Official Title: **A Phase 1/2 Study of INCB053914 in Subjects With Advanced Malignancies**

NCT Number: NCT02587598

Document Date: Clinical Study Protocol Version 8: 18 December 2019

16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

The documents listed below are enclosed.

Protocol Amendment 1 – Summary of Changes	17 JUL 2015
Protocol Amendment 2 – Summary of Changes	30 OCT 2015
Protocol Amendment 3 – Summary of Changes	13 JUL 2016
Protocol Amendment 4 – Summary of Changes	26 AUG 2016
Protocol Amendment 5 – Summary of Changes	13 DEC 2016
Protocol Amendment 6 – Summary of Changes	15 MAR 2017
Protocol Amendment 7 – Summary of Changes	25 FEB 2019
Protocol Amendment 8 – Summary of Changes	18 DEC 2019
Protocol Amendment 8	18 DEC 2019

Clinical Study Protocol

INCB 53914-101 / NCT02587598

A Phase 1/2 Study of INCB053914 in Subjects With Advanced Malignancies

Product:	**INCB053914**
IND Number:	**126,097**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**03 JUN 2015**
Amendment (Version) 1:	**17 JUL 2015**
Amendment (Version) 2:	**30 OCT 2015**
Amendment (Version) 3:	**13 JUL 2016**
Amendment (Version) 4:	**26 AUG 2016**
Amendment (Version) 5:	**13 DEC 2016**
Amendment (Version) 6:	**15 MAR 2017**
Amendment (Version) 7:	**25 FEB 2019**
Amendment (Version) 8:	**18 DEC 2019**

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INVESTIGATOR'S AGREEMENT

I have read the INCB 53914-101 Protocol Amendment 8 (Version 8 dated 18 DEC 2019) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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SYNOPSIS

Name of investigational product: INCB053914	
Title of study: A Phase 1/2 Study of INCB053914 in Subjects With Advanced Malignancies	
Protocol number: INCB 53914-101	**Study Phase:** 1/2
Indication: Advanced malignancies, including acute leukemia, high-risk myelodysplastic syndrome (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPN), myelofibrosis (MF), multiple myeloma (MM), and lymphoproliferative neoplasms.	

Primary Objectives:

- All parts: To evaluate the safety and tolerability of INCB053914 as a monotherapy and in combination with standard-of-care (SOC) agents in subjects with advanced malignancies.
- Part 4 only:
  - To evaluate the efficacy of INCB053914 in combination with cytarabine in subjects with relapsed or refractory acute myeloid leukemia (AML) based on objective remission rate (ORR).
  - To evaluate the efficacy of INCB053914 in combination with azacitidine in subjects with newly diagnosed AML who are 65 years or older and unfit for intensive chemotherapy based on ORR.

Secondary Objectives:

- All parts: To evaluate the pharmacokinetics (PK) of INCB053914 when administered alone in the fasted state, the effect of food on the INCB053914 PK, and the PK when administered in combination with SOC agents in the fasted state.
- All parts: To assess the pharmacodynamics (PD) of INCB053914 as a monotherapy and in combination with SOC agents in subjects with advanced malignancies.

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Primary Endpoint:

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs) and DLTs; through physical examinations; by evaluating changes in vital signs and ECGs; and through clinical laboratory blood and urine sample evaluations.
- Part 4 only: ORR, defined as the proportion of subjects who achieve CR or complete remission with incomplete hematologic recovery (CRi).

Secondary Endpoints:

- Pharmacokinetics of INCB053914, including C_{max}, T_{max}, C_{min}, AUC_{0-t}, and Cl/F at Protocol-specified timepoints.
- Pharmacodynamic profile of INCB053914 defined by phosphorylation of Bcl-2–associated death promoter protein.

[redacted]

Overall Study Design:

This is an open-label, dose-escalation study of the PIM kinase inhibitor INCB053914 as monotherapy and in combination with SOC agents in subjects with advanced malignancies. Subjects will receive INCB053914 in 21- or 28-day cycles (as applicable to regimen schedules) until withdrawal criteria are met. Alternative administration schedules may be assessed if indicated by emerging safety, PK, or PD data. The study will be conducted in 4 parts: Parts 1 and 2 will evaluate INCB053914 as monotherapy and Parts 3 and 4 will evaluate INCB053914 in combination with select SOC agents. Part 1 (monotherapy dose escalation) will be conducted in 2 disease-specific treatment groups (Treatment Groups A and B) and will determine the maximum tolerated dose (MTD) of INCB053914 and/or a tolerated pharmacologically active dose (PAD [defined as a plasma concentration exceeding average PK that is projected to inhibit pBAD level > 50% for approximately 12 hours]) that will be taken forward into Part 2 of the study (ie, the recommended Phase 2 dose [RP2D]). Part 2 (monotherapy dose expansion) will further evaluate the safety, efficacy, PK, and PD of the RP2D in specific disease indications in which PIM kinases are particularly relevant, including leukemias and myeloproliferative and lymphoproliferative disorders, such as AML, MDS/MPN, MF, DLBCL, and MM. Part 3 (combination dose-finding) will comprise of 3 disease-specific combination treatment groups (Combination Treatment Groups A, B, and C [C-TGA, C-TGB, C-TGC]) and will determine the optimal doses of INCB053914 in combination with the selected SOC agents based on the MTD and/or tolerated

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PAD at the discretion of the sponsor and investigators. Part 4 (combination dose expansion) further evaluate the safety, efficacy, PK, and PD of the selected combination dose regimens identified in Part 3 in up to 3 expansion cohorts in specific indications relevant to the drug combinations (2 AML; 1 MF). A Simon 2-stage design will be implemented in the 2 AML combination expansion cohorts (Part 4).

Part 1 Monotherapy Dose Escalation

Between 3 and up to approximately 30 subjects will be enrolled into each of 2 treatment groups. Treatment Group A (TGA) will include acute leukemia, high-risk MDS, and MDS/MPNs (including atypical chronic myeloid leukemia [aCML], chronic myelomonocytic leukemia [CMML], myelodysplastic/myeloproliferative neoplasm unclassifiable [MDS/MPN-U], and refractory anemia with ring sideroblasts and thrombocytosis [RARS-T]). Treatment Group B (TGB) will include MM, lymphoma, and other lymphoproliferative neoplasms. Dose escalation for TGA and TGB will proceed independently, with each treatment group following a 3 + 3 design. At least 3 subjects will be enrolled and treated in each cohort. If no dose-limiting toxicities (DLTs) are observed in the initial 3 subjects, the next cohort will begin enrollment at the next higher dose level. If 1 DLT is observed in the first 3 subjects, 3 additional subjects will be enrolled in that cohort. If a DLT occurs in one-third or more of the total cohort (ie, $\geq$ 2 of 6 subjects), then the MTD will be deemed to have been exceeded, and the next lower dose level will be deemed to be the MTD. Thus, the MTD will be defined as 1 dose level below that at which one-third or more of subjects in a particular cohort report DLTs. If the first cohort exceeds the MTD, a dose de-escalation will be considered. The initial dose level in each treatment group will be 100 mg once daily (QD), with dose increases up to 2-fold until a Grade 2 toxicity that has a reasonable possibility of being related to INCB053914 is observed in that treatment group or until a total daily dose of 300 mg has been reached in that treatment group, after which dose increases will be limited to $\leq$ 50%. Each subject will be observed for 1 cycle to be evaluable to assess safety and tolerability of the dose. The RP2D will be selected based on the totality of the data within each treatment group for further investigation in the expansion cohorts, and it is possible that the RP2D could be different among disease types. If there is a distinct discrepancy in tolerability among different disease types in the same treatment group, separate disease-specific dose-escalation schedules may be initiated. If a PAD is reached before the MTD, the PAD may be selected as the RP2D based on the clinical data at the discretion of the sponsor. The sponsor, in consultation with participating investigators, may elect to expand a dose cohort(s) deemed tolerable, to up to 12 subjects, in order to obtain supplemental PK, PD, and safety data.

Part 2 Monotherapy Dose Expansion

Upon identification of the RP2D(s), up to 5 expansion cohorts will enroll subjects to further determine safety, tolerability, efficacy, PK, and PD of the selected dose(s) as follows:

- TGA Expansion Cohort 1 (TGA E1): At least 5 and up to approximately 15 subjects with AML will be enrolled and treated at the RP2D identified in Part 1 TGA.
- TGA Expansion Cohort 2 (TGA E2): At least 5 and up to approximately 15 subjects with MDS/MPN (including aCML, CMML, MDS/MPN-U, and RARS-T) will be enrolled and treated at the RP2D identified in Part 1 TGA.
- TGA Expansion Cohort 3 (TGA E3): At least 5 and up to approximately 15 subjects with MF will be enrolled and treated at the RP2D identified in Part 1 TGA.
- TGB Expansion Cohort 1 (TGB E1): At least 5 and up to approximately 15 subjects with MM will be enrolled and treated at the RP2D identified in Part 1 TGB.
- TGB Expansion Cohort 2 (TGB E2): At least 5 and up to approximately 15 subjects with DLBCL will be enrolled and treated at the RP2D identified in Part 1 TGB.

Individual dose titration will be permitted according to Protocol-defined safety parameters. Subjects will continue to receive INCB053914 in 21-day cycles until withdrawal criteria are met.

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Part 3 Combination Dose-Finding

Part 3 will include dose-finding to optimize the combination doses. Dose-finding will use a 3 + 3 design to evaluate different doses of INCB053914 in combination with SOC agents in the following treatment groups:

- Combination Treatment Group A (C-TGA): INCB053914 + I-DAC in subjects with relapsed/refractory AML.
- Combination Treatment Group B (C-TGB): INCB053914 + azacitidine in subjects with relapsed/refractory AML or newly diagnosed AML (*de novo* or secondary) in subjects ≥ 65 years at screening and unfit to receive intensive chemotherapy.
- Combination Treatment Group C (C-TGC): INCB053914 + ruxolitinib in subjects with primary or secondary MF (PPV-MF or PET-MF) who are currently experiencing a suboptimal response on ruxolitinib monotherapy, defined as follows:
  - Palpable spleen of > 10 cm below the left subcostal margin on physical examination at the screening visit OR
  - Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical exam AND active symptoms of MF at the screening visit as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form.

The starting dose of INCB053914 in the combination treatment groups will be a PAD and 1 dose level below the highest tolerated dose of INCB053914 monotherapy identified in Part 1 of this study. Starting doses of the SOC combination agents will be selected from conventional dose regimens and will remain the same for all dose-finding and dose-expansion cohorts. INCB053914 doses will not exceed the monotherapy MTD to be identified in Part 1.

Combination treatment groups will escalate independently and in parallel until the MTD or optimal doses of the combination is identified and will be followed by independent expansion cohorts at the selected dose(s). The sponsor, in consultation with participating investigators, may elect to expand a dose cohort(s) deemed tolerable, to up to 12 subjects, in order to obtain supplemental PK, PD, and safety data.

Part 4 Combination Expansion

Upon identification of the RP2D combination regimens in Part 3, up to 3 expansion cohorts will enroll to further determine safety, tolerability, efficacy, PK, and PD in the subject populations as detailed below. The 2 AML expansion cohorts will use a Simon 2-stage design to evaluate the efficacy of the combination regimens.

- **C-TGA Expansion Cohort 1 (C-TGA E1)** will enroll subjects with relapsed/refractory (r/r) AML who will be treated with INCB053914 in combination with I-DAC using the regimen identified from the Part 3 dose-finding. The approximate numbers of subjects for Stage 1 and Stage 2 are described in the Statistical Methods section of this synopsis. If an insufficient number of responders are observed in the cohort at Stage 1, further enrollment in the cohort will be terminated.
- **C-TGB Expansion Cohort 1 (C-TGB E1)** will enroll subjects with newly diagnosed AML (*de novo* or secondary) who are ≥ 65 years at screening and unfit to receive intensive chemotherapy and who will be treated with INCB053914 in combination with azacitidine using the regimen identified from the Part 3 dose-finding. The approximate numbers of subjects for Stage 1 and Stage 2 are described below in the section of "Statistical Methods." If an insufficient number of responders are observed in the cohort at Stage 1, further enrollment in the cohort will be terminated.
- **C-TGC Expansion Cohort 1 (C-TGC E1)** will enroll up to 16 subjects with PMF or secondary MF (PPV-MF or PET-MF) who are currently experiencing a suboptimal response on ruxolitinib monotherapy and who will be treated with INCB053914 in combination with ruxolitinib using the dose identified from the Part 3 dose-finding.

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- **Optional C-TGA Expansion Cohort 2 (C-TGA E2)**
  If the Part 3 C-TGB dose-finding does not yield a tolerable combination of INCB053914 and azacitidine, or if the Part 4 C-TGB E1 Simon Stage 1 does not yield favorable efficacy data, then the sponsor may elect to evaluate INCB053914 in combination with a low-dose cytarabine (L-DAC) regimen in this population. This option will use an INCB053914 dose deemed tolerable in combination with I-DAC and will reference safety and tolerability data obtained from the Part 3 C-TGA dose-finding. If the sponsor and investigators believe that the optimal dose regimen of INCB053914 in combination with L-DAC will be different from that of INCB053914 in combination I-DAC, a separate dose-finding cohort will be initiated to identify the optimal dose regimen of INCB053914 in combination with L-DAC.

Study Population:

Parts 1 and 2

Subjects diagnosed with acute leukemia, high-risk MDS, MDS/MPN, MF, MM, or lymphoproliferative neoplasms that are unresponsive to currently available therapy and have no SOC options in the opinion of the investigator.

Parts 3 and 4

Subjects diagnosed with relapsed/refractory AML, subjects with newly diagnosed AML who are ≥ 65 years of age and unfit for intensive chemotherapy, and subjects with primary or secondary MF who are currently experiencing a suboptimal response on ruxolitinib monotherapy.

Key Inclusion Criteria:

- Men and women, aged 18 years or older. Subjects in the C-TGB Expansion Cohort 1 (C-TGB E1) with newly diagnosed AML must be ≥ 65 years old.
- Part 1 monotherapy dose escalation
  - TGA: Subjects with histologically confirmed diagnosis of acute leukemia, high-risk MDS, or MDS/MPN (including aCML, CMML, MDS/MPN-U, and RARS-T).
  - TGB: Subjects with MM, lymphoma, and other lymphoproliferative neoplasms.

  Part 2 monotherapy dose expansion

  Subjects with histologically confirmed and measureable/evaluable disease:
  - TGA Expansion Cohort 1 (TGA E1): AML.
  - TGA Expansion Cohort 2 (TGA E2): MDS/MPN.
  - TGA Expansion Cohort 3 (TGA E3): MF.
  - TGB Expansion Cohort 1 (TGB E1): MM.
  - TGB Expansion Cohort 2 (TGB E2): DLBCL.

  Part 3 combination dose-finding

  Subjects with histologically confirmed and measureable/evaluable disease:
  - Combination Treatment Group A (C-TGA): relapsed/refractory AML. Subjects with acute promyelocytic leukemia are excluded.
  - Combination Treatment Group B (C-TGB): relapsed/refractory AML or subjects ≥ 65 years of age with newly diagnosed, histologically confirmed and measureable/evaluable AML (*de novo* or secondary) and unfit for intensive chemotherapy. Subjects with acute promyelocytic leukemia are excluded.
  - Combination Treatment Group C (C-TGC): primary or secondary MF who are currently experiencing a suboptimal response on ruxolitinib monotherapy defined as follows:
    - Palpable spleen of > 10 cm below the left subcostal margin on physical examination at the screening visit OR

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- Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical exam AND active symptoms of MF at the screening visit as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form.

Part 4 combination expansion

Subjects with histologically confirmed and measureable/evaluable disease:

- C-TGA Expansion Cohort 1 (C-TGA E1): relapsed/refractory AML. Subjects with acute promyelocytic leukemia are excluded.
- C-TGB Expansion Cohort 1 (C-TGB E1): newly diagnosed AML (*de novo* or secondary) who are ≥ 65 years and unfit to receive intensive chemotherapy. Subjects with acute promyelocytic leukemia are excluded.
- C-TGC Expansion Cohort 1 (C-TGC E1): primary or secondary MF who are currently experiencing a suboptimal response on ruxolitinib monotherapy defined as follows:
  - Palpable spleen of > 10 cm below the left subcostal margin on physical examination at the screening visit OR
  - Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical exam AND active symptoms of MF at the screening visit as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form.

- Parts 1 and 2
  - Must be unresponsive to currently available therapy and there is no further SOC therapy available in the judgment of the investigator.
  - Must not currently be a candidate for curative treatment, including hematopoietic stem cell transplant.
- Parts 3 and 4
  - Subjects with relapsed/refractory AML must have received either induction chemotherapy for AML or hypomethylating agents for hematologic disease before AML.
  - Elderly subjects (≥ 65 years) with newly diagnosed AML (*de novo* or secondary) must be treatment-naive and unfit for intensive chemotherapy.
  - Subjects with MF must be receiving ruxolitinib monotherapy at a stable dose for ≥ 8 weeks before Study Day 1. One dose reduction due to toxicities within the 8 weeks before Study Day 1 will be permitted. Acceptable doses are 5 mg twice daily (BID) to 25 mg BID; QD doses are not allowed.
- Willingness to undergo a pretreatment bone marrow biopsy and/or aspirate (as appropriate to disease), or archival sample obtained since completion of most recent therapy (as appropriate to subjects with existing bone marrow disease or for whom bone marrow examination is a component of disease status assessment). If a biopsy is not possible or contraindicated, or the tissue requirement cannot be satisfied, this requirement may be waived with approval from the medical monitor.
- ECOG performance status:
  - Part 1: 0 or 1.
  - Parts 2 through 4: 0, 1, or 2.
- Life expectancy > 12 weeks or ≥ 24 weeks for Part 3 and Part 4 MF subjects.

