample for cytogenetics should be used.

Details on sampling procedures, sample storage and shipment are given in the Sample Handling Manual.

Allowed pharmacodynamic sampling assessment windows are as follows:

- Pre-dose assessments: within 2 hours
- Assessments < 2 hours: ±5 minutes
- Assessments 2–24 hours: ±5% (equal to 3 mins/hr)
- Assessments > 24 hours: ±2 hours

Pharmacodynamics samples will be destroyed no later than five years after the final CSR. These samples may be used for additional exploratory biomarker profiling, identification, assay development purposes, and assay validation during the development of study or compound-related assays after the mentioned intended uses.

8.7 BIOMARKERS, GENETIC ANALYSIS

8.7.1 DNA Sequencing

Fresh blood for PV-derived DNA and RNA will be collected at baseline for analysis of TP53 and JAK2 mutational status as well as transcript quant for exploratory research on non-inherited biomarkers. Further, DNA and/or RNA extraction will be performed on post-treatment specimens for exploratory research on changes in non-inherited biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways, or immune-related markers, and also tumor mutation burden).

The following samples will be collected for genetic analysis:

- **Nucleic acid Whole Blood** analysis to include, but are not limited to JAK2 and p53 mutation status (gene sequencing)
- **Paxgene Whole Blood** analysis to include, but not limited to mRNA level of gene expression of various genes.
- **Cytogenetics Whole Blood** for cytogenetics by local routine karyotyping if bone marrow aspirate sample insufficient/inconclusive.

Details on processes for collection and shipment of these samples can be found in the Sample Handling Manual.

Whole blood samples and residual DNA and RNA from these will be destroyed no later than five years after the final CSR. These samples may be used for additional exploratory biomarker profiling, identification, assay development purposes, and assay validation during the development of study or compound-related assays after the mentioned intended uses.

8.7.2 Samples for Research Biosample Repository

Overview of the Research Biosample Repository

The Roche Research Biosample Repository (RBR) is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage and analysis of these specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens will be collected from patients who give specific consent to participate in this optional RBR. Collected specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression.
- To increase knowledge and understanding of disease biology.

- To study treatment response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site.

Sample Collection

IF RBR consent is provided, leftover biomarker samples and any derivatives thereof will be stored in the RBR.

Additionally, the following sample will be collected for identification of dynamic (non-inherited) biomarkers:

- Serum to assess exploratory biomarkers

The following samples will be collected for identification of genetic (inherited) biomarkers:

- Blood for DNA extraction

The samples collected for DNA extraction include, but are not limited to, genomic analysis and may be sent to one or more laboratories for analysis.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For all samples, dates of consent and specimen collection should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the separate Laboratory Manual.

RBR specimens will be stored and used until no longer needed or until they are exhausted. The RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., Health Authority requirements).

The repository specimens will be subject to the confidentiality standards (as described under Confidentiality in Appendix 7.

8.8 HEALTH ECONOMICS

Health Economics parameters will not be evaluated in this study.

8.9 TIMING OF STUDY ASSESSMENTS

8.9.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) for enrolled patient and for patients who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments must be completed and reviewed to confirm that patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Screening and pre-treatment assessments will be performed as described in the SoA (see Section 1.2). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 72 hours prior to first dose may be used (and do not need to be repeated for screening).

8.9.2 Assessments during Treatment

Under no circumstances will patients who enroll in this study and have completed treatment as specified, be permitted to be allocated a new enrollment number and re-enroll in the study.

All assessments must be performed as per SoA (see Section 1.2). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments. COA assessments should be performed prior to the completion of other study assessments.

8.9.3 Assessments at Study Completion/Early Termination Visit

Patients who discontinue from the study for any reason will be asked to return to the clinic to complete an End-of-Study (EOS) visit 28 days after the last dose.
If discontinuation is due to progression of disease, the EOS visit should be completed on the day the response assessment shows progressive disease instead of the next scheduled visit. See Section 1.2 for the assessment to be performed at the study completion visit.

8.9.4 Follow-Up Assessments

After the study completion/early termination visit, adverse events should be followed as outlined in Sections 8.3.1 and 8.3.2.