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Key Exclusion Criteria:

- Inadequate bone marrow function demonstrated by any of the following:

Laboratory Parameter	TGB (Part 1)	TGB (Part 2)	C-TGC (Parts 3 and 4)
Hemoglobin (g/dL)	< 8.0	< 8.0	Subjects unwilling to receive red blood cell transfusions to treat low hemoglobin levels are excluded.
Platelets ($\times 10^9$/L)	< 75	< 50	< 50 in 2 weeks before screening or platelet transfusions within 4 weeks of screening.
Absolute neutrophils ($\times 10^9$/L)	< 1.0	< 1.0	< 0.5 in the 2 weeks before screening.

Note: No specific hematologic exclusion criteria apply for TGA (Parts 1 and 2), Part 3 C-TGA and C-TGB, and Part 4 C-TGA E1 and C-TGB E1 Cohorts.

- Inadequate organ function demonstrated by any of the following, unless approved by the medical monitor:

  Part 1 and Part 3:

  - Total bilirubin > upper limit of normal (ULN; except total bilirubin > ULN is acceptable if direct bilirubin is ≤ 1.2 × ULN. Subjects with Gilbert's syndrome who have total bilirubin ≤ 2 × ULN may be enrolled with medical monitor approval).
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 × ULN.
  - Creatinine clearance < 50 mL/min (< 30 mL/min for MM) based on Cockroft-Gault formula or 24-hour urine analysis.

  Part 2 and Part 4:

  - Total bilirubin > ULN (except total bilirubin > ULN is acceptable if direct bilirubin is ≤ 1.2 × ULN. Subjects with Gilbert's syndrome who have total bilirubin ≤ 2 × ULN may be enrolled with medical monitor approval).
  - AST or ALT > 1.5 × ULN.
  - Creatinine clearance < 40 mL/min (< 30 mL/min for MM) based on Cockroft-Gault formula or 24-hour urine analysis.

- Receipt of anticancer medications or investigational drugs within the following interval before the first administration of study drug (note: subjects enrolling in C-TGC must continue to receive their ruxolitinib throughout the study):
  - < 5 half-lives or 14 days, whichever is longer, for any investigational agent.
  - < 28 days for any antibodies or biological therapies.
  - < 5 half-lives for all other nonbiologic anticancer medications, or sponsor approval.
  - < 6 weeks for mitomycin-C or nitrosoureas.
  - The following are allowed: hydroxyurea for controlling proliferative disease and low-dose corticosteroids (prednisone or equivalent ≤ 10 mg per day). Hydroxyurea should not be used within 48 hours before and on the day of PD sample collection or during or 72 hours before or after azacitidine administration. Note: Concomitant hydroxyurea is prohibited in subjects with MF within 8 weeks before enrolling (Day 1) into C-TGC.
- Unless approved by the medical monitor, may not have received an allogeneic hematopoietic stem cell transplant within 6 months before treatment, or have active graft-versus-host disease following allogeneic transplant, or have received immunosuppressive therapy (including, but not limited to, cyclosporine, tacrolimus, mycophenolate mofetil, or corticosteroids [> 10 mg/day prednisone equivalent]) following allogeneic transplant within 2 weeks of Cycle 1 Day 1.
- Unless approved by the medical monitor, may not have received autologous hematopoietic stem cell transplant within 3 months before treatment.

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- Has any unresolved toxicity ≥ Grade 2 from previous anticancer therapy except for stable chronic toxicities (≤ Grade 2) not expected to resolve, such as stable Grade 2 peripheral neuropathy.
- Radiotherapy within the 2 weeks before initiation of treatment. Palliative radiation treatment to nonindex or bone lesions performed less than 2 weeks before treatment initiation may be considered with medical monitor approval. In Part 3 and Part 4, MF subjects may not have had splenic irradiation within 6 months of the first dose of INCB053914.
- Part 1 and Part 3 only: Type 1 diabetes or uncontrolled Type 2 diabetes.
- Part 1 and Part 3 only: Hemoglobin A1c (HbA1c) > 8.0% (all subjects will have HbA1c tested at screening).
- Part 1 and Part 3: Any history of disease involving the central nervous system (CNS).

  Part 2 and Part 4: Known active disease involving the CNS, for example, brain metastasis or spinal cord compression, except primary CNS lymphoma.
- History of clinically significant or uncontrolled cardiac disease, including recent (within last 6 months) unstable angina or acute myocardial infarction, or New York Heart Association Class III or IV congestive heart failure, or clinically significant arrhythmias not controlled by medication. Subjects with a pacemaker and well-controlled rhythm for at least 1 month before the first dose of study drug will be allowed.
- Part 1 and Part 3: Current diagnosis of any chronic or acute respiratory condition or ongoing sequelae from any previously diagnosed respiratory condition that is significant in the judgment of the investigator or the sponsor's medical monitor.

  Part 2 and Part 4: Current diagnosis of any severe or uncontrolled obstructive or restrictive respiratory condition (eg, Global Initiative for Chronic Obstructive Lung Disease [GOLD] 3 or GOLD 4 chronic obstructive pulmonary disease).
- Gastroesophageal reflux disease not controlled by medication (ie, currently symptomatic) within 30 days before Cycle 1 Day 1.
- Prior receipt of a PIM inhibitor.
- Excessive alcohol use (eg, > 2 drinks per day).
- Excessive chronic acetaminophen use (> 2 g per day).

Study Drugs and SOC Medications, Dosages and Modes of Administration:

Part 1 and Part 2 Monotherapy

INCB053914 tablets (15 mg and 50 mg strength) will be administered orally in 21-day treatment cycles. The initial dose will be 100 mg QD. Dose escalation during Part 1 of the study will proceed using the dose-escalation rules described above. Dose increases will be accomplished using the following options: 1) increasing the number of tablets taken at each QD administration, or 2) increasing administration frequency to BID, or 3) increasing the number of tablets taken at 1 or more dose administrations and increasing the frequency to BID. The sponsor may implement alternate administration, such as intermediate doses, alternate dose regimens, or alternate formulations, depending upon PK, PD, and safety results.

Part 3 and Part 4 Combination Therapy

Conventional regimens of the SOC combination agents will be used throughout Part 3 and Part 4 of the study. In the Part 3 dose-finding cohorts, the assigned dose of INCB053914 will be dependent upon cohort assignment. In the Part 4 combination expansion cohorts, the dose of INCB053914 will depend upon the optimal dose combinations identified in the respective dose-finding cohorts in Part 3.

INCB053914: Except as noted in the Protocol, INCB053914 will be self-administered orally BID beginning with the Cycle 1 Day 1 morning dose and continuously thereafter in 21- or 28-day cycles depending upon the treatment group regimen until treatment withdrawal criteria are met. All BID doses

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will be taken in the morning and evening, approximately 12 hours apart and at least 2 hours after a meal. The starting dose of INCB053914 in Part 3 will be a PAD and 1 dose level below the highest tolerated dose of INCB053914 monotherapy identified in Part 1 of this study. At the current data cutoff date, the highest tolerated dose of INCB053914 monotherapy in Part 1 was 80 mg BID, so the planned starting dose for Part 3 will be 65 mg BID. An alternative starting dose may be selected pending emerging safety, PK, and PD data in Part 1.

Cytarabine: In the Part 3 C-TGA dose-finding cohorts and Part 4 combination expansion 1 (C-TGA E1) cohort, I-DAC will be administered to subjects with relapsed/refractory AML as an open-label commercial product at a dose of 1 g/m² per day, 2-hour infusion on Days 1 through 5. A second induction cycle may be started between 15 days and 8 weeks after initiation of Cycle 1, at the discretion of the investigator, in subjects with residual leukemia upon bone marrow assessment during initial induction, provided all drug-related toxic effects had resolved to ≤ Grade 1. Up to 2 additional cycles may be given as consolidation therapy in subjects who achieved complete remission (CR) or complete remission with incomplete platelet recovery, at the discretion of the investigator. The start of subsequent induction or consolidation cycles of I-DAC should be coordinated with the Day 1 of the INCB053914 21-day visit cycle when feasible.

If the Part 3 C-TGB dose-finding does not yield a tolerable combination of INCB053914 and azacitidine, or if the Part 4 C-TGB E1 Simon Stage 1 does not yield favorable efficacy data, then the sponsor may elect to evaluate INCB053914 in combination with a L-DAC regimen to treat elderly subjects (≥ 65 years) with newly diagnosed AML (*de novo* or secondary) who are unfit for intensive chemotherapy. In this event, L-DAC will be administered as an open-label commercial product at a dose of 20 mg subcutaneously (SC) on Days 1 through 10 of a 28- to 42-day cycle, depending upon hematologic recovery. Low-dose cytarabine therapy may continue until Protocol withdrawal criteria are met, or until subject's condition worsens, per investigator's clinical judgment, and warrants withdrawal.

Azacitidine: In the Part 3 C-TGB dose-finding cohorts and Part 4 C-TGB E1 expansion cohort, azacitidine will be administered as an open-label commercial product at a dose of 75 mg/m^2 SC or intravenously (IV) for 7 days during 9-day or less period (ie, a 2-day break allowed on week-end, if needed) of each 28-day treatment cycle.

Ruxolitinib: In the Part 3 C-TGC dose-finding cohorts and Part 4 C-TGC E1 expansion cohort, ruxolitinib will be administered as an open-label commercial BID oral treatment using the dose designated as the stable dose at the time of the screening visit for each subject. Acceptable doses are 5 mg BID to 25 mg BID. Doses of ruxolitinib should be self-administered approximately 12 hours apart without regard to food.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinical site as part of a 21-day cycle or 28-day cycle depending upon treatment regimens.

Study visits are as follows:

<u>Parts 1 and 2</u>:

- Screening
- Cycle 1: Day 1, Day 2, Day 8 (± 3 days), Day 15 (± 3 days)
- Cycle 2 and beyond: Day 1 (± 3 days), Day 2 (Cycle 2 – food-effect only), and Day 11 (± 4 days)
- End of treatment (+ 3 days from last dose of study medication)
- Safety follow-up (30-35 days after end of treatment)
- Disease status follow-up (every 9 weeks)
- Survival follow-up (every 12 weeks)

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Parts 3 and 4:

- Screening
- Cycle 1 Day 1 and Day 1 of each subsequent cycle or at appropriate intervals. Additional study visits may be required during some cycles for safety, efficacy, PK, and PD assessments as described below.
- End of treatment (+ 3 days from last dose of study medication)
- Safety follow-up (30-35 days after end of treatment)
- Disease status follow-up (every 9 weeks; except Part 3 C-TGC and Part 4 C-TGC E1)
- Survival follow-up (every 12 weeks)

Local Laboratory Tests:

All study visits will include sample collection for hematology and chemistry (including liver function panels). Coagulation, lipid, and urinalysis testing will be performed at defined intervals throughout the treatment phase. Additionally, the screening visit will include hepatitis serology testing and pregnancy testing. Subjects with diseases that are typically monitored though bone marrow examination, for example, AML, MDS, MDS/MPN, MF, and MM, will have bone marrow aspirate/biopsy at screening and as part of the disease response assessment performed by a local laboratory.

Central Laboratory Tests:

Pharmacokinetic and PD/tumor tissue samples will be collected at specific study timepoints and shipped to the sponsor or designee for analysis.

Clinical Assessments:

Adverse event assessments, physical examinations, vital signs, ECOG performance status, skeletal survey, and tumor/disease response assessments will be performed by the investigative site. Electrocardiograms (ECGs) will be performed at the site; data will be submitted to a central reader. An objective assessment of disease status will be performed for all subjects at screening, appropriate to the malignancy type. Subsequent disease assessments for AML, MDS, MPN, MM, and subsets of lymphoproliferative disorders will be performed at each cycle (excluding definitive bone marrow examination, which occurs at specified intervals for AML, MDS, MDS/MPN and MF, and otherwise to confirm complete response); subsequent disease assessments for lymphoma will be conducted every 9 weeks.

Estimated Duration of Participation: Subjects may continue on study until withdrawal criteria are met. Treatment duration will vary significantly between subjects but is expected to average approximately 4 to 6 months.

Estimated Number of Subjects:

Part 1: Approximately 3 to 30 subjects per treatment group.

Part 2: Up to 75 subjects.

Part 3: Approximately 3 to 10 subjects per dose-finding treatment group

Part 4: Up to 102 subjects.

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Statistical Methods:

Part 1 consists of a 3 + 3 dose-escalation design in INCB059314 monotherapy for 2 disease-specific treatment groups. Dose escalation for TGA and TGB will proceed independently. Approximately 3 to 6 subjects will be enrolled in each dose cohort. The total number of subjects will depend on the frequency of DLTs and the number of dose levels tested before the MTD or PAD is reached.

Part 2 will include up to 5 expansion cohorts to further evaluate the safety, tolerability, efficacy, PK and PD of RP2Ds selected from Part 1. Within each cohort, at least 5 and up to approximately 15 subjects will be enrolled and treated at the RP2D identified in the corresponding treatment group. With 5 subjects enrolled, there is an 83% probability of observing at least 1 responder if the true underlying response rate is 30%.

Part 3 will use a 3 + 3 design to evaluate different doses of INCB053914 in combination with cytarabine, azacitidine, or ruxolitinib in 3 treatment groups. Dose escalation for 3 treatment groups will proceed independently. Approximately 3 to 6 subjects will be enrolled in each dose cohort. The total number of subjects will depend on the frequency of DLTs and the number of dose levels tested before the MTD or PAD is reached.

In Part 4, up to 4 expansion cohorts will be included to further evaluate the safety, tolerability, efficacy, PK, and PD of RP2Ds selected from Part 3. A Simon 2-stage design (Simon 1989) will be used for combination expansion cohorts C-TGA E1, C-TGB E1, and the optional C-TGA E2. The response rates for the historical control (p_0), desired response rates for the combination (p_1), number of subjects needed in Stage 1 (n_1) and Stage 2 (n_2), total number of subjects in both stages (n), first stage threshold declaring cohort undesirable (r_1), the upper-limit of the number of responses in n patients such that futility of the drug is concluded (r), and probability of early termination under p_0 (PET[p_0]) are provided for each expansion cohort. The calculation is based on a 1-sided Type I error of 0.05 and power of 80%.

Cohort	p_0	p_1	n_1	n_2	n	r_1	r	PET(p_0)
C-TGA E1	20%	40%	13	30	43	3	12	0.7473
C-TGB E1	20%	40%	13	30	43	3	12	0.7473
C-TGA E2 (optional)	20%	40%	13	30	43	3	12	0.7473

Up to 16 subjects will be enrolled in the C-TGC E1 cohort. [redacted]

Descriptive statistics will be provided where appropriate. Continuous endpoints will be summarized with number of subjects, mean, standard deviation, minimum, median, and maximum for each cohort. Categorical endpoints will be summarized with frequency and percentages for each category by cohort.

In the expansion cohorts, ORR will be estimated with 95% exact confidence interval. [redacted]

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this clinical study Protocol.

Term	Explanation
aCML	atypical chronic myeloid leukemia
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
Ara-C	cytarabine
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration-time curve
BID	twice daily
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma or serum concentration
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
CR	complete response/remission
CRc	cytogenetic complete remission
CRi	complete remission with incomplete recovery
CRm	molecular complete remission
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C-TGA	Combination Treatment Group A
C-TGA E1	Combination Treatment Group A Expansion Cohort 1
C-TGA E2	Combination Treatment Group A Expansion Cohort 2
C-TGB	Combination Treatment Group B
C-TGB E1	Combination Treatment Group B Expansion Cohort 1
C-TGC	Combination Treatment Group C
C-TGC E1	Combination Treatment Group C Expansion Cohort 1
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
[redacted]	[redacted]

Term	Explanation
EBMT	European Group for Blood and Marrow Transplant
EDC	electronic data capture
EOT	end of treatment
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FDG-PET	positron emission tomography using [^{18}F] fluorodeoxyglucose
FISH	fluorescence *in situ* hybridization
FLC	free light chain
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HBV-DNA	hepatitis B virus deoxyribonucleic acid
HCV	hepatitis C virus
HCV-RNA	hepatitis C virus ribonucleic acid
HDL	high-density lipoprotein
HED	human equivalent dose
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
I-DAC	intermediate-dose cytarabine
IEC	independent ethics committee
IgM	immunoglobulin M
IL	interleukin
IN	Investigator Notification
INR	international normalized ratio

Term	Explanation
IRB	institutional review board
IMWG	International Myeloma Working Group
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWG	International Working Group
IV	intravenously
L-DAC	low-dose cytarabine
LDi	longest diameter
LFT	liver function test
LDL	low-density lipoprotein
MDS	myelodysplastic syndrome
MDS/MPN-U	myelodysplastic/myeloproliferative neoplasms unclassifiable
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MM	multiple myeloma
MPN	myeloproliferative neoplasms
[redacted]	[redacted]
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
ORR	objective remission rate
[redacted]	[redacted]
PAD	pharmacologically active dose
PASK	PAS kinase
pBAD	phosphorylated Bcl-2–associated death promoter protein
PD	pharmacodynamics
PET	positron emission tomography
PET-MF	post–essential thrombocythemia myelofibrosis
PHL	potential Hy's law
[redacted]	[redacted]
P-gp	P-glycoprotein 1
PIM	proviral integration site of Moloney murine leukemia virus
PK	pharmacokinetics
PMF	primary myelofibrosis
PPD	primary progressive disease
PPV-MF	post–polycythemia vera myelofibrosis
PR	partial remission
PRBC	packed red blood cells

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Term	Explanation
PT	prothrombin time
QTcF	QT interval corrected using the Fridericia formula
QD	once daily
RARS-T	refractory anemia with ring sideroblasts and thrombocytosis
RBC	red blood cell
RD	resistant disease
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SC	subcutaneously
SD	stable disease
SDi	smallest diameter
SOC	standard-of-care
SUSAR	suspected unexpected serious adverse reaction
TGA	Treatment Group A
TGA E1	Treatment Group A Expansion Cohort 1
TGA E2	Treatment Group A Expansion Cohort 2
TGA E3	Treatment Group A Expansion Cohort 3
TGB	Treatment Group B
TGB E1	Treatment Group B Expansion Cohort 1
TGB E2	Treatment Group B Expansion Cohort 2
TGC	Treatment Group C
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
UPM	unit probability mass
Vd_{ss}	volume of distribution at steady state
WBC	white blood cell

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1. INTRODUCTION

1.1. Background

Protein kinases regulate diverse biological processes, including cell growth, survival, and differentiation, and play specialized roles in a host of human diseases, including cancer. One such family of kinases involved is the proviral integration site of Moloney murine leukemia virus (PIM) family of serine/threonine kinases. Three members of this kinase family, PIM1, PIM2, and PIM3, were initially identified in mouse models of cancer. Subsequently, overexpression of permutations of these kinases has been demonstrated in multiple types of human cancers, predominantly in hematological malignancies. Enhanced activity of PIM kinases contributes to the development of malignancies by promoting tumor cell proliferation and survival. As opposed to numerous other cancer-related protein kinases, which require activation by phosphorylation, ligand engagement, or genetic modification (mutation or translocation), the PIM kinases are constitutively active (Qian et al 2005), and in fact, most known mutations in the PIM somatic hypermutation region do not alter kinase activity significantly (Kumar et al 2005). Expression of PIM kinases is induced by cytokines and growth factors. Among the cytokines activating the transcription of PIM kinases are those which signal through the Janus kinase/signal transducer and activator of transcription pathway, such as interleukin (IL) 6, IL-10, and granulocyte macrophage colony–stimulating factor.

Dysregulated expression of PIM kinases is detected in a wide variety of hematologic and solid cancers. Overexpression of various family members have been noted in multiple myeloma (MM), acute myeloid leukemia (AML), pancreatic and hepatocellular cancers (Amson et al 1989, Claudio et al 2002, Fujii et al 2005, Li et al 2006, Mizuki et al 2003). Additionally, PIM1 overexpression is associated with poor prognosis in mantle cell lymphoma, esophageal, gastric, and head and neck cancers (Hsi et al 2008, Liu et al 2010, Peltola et al 2009, Warnecke-Eberz et al 2009). PIM1 is overexpressed in Myc driven prostate tumors (Ellwood-Yen et al 2003) while PIM2 overexpression is associated with an aggressive clinical course in a subset of diffuse large B-cell lymphoma (DLBCL) patients (Gomez-Abad et al 2011). Overexpression is often seen where Myc is overexpressed and PIM kinases can convey resistance to traditional chemotherapeutic agents and radiation (Chen et al 2009, Isaac et al 2011, Peltola et al 2009). As such, these data suggest that inhibition of PIM kinases may result in therapeutic benefit in cancer patients. INCB053914 is a selective inhibitor of PIM1, PIM2, and PIM3 and is proposed for the treatment of advanced malignancies.

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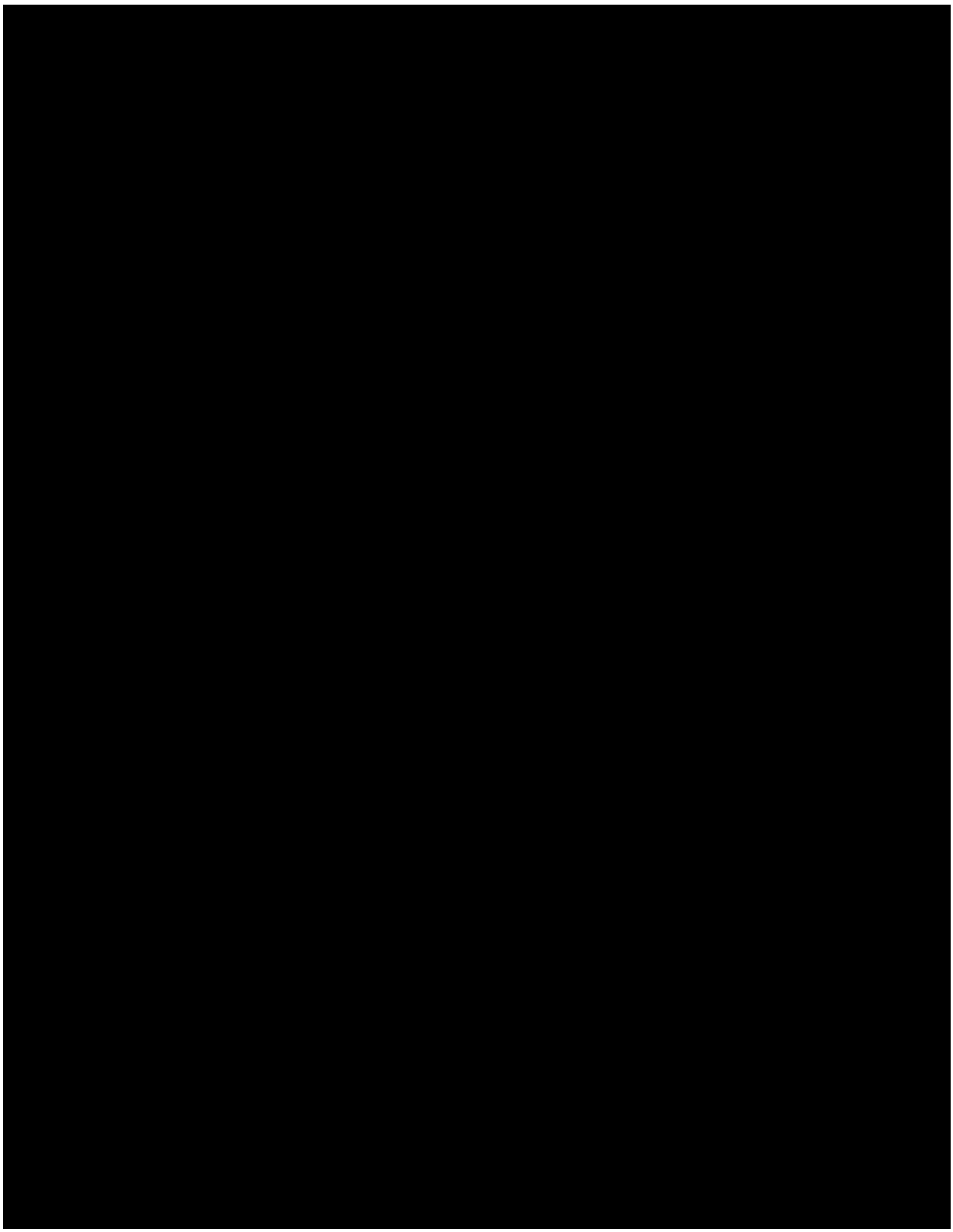

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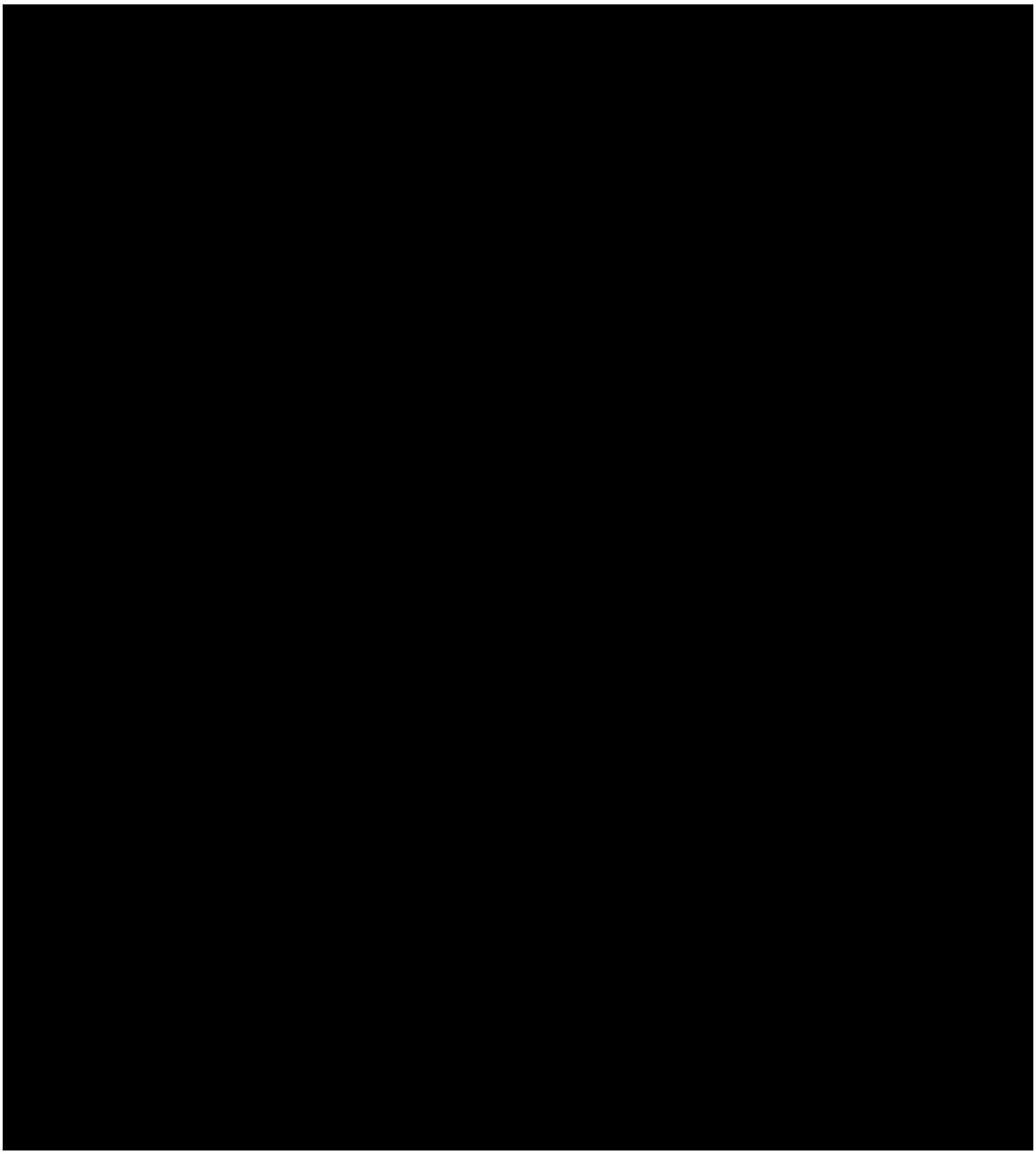

1.3. Overview of Standard-of-Care Agents Selected for Combination

1.3.1. Cytarabine

Cytarabine is an antimetabolic, neoplastic cytotoxic agent that exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G_1 phase to the S-phase. Although its mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of

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DNA polymerase (Cytarabine 2016). Cytarabine has served as one of the lynchpin treatments to induce remission in AML for over 30 years (Löwenberg et al 1999). Cytarabine in combination with other approved anticancer drugs is indicated for remission induction in acute nonlymphocytic leukemia of adults and children (Cytarabine 2016), and cytarabine monotherapy or in combination is also used widely in relapsed or refractory AML patients (NCCN Guidelines). In the Phase 3 VALOR study (Ravandi et al 2015), where vosaroxin plus cytarabine was compared with placebo plus cytarabine in subjects with first relapsed or refractory AML, mOS was 7.5 months in the vosaroxin group (n = 356) versus 6.1 months in the intermediate-dose cytarabine (I-DAC) group (n = 350), with HR = 0.87, p = 0.061 unstratified, and p = 0.024 stratified by prespecified randomization factors, with complete remission rate (CR) 30% versus 16%, and remission rate (CR/CRp/CRi) 37% versus 19%. Of subjects in the I-DAC arm, 84% experienced treatment-emergent adverse events (TEAEs) ≥ Grade 3 (all grade and all causality), of which the majority were hematological adverse events (AEs; febrile neutropenia, anemia, thrombocytopenia, and neutropenia), and most of nonhematologic AEs were Grades 1 and 2, including nausea, constipation, diarrhea, pyrexia, headache, and fatigue.

1.3.2. Azacitidine

Azacitidine is a nucleoside metabolic inhibitor that is approved by the FDA for the treatment of patients with several different subtypes of myelodysplastic syndrome (MDS; Vidaza 2016). Azacitidine is thought to have 2 main mechanisms of antineoplastic action: cytotoxicity, resulting from incorporation into RNA and DNA, and DNA hypomethylation, restoring normal growth control and differentiation in hematopoietic cells (Kaminskas et al 2005). Azacitidine is recommended as a low-intensity induction therapy in AML, primarily in patients who are unfit for high- or intermediate-intensity regimens, especially in patients ≥ 60 years (NCCN Guidelines). In the AZA-AML-001 study (Dombret et al 2015), azacitidine (n=241) was compared with conventional therapies (best supportive care, low-dose cytarabine (L-DAC), and standard induction therapy) (n=247) in patients age ≥65 years with newly diagnosed AML with >30% bone marrow blasts; mOS was improved (10.4m vs 6.5m, HR=0.85, P=0.10009), however, which did not reach statistical significance; mOS did reach statistical significance (12.1m vs 6.9m, HR=0.76, P=0.019) when the patients were censored at the start of subsequent AML therapy by prespecified sensitivity analysis; also, patients with poor-risk cytogenetics (HR=0.68) and with myelodysplasia-related changes (HR=0.69) benefited significantly from azacitidine; even though the study was not powered to compare azacitidine with individual conventional therapy, the OS of patients treated with azacitidine or L-DAC (n=154 vs 158) did not different significantly, and comparable survival rates were also observed comparing azacitidine with standard induction therapy (n=43 vs 44), and azacitidine is superior to best supportive care by post hoc analysis; azacitidine achieved a CR of 19.5% vs 21.9% with conventional therapies, CR/CRi 27.8% vs 25.1%; the most common TEAEs ≥G3 occurring in ≥20% of patients in the azacitidine arm were febrile neutropenia, neutropenia, thrombocytopenia, pneumonia, anemia. Although there has been limited investigation into the use of azacitidine in relapsed/refractory AML, Al-Ali et al (2012) reported a 10% overall response rate (including hematologic improvement) in subjects who were resistant to primary chemotherapy. Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase. Cytochrome P450 enzyme induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely, and metabolic drug-drug interaction between INCB053914 and azacitidine is not anticipated.

1.3.3. Ruxolitinib

Ruxolitinib, a potent and selective inhibitor of JAKs 1 and 2, is approved for use in patients with intermediate- or high-risk MF, including primary myelofibrosis (PMF), post–polycythemia vera myelofibrosis (PPV-MF), and post–essential thrombocythemia myelofibrosis (PET-MF). Registration studies showed improvement in spleen size, symptom burden, and overall survival (OS) with ruxolitinib use in this patient population (Harrison et al 2012, Cervantes et al 2013, Mesa et al 2013a, Mesa et al 2013b, Verstovsek et al 2012, Verstovsek et al 2013, Vannucchi et al 2015).

In the 2 pivotal, Phase 3 studies of ruxolitinib in MF, INCB 18424-351 and CINC424A2352, 301 subjects had a median duration of exposure to ruxolitinib of 9.6 months (range, 2 weeks to 17 months). The majority of subjects (55.8%) were treated for at least 9 months. The most frequently reported AEs were thrombocytopenia and anemia. Hematologic AEs (any CTCAE grade) included anemia (81.7%), thrombocytopenia (67.4%), and neutropenia (15.3%). Anemia, thrombocytopenia, and neutropenia are dose-related effects. The 3 most frequently reported nonhematologic AEs were bruising (18.6%), dizziness (14.0%), and headache (12.6%). The 3 most frequently reported nonhematologic laboratory abnormalities were elevated alanine aminotransferase (ALT; 26.2%), elevated aspartate aminotransferase (AST; 18.6%), and hypercholesterolemia (16.6%). In Phase 3 clinical studies, discontinuation because of AEs, regardless of causality, was observed in 9.6% of subjects.