8.9.5 Assessments at Unscheduled Visits

Assessments as listed in Section 1.2 as deemed necessary by the Investigator and/or Sponsor, in particular for safety, will be performed at unscheduled visits.

8.9.6 Patient Engagement Application

The Smartphone Patient Engagement Application is an optional service that patients can opt-in to use to remind them of activities/tasks relevant to study compliance, e.g., attend study visits. The application also provides supportive guides to help patients to be aware of visit procedures, study information and instructions. Additional details are found in Appendix 13.

9. STATISTICAL CONSIDERATIONS

The data will be listed and summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and PK and biomarker measurements. No formal hypothesis testing is planned in the study. All the analyses will be descriptive.

9.1 STATISTICAL HYPOTHESES

This section is not applicable.

9.2 SAMPLE SIZE DETERMINATION

9.2.1 Sample Size in Ruxolitinib-Naïve Patients

Approximately 20 efficacy-evaluable patients without prior ruxolitinib exposure will be enrolled.

For 12 patients who are ruxolitinib-naïve with splenomegaly, observing a composite response rate of 50% (6/12) would provide a posterior probability of 85% that the true rate is greater than a 35% response rate. A 35% composite response rate is the minimum response rate to be considered of interest (Vannuchi et al. 2015).

Assuming a true composite endpoint rate of 60%, there is an 84% probability of observing at least 6 responders out of 12 patients.

In 20 ruxolitinib-naive patients, observing a Hct control rate of 70% (14/20) would provide a posterior probability of 80% that the true rate is greater than 60%. Assuming a true Hct control rate of 75%, there is a 79% probability of observing at least 14 responders out of 20 patients.

Based on the results from *the trials RESPONSE and* RESPONSE-2 in patients *with and* without splenomegaly, a 60% Hct control rate is the minimum response rate to be considered of interest. For 8 patients who are ruxolitinib-naïve without splenomegaly, observing a Hct control rate of 75% (6/8) would provide a posterior probability of 79% that the true rate is greater than 60%. Assuming a true Hct control rate of 75%, there is a 68% probability of observing at least 6 responders out of 8 patients.

For all 20 ruxolitinib-naïve patients, observing CHR of 45% (9/20) would provide a posterior probability of 81% that the true rate is greater than 35%. Assuming a true rate of 50%, there is 75% probability of observing at least 9/20 responders. Up to 20 additional patients may be enrolled to confirm safety, efficacy, and/or PK.

9.2.2 ***Sample Size in Ruxolitinib-Resistant or Intolerant Patients***

Approximately 20 efficacy-evaluable, ruxolitinib-resistant or intolerant patients will be enrolled in the initial phase of the study. Approximately 40 additional patients may be enrolled for further evaluation of safety and efficacy if warranted by results in the initial phase of the study and upon the discretion of the Sponsor, in a cohort expansion phase.

In this population, a Hct control rate of 30% is considered to be clinically meaningful. Observing a Hct control rate of 40% (8/20) would provide a posterior probability of 82% that the true rate is greater than 30%. Assuming a true Hct control rate of 40%, there is a 75% probability of observing at least 7 responders out of 20 patients.

From the initial phase, if the proportion of responders based on Hct control is above 30% in the ruxolitinib-resistant or intolerant cohort, the Sponsor may decide to enroll approximately an additional 40 patients with the goal of registration (expansion cohort), that would be considered the totality of available efficacy and safety data. The minimum sample size of 60 (40 patients from the expansion plus 20 patients from the initial phase) is expected to give sufficiently narrow confidence intervals. Based on a sample size of N =60, the following table shows corresponding lower bounds of the two-sided 95% confidence interval for a range of potential observed response rates.

Table 9 Lower Limit of Two-Sided 95% Confidence Interval for a Range of Potential Observed Response Rates based on a Sample Size of 60 Patients

Observed Response Rate	*Lower Limit of Two-Sided 95% Confidence Interval (exact Clopper-Pearson method)*
35% (21/60)	*23.1*
40% (24/60)	*27.6*
45% (27/60)	*32.1*
50% (30/60)	*36.8*
55% (33/60)	*41.6*
60% (36/60)	*46.5*

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following *two main* populations *(and combined populations) will be described as* defined in Table 10*:*

- *Ruxolitinib-naïve patients*
- *Ruxolitinib-resistant or intolerant patients*

Additional populations may be defined in the Statistical Analysis Plan (SAP).