1.4. Potential Risks and Benefits of the Treatment Regimens

1.4.1. Potential Risks of INCB053914 Based on Preclinical Safety

Nonclinical safety studies with INCB053914 included single and repeat-dose studies of up to 28 days in duration in rats and dogs using a QD dose regimen. In the 28-day pivotal GLP studies, doses were 0 mg/kg, 55 mg/kg, 110 mg/kg, and 250 mg/kg per day for the rat and 0 mg/kg, 3 mg/kg, 10 mg/kg, and 30 mg/kg per day for the dog. The target organs observed in the pivotal 28-day GLP studies included the liver, the hematopoietic system, and the respiratory tract. Liver effects were primarily seen in the bile ducts (ie, proliferation, epithelial degeneration/necrosis, periportal inflammation). The hematopoietic effects (ie, hematologic changes, bone marrow hypocellularity) were attributed to the pharmacology of PIM inhibition. Respiratory tract findings (inflammation/hemorrhage), which were the cause of mortality in both species, resulted from aspiration of the drug and or stomach contents following reflux (rats) or emesis (dogs) and thus are not considered to be related to a systemic effect of INCB053914.

The main INCB053914-related target organ toxicity following repeat-dose exposure to INCB053914 in both rats and dogs was hepatotoxicity. In the 28-day rat GLP study, minimal to moderate biliary changes were observed in all high-dose animals (250 mg/kg per day; human equivalent dose [HED] = 2400 mg), characterized as bile duct proliferation with epithelial degeneration/necrosis and periportal inflammation. These findings were accompanied by minimal to mild hepatocellular necrosis in some animals. Hepatocellular necrosis may have been secondary to the biliary changes, as there were no findings of hepatocellular necrosis in the absence of biliary change, whereas biliary changes without necrosis were frequently observed. No fibrosis was observed. In rats, there were no changes in serum chemistry parameters associated with biliary changes in the absence of hepatocellular necrosis. However, elevated

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serum ALT, AST, and sorbitol dehydrogenase levels were observed in animals with mild to moderate hepatocellular necrosis. Minimal biliary changes were observed in 1 male and 1 female at the mid dose (110 mg/kg per day; HED = 1056 mg), with no hepatocellular necrosis. There were no histologic findings in the liver of high-dose animals after a 4-week recovery period, suggesting that these findings were fully reversible. In the 28-day dog study, minimal biliary hyperplasia was observed in a single high-dose dog (30 mg/kg per day; HED = 972 mg), with associated increases in serum alkaline phosphatase (ALP), gamma-glutamyl transferase, and transient body weight loss. There were no histologic findings in the liver of high-dose animals after a 4-week recovery period.

Bone marrow effects consistent with the pharmacologic activity of INCB053914 were observed in both rats and dogs. In the 28-day study in rats, hypocellularity of bone marrow was observed in animals dosed with ≥ 10 mg/kg (HED = 324 mg), and lower reticulocyte and platelet counts were observed in high-dose males (30 mg/kg per day; HED = 972 mg). In dogs, hematologic changes (lower total leukocyte and absolute neutrophil, monocyte, eosinophil, basophil, platelet, and reticulocyte counts) were observed at all doses in the 28-day study, although there were no histologic changes in the bone marrow. Slightly lower reversible values of the mean corpuscular volume, mean corpuscular hemoglobin, and/or mean corpuscular hemoglobin concentration accompanied by slight increase of hemoglobin distribution width were observed on 10-day and 28-day rat studies. Comparable hematologic findings were noted in high-dose males in the 28-day dog study. Similar hematologic findings have been described in a PIM 1/2/3 triple knockout mouse model (Mikkers et al 2004).

In the 28-day studies, mortality was observed in rats at the mid (110 mg/kg per day; HED = 1056 mg; 1 female) and high dose (250 mg/kg per day; HED = 2400 mg; males and females), and 2 dogs (one mid [10 mg/kg per day; HED 324 mg] and one high dose [30 mg/kg per day; HED 972 mg]) were euthanized in extremis. Deaths in both species were due to respiratory findings consistent with aspiration. In rats, these findings were attributed to aspiration following reflux of INCB053914 formulation and/or stomach contents (as evidenced primarily by acute necrotizing inflammation of larynx, trachea, and lung), and in dogs were attributed to aspiration following emesis. These findings were likely mediated by local concentrations and irritant effects of the drug in the stomach and/or upper respiratory tract (as evidenced by acute inflammation and hemorrhage in the trachea and large bronchi), not systemic exposure. Furthermore, the findings in rats are typical of those described with gavage-related reflux and so could, at least in part, be associated with the oral gavage delivery of the compound (Damsch et al 2011b). Hence, respiratory findings were attributed to high local INCB053914 concentrations in the stomach leading to reflux/emesis and aspiration. Emesis, while compound-related, is a common finding in dogs; also, dogs are prone to aspiration. Reflux and aspiration, while uncommon in rats, have been described following oral gavage administration of irritating compounds (Damsch et al 2011a, Damsch et al 2011b), which would not be relevant for patients administered tablets. Moreover, the high gastric concentrations associated with these findings in rats would not be achieved over the projected dose range for clinical studies of INCB053914. Symptoms such as nausea, vomiting, reflux, and heartburn are easily monitored in patients. Thus, these findings are not considered relevant for human subjects and were not used in defining the safe starting dose.

The following histologic findings were noted in the rats administered 500 mg/kg per day (HED = 4800 mg) in the 10-day range-finding study: ulceration of the nonglandular stomach,

diffuse acinar cell hypertrophy in the salivary gland, reduced luminal sperm in the epididymides, diffuse hypertrophy of the adrenal cortex. These findings occurred at exposures representing high multiples of anticipated human exposure and were not observed on 28-day study.

INCB053914 is an inhibitor of PASK and theoretically may have an effect on glucose metabolism. Glucose levels will be appropriately monitored in clinical studies.

INCB053914 was negative in the Ames mutagenicity assay.

The proposed safe starting dose for the Phase 1 study is based on liver findings in rats and dogs. The no-observed-adverse-effects levels for these findings were 110 mg/kg per day in rats (660 mg/m^2 per day) and 30 mg/kg per day in dogs (600 mg/m^2 per day) in the 28-day pivotal studies. The HEDs associated with these doses are 1056 mg and 960 mg, respectively; applying a 10-fold safety factor for the rat and 6-fold safety factor in the dog results 106 mg and 162 mg, respectively. Thus, a starting dose of INCB053914 100 mg QD is proposed for the first in human study.

Lower mean testis, epididymis and prostate gland weights that correlated with microscopic findings of testes immaturity were noted in all treatment groups of a 3-month dog study. Immaturity in the testes persisted post-42 day recovery period at the two highest doses (10 mg/kg and 20 mg/kg per day).

Refer to the INCB053914 IB for more details on the nonclinical toxicology.

1.4.2. Potential Risks of INCB053914 Based on Preliminary Clinical Experience

As of 31 DEC 2016, 34 subjects with various hematologic malignancies had been enrolled in Part 1 of the study (monotherapy dose escalation) and received starting doses of INCB053914 of either 100 mg QD (n = 4; all in Treatment Group A [TGA]), 50 mg BID (n = 11; 6 in TGA, 4 in Treatment Group B [TGB] and 1 in Treatment Group C [TGC]), 65 mg BID (n = 4; all in TGA), 80 mg BID (n = 3; all in TGA), 100 mg BID (n = 6; 4 in TGA and 2 in TGB), or 115 mg BID (n = 6; all in TGA) continuous study drug administration for 21-day cycles. As of the data cutoff date, 2 dose-limiting toxicities (DLTs) have been observed. Two of 6 subjects experienced DLTs (1 subject with AML experienced Grade 3 rash and 1 subject with AML experienced Grade 4 ALT elevation) in the TGA 115 mg BID cohort; as such 115 mg BID was deemed to be the nontolerated dose for TGA. Subsequent to the determination of the nontolerated dose , a 100 mg BID cohort was opened for enrollment in TGA. One subject with AML in the TGA 100 mg BID cohort experienced Grade 3 ALT/AST elevation and Grade 3 rash toxicities in Cycle 2. Additionally, after the 31 DEC 2016 data cutoff date, it was reported that 1 subject with DLBCL in the TGB 100 mg BID cohort experienced a DLT of Grade 3 ALT elevation.

Aside from the DLTs reported, which have been asymptomatic, INCB053914 has been generally well tolerated. Based on preliminary unaudited data as of 31 DEC 2016, 32 of the 34 enrolled subjects (94%) reported a TEAE. The most common AEs reported (> 25% incidence, any causality) were anemia (38%), ALT increased (35%), fatigue (35%), AST increased (32%), nausea (32%), and diarrhea (26%). Twenty-seven subjects (79%) reported a Grade 3 or greater AE (CTCAE v4.03). The most common Grade 3/4 AEs reported (≥ 15% incidence, any causality) were anemia (35%), platelet count decreased/thrombocytopenia (24%), febrile neutropenia (21%), and pneumonia (15%). Seventeen subjects (50%) reported an AE that led to an interruption, reduction, or withdrawal of study drug. There were treatment-emergent serious

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adverse events (SAEs) reported in 20 subjects (59%), 9 of which were considered related to study drug as per investigator assessment. The most common SAEs reported of any causality were febrile neutropenia (21%) and pneumonia (15%), while the most common SAEs reported as related to study drug were maculopapular rash (9%), ALT increased (6%), and AST increased (6%).

As of 31 DEC 2016, 6 of 34 subjects continue to receive study drug; 28 of 34 subjects permanently discontinued treatment (20 because of disease progression, 3 because of an AE, 2 because of death, 2 because of subject decision, and 1 because of physician decision). Seventeen subjects have died as of the cutoff date (12 from disease progression, 3 from unknown causes, 1 from disease-related intracerebral hemorrhage, and 1 from disease-related pneumonia/sepsis).

1.4.2.1. ALT/AST Elevations

As of 31 DEC 2016, based on a review of raw, unaudited laboratory data, 22 subjects with baseline AST or ALT values within normal limits (62%) experienced treat-emergent ALT or AST elevations of any grade.

Eighteen subjects across all cohorts experienced treatment-emergent Grade 1 (worst grade) ALT or AST elevation. None of these subjects required dose interruptions or modifications.

Two subjects in the TGA 100 mg QD cohort experienced Grade 2 ALT elevations, and study drug administration was interrupted per the guidelines in Protocol Amendment 2. The ALT elevation resolved (values returned to baseline or Grade 1) in approximately 1 week after dose interruption, and study drug administration was restarted at a lower dose (50 mg QD) per Protocol guidelines. No further issue occurred.

As noted above, ALT and AST elevations ≥ Grade 3 have been reported in 3 subjects; 1 subject (Grade 4 ALT/Grade 3 AST) in the TGA 115 mg BID cohort and 1 subject (Grade 3 ALT/AST) in the TGA 100 mg BID cohort as of the 31 DEC 2016 cutoff date, as well as 1 subject (Grade 3 ALT) in the TGB 100 mg BID cohort after the data cutoff date. Study drug was interrupted in all 3 cases. The ALT and AST levels in the 2 subjects who received 100 mg BID were resolved after approximately 1 week off study drug. The ALT in the subject who received 115 mg BID also showed significant improvement immediately after treatment interruption; however, the subject's liver function test (LFT) elevation was considered not resolved at the time of death due to disease progression, which occurred 3 days after treatment interruption.

Investigators should closely monitor serum chemistry and coagulation markers of liver function as noted in the relevant schedules of assessments in Section 6, treatment interruption guidelines in Section 5.2.4, and assessment of potential Hy's law (PHL) cases as noted in Appendix S.

1.4.2.2. Rash

As of the 31 DEC 2016 data cutoff date, 3 subjects (2 in the TGA 115 mg BID cohort and 1 in the TGA 100 mg BID cohort) have experienced Grade 3 treatment-emergent maculopapular rashes. The majority of these rashes have been nonpruritic and asymptomatic, but did warrant treatment interruption, and all resolved with or without supportive care.

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1.4.3. Potential Risks Related to Standard-of-Care Agents Selected for Combination

1.4.3.1. Cytarabine

Cytarabine is a potent bone marrow suppressant, and as such, dose and schedule-dependent pancytopenias, as well as cellular changes in the morphology of bone marrow and peripheral smears, can be expected as a result of cytarabine treatment. Subjects receiving this drug must be under close medical supervision and during induction therapy; bone marrow and peripheral blood parameters will be monitored according to the Protocol schedule, local institutional guideline, or as clinically indicated. Infections in any location of the body may be associated with the use of cytarabine.

Other frequent toxicities following cytarabine treatment include anorexia, hepatic dysfunction, nausea, fever, vomiting, rash, diarrhea, thrombophlebitis, oral and anal inflammation, or ulceration and bleeding (all sites). Periodic checks of liver and kidney functions should be performed in subjects receiving cytarabine treatment according to the Protocol schedule, local institutional guideline, or as clinically indicated.

A complete discussion of risks associated with cytarabine can be found at http://dailymed.nlm.nih.gov/.

1.4.3.2. Azacitidine

The primary DLT observed with azacitidine therapy is myelosuppression, typically manifesting as leukopenia, anemia, thrombocytopenia, and/or neutropenia. Hematologic toxicities are reversible and are managed through dose interruptions and/or reductions. Subjects will have blood counts monitored weekly during the first cycle of treatment and before starting each course of therapy thereafter, at minimum. Azacitidine has also been associated with severe adverse reactions, including hepatic coma and renal failure. Subjects with significant baseline hepatic or renal impairment are excluded from this clinical study. Additional adverse reactions associated with the use of azacitidine ($\geq$ 20%) include nausea, vomiting, constipation, diarrhea, fever, dyspnea, petechiae, and ecchymosis. Periodic checks of bone marrow, liver, and kidney functions should be performed in subjects receiving azacitidine treatment according to the Protocol schedule, local institutional guideline, or as clinically indicated. A complete discussion of risks associated with azacitidine can be found at http://dailymed.nlm.nih.gov/.

1.4.3.3. Ruxolitinib

The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoietic proliferation attributable to the inhibition of growth factor pathways associated with JAK inhibition. Dose-dependent, reversible thrombocytopenia has been observed in studies of subjects with MF. Anemia and, less frequently, neutropenia have also been observed in studies in subjects with MF. Increased rates of infection and anemia are potential risks of myelosuppression, and there are multiple sequelae of anemia, including the burden and risks of transfusion. A complete discussion of risks associated with ruxolitinib can be found at http://dailymed.nlm.nih.gov/.

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1.4.4. Potential Risks Related to the Combination of INCB053914 and Selected Standard-of-Care Agents

INCB053914 has not been combined with cytarabine, azacitidine, or ruxolitinib in the clinic previously. Therefore, the safety profiles of each combination are unknown. The most common AE associated with the standard-of-care (SOC) agents is myelosuppression. The expected treatment-emergent AE of INCB053914 is ALT/AST elevation. The effects of each combination are being assessed in this Protocol. There is not an expected overlap or interaction between INCB053914 and the SOC agents. Hematology and blood chemistry, including LFT panels, will be closely monitored in all study subjects. In addition, all AEs will be monitored to identify occurrences of any new safety signal or potentiation of any SOC agent-related side effects.

1.4.5. INCB053914 Potential Benefits

INCB053914 represents a novel compound that demonstrates potent inhibitory activity across several PIM kinases, including PIM1, PIM2, and PIM3. Because PIM kinases have been shown to play a role in many hematologic malignancies, PIM kinase inhibition may provide a method to treat these diseases either alone or in combination with chemotherapeutics or other targeted agents. The degree of PIM inhibition that is being targeted in the current study may result in clinical benefit.

1.5. Study Rationale

In many advanced malignancies, dysregulated cytokine and growth factor receptor signaling results in the overexpression of PIM kinases and support the establishment, growth, and survival of tumors. Therefore selective inhibition of PIM proteins may be efficacious in the treatment of these diseases. Preliminary data from ongoing Phase 1 studies with the pan-PIM inhibitor PIM447 (formerly LGH447) have shown a tolerable safety profile for the class with preliminary indications of efficacy in relapsed and refractory MM. The planned study will evaluate the safety, tolerability, and pharmacological activity of INCB053914 in subjects with advanced malignancies. An expansion phase will further evaluate the safety, tolerability, and preliminary efficacy of the recommended Phase 2 dose (RP2D) of INCB053914 in selected malignancies.

1.5.1. Rationale for Combining INCB053914 With Cytarabine and Azacitidine in AML

For relapsed or refractory AML, high-dose cytarabine monotherapy or cytarabine-based combination regimens are often used as aggressive salvage therapy, and L-DAC or hypomethylating agents such as azacitidine is used as less aggressive therapy. For newly diagnosed AML in patients ≥ 60 years old, azacitidine is recommended as a low-intensity induction therapy, primarily in patients who are unfit for high- or intermediate-intensity regimens; L-DAC is also one of the recommended treatment regimens in this population (NCCN Guidelines). However, in both disease populations, all the conventional therapy regimens result in limited efficacy, and as such, new approaches are urgently needed and patients are encouraged to enroll in clinical trials. It is hypothesized that the combination of INCB053914 with either cytarabine or azacitidine will be able to achieve better clinical efficacy in order to increase clinical remission rate and duration and OS.

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1.5.2. Rationale for Combining INCB053914 With Ruxolitinib in Myelofibrosis

Despite statistically significant improvements in signs and symptoms of MF and OS rates, compared with either placebo or best available therapy demonstrated in the registration studies, ruxolitinib monotherapy fails to provide adequate and/or sustained response for some patients. A subgroup analysis of the Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment I study did not identify subgroups (age, MF subtype, International Prognostic Scoring System risk group, baseline ECOG score, baseline platelet or hemoglobin level, baseline spleen volume quartile, baseline symptom burden quartile, or presence/absence of V617F mutation) that did not benefit from ruxolitinib therapy (Verstovsek et al 2013); however, additional systemic and genetic factors may influence the response magnitude and duration in an individual patient. It is possible that for some patients, declining hemoglobin or platelet counts associated with ruxolitinib use preclude maintenance at optimal ruxolitinib dosages. Alternatively, some patients may have increases in inflammatory pathway signaling that are not JAK-mediated as a primary driver for their disease. Therefore, new approaches such as combination therapy are needed to provide adequate and/or sustained responses for MF patients who do not achieve such with ruxolitinib monotherapy.

Mazzacurati et al (2015) recently treated JAK2-V617F–dependent MPN model cells and primary MPN patient cells with a combination of pan-PIM inhibitors and ruxolitinib. While PIM inhibitor monotherapy had little effect on MPN model cell line, the combination therapy demonstrated a synergistic effect on MPN cell growth due to enhanced apoptosis, as well as a synergistic suppression of colony formation of primary MPN cells. Moreover, PIM inhibitors resensitized ruxolitinib-resistant MPN cells to ruxolitinib by inducing apoptosis. Finally, exogenous expression of PIM1 induced ruxolitinib resistance in MPN model cells. These data suggest that PIM kinases may play a role in MPNs and that combining a pan-PIM inhibitor such as INCB053914 with the JAK inhibitor ruxolitinib may offer an efficacious approach to treating patients with MF who have been unable to achieve a satisfactory response on ruxolitinib monotherapy.

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2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- All parts: To evaluate the safety and tolerability of INCB053914 as a monotherapy and in combination with SOC agents in subjects with advanced malignancies.
- Part 4 only:
  - To evaluate the efficacy of INCB053914 in combination with cytarabine in subjects with relapsed or refractory AML based on objective remission rate (ORR).
  - To evaluate the efficacy of INCB053914 in combination with azacitidine in subjects with newly diagnosed AML who are 65 years or older and unfit for intensive chemotherapy based on ORR.

2.1.2. Secondary Objectives

- All parts: To evaluate the PK of INCB053914 when administered alone in the fasted state, the effect of food on the INCB053914 PK, and the PK when administered in combination with SOC agents in the fasted state.
- All parts: To assess the PD of INCB053914 as a monotherapy and in combination with SOC agents in subjects with advanced malignancies.

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2.2. Study Endpoints

2.2.1. Primary Endpoint

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs and DLTs; through physical examinations; by evaluating changes in vital signs and electrocardiograms (ECGs); and through clinical laboratory blood and urine sample evaluations.
- Part 4 only: ORR, defined as the proportion of subjects who achieve complete remission (CR) or complete remission with incomplete hematologic recovery (CRi).

2.2.2. Secondary Endpoints

- Pharmacokinetics of INCB053914, including C_{max}, T_{max}, C_{min}, AUC_{0-t}, and Cl/F at timepoints specified in Section 6.
- Pharmacodynamic profile of INCB053914 defined by phosphorylation of Bcl-2–associated death promoter protein.

[redacted]

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3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Study Population

3.1.1. Parts 1 and 2

Subjects diagnosed with acute leukemia, high-risk MDS, MDS/MPN, MF, MM, or lymphoproliferative neoplasms that are unresponsive to currently available therapy and have no SOC options in the opinion of the investigator.

3.1.2. Parts 3 and 4

Subjects diagnosed with relapsed/refractory AML, subjects with newly diagnosed AML who are ≥ 65 years of age and unfit for intensive chemotherapy, and subjects with primary or secondary MF who are currently experiencing a suboptimal response on ruxolitinib monotherapy.

3.2. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

1. Men and women, aged 18 or older. Subjects in the Part 4 C-TGB Expansion Cohort 1 (C-TGB E1) and the optional C-TGA Expansion Cohort 2 (C-TGA E2) must be ≥ 65 years old.
2. Part 1 monotherapy dose escalation
   a. TGA: Subjects with histologically confirmed diagnosis of acute leukemia, high-risk MDS, or MDS/MPN (including atypical chronic myeloid leukemia [aCML], chronic myelomonocytic leukemia [CMML], myelodysplastic/myeloproliferative neoplasm unclassifiable [MDS/MPN-U], and refractory anemia with ring sideroblasts and thrombocytosis [RARS-T]).
   b. TGB: Subjects with MM, lymphoma, and other lymphoproliferative neoplasms.

   Part 2 monotherapy dose expansion
   Subjects with histologically confirmed and measureable/evaluable disease:

   c. TGA Expansion Cohort 1 (TGA E1): AML.
   d. TGA Expansion Cohort 2 (TGA E2): MDS/MPN.
   e. TGA Expansion Cohort 3 (TGA E3): MF.
   f. TGB Expansion Cohort 1 (TGB E1): MM.
   g. TGB Expansion Cohort 2 (TGB E2): DLBCL.

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Part 3 combination dose-finding

Subjects with histologically confirmed and measureable/evaluable disease:

h. Combination Treatment Group A (C-TGA): relapsed/refractory AML. Subjects with acute promyelocytic leukemia are excluded.
i. Combination Treatment Group B (C-TGB): relapsed/refractory AML or subjects ≥ 65 years of age with newly diagnosed AML (*de novo* or secondary) and unfit for intensive chemotherapy. Subjects with acute promyelocytic leukemia are excluded.
j. Combination Treatment Group C (C-TGC): primary or secondary MF who are currently experiencing a suboptimal response on ruxolitinib monotherapy, defined as follows:

   – Palpable spleen of > 10 cm below the left subcostal margin on physical examination at the screening visit OR

   – Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical exam AND active symptoms of MF at the screening visit as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form (Appendix O).

Part 4 combination expansion

Subjects with histologically confirmed and measureable/evaluable disease:

k. C-TGA Expansion Cohort 1 (C-TGA E1): relapsed/refractory AML. Subjects with acute promyelocytic leukemia are excluded.
l. C-TGB Expansion Cohort 1 (C-TGB E1): newly diagnosed AML (*de novo* or secondary) who are ≥ 65 years and unfit to receive intensive chemotherapy. Subjects with acute promyelocytic leukemia are excluded.
m. C-TGC Expansion Cohort 1 (C-TGC E1): primary or secondary MF who are currently experiencing a suboptimal response on ruxolitinib monotherapy, defined as follows:

   – Palpable spleen of > 10 cm below the left subcostal margin on physical examination at the screening visit OR

   – Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical exam AND active symptoms of MF at the screening visit as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form (Appendix O).

3. Parts 1 and 2

   a. Must be unresponsive to currently available therapy, and there is no further SOC therapy available in the judgment of the investigator.
   b. Must not currently be a candidate for curative treatment, including hematopoietic stem cell transplant.

   Parts 3 and 4

   c. Subjects with relapsed/refractory AML must have received either induction chemotherapy for AML or hypomethylating agents for hematologic disease before AML.

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d. Elderly subjects (≥65 years) with newly diagnosed AML must be treatment-naive and unfit for intensive chemotherapy.
e. Subjects with MF must be receiving ruxolitinib monotherapy at a stable dose for ≥ 8 weeks before Study Day 1. One dose reduction due to toxicities within the 8 weeks before Study Day 1 will be permitted. Acceptable doses are 5 mg BID to 25 mg BID; QD doses are not allowed.

4. Willingness to undergo a pretreatment bone marrow biopsy and/or aspirate (as appropriate to disease), or archival sample obtained since completion of most recent therapy (as appropriate to subjects with existing bone marrow disease or for whom bone marrow examination is a component of disease status assessment). If a biopsy is not possible or contraindicated, or the tissue requirement cannot be satisfied, this requirement may be waived with approval from the medical monitor.
5. ECOG performance status:
   a. Part 1: 0 or 1.
   b. Parts 2 through 4: 0, 1, or 2.
6. Life expectancy > 12 weeks or ≥ 24 weeks for Part 3 and Part 4 MF subjects.
7. Willingness to avoid pregnancy or fathering children based on the following criteria:
   a. Postmenopausal woman (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age.)
   b. Woman of childbearing potential who has a negative serum pregnancy test at screening and before the first dose on Day 1 who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
   c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study medication. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

3.3. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Inadequate bone marrow function demonstrated by any of the following:

Laboratory Parameter	TGB (Part 1)	TGB (Part 2)	C-TGC (Parts 3 and 4)
Hemoglobin (g/dL)	< 8.0	< 8.0	Subjects unwilling to receive red blood cell transfusions to treat low hemoglobin levels are excluded.
Platelets (× 10^9/L)	< 75	< 50	< 50 in 2 weeks before screening or platelet transfusions within 4 weeks of screening.
Absolute neutrophils (× 10^9/L)	< 1.0	< 1.0	< 0.5 in the 2 weeks before screening.

Note: No specific hematologic exclusion criteria apply for TGA (Parts 1 and 2), Part 3 C-TGA and C-TGB, and Part 4 C-TGA E1 and C-TGB E1 cohorts.

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2. Inadequate organ function demonstrated by any of the following, unless approved by the medical monitor:

   Part 1 and Part 3

   a. Total bilirubin > upper limit of normal (ULN; except total bilirubin > ULN is acceptable if direct bilirubin is ≤ 1.2 × ULN. Subjects with Gilbert's syndrome who have total bilirubin ≤ 2 × ULN may be enrolled with medical monitor approval).
   b. AST or ALT > 1.5 × ULN.
   c. Creatinine clearance < 50 mL/min (< 30 mL/min for MM) based on Cockroft-Gault formula or 24-hour urine analysis.

   Part 2 and Part 4

   d. Total bilirubin > ULN (except total bilirubin > ULN is acceptable if direct bilirubin is ≤ 1.2 × ULN. Subjects with Gilbert's syndrome who have total bilirubin ≤ 2 × ULN may be enrolled with medical monitor approval).
   e. AST or ALT > 1.5 × ULN.
   f. Creatinine clearance < 40 mL/min (< 30 mL/min for MM) based on Cockroft-Gault formula or 24-hour urine analysis.

3. Receipt of anticancer medications or investigational drugs within the following interval before the first administration of study drug (note: subjects enrolling in C-TGC must continue to receive their ruxolitinib throughout the study):

   a. < 5 half-lives or 14 days, whichever is longer, for any investigational agent.
   b. < 28 days for any antibodies or biological therapies.
   c. < 5 half-lives for all other nonbiologic anticancer medications, or sponsor approval.
   d. < 6 weeks for mitomycin-C or nitrosoureas.
   e. The following are allowed: hydroxyurea for controlling proliferative disease and low-dose corticosteroids (prednisone or equivalent ≤ 10 mg per day). Hydroxyurea should not be used within 48 hours before and on the day of PD sample collection or during or 72 hours before or after azacitidine administration. Note: Concomitant hydroxyurea is prohibited in subjects with MF within 8 weeks before enrolling (Day 1) into C-TGC.

4. Unless approved by the medical monitor, may not have received an allogeneic hematopoietic stem cell transplant within 6 months before treatment, or have active graft-versus-host disease following allogeneic transplant, or have received immunosuppressive therapy (including, but not limited to, cyclosporine, tacrolimus, mycophenolate mofetil, or corticosteroids [> 10 mg/day prednisone equivalent]) following allogeneic transplant within 2 weeks of Cycle 1 Day 1.

5. Unless approved by the medical monitor, may not have received autologous hematopoietic stem cell transplant within 3 months before treatment.

6. Has any unresolved toxicity ≥ Grade 2 from previous anticancer therapy except for stable chronic toxicities (≤ Grade 2) not expected to resolve, such as stable Grade 2 peripheral neuropathy.

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7. Radiotherapy within the 2 weeks before initiation of treatment. Palliative radiation treatment to nonindex or bone lesions performed less than 2 weeks before treatment initiation may be considered with medical monitor approval. In Part 3 and Part 4, MF subjects may not have had splenic irradiation within 6 months of the first dose of INCB053914.
8. Part 1 and Part 3 only: Hemoglobin A1c (HbA1c) > 8.0% (all subjects will have HbA1c tested at screening).
9. Part 1 and Part 3: Any history of disease involving the central nervous system (CNS).

   Part 2 and Part 4: Known active disease involving the CNS, for example, brain metastasis or spinal cord compression, except primary CNS lymphoma.
10. Known HIV infection.
11. Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as defined in Section 7.5.5.3.
12. Active and uncontrolled infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment.
13. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 470 milliseconds is excluded. For subjects with an intraventricular conduction delay (QRS interval 120 msec), the JTc interval may be used in place of the QTc with sponsor approval. Subjects with left bundle branch block are excluded. QTc prolongation due to a pacemaker may enroll if the JT is normal or with MM approval.
14. History of clinically significant or uncontrolled cardiac disease, including recent (within last 6 months) unstable angina or acute myocardial infarction, or New York Heart Association Class III or IV congestive heart failure, or clinically significant arrhythmias not controlled by medication. Subjects with a pacemaker and well-controlled rhythm for at least 1 month before the first dose of study drug will be allowed.
15. Part 1 and Part 3: Current diagnosis of any chronic or acute respiratory condition or ongoing sequelae from any previously diagnosed respiratory condition that is significant in the judgment of the investigator or the sponsor's medical monitor.

    Part 2 and Part 4: Current diagnosis of any severe or uncontrolled obstructive or restrictive respiratory condition (eg, Global Initiative for Chronic Obstructive Lung Disease [GOLD] 3 or GOLD 4 chronic obstructive pulmonary disease).
16. Gastroesophageal reflux disease not controlled by medication (ie, currently symptomatic or endoscopic evidence of esophagitis) within 30 days before Cycle 1 Day 1.
17. Prior receipt of a PIM inhibitor.
18. Current use of prohibited medication as described in Section 5.2.8.2.
19. Use of any potent CYP3A4 inhibitors or inducers (Appendix M) within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug.

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20. Subject has known hypersensitivity or severe reaction to any of the active substances or excipients in INCB053914, cytarabine, azacitidine, ruxolitinib, or similar compounds as appropriate to the relevant treatment group.
21. Subjects who, in the opinion of the investigator, are unable or unlikely to comply with the dose regimen and study evaluations.
22. Currently breastfeeding.
23. Any condition in the investigator's judgment that would interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
24. Unable to swallow and retain oral medication.
25. Unable to comprehend or unwilling to sign the informed consent form (ICF).
26. Any known contraindications to the use of cytarabine, azacitidine, or ruxolitinib as appropriate to the relevant treatment group.
27. Excessive alcohol use (eg, > 2 drinks per day).
28. Excessive chronic acetaminophen use (> 2 g per day).
29. Part 1 and Part 3 only: Type 1 diabetes or uncontrolled Type 2 diabetes.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, dose-escalation study of the PIM kinase inhibitor INCB053914 as monotherapy and in combination with SOC agents in subjects with advanced malignancies. Subjects will receive INCB053914 in 21- or 28-day cycles (as applicable to regimen schedules) until withdrawal criteria are met. The study will be conducted in 4 parts: Parts 1 and 2 will evaluate INCB053914 as monotherapy (Figure 1) and Parts 3 and 4 will evaluate INCB053914 in combination with select SOC agents (Figure 2). Part 1 (monotherapy dose escalation) will be conducted in 2 disease-specific treatment groups (Treatment Groups A and B) and will determine the maximum tolerated dose (MTD) of INCB053914 and/or a tolerated pharmacologically active dose (PAD [defined as a plasma concentration exceeding average PK that is projected to inhibit pBAD level > 50% for approximately 12 hours]) that will be taken forward into Part 2 of the study (ie, the RP2D). Part 2 (monotherapy dose expansion) will further evaluate the safety, efficacy, PK, and PD of the RP2D in specific disease indications in which PIM kinases are particularly relevant, including leukemias and myeloproliferative and lymphoproliferative disorders, such as AML, MDS/MPN, MF, DLBCL, and MM. Part 3 (combination dose-finding) will consist of 3 disease-specific combination treatment groups (Combination Treatment Groups A, B, and C [C-TGA, C-TGB, C-TGC]) and will determine the optimal doses of INCB053914 in combination with the selected SOC agents based on the MTD and/or tolerated PAD at the discretion of the sponsor and investigators. Part 4 (combination dose expansion) will further evaluate the safety, efficacy, PK, and PD of the selected combination dose regimens identified in Part 3 in up to 3 expansion cohorts in specific indications relevant to

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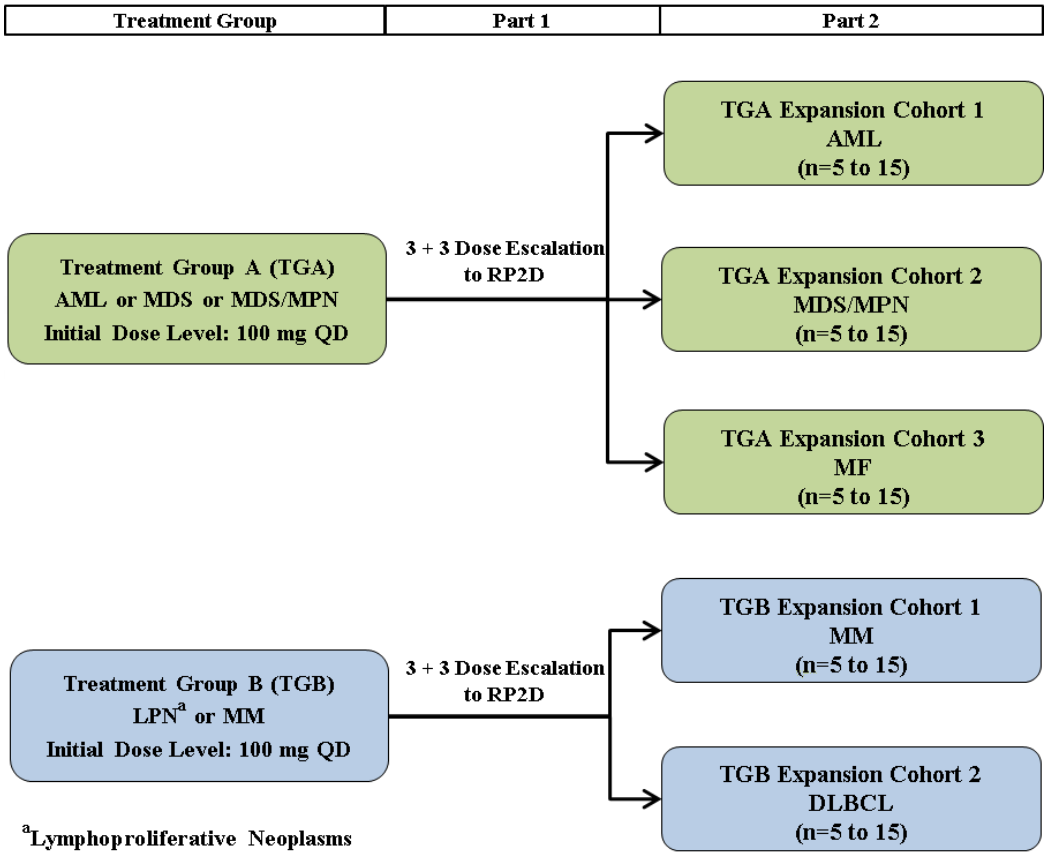
the drug combinations (2 AML; 1 MF). A Simon 2-stage design will be implemented in the 2 AML combination expansion cohorts (Part 4).