Table 10 Analysis Populations *for Ruxolitinib-Naïve and Ruxolitinib-Resistant or Intolerant Patients*

Description Analyses Per Population and Combined Populations	
Efficacy	Primary efficacy population consists of patients who have completed at least 32 weeks of treatment or withdrew prior to Week 32 due to NR or progressive disease. There will also be an early-look efficacy population consisting of patients who have completed at least 3 and/or 5 cycles.
Safety	All patients who received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
PK	All patients who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Patients will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.
Pharmacodynamic	All patients who had at least one pre-dose and one post-dose pharmacodynamic assessment will be included and analyzed.

ITT = intent-to-treat; NR = no response; PK = pharmacokinetic.

9.4 STATISTICAL ANALYSES

9.4.1 Demographics and Baseline Characteristics

Demographics, including age, sex, weight, and height, as well as baseline characteristics such as prior cancer therapies, ECOG status, and medical history, will be described using basic summary statistics.

9.4.2 Efficacy Analyses

The efficacy analyses will include all patients in the efficacy analysis populations as defined in Table 10.

The primary analysis will be triggered by at least *20 efficacy-evaluable,* ruxolitinib-*naïve patients, or at least 20* efficacy-evaluable*, ruxolitinib-resistant or intolerant* patients. Primary, secondary, and exploratory endpoints (see Table 3) will be analyzed using listings and summary statistics as appropriate. No formal statistical model and no formal hypothesis testing are planned in this study.

Patients with missing assessments (hematology and/or splenic imaging) that prevent evaluation of efficacy endpoints will be considered NR. To be considered as having Hct control (absence of phlebotomy eligibility) between Week 8 and Week 32, the patient cannot miss more than one scheduled Hct assessment during this period.

A detailed description of the statistical methods that will be used for the efficacy analyses will be provided in the SAP.

Interim analyses may be performed to evaluate preliminary results and to confirm continuous positive benefit/risk profile (see Section 9.5).

9.4.3 Safety Analyses

All safety analyses will be based on the safety analysis populations.

Safety will be determined by AE, laboratory tests, vital signs, and electrocardiograms. Descriptive statistics will be used to summarize all safety data.

Exposure to study medication will be summarized by total duration of study medication, number of cycles started and cumulative dose using descriptive statistics.

All clinical laboratory data will be stored on the database in the units in which they were reported. Patient's listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing. See Appendix 9 for details on standard reference ranges and data transformation and the definition of laboratory abnormalities.

Table 11 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for AE will be coded by the Sponsor using the latest MedDRA version available at time of CCOD. AE severity will be graded according to NCI CTCAE v4.0. AE will be summarized by mapped term and appropriate thesaurus level. Individual patient listings will be produced. Safety analyses will include, but not be limited to, incidence rates for adverse events including mortality, adverse event severity, seriousness, and adverse events leading to discontinuation. The incidence of treatment discontinuation for reasons other than disease progression will be summarized.
Clinical laboratory tests	Laboratory test values will be presented in SI units by individual listings with flagging of values outside the normal ranges. In addition, tabular summaries will be produced, as appropriate. Shifts in NCI CTCAE v4.0 grades from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters. Individual patient listings will be produced. See Appendix 9 for details on standard reference ranges, data transformation, and the definition of laboratory abnormalities.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate. Individual patient listings will be produced.
ECG data analysis	ECG data will be presented by individual listings. In addition, tabular summaries will be used, as appropriate. Incidence of clinically significant ECG abnormalities will be reported in patient listings and change from baseline summarized in tables.
Concomitant medications	The original terms recorded on the patient's eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms using MedDRA version available at time of CCOD. Concomitant medications will be presented in summary tables and listings.

AE = adverse event; CCOD = clinical cut-off date; eCRF = electronic Case Report Form; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SI = International System of Units.