Pending emerging scientific and/or clinical data, all of the cohorts in each part may not open in parallel, and/or certain cohort(s) may not open for enrollment.

Figure 1: Monotherapy Study Design



4.1.1. Part 1 Monotherapy Dose Escalation

Between 3 and up to approximately 30 subjects will be enrolled into each of 2 treatment groups. Treatment Group A will include acute leukemia, high-risk MDS, and MDS/MPNs (including aCML, CMML, MDS/MPN-U, and RARS-T). Treatment Group B will include MM, lymphoma, and other lymphoproliferative neoplasms. Dose escalation for TGA and TGB will proceed independently, with each treatment group following a 3 + 3 design. At least 3 subjects will be enrolled and treated in each cohort. If no DLTs are observed in the initial 3 subjects, the next cohort will begin enrollment at the next higher dose level. If 1 DLT is observed in the first 3 subjects, 3 additional subjects will be enrolled in that cohort. If a DLT occurs in one-third or more of the total cohort (ie, $\geq$ 2 of 6 subjects), then the MTD will be deemed to have been exceeded, and the next lower dose level will be deemed to be the MTD. Thus, the MTD will be defined as 1 dose level below that at which one-third or more of subjects in a particular cohort report DLTs. If the first cohort exceeds the MTD, a dose de-escalation will be considered. The

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initial dose level in each treatment group will be 100 mg QD, with dose increases up to 2-fold until a Grade 2 toxicity that has a reasonable possibility of being related to INCB053914 is observed in that treatment group or until a total daily dose of 300 mg has been reached in that treatment group, after which dose increases will be limited to ≤ 50%. The sponsor, in consultation with participating investigators, may implement alternate administration, such as intermediate doses, alternate dose regimens, or alternate formulations, depending on emerging PK, PD, and safety results. Each subject will be observed for 1 cycle to be evaluable to assess safety and tolerability of the dose. The RP2D will be selected based on the totality of the data within each treatment group for further investigation in the expansion cohorts, and it is possible that the RP2D could be different among disease types. If there is a distinct discrepancy in tolerability among different disease types in the same treatment group, separate disease-specific dose-escalation schedules may be initiated. If a PAD (defined as a plasma concentration exceeding average PK that is projected to inhibit pBAD level > 50% for approximately 12 hours) is reached before the MTD, the PAD (rather than the MTD) may be selected as the RP2D based on the clinical data at the discretion of the sponsor. The sponsor, in consultation with participating investigators, may elect to expand a dose cohort(s) deemed tolerable, to up to 12 subjects, in order to obtain supplemental PK, PD, and safety data.

4.1.2. Part 2 Monotherapy Dose Expansion

Upon identification of the RP2D(s), up to 5 expansion cohorts will enroll subjects to further determine safety, tolerability, efficacy, PK, and PD of the selected dose(s) as follows:

- **TGA Expansion Cohort A1**: At least 5 and up to approximately 15 subjects with AML will be enrolled and treated at the RP2D identified in Part 1 TGA.
- **TGA Expansion Cohort A2**: At least 5 and up to approximately 15 subjects with MDS/MPN (including aCML, CMML, MDS/MPN-U, and RARS-T) will be enrolled and treated at the RP2D identified in Part 1 TGA.
- **TGA Expansion Cohort A3**: At least 5 and up to approximately 15 subjects with MF will be enrolled and treated at the RP2D identified in Part 1 TGA.
- **TGB Expansion Cohort B1**: At least 5 and up to approximately 15 subjects with MM will be enrolled and treated at the RP2D identified in Part 1 TGB.
- **TGB Expansion Cohort B2**: At least 5 and up to approximately 15 subjects with DLBCL will be enrolled and treated at the RP2D identified in Part 1 TGB.

Individual dose titration will be permitted according to Protocol-defined safety parameters. Subjects will continue to receive INCB053914 in 21-day cycles until withdrawal criteria are met.

Part 2 will also include a food-effect study. At least 12 and up to 18 subjects across all expansion cohorts who are able to participate in the food study will have additional PK assessments on Cycle 2 Day 1 and Cycle 2 Day 2, as per Section 7.8.4.

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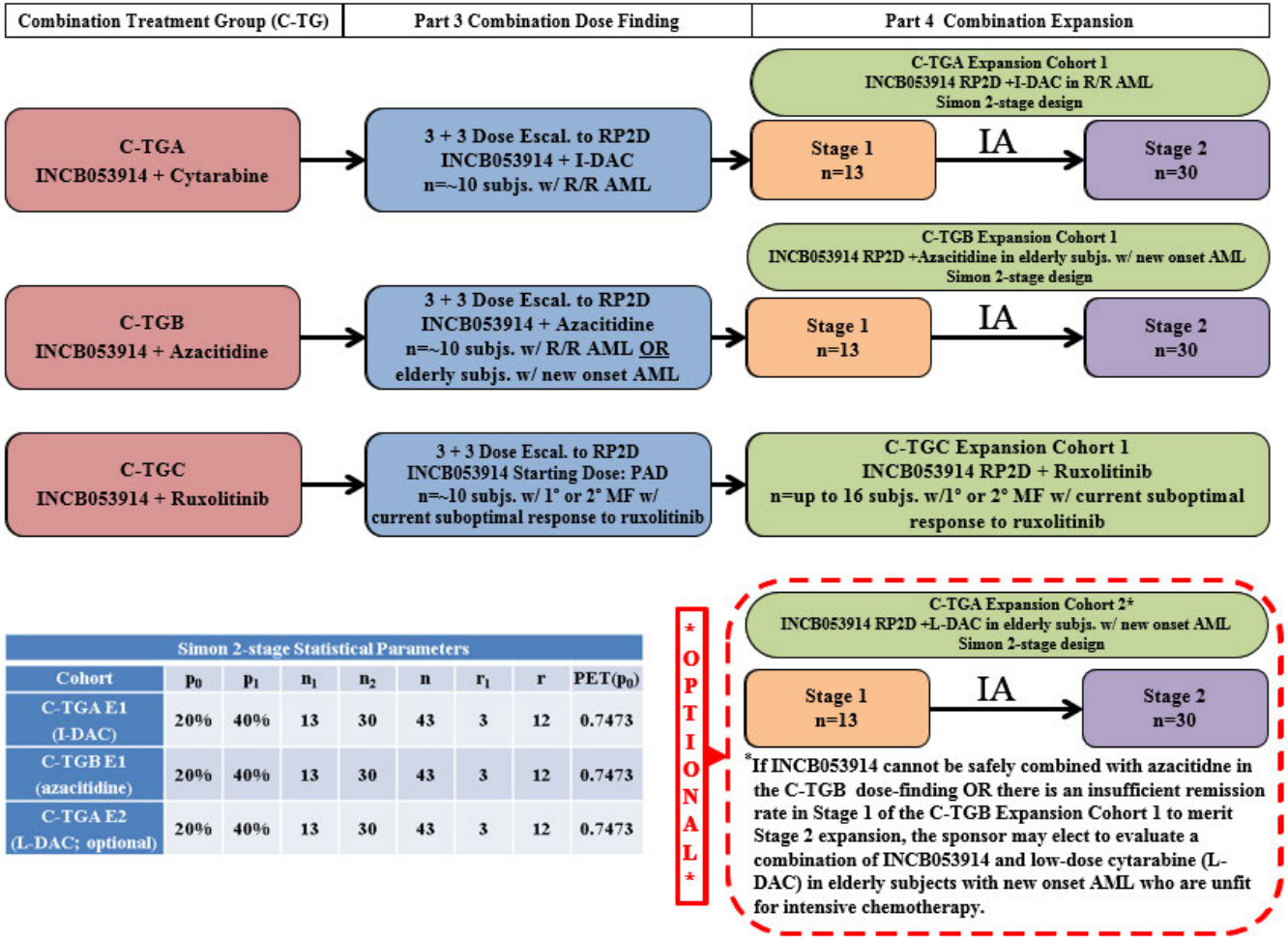
Figure 2: Combination Therapy Study Design



Simon 2-stage Statistical Parameters								
Cohort	p_0	p_1	n_1	n_2	n	r_1	r	PET(p_0)
C-TGA E1 (I-DAC)	20%	40%	13	30	43	3	12	0.7473
C-TGB E1 (azacitidine)	20%	40%	13	30	43	3	12	0.7473
C-TGA E2 (L-DAC; optional)	20%	40%	13	30	43	3	12	0.7473

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4.1.3. Part 3 Combination Therapy Dose-Finding

Part 3 (combination dose-finding) will comprise up to 3 disease-specific treatment groups (Combination Treatment Groups A through C [C-TGA – C-TGC]) and will determine the MTD and/or a tolerated PAD of INCB053914 in combination with 3 SOC agents. The combination dose-finding will use a 3 + 3 design to identify an optimal dose regimen in up to 3 different combination expansion cohorts.

- **Combination Treatment Group A (C-TGA)**: INCB053914 + cytarabine in subjects with relapsed/refractory AML.
- **Combination Treatment Group B (C-TGB)**: INCB053914 + azacitidine in subjects with relapsed/refractory AML or elderly subjects (≥ 65 years) with newly diagnosed AML (*de novo* or secondary) who are unfit to receive intensive chemotherapy.
- **Combination Treatment Group C (C-TGC)**: INCB053914 + ruxolitinib in subjects with primary or secondary MF (PPV-MF or PET-MF) who are currently experiencing a suboptimal response on ruxolitinib monotherapy, defined as follows:
  - Palpable spleen of > 10 cm below the left subcostal margin on physical examination at the screening visit OR
  - Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical exam AND active symptoms of MF at the screening visit as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form (Appendix O).

4.1.3.1. Standard-of-Care Agent Combination Cohort Dose-Finding Strategy

Between 3 and up to approximately 10 subjects will be enrolled into cohorts under each of the SOC treatment groups, C-TGA, C-TGB, and C-TGC, as described above. Dose-finding for C-TGA, C-TGB, and C-TGC will proceed independently, with each treatment group following a 3 + 3 cohort design. At least 3 subjects will be enrolled and treated at each dose level. If no DLTs are observed in the initial 3 subjects, the next cohort will begin enrollment at the next higher dose level of INCB053914. If 1 DLT is observed in the first 3 subjects, 3 additional subjects will be enrolled in that cohort. If a DLT occurs in one-third or more of the total cohort (ie, ≥ 2 of 6 subjects), then the MTD will be deemed to have been exceeded, and the next lower dose level will be deemed to be the MTD. Thus, the MTD will be defined as 1 INCB053914 dose level below that at which one-third or more of subjects in a particular cohort report DLTs. If the first cohort exceeds the MTD, a dose de-escalation of INCB053914 will be considered.

A conventional regimen of the SOC agents will be used in all dose-finding cohorts within a given SOC combination treatment group and will remain fixed throughout the dose-finding portion of the study.

The starting dose of INCB053914 in the combination treatment groups will be a PAD and 1 dose level below the highest tolerated dose of INCB053914 monotherapy identified in Part 1 of this study. At the current data cutoff date, the highest tolerated dose of INCB053914 monotherapy was 80 mg BID, which also met the criteria of protocol-defined PAD; thus, the planned starting dose for Part 3 will be 65 mg BID (Dose Level 1 dose). The INCB053914 dose used in Part 3

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will never exceed the monotherapy MTD dose to be identified in Part 1 of the study. Table 1, Table 2, and Table 3 summarize the planned starting doses to be used in the SOC combination dose-finding cohorts. An alternative starting dose and/or subsequent INCB053914 doses (Dose Level 1, 2, and/or 3) may be selected pending emerging safety, PK, and PD data in Part 1.

The sponsor, in consultation with participating investigators, may implement alternate INCB053914 administration, such as intermediate doses, alternate dose regimens, or alternate formulations, depending on emerging PK, PD, and safety results. Each subject will be observed for 1 cycle to be evaluable to assess safety and tolerability of the assigned INCB053914 dose in combination with the chosen SOC regimen. The sponsor, in consultation with participating investigators, may elect to expand a dose cohort(s) deemed tolerable, to up to 12 subjects, in order to obtain supplemental PK, PD, and safety data. The INCB053914 RP2D of the combination treatment group will be selected based on the totality of the data within each treatment group for further investigation in the expansion cohorts, and it is possible that the RP2D could be different among disease types.

Table 1: Planned C-TGA Combination Dose-Finding Cohorts

Dose Level	I-DAC dose	INCB053914 Dose[a]
-1	1 g/m^2; given as 2-hour infusion on Days 1-5	50 mg BID
1 (starting dose)	**1 g/m^2; given as 2-hour infusion on Days 1-5**	**65 mg BID**
2	1 g/m^2; given as 2-hour infusion on Days 1-5	80 mg BID
3	1 g/m^2; given as 2-hour infusion on Days 1-5	100 mg BID

[a] INCB053914 starting dose and subsequent cohort doses may change based on emerging Part 1 safety, PK, and PD data.

Table 2: Planned C-TGB Combination Dose-Finding Cohorts

Dose Level	Azacitidine Dose	INCB053914 Dose[a]
-1	75 mg/m^2 SC or IV; given on Days 1-5 and 8-9 of a 28-day cycle	50 mg BID
1 (starting dose)	**75 mg/m^2 SC or IV; given on Days 1-5 and 8-9 of a 28-day cycle**	**65 mg BID**
2	75 mg/m^2 SC or IV; given on Days 1-5 and 8-9 of a 28-day cycle	80 mg BID
3	75 mg/m^2 SC or IV; given on Days 1-5 and 8-9 of a 28-day cycle	100 mg BID

IV = intravenously; SC = subcutaneously.
[a] INCB053914 starting dose and subsequent cohort doses may change based on emerging Part 1 safety, PK, and PD data.

Table 3: Planned C-TGC Dose-Finding Cohorts

Dose Level	Ruxolitinib Dose	INCB053914 Dose[a]
-1	Subject's current stable dose (between 5 mg BID and 25 mg BID)	50 mg BID
1 (starting dose)	**Subject's current stable dose (between 5 mg BID and 25 mg BID)**	**65 mg BID**
2	Subject's current stable dose (between 5 mg BID and 25 mg BID)	80 mg BID
3	Subject's current stable dose (between 5 mg BID and 25 mg BID)	100 mg BID

[a] INCB053914 starting dose and subsequent cohort doses may change based on emerging Part 1 safety, PK, and PD data.

See Sections 5.1.4, 5.1.5, and 5.1.6 for information on the specific dose regimens for cytarabine, azacitidine, and ruxolitinib, respectively.

4.1.4. Part 4 Combination Expansion Cohorts

Upon identification of the RP2D combination regimens in the combination dose-finding treatment groups, up to 4 expansion cohorts will enroll to further determine safety, tolerability, efficacy, PK, and PD in the subject populations. The 2 AML expansion cohorts will use a Simon 2-stage design to evaluate the efficacy of the combination regimens.