9.4.4 Pharmacokinetic Analyses

The PK evaluations for this study are as follows:

- Maximum concentration (C_{max})
- Trough concentration (C_{trough})
- Time of maximum concentration (t_{max})
- Clearance (CL) or apparent clearance (CL/F) for drugs given extra-vascularly

- Volume or apparent volume of distribution (Vd_{ss}/F)
- Area under the curve (AUC)
- Half-life ($t_{1/2}$)
- Potentially other parameters derived

All PK parameters will be presented by listings and descriptive summary statistics as appropriate.

Individual and mean plasma idasanutlin concentration versus time data will be tabulated and plotted by dose level. The plasma PK of idasanutlin will be summarized by estimating total exposure (AUC), maximum concentration, total clearance, volume of distribution at steady-state, and terminal half-life. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum). Inter- patient variability and drug accumulation will be evaluated.

Both non-compartmental analysis (NCA) and population PK (popPK) as well as potential association with effects (efficacy, AEs, and biomarkers) will also be applied or explored with results either reported in the CSR or a separate report.

Additional PK analyses will be conducted as appropriate.

9.4.5 Pharmacodynamic Analyses

All pharmacodynamic parameters will be presented by listings and descriptive summary statistics as appropriate.

9.4.6 Clinical Outcome Assessment Analyses

The MPN-SAF TSS, EORTC QLQ-C30, and PGIC will be used to measure symptoms of PV, physical functioning, global health status/HRQoL, and change in condition. Data will be used to derive summary scores at each timepoint. Appropriate summary statistics (frequency, mean, standard deviation, median, and range) of absolute scores will be calculated for the PGIC and all scales of the MPN-SAF TSS and EORTC QLQ-C30, at each assessment point, for all patients. Individual trajectories (e.g., spaghetti plots) and line graphs will be used to chart patient- and mean-level change over the course of the study. Mean change from baseline to each follow-up assessment point will be calculated for the scales of the MPN-SAF TSS and EORTC QLQ-C30. Frequencies will be used to show the distribution of responses to the PGIC at each assessment point. Results will be further stratified by splenomegaly at baseline. COA completion and compliance rates will be summarized at each assessment point with reasons for missing data.

9.4.7 Exploratory Analyses

The exploratory outcome measures for this study include but are not limited to the following:

- Molecular Response by percent reduction in baseline JAK2V617F (or JAK2 exon 12 mutation) allele burden at end of Cycle 3, end of Cycle 5, Week 32, and every 3 cycles up to 2 years post initial dose compared to baseline. Other genes potentially relevant to PV and/or to drug response may also be assessed at different timepoints.
- Histologic Response changes in bone marrow histopathologic abnormalities and reduction in baseline reticulin/collagen fibrosis (with fibrosis grading per European consensus on grading bone marrow fibrosis and assessment of cellularity (Thiele et al. 2005) at Week 32, and every 6 cycles per Principal Investigator (PI)'s discretion in context of CHR up to 2 years post initial dose compared to baseline.
- Assessment of Cytogenetic Response at Week 32, and every 6 cycles per PI discretion in context of CHR up to 2 years post initial dose compared to baseline.

9.5 INTERIM ANALYSES

No formal testing for efficacy will be carried out in this study and therefore no prospectively planned interim analyses are planned. The Sponsor may review the data at various timepoints during the course of the study to evaluate information that may emerge during the course of this study.

Interim analyses may be performed and interpreted by members of the Sponsor study team and senior management personnel as appropriate.

9.6 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol violations, and discontinuations from the study will be listed. The incidence of treatment discontinuation for reasons other than disease progression will be tabulated.

Variables from the eCRF used to establish the number of patients who reached the various stages of the study, withdrew, and the reasons for withdrawal will be described in the SAP.

10. REFERENCES

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11. APPENDICES

The following section includes standard appendices including:

- Regulatory, Ethical, and Study Oversight Considerations (Appendix 7).
- Adverse Events: Definitions and Evaluating, Followup and Reporting (Appendix 10).
- Procedures for Recording Adverse Events (Appendix 11).
- Contraceptive Guidance and Collection of Pregnancy Information (Appendix 6).

Additional study-related appendices are in order of appearance in the protocol.

Appendix 1
Modified ELN Criteria for Hematologic Response in PV Patients

Response Grade	Definition
Complete response (CR)	(1) Hct $<45\%$ without phlebotomy * AND (2) Platelet count $\leq 400 \times 10^9$/L AND (3) White blood cell count $\leq 10 \times 10^9$/L, AND (4) Normal spleen size on imaging AND (5) No disease-related symptoms#
Partial response (PR)	In patients who do not fulfill the criteria for complete response: Hct $<45\%$ without phlebotomy * OR response in 3 or more of the other criteria.
No response (NR)	Any response that does not satisfy partial response.
Progressive disease (PD)	Defined by occurrence of increased bone marrow fibrosis from baseline, and/or transformation to MF, MDS or Acute Leukemia.

* *Defined as protocol-specified ineligibility for phlebotomy between Weeks 8–32 and ≤1 instance of phlebotomy eligibility between first dose and Week 8. (Definition of eligibility for phlebotomy: a Hct of ≥45% that was ≥3% higher than baseline level or a Hct of >48%.)*

\# Disease-related symptoms as described in Section 8.3.8.

Reference

Adapted from: Barosi G, Birgegard G, Finazzi G, et al. Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. Blood. 2009;113:4829–33.

Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-RMT consensus project. Blood, 2013;121:4778–81.

Appendix 2
Molecular Response Criteria for PV Patients

Response Grade	Definition
Complete response	Reduction of any specific molecular abnormality to undetectable levels.
Partial response*	(1) A reduction of ≥50% from baseline value in patients with <50% mutant allele burden at baseline OR (2) A reduction of ≥25% from baseline value in patients with >50% mutant allele burden at baseline.
No response	Any response that does not satisfy partial response.

* Applies only to patients with a baseline value of mutant allele burden greater than 10%.

Reference

Barosi G, Birgegard G, Finazzi G, et al. Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. Blood. 2009;113:4829-4833.

Appendix 3
Fibrosis Grading and Histologic Response Criteria for PV Patients

Fibrosis Grading per European Consensus 2005:

Grade	
0	Scattered linear reticulin with no intersections (cross-overs) corresponding to normal bone marrow.
1	Loose network of reticulin with many intersections, especially in perivascular areas.
2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis.
3	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

Histologic Response Criteria:

Response
Histologic Remission (including disappearance of trilineage hyperplasia, age-adjusted normocellularity and absence of reticulin fibrosis [Grade 0])
No change from Baseline
Worsening of Histology from Baseline*

* If "Worsening of Histology from Baseline" is recorded please review and select the "Details of Transformation" from the following list.

- Transformation to Myelofibrosis
- Transformation to MDS
- Transformation to Acute Leukemia
- No Transformation

References

Barosi G, Birgegard G, Finazzi G, et al. Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. Blood. 2009;113:4829–33.

Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood. 2013;121:4778–81.

Appendix 4
WHO 2016 Diagnostic Criteria For PV

2016 WHO diagnostic criteria for PV

(Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion)

Major criteria	
Criterion 1 (clinical)	
Hb, or	>16.5 g/dL in men, >16.0 g/dL in women
Hematocrit, or	>49% in men, >48% in women
Red cell mass	Increased 25% above mean normal predicted value
Criterion 2 (morphologic)	
BM morphology*	Hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature MKs (differences in size)
Criterion 3 (genetic)	
JAK2V617F, or	Presence
JAK2 exon 12 mutation	Presence
Minor criterion	
Serum Epo level	Subnormal

*Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels > 18.5 g/dL in men (hematocrit, 55.5%) or > 16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present.

Reference

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.

Appendix 5
Cockcroft Gault Formula for Calculation of Creatinine Clearance

Creatinine Clearance (mL/min) for Males:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age [years]} \times \text{body weight [kg]})}{(72 \times \text{serum creatinine [mg/dL]})}$$

Creatinine Clearance (mL/min) for Females:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age [years]} \times \text{body weight [kg]})}{(72 \times \text{serum creatinine [mg/dL]})} \times 0.85$$

Appendix 6
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

- A post-menopausal state is defined as no menses for 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 1 below.