- **C-TGA Expansion Cohort 1 (C-TGA E1)** will enroll subjects with relapsed/refractory (r/r) AML who will be treated with INCB053914 in combination with I-DAC using the regimen identified from the Part 3 dose-finding. This cohort will use a Simon 2-stage design, details of which can be referenced in Section 9.2.4. If an insufficient number of responders are observed in the cohort at Stage 1, further enrollment in the cohort will be terminated.
- **C-TGB Expansion Cohort 1 (C-TGB E1)** will enroll subjects with newly diagnosed AML (*de novo* or secondary) who are ≥ 65 years at screening and unfit to receive intensive chemotherapy and who will be treated with INCB053914 in combination with azacitidine using the regimen identified from the Part 3 dose-finding. This cohort will use a Simon 2-stage design, details of which can be referenced in Section 9.2.4. If an insufficient number of responders are observed in the cohort at Stage 1, further enrollment in the cohort will be terminated.
- **C-TGC Expansion Cohort 1 (C-TGC E1)** will enroll up to 16 subjects with PMF or secondary MF (PPV-MF or PET-MF) who are currently experiencing a suboptimal response on ruxolitinib monotherapy and who will be treated with INCB053914 in combination with ruxolitinib using the dose identified from the Part 3 dose-finding.
- **Optional C-TGA Expansion Cohort 2 (C-TGA E2)**

  If the Part 3 C-TGB dose-finding does not yield a tolerable combination of INCB053914 and azacitidine, or if the Part 4 C-TGB E1 Simon Stage 1 does not yield favorable efficacy data, then the sponsor may elect to evaluate INCB053914 in combination with a L-DAC regimen in this population. This option will use an INCB053914 dose deemed tolerable in combination with I-DAC and will reference safety and tolerability data obtained from the Part 3 C-TGA dose-finding. If the sponsor and investigators believe that the optimal dose regimen of INCB053914 in combination with L-DAC will be different from that of INCB053914 in combination I-DAC, a separate dose-finding cohort will be initiated to identify the optimal dose regimen of INCB053914 in combination with L-DAC.

4.2. Measures Taken to Avoid Bias

This is an open-label study; no comparisons will be made between subjects or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

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4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Approximately 3 to 30 subjects per treatment group may be enrolled in Part 1 of the study, and up to 75 subjects may be enrolled in Part 2. In Part 3, approximately 3 to 10 subjects will be enrolled per treatment group, and in Part 4, up to 102 subjects may be enrolled.

4.3.2. Replacement of Subjects

In Part 1 and Part 3, if a subject is not evaluable (eg, at least 80% of the prescribed study drug and SOC agent doses during the first cycle are not taken due to dose interruption, reduction, or discontinuation), another subject will be enrolled at this dose level. Subjects who report DLTs will be considered evaluable for the purpose of determining the safety and tolerability of the dose.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may continue to receive study treatment in continuous 21- or 28-day cycles depending upon the treatment regimen. If the subject discontinues all study treatment, the subject will enter follow-up (see Section 6.4). Subjects may continue on study until withdrawal criteria are met. Treatment duration will vary significantly between subjects but is expected to average approximately 4 to 6 months.

4.5. Overall Study Duration

The study begins when the first subject signs the informed consent. The end of the study will occur when all subjects have discontinued study drug and have completed the safety follow-up visit; the sponsor may elect to continue to monitor survival outcome and subsequent therapies for subjects enrolled in Parts 2 and 4. The overall study duration is expected to be approximately 42 months.

4.6. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination, and send a copy of the notification to the sponsor or sponsor's designee and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively or if required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

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5. TREATMENT

5.1. Study Drug and Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Upon screening a subject, study sites will contact the IRT in order to receive a subject number.

All subject numbers will be 6 digits; the first 3 digits will be the site number and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who fail screening, withdraw consent, or discontinue from the study after being assigned a subject number will retain their initial number.

Upon enrolling the subject, the site staff will contact the IRT to register the quantity of study drug allocated at the initial visit and all subsequent visits at which study drug is dispensed. Refer to the IRT manual for detailed information.

5.1.2. Randomization and Blinding

Not applicable.

5.1.3. INCB053914

5.1.3.1. Description and Administration

INCB053914 drug product is formulated as immediate release (IR) tablets.

INCB053914 will be self-administered orally BID beginning with the Cycle 1 Day 1 morning dose and continuously thereafter in 21- or 28-day cycles, or appropriate visit intervals, depending on the treatment group regimen until treatment withdrawal criteria are met. Exceptions are noted in the Schedule of Assessment tables (Table 6, Table 9, Table 12, Table 15, Table 18), when the morning dose will be administered in the clinic to accommodate PK sample collection. Dose increases will be accomplished using the following options: 1) increasing the number of tablets taken at each QD administration, or 2) increasing administration frequency to BID, or 3) increasing the number of tablets taken at 1 or more dose administrations and increasing the frequency to BID. The sponsor may implement alternate administration, such as intermediate doses, alternate dose regimens, or alternate formulations, depending upon PK, PD, and safety results. All BID doses will be taken with water in the morning and evening, approximately 12 hours apart and at least 2 hours after a meal. If possible, subjects should refrain from eating for 1 hour after administration

See Section 10.2 for details regarding the accountability, handling, and disposal of study drug.

Refer to the INCB053914 IB for additional detail about the respective investigational products.

5.1.3.2. Supply, Packaging, and Labeling

INCB053914 will be provided as 15 mg and 50 mg round, white to off-white tablets packaged in high-density polyethylene bottles. The 15 mg tablets will be smaller than the 50 mg tablets.

No preparation of INCB053914 is required.

All Incyte investigational product will be labeled with the following statement, "Caution: New Drug—Limited by the United States law to investigational use," or in accordance with local regulatory requirements as applicable.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

5.1.3.3. Storage

INCB053914 drug product should be stored according to the conditions stipulated on the investigational product labels.

5.1.3.4. Instructions to Subjects for Handling Study Drug

The subject must be instructed in the handling of study medication as follows:

- To store the study medication according to the conditions listed on the investigational product bottle label.
- To only remove from the study drug bottle(s) the amount of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- When taking the study drug at home, take the tablets with a glass of water at least 2 hours after the last meal. It is preferable to refrain from food or drink (other than water) for 1 hour after the dose (unless otherwise advised by the sponsor after completion of food-effect testing).
- To report any missed doses, including any missed injections of cytarabine or azacitidine.
- If the subject vomits after taking study medication, the subject should not take another dose.
- To keep study drug in a safe place and out of reach of children.
- To bring all used and unused study medication bottles and syringes (if applicable) to the site at each visit.
- If a dose of INCB053914 is missed by more than 4 hours, that dose should be skipped, and the next scheduled dose should be administered at the usual time.

5.1.4. Cytarabine

In the Part 3 C-TGA dose-finding cohorts and Part 4 combination expansion 1 (C-TGA E1) cohort, I-DAC will be administered to relapsed/refractory AML subjects as an open-label commercial product at a dose of 1 g/m² per day, 2-hour infusion on Days 1 through 5. A second induction cycle may be started between 15 days and 8 weeks after initiation of Cycle 1, at the discretion of the investigator, in subjects with residual leukemia upon bone marrow assessment during initial induction, provided all drug-related toxic effects had resolved to ≤ Grade 1. Up to 2 additional cycles may be given as consolidation therapy in subjects who achieved CR or

complete remission with incomplete platelet recovery, at the discretion of the investigator. The start of subsequent induction or consolidation cycles of I-DAC should be coordinated with the Day 1 of the INCB053914 21-day visit cycle when feasible.

If the Part 3 C-TGB dose-finding does not yield a tolerable combination of INCB053914 and azacitidine, or if the Part 4 C-TGB E1 Simon Stage 1 does not yield favorable efficacy data, then the sponsor may elect to evaluate INCB053914 in combination with a L-DAC regimen to treat elderly subjects (≥ 65 years) with newly diagnosed AML (*de novo* or secondary) who are unfit for intensive chemotherapy. In this event, L-DAC will be administered as an open-label commercial product at a dose of 20 mg SC on Days 1 through 10 of a 28- to 42-day cycle, depending upon hematologic recovery. Low-dose cytarabine therapy may continue until Protocol withdrawal criteria are met, or until subject's condition worsens, per investigator's clinical judgment, and warrants withdrawal.

Cytarabine dose modifications for toxicity may be made at the investigator's discretion.

Investigative sites must provide subjects with administration and storage instructions, as per cytarabine package insert or institution standard, for L-DAC SC syringes dispensed to subjects for administration away from the investigative site.

5.1.5. Azacitidine

In the Part 3 C-TGB dose-finding cohorts and Part 4 C-TGB E1 expansion cohort, azacitidine (Vidaza 2016) will be administered as an open-label commercial product at a dose of 75 mg/m^2 SC or IV for 7 days during 9-day or less period (ie, a 2-day break allowed on weekend, if needed) of each 28-day treatment cycle. Dose modifications for toxicity will be permitted at the discretion of the investigator.

Azacitidine dose modifications for toxicity may be made at the investigator's discretion.

Investigative sites must provide subjects with administration and storage instructions, as per Vidaza® package insert or institution standard, for azacitidine SC syringes dispensed to subjects for administration away from investigative site.

5.1.6. Ruxolitinib

In the Part 3 C-TGC dose-finding cohorts and Part 4 C-TGC E1 expansion cohort, ruxolitinib (Jakafi 2016) will be administered as an open-label commercial BID oral treatment using the dose designated as the stable dose at the time of the screening visit for each subject. Acceptable doses are 5 mg BID to 25 mg BID.

Doses of ruxolitinib should be self-administered approximately 12 hours apart without regard to food.

Note that subjects must be instructed to withhold the morning dose or ruxolitinib until reaching the clinic for each study visit where administration will occur. The dose may need to be reduced or interrupted for declining platelet count or ANC as described in Section 5.2.4 and will be increased or restarted with recovery of hematologic parameters.

Ruxolitinib should be stored in accordance with the Jakafi® package insert.

5.1.7. Treatment Compliance

Treatment compliance with all study-related medications should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB053914 will be calculated, by the sponsor, based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring all study-related medications with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

5.2. Treatment of Subjects

5.2.1. Starting Dose

The starting dose of INCB053914 in Part 1 will be 100 mg QD. Dose escalation in Part 1, dose-finding in Part 3, and the determination of the Part 2 monotherapy dose and Part 4 combination regimens will proceed as per Section 4.1.

5.2.2. Dose Modifications

Dose interruptions and modifications may occur for individual study subjects. The identification of DLTs will define the doses used in planned cohorts. Further, the occurrence of DLTs and other toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects.

Subjects enrolled in the dose-escalation or dose-finding portion of the study will have the option of escalating to a dose found to be tolerated in a subsequent cohort (see Section 5.2.6).

5.2.3. Dose-Limiting Toxicity and Determination of Maximum-Tolerated Dose

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 4 occurring up to and including Day 21 or Day 28 (per regimen cycle schedule), except those with a clear alternative explanation (eg, disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. All DLTs will be assessed by the investigator using CTCAE v4.03 criteria. Subjects who receive at least 80% of the INCB053914 doses at the level assigned 80% of the planned doses for the SOC agents or have a DLT will be considered evaluable for determining tolerability of the dose. Subjects receiving dose reductions (but not meeting DLT criteria) that result in < 80% of the prescribed dose being administered will not be considered evaluable for the purposes of determining the MTD and will be replaced.

Individual subject dose reductions may be made based on events observed at any time during treatment with study drug; however, for the purposes of dose cohort escalation/de-escalation/dose-finding and determining the MTD of INCB053914 monotherapy or the optimal doses of INCB053914 in combination with the selected SOC agents, decisions will be made based on events that are observed from the first day of study drug administration through and including the final day of Cycle 1 (Day 21 or Day 28). A lower MTD may subsequently be determined based on relevant toxicities that become evident after Day 21 or Day 28, respectively.

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Table 4: Definition of Dose-Limiting Toxicity

Toxicity		
Nonhematologic		
• Any ≥ Grade 3 nonhematologic toxicity EXCEPT the following: – Nausea, vomiting, and diarrhea responding to supportive therapy within 48 hours. – Alopecia		
Hematologic[a]		
Parameter	**Treatment Group**	**Toxicity**
Anemia	Part 1 TGB	Grade 4, unexplained by underlying disease.
	Part 1 TGA Part 3 C-TGA, C-TGB, C-TGC	Not applicable.
Neutropenia	Part 1 TGB	Grade 4 lasting > 5 days.
	Part 1 TGA Part 3 C-TGA, C-TGB	Grade 4 with a hypocellular bone marrow lasting ≥ 6 weeks after the start of a course in the absence of residual disease.
	Part 3 C-TGC	Grade 4 lasting > 3 days after ruxolitinib interruption (to rule out ruxolitinib related transient decreases in WBCs because of margination). (When the clinical status of the subject allows, investigators are encouraged to wait 24 hours before starting myeloid growth factors to determine if WBC margination is contributing to the degree of neutropenia.)
Febrile neutropenia	Part 1 TGB	Febrile neutropenia of any duration (ANC < 1.0×10^9/L and fever ≥ 38.5°C).
	Part 1 TGA Part 3 C-TGA, C-TGB	Not applicable.
	Part 3 C-TGC	Grade 4 febrile neutropenia that does not clinically resolve within 7 days in the setting of optimal interventions.
Thrombocytopenia	Part 1 TGB	Grade 4 or Grade 3 with bleeding, or any requirement for platelet transfusion.
	Part 1 TGA Part 3 C-TGA, C-TGB	Grade 4 with a hypocellular bone marrow lasting ≥ 6 weeks after the start of a course in the absence of residual disease.
	Part 3 C-TGC	Grade 4 thrombocytopenia with bleeding.
TGB only: A treatment delay > 14 days because of a hematologic toxicity of any grade will also be considered a DLT.		
Other toxicities not meeting DLT criteria:		
• While the rules for adjudicating DLTs in the context of dose escalation are specified above, an AE not listed above may be defined as a DLT after a consultation with the sponsor and investigators, based on the emerging safety profile.		

ANC = absolute neutrophil count.

[a] Cytopenias and/or myelosuppression are expected outcomes of the disease processes of and treatments used for the malignancies evaluated in Part 1 TGA and Part 3 C-TGA, C-TGB, and C-TGC and per se will not constitute DLTs except as noted in this table.

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5.2.3.1. Management of Dose-Limiting Toxicities or Other Urgent Situations

In all cases, investigators may employ any measures or concomitant medications (following discussion with the sponsor when feasible), necessary to optimally treat the subject.

5.2.3.2. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or appears to have stabilized for a minimum of 4 weeks. During follow-up, subjects should be seen as often as medically indicated to assure safety.

5.2.3.3. Procedures for Cohort Review and Dose Escalation

Regular telephone conferences will be scheduled by the sponsor with study investigators in order to review cohort-specific data and overall safety data, to agree on dose escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

5.2.4. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Treatment with INCB053914, L-DAC, azacitidine, or ruxolitinib may be delayed up to 2 weeks (≤ 14 days) to allow for resolution of toxicity. The second induction or consolidation cycles of I-DAC may be delayed until subject has recovered from I-DAC–related toxicities. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been delayed for more than 14 days before restarting treatment with INCB053914, L-DAC, azacitidine, or ruxolitinib.

Because subjects may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, these dose reduction rules are provided as guidelines (see Table 5). Individual decisions regarding dose reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug or SOC agents, and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules. Hematologic events (eg, thrombocytopenia, anemia, neutropenia) occurring in Part 1 TGB precipitating dose interruptions during Cycle 1 of treatment will be evaluated as potential DLTs (Table 4) and managed as per the guidelines in Section 5.2.3. Hematologic AEs that precipitate dose interruptions should be monitored for recovery at least every 3 days, if feasible.