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent [a] (Failure rate of < 1% per year when used consistently and correctly)
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User-Independent [a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion **Vasectomized partner** *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

3. PREGNANCY TESTING

For all women enrolled in the study: blood sample and urine pregnancy tests will be performed during the Screening Period (within 7 days of C1D1) and then according to Schedule of Activity tables (see Section 1.2). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

4. COLLECTION OF PREGNANCY INFORMATION

- **Male participants with partners who become pregnant**

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study (see Section 8.3.6). This applies only to male participants who receive idasanutlin.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study drug. After obtaining the necessary signed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the patient should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- **Female participants who become pregnant**

Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.6). Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the patient should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 10. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

5 ABORTIONS

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Appendix 7
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC) *and applicable local, regional, and national laws*.

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the participant (e.g., advertisements, diaries etc), and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments.

The Investigator should follow the requirements for reporting all adverse events to the Sponsor. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form (and ancillary sample ICFs such as a Child's Assent or Caregiver's ICF, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample

ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant's legally authorized representative.

The Consent Forms must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the participant or the participant's legally authorized representative. All signed and dated Consent Forms must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR specimens. Participants who decline to participate will not provide a separate signature.

The Investigator should document whether or not the participant has given consent to participate by completing the RBR Sample Informed Consent eCRF.

In the event of death or loss of competence of a subject who is participating in the Research, the participant's specimens and data will continue to be used as part of the RBR.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

1.4. CONFIDENTIALITY

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Confidentiality for Research Biosample Repository

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data derived from RBR specimen analysis on individual participants will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with investigators or patients unless required by law.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR specimen data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Monitoring and Oversight Research Biosample Repository

Specimens collected for the Research Biosample Repository will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to participant participation in Research Biosample Repository for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

1.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLV).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

For information regarding the retention of records and documents, see Section 2.2 of Appendix 7.

2.1.2. Source Data Records

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable Health Authorities.

2.1.3. Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the

electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. *After that period of time, the documents may be destroyed, subject to local regulations.*

No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or any non-substantial changes, as defined by regulatory requirements.

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. This allows the Sponsor to protect proprietary

information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

2.3.3. Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

3. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study treatment development

Withdrawal from the Research Biosample Repository

Participants who give consent to provide specimens for the RBR have the right to withdraw their specimens at any time for any reason. *After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient.* If a participant wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the participant's wishes using the RBR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the Research Biosample Repository Withdrawal of Informed Consent eCRF.

If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A participant's withdrawal from Study NP39761 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from Study NP39761. Data already generated before time of withdrawal of consent to Research Biosample Repository will still be used.

Appendix 8
ECOG Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours.
3	Capable of only limited self-care; confined to a bed or chair > 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 9
Clinical Laboratory Tests

All study-required safety laboratory assessments will be performed by a local laboratory. Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	CBC, including red blood cell count (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count, white blood cell count (WBC) with differential count (i.e., neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and if present, blasts and other cells). Differential may be manual or automated, but **must** occur with each hematology assessment with emphasis on determination of the presence of peripheral blasts.
Clinical Chemistry[1]	Sodium, potassium, magnesium, chloride bicarbonate, calcium, phosphorus, albumin, total bilirubin, direct bilirubin, AST, ALT, ALP, LDH, creatinine, creatine kinase, blood urea nitrogen (BUN) or urea, uric acid, total protein, glucose, erythropoietin, iron.
Viral Serology	HIV (HIV-1/2 antibody), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody.
Pregnancy Test	All women of childbearing potential (including those who have had a tubal ligation) will have a blood pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.
Urinalysis	Urinalysis (dipstick; pH, glucose, blood, protein, ketones and bilirubin). If there is a clinically significant positive result (confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture. The results of each test must be entered into the CRF.

[1] All events of ALT $\geq 3 \times$ upper limit of normal (ULN) and bilirubin $\geq 2 \times$ ULN ($>35\%$ direct bilirubin) or ALT $\geq 3 \times$ ULN and international normalized ratio (INR) > 1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[2] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

Additional statistical considerations for Clinical Laboratory Data

Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

Definition of Laboratory Abnormalities

For all laboratory parameters included, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

Appendix 10
Adverse Events: Definitions and Evaluating, Follow-up and Reporting

1. Definition of Adverse Events

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events Meeting the AE Definition:

- Any deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be a serious adverse event (SAE) even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- **Results in death. Is life-threatening.**

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization (see Appendix 11)**

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- **Other significant events:**

  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent

one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

3. Recording of Adverse Event and/or Serious Adverse Event

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the eCRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by the Medical Monitor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Medical Monitor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

a) Assessment of Severity

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria [e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria; see below]); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity (see below).

Table 1 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to adverse event[d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event, per the definition of serious adverse event.

[d] Grade 4 and 5 events must be reported as serious adverse events, per the definition of serious adverse event.

b) Assessment of Causality

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment.
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study treatment, or reintroduction of study treatment.
- Known association of the event with the study treatment or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

For participant receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

4. Follow-up of AEs and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

5. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Idasanutlin Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Appendix 11
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

1. Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

2. Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

3. Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event

worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

4. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

6. Abnormal Liver Function Tests

Idasanutlin has hepatic toxicity as a potential risk. Accordingly, ALT, AST and bilirubin will be monitored throughout the trial as specified in Section 1.2. Patients with active hepatitis will be not eligible for treatment (see Exclusion Criteria Section 5.2). Patients at screening must also have adequate hepatic function. In the case of an abnormal liver function test on trial, participants will be managed as described in Section 8.3.9.

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN.
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest.

7. Overdose

Any study treatment overdose, or incorrect administration of study treatment, should be noted on the Study Treatment Administration eCRF.

All adverse events associated with an overdose, or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
3. Obtain a blood sample for PK analysis within 24 hours from the date of the last dose of study treatment, if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the CRF.

8. Deaths

All deaths that occur during the protocol-specified adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, ″unexplained death″ should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), ″unexplained death″ should be replaced by the established cause of death. The term ″sudden death″ should not be used unless combined with the presumed cause of death (e.g., ″sudden cardiac death″).

Deaths attributed to progression of PV will not be reported as an AE, instead will be reported on the Death Attributed to Progressive Disease eCRF.

9. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

10. Lack of Efficacy or Worsening of Polycythemia Vera

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on ELN response and hematocrit control criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

11. Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Appendix 10), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The participant has not suffered an adverse event.
- Hospitalization due solely to progression of the underlying cancer.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

12. Clinical Outcome Assessment Data

Adverse event reports will not be derived from COA data by the Sponsor, and safety analyses will not be performed with use of the COA data. Although sites are not expected to review the COA data, it is possible that an investigator could become aware of COA data that may be indicative of an adverse event. Under these circumstances, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

13. Post-Study Adverse Events and Serious Adverse Events

If the Investigator becomes aware of any other serious adverse event occurring after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event Reporting Form using the fax number or email address provided to investigators.

14. Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Events That Occur after Study Drug Initiation

For reports of serious adverse events and non-serious adverse events of special interest (see Sections 8.3.5 and 8.3.6) that occur after initiation of study drug, investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Appendix 12
Preferred Term Examples for AESIs

Gastrointestinal non-specific symptoms and therapeutic procedures (SMQ-narrow)
Abdominal discomfort
Abdominal distension
Abdominal pain
Abdominal pain lower
Abdominal pain upper
Abdominal symptom
Abdominal tenderness
Abnormal faeces
Aerophagia
Anorectal discomfort
Bowel movement irregularity
Change of bowel habit
Constipation
Defaecation urgency
Diarrhoea
Epigastric discomfort
Eructation
Faecal volume decreased
Faecal volume increased
Faeces hard
Faeces soft
Flatulence
Frequent bowel movements
Gastrointestinal pain
Gastrointestinal sounds abnormal
Gastrointestinal toxicity
Infrequent bowel movements
Nausea
Non-cardiac chest pain
Oesophageal discomfort
Oesophageal pain
Premenstrual cramps
Vomiting
Supraventricular tachyarrhythmias (SMQ-narrow)
Arrhythmia supraventricular
Atrial fibrillation
Atrial flutter
Atrial parasystole
Atrial tachycardia
Junctional ectopic tachycardia
Sinus tachycardia
Supraventricular extrasystoles
Supraventricular tachyarrhythmia
Supraventricular tachycardia

Haematopoietic cytopenias (SMQ-narrow)
Haematopoietic cytopenias affecting more than one type of blood cell (SMQ-narrow)
Aplastic anaemia
Autoimmune aplastic anaemia
Bicytopenia
Bone marrow failure
Cytopenia
Febrile bone marrow aplasia
Full blood count decreased
Gelatinous transformation of the bone marrow
Pancytopenia
Panmyelopathy
Haematopoietic erythropenia (SMQ-Narrow)
Anaemia macrocytic
Aplasia pure red cell
Aplastic anaemia
Erythroblast count decreased
Erythroid maturation arrest
Erythropenia
Hypoplastic anaemia
Microcytic anaemia
Proerythroblast count decreased
Red blood cell count decreased
Reticulocyte count decreased
Reticulocytopenia
Haematopoietic leukopenia (SMQ-Narrow)
Agranulocytosis
B-lymphocyte count decreased
Band neutrophil count decreased
Band neutrophil percentage decreased
Basophil count decreased
Basophilopenia
Cyclic neutropenia
Eosinopenia
Eosinophil count decreased
Febrile neutropenia
Granulocyte count decreased
Granulocytes maturation arrest
Granulocytopenia
Idiopathic neutropenia
Leukopenia
Lymphocyte count decreased
Lymphopenia
Metamyelocyte count decreased
Monoblast count decreased
Monocyte count decreased
Monocytopenia
Myeloblast count decreased
Myelocyte count decreased
Neutropenia

Neutropenic infection
Neutropenic sepsis
Neutrophil count decreased
Promyelocyte count decreased
Pure white cell aplasia
Radiation leukopenia
T-lymphocyte count decreased
White blood cell count decreased
Haematopoietic thrombocytopenia (SMQ-Narrow)
Acquired amegakaryocytic thrombocytopenia
Heparin-induced thrombocytopenia
Megakaryocytes decreased
Platelet count decreased
Platelet maturation arrest
Platelet production decreased
Platelet toxicity
Thrombocytopenia

Appendix 13
Patient Engagement Application

The Patient Engagement Application is a Smartphone system, referred to as an “app” that can be used by a patient or the legally authorized representative of a patient in the NP39761 study.

The app is an optional service that patients can opt-in to use to remind them of activities/task relevant to study compliances like when to take their study medication, attend site visit, track goals. The app also provides supportive guides to help patients be aware of visit procedures, study information and instructions.

The app’s interactive features are intended to be a companion to the user during the course of a trial and include the following modules:

- Study Information: targeted study information throughout the duration of the study.
- Visit Schedule: site visit reminder based on predefined Schedule of Assessments
- Goals: ability to implement study defined or personal goal targets (e.g., weight, exercise, sleep, etc.).
- Reminders: reminders for activities/task relevant to study compliances.
- Site Information: module where patients can enter their site contacts details.

The app is available for download to smartphone devices that support iOS or Android. The app will contain study-specific information only once activated by a patient. The study coordinator will provide the patient with a secure activation code, which they can use to activate the app upon their first use.

The app does not collect any patient-identified information or clinical data. This app is intended for informational purposes only. It is not a substitute for professional medical advice. Patients should contact the study site investigator or coordinator with any medical questions or concerns.

Appendix 14
Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

Symptom	**1 to 10 (0 if absent) ranking (1 is most favorable and 10 least favorable)**
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past **24 hours**	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the PAST 24 HOURS how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early Satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night Sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone Pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Appendix 15
European Organization for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire (EORTC QLQ-C30)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 16
Patient Global Impression of Change (PGIC)

Patient Global Impression of Change

Since the start of the treatment you've received in this study, your polycythemia vera (PV) symptoms are (select one):

☐Very much improved
☐Much improved
☐Minimally improved
☐No change
☐Minimally worse
☐Much worse
☐Very much worse