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Table 5: Guidelines for Interruption and Restarting of Study Drug

CHEMISTRY		
Adverse Event	**Trigger**	**Action Taken**
ALT and/or AST elevation	Grade 1	• Continue study drug: –Monitor LFTs at least weekly until < Grade 1 or baseline. –Carefully examine subject's concomitant medications for any that may contribute to LFT elevations. Hold these concomitant medications or switch to an alternative; consult medical monitor if needed. –Subjects with persistent but stable low-grade elevations (eg, < 1.5 × ULN) may revert to the routine LFT evaluation schedule as noted in Section 6.
	Grade 2	• Continue study drug: –Take actions as noted for Grade 1 elevations until LFTs have resolved to ≤ Grade 1 or baseline. –Refer to Appendix S for PHL case evaluation. –If Grade 2 elevation lasts ≤ 14 days, no action required. –If Grade 2 elevation lasts > 14 days, interrupt drug, monitor LFTs at least weekly, AND: ▪ If resolved within 14 days after interruption, resume study drug at the same dose, monitor LFTs at least weekly during the next month and according to Protocol schedule thereafter. ▪ If LFTs do not resolve to ≤ Grade 1 or baseline within 14 days after interruption lasts, discuss with medical monitor.
	Grade 3 or 4	• Refer to Appendix S for PHL case evaluation • Complete a coagulation panel on the subject. • Interrupt study drug and monitor LFTs at least weekly until ≤ Grade 1 or baseline: –If resolved within 14 days after interruption subject may resume study drug at next lower dose (or at 25% reduction [Part 2 or Part 4], rounded down to the nearest strength). –If LFTs do not resolve to ≤ Grade 1 or baseline within 14 days after interruption, discuss with medical monitor. • Carefully examine subject's concomitant medications for any that may contribute to LFT elevations. Hold these concomitant medications or switch to an alternative; consult medical monitor if needed.
Total bilirubin elevation	> 2 ×ULN	• Refer to Appendix S for PHL case evaluation • If > 3 × ULN, interrupt treatment.
ALT and/or AST > 3.0 × ULN AND total bilirubin > 2.0 × ULN (Hy's law)		• Interrupt treatment • Refer to Appendix S for PHL case evaluation
• ***Monitor LFTs according to Protocol schedule or more frequently if clinically indicated.*** • ***If Grade 2 or Grade 3 AST or ALT elevations recur upon restart of study drug, follow guidelines above, and if eligible to restart, resume study drug at next lower dose (or at 25% reduction [Part 2 or Part 4], rounded down to the nearest strength). If Grade 4 elevation recurs upon restart of study drug, discontinue study drug.*** • ***In subjects with liver metastasis-related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.*** • ***Actions taken with any of the SOC combination agents in response to LFT elevations should be in accordance with the respective agents prescribing information.***		

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Table 5: Guidelines for Interruption and Restarting of Study Drug (Continued)

HEMATOLOGY			
Parameter	**Subjects**	**Trigger**	**Action Taken**
Platelet count ($\times 10^9$/L)	Part 1 TGB	≥ 25 to < 50 sustained for > 7 days OR w/associated bleeding	• Hold until resolved to ≥ 50. • Restart study drug at same dose and monitor.
		< 25	• Hold until resolved to ≥ 50. • If recovery to ≥ 50 in ≤ 7 days, restart study drug at same dose and monitor. If recovery to ≥ 50 in > 7 days, restart study drug at next lower dose and monitor.
	Part 2 TGB Expansion Cohorts	< 25	• Hold until resolved to ≥ 25. • If recovery to ≥ 25 in ≤ 7 days, restart study drug at same dose and monitor. If recovery to ≥ 25 in > 7 days, restart study drug at next lower dose and monitor.
	Part 1 TGA Part 2 TGA Expansion Cohorts	N/A	Thrombocytopenia should be managed as per institutional standard, relevant to the underlying disease. If there is a suspected causal relationship to INCB053914 in the setting of a decreasing platelet count, hold INCB053914 and discuss with the medical monitor.
	Part 3 All Cohorts Part 4 All Cohorts	≥ 50% decrease from baseline platelet count (**Subjects with baseline platelet count < 75**)	• Evaluate underlying disease based on peripheral blood and bone marrow assessment as needed. • Consider dose interruption if cytopenias are NOT due to underlying disease or treatment with standard-of-care agents. • Restart study drug at next lower dose (or 25% reduction if in expansion cohort, rounded down to the nearest tablet strength); monitor as clinically indicated.
ANC ($\times 10^9$/L)	Part 1 TGB Part 2 TGB Expansion Cohorts	< 0.5	• Hold until resolved to ≥ 0.5. • If recovery to ≥ 0.5 in ≤ 7 days, restart study drug at same dose and monitor. If recovery to ≥ 0.5 in > 7 days, restart study drug at next lower dose and monitor.
	Part 1 TGA Part 2 TGA Expansion Cohorts	N/A	Neutropenia should be managed as per institutional standard, relevant to the underlying disease. If there is a suspected causal relationship to INCB053914 in the setting of a decreasing ANC, hold INCB053914 and discuss with the medical monitor.
	Part 3 All Cohorts Part 4 All Cohorts	≥ 50% decrease from baseline ANC (**Subjects with baseline ANC < 1.0 only**)	• Evaluate underlying disease based on peripheral blood and bone marrow assessment as needed. • Consider dose interruption if cytopenias are NOT due to underlying disease or treatment with standard-of-care agents. • Restart study drug at next lower dose (or 25% reduction if in expansion cohort, rounded down to the nearest tablet strength); monitor as clinically indicated.

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Table 5: Guidelines for Interruption and Restarting of Study Drug (Continued)

HEMATOLOGY			
Parameter	**Subjects**	**Trigger**	**Action Taken**
Hemoglobin (g/dL)	All treatment groups/cohorts	< 6.5	• Hold until resolved to ≥ 6.5, restart at same dose, and monitor. • If recovery to ≥ 6.5 does not occur within 14 days of dose interruption or is refractory to transfusion support, discontinue study drug treatment(s) and follow-up per Protocol.
OTHER TOXICITIES			
Adverse Event		**Action Taken**	
Any Grade 1 or Grade 2 toxicity.		Continue study drug treatment and treat the toxicity; monitor as clinically indicated.	
Any Grade 3 toxicity, if clinically significant and not manageable by supportive care.		• Interrupt study drug up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1 or to baseline. • Resume study drug at same dose. If assessed as related to study drug, resume at next lower dose (or 25% reduction, whichever is the smaller increment, rounded down to the nearest pill strength); monitor as clinically indicated.	
Any recurrent Grade 3 toxicity after 2 dose reductions.		Discontinue study drug and follow-up per Protocol. (Exceptions require approval of sponsor.)	
Any other Grade 4 toxicity.		Discontinue study drug and follow-up per Protocol.	

Note: Dose reductions in Part 2 or Part 4 will use the next lowest dose evaluated in Part 1 or combination regimen in Part 3, respectively.

Up to 2 dose reductions of cytarabine, azacitidine, and ruxolitinib may be made at the discretion of the investigator.

5.2.5. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity related to study drug treatment will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug which, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures, or is considered to not be in the subject's best interest.
- An AE requiring more than 2 dose reductions, unless further dose reductions are approved by the medical monitor.
- Persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the medical monitor.

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5.2.6. Dose Increases

Intrasubject dose escalation will be permitted in Part 1 and Part 3 with sponsor preapproval in the following circumstances:

- The Protocol eligibility criteria are met at the time of escalation (hepatitis serology and pregnancy testing do not need to be repeated).
- The subject has received ≥ 4 cycles of study drug without drug-related toxicity ≥ Grade 2.
- The next dose level(s) has been determined to be safe based on the MTD criteria.
- Subjects in the monotherapy groups must be willing to submit to the PK sampling and ECG schedule as in Cycle 1 of Table 8. Supplemental PK sampling at the escalated dose is optional for subjects in the SOC combination groups and should be considered only if the subject is continuing to receive the combination agent.
- In the opinion of the investigator, the subject does not have any concurrent condition or circumstance that would complicate the dose escalation or PK sampling or pose increased risk to the subject.

5.2.7. Withdrawal of Subjects From Study Treatment

5.2.7.1. Withdrawal Criteria

Subjects **must** be withdrawn from treatment for the following reasons:

- Disease progression or treatment failure has occurred, as assessed by the appropriate disease-specific assessment criteria. If, in the investigators opinion, the subject is receiving clinical benefit despite meeting criteria for progressive disease, the subject may continue to receive treatment with sponsor approval.
- An AE defined as unacceptable toxicity occurs (see Section 5.2.5).
- The subject becomes pregnant.
- Consent is withdrawn.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A subject **may** be discontinued from study treatment as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

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5.2.7.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study and the end-of-treatment (EOT) visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit. These visits are described in Sections 6.3 and 6.4. The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the electronic case report form (eCRF).

If a subject is withdrawn from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed (see Section 6.3).
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

5.2.8. Concomitant Medications

All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 30 days before enrollment (Cycle 1 Day 1) will be recorded in the eCRF. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

5.2.8.1. Restricted Medications

- Chronic use of systemic corticosteroid doses ≤ 10 mg/day prednisone (or equivalent) is permitted but discouraged from the screening visit through the EOT visit or last dose of study drug.
- Short courses of systemic corticosteroid doses > 10 mg/day prednisone (or equivalent) are permitted (eg, for transfusion reaction prophylaxis) but discouraged from the screening visit through the EOT visit or last dose of study drug.
- Chronic acetaminophen use is discouraged; however, if it is required and no alternative therapies are available, acetaminophen less than 2 g per day is permitted.
- Use of weak or moderate inducers or inhibitors of CYP3A4 (Appendix M) is discouraged, and investigators should seek other options where possible.
- P-glycoprotein substrates with a narrow therapeutic index (Appendix N) should be used with caution.

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- Hydroxyurea should not be used within 48 hours before and on the day of PD sample collection or during or 72 hours before or after azacitidine administration. Hydroxyurea is prohibited in C-TGC subjects.
- For subjects taking INCB053914 in combination with ruxolitinib only:
  - Aspirin in doses exceeding 125 mg/day is not permitted. Low-dose aspirin (≤ 125 mg/day) is permitted.
  - Caution should be used when administering ibuprofen or other nonsteroidal anti-inflammatory drugs with long elimination half-lives; subjects should be monitored closely for toxicity, especially for myelosuppression and renal and gastrointestinal toxicity.

Additional timed PK testing following the serial timepoints schedule for the respective monotherapy or combination regiment may be required if subjects initiate or require a dose modification of inhibitors or inducers of CYP3A4 or of P-gp substrates during the study.

5.2.8.2. Prohibited Medications

The following medications are prohibited:

- Any concomitant anticancer therapy to treat the disease under study.
- Potent inducers and inhibitors of CYP3A4 with the exception of topical ketoconazole, based on its low overall bioavailability (see Appendix M).
- Any investigational study drug, for any indication.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments relevant to subjects' study part, treatment group and combination regimen, as applicable (see Table 6, Table 9, Table 12, Table 15, and Table 18), and all laboratory assessments will be performed as indicated in Table 7, Table 10, Table 13, Table 16, and Table 19. The order of assessments is suggested by the order of mention within the schedule. Table 21 presents a summary of clinical laboratory analytes to be assessed. The following tables outline the PK, PD, and ECG schedule during Cycle 1 and Cycle 2 where applicable: Table 8, Table 11, Table 14, Table 17, and Table 20. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

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Table 6: Schedule of Assessments for INCB053914 Monotherapy Cohorts

Visit Day / Evaluation/Window	Section	Screening	Treatment (21-Day Cycles)							EOT	Follow–Up		
			Cycle 1				Cycle 2 and Beyond				Safety	Disease Status	Survival
			D1	D2	D8	D15	D1	D2[a]	D11		30-35 Days After EOT	Every 9 Weeks	Every 12 Weeks
		Day -28 to Day -1	± 3 Days						± 4 Days	+ 3 Days			
Informed consent	7.1	X											
Inclusion/exclusion criteria	3	X	X										
Contact IRT	7.2	X	X				X			X			
Medical and cancer history	7.3.1	X											
Prior/concomitant medications	7.4	X	X	X	X	X	X	X	X	X	X		
Administer INCB053914 in clinic	Table 8		X	X	X	X	X	X					
Drug dispense/compliance check[b]	5.1.7		X	X	X	X	X		X	X[c]			
Comprehensive physical exam	7.5.2.1	X								X	X		
Targeted physical exam	7.5.2.2		X	X	X	X	X	X	X				
ECOG performance status	7.7.1	X	X				X			X	X		
Vital signs/height/weight[d]	7.5.3	X[d]	X[d]	X	X	X	X[d]	X	X	X[d]	X[d]		
12-lead ECG	7.5.4	X				X	X			X	X		
Timed 12-lead ECG[e]	7.5.4.3		X		X								
[redacted]													
AE assessment[f]	7.5.1	X	X	X	X	X	X	X	X	X	X		
Laboratory assessments	Table 7	X	X	X	X	X	X	X	X	X	X		
[redacted]													
Provide reminder card	7.10.2	X	X	X	X	X	X	X	X	X			
[redacted]													

CR = complete response/remission.

[a] Applicable to Part 2 subjects in the food-effect study at Cycle 2 only. See Section 7.8.4 for details.

[b] All study drug for Cycle 1 will be dispensed at Cycle 1 Day 1; subject will bring unused study drug to clinic for compliance check on Cycle 1 Days 2, 8, and 15. Drug will only be dispensed at Day 1 of all subsequent cycles and will bring unused study drug to clinic for compliance check on Day 11.
[c] EOT visit – compliance check only.
[d] Height only assessed at screening. Weight is only required at screening, Day 1 of each cycle, EOT, and the follow-up visit
[e] See Table 8 for timepoints and collection windows.
[f] Subjects must be followed for AEs for 30 days (+ 5 days) after the EOT visit (or after the last dose of study drug if the EOT visit was not performed).

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Table 7: Laboratory Assessments for INCB053914 Monotherapy Cohorts

Visit Day / Evaluation/Window	Section	Screening	Treatment (21-Day Cycles)							EOT	Safety Follow-Up
			Cycle 1				Cycle 2 and Beyond				
		Day -28 to Day -1	D1	D2	D8	D15	D1	D2	D11		
					± 3 Days				± 4 Days	+ 3 Days	EOT + 30-35 Days
Overnight fast before assessments	Table 8		X		X		X[a]				
Comprehensive blood chemistries	Table 21	X[b]	X[b]	X	X	X	X		X	X	X
Hematology with differential	Table 21	X[b]	X[b]	X	X	X	X		X	X	X
LFT panel[c]	Table 21	X[b]	X[b]	X	X	X	X		X	X	X
Coagulation panel[c]	Table 21	X[b]	X[b]		X	X	X			X	X
Urinalysis	Table 21	X					X[d]			X	X
Lipid panel	Table 21	X					X[d]				
Hepatitis screening	Table 21	X									
Serum pregnancy test	7.5.5.2	X	X[e]								X
PK – plasma[f,g]	7.8.1		X	X	X	X	X[f]				
PK – food effect[g]	7.8.4						X	X			
PD – whole blood[g]	7.9.4		X		X						
PK – urine[g]	7.8.2				X						
[redacted]											

[a] Applicable to Part 2 subjects in the food-effect study at Cycle 2 only. See Section 7.8.4 for details.
[b] Blood chemistry (including LFTs) and hematology screening assessments used to determine eligibility must be collected within 14 days before Cycle 1 Day 1. Cycle 1 Day 1 blood chemistry, hematology, LFT panel, and coagulation panel assessments may be omitted if the screening assessments were performed within 3 days before Cycle 1 Day 1.
[c] Additional LFT and coagulation monitoring may be required as per Table 5 and Appendix S.
[d] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles there after (eg, Cycle 10, Cycle 13, etc).
[e] If screening serum pregnancy testing is performed within 7 days of treatment initiation, it does not need to be repeated at Cycle 1 Day 1.
[f] Untimed PK sample should be performed at Cycle 2 Day 1; however, Cycle 2 Day 1 untimed PK does not apply to subjects in the food-effect study.
[g] See Table 8 for sample collection details. The Cycle 2 PK samples only pertain to Part 2 subjects who participate in the food-effect study.
[redacted]

Table 8: Pharmacokinetic, Pharmacodynamic, and Electrocardiogram Assessments for INCB053914 Monotherapy Cohorts

Visit	Assessment	Fasting Requirement	HOLD AM Dose	Predose	Dose	Time Postdose					
						1 h ± 15 min		2 h ± 15 min	4 h ± 15 min	6 h ± 30 min	8 h ± 30 min
C1D1	ECG	Fast overnight	n/a	3X	♦		snack/meal	3X	3X	3X	
	PK plasma			≤ 15 min after ECG		X		≤ 15 min after ECG	≤ 15 min after ECG		X
	PD whole blood			≤ 15 min after ECG		X		≤ 15 min after ECG	≤ 15 min after ECG		
C1D8	ECG	Fast overnight	X	3X	♦		snack/meal	3X	3X	3X	
	PK plasma			≤ 15 min after ECG		X		≤ 15 min after ECG	≤ 15 min after ECG		X
	PD whole blood			≤ 15 min after ECG		X		≤ 15 min after ECG	≤ 15 min after ECG		
	Urine PK			N/A		Collect urine over 8 hours following study drug administration.					
C1D2/ C1D15	PK plasma	none	X	X	♦						
C2D1[a]	PK plasma	none	X	X	♦						
Food-Effect Study Subjects Only											
C2D1	PK plasma	Fast overnight	X	X	♦[b]	X	snack/meal	X	X		X
C2D2	PK plasma	none	X	X	♦						

[a] This trough sample is not required for subjects participating in the food-effect study.
[b] High-fat meal to be consumed within a 25-minute period, followed by study drug administration 5 minutes after completing the meal.

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Table 9: Schedule of Assessments for I-DAC Combination Cohorts

Visit Day / Evaluation/Window	Section	Screening: Day -28 to Day -1	Treatment[a] 21-Day Cycles (Anchored to INCB053914 Schedule) Cycle 1 D1	Cycle 1 D5	Cycle 1 D15 ± 1 Days	Subsequent Cycles D1	Subsequent Cycles D11 ± 4 Days	EOT + 3 Days	Follow-Up Safety 30-35 Days After EOT	Follow-Up Disease Status Every 9 Weeks	Follow-Up Survival Every 12 Weeks
Informed consent	7.1	X									
Inclusion/exclusion criteria	3	X	X								
Contact IRT	7.2	X	X			X		X			
Medical and cancer history	7.3.1	X									
Prior/concomitant medications	7.4	X	X	X	X	X	X	X	X		
Administer cytarabine[b]	5.1.4		Induction			Reinduction/consolidation[c]					
Administer INCB053914 in clinic	Table 11		X	X	X						
Drug dispense/compliance check[d]	5.1.7		X		X	X	X	X[e]			
Comprehensive physical exam	7.5.2.1	X						X	X		
Targeted physical exam	7.5.2.2		X	X	X	X	X				
ECOG performance status	7.7.1	X	X			X		X	X		
Vital signs/height/weight[f]	7.5.3	X[f]	X[f]	X[g]	X	X[f]	X	X[f]	X[f]		
[redacted]											
12-lead ECG	7.5.4	X	X			X		X	X		
AE assessment[h]	7.5.1	X	X	X	X	X	X	X	X		
Laboratory assessments	Table 10	X	X	X[g]	X	X	X	X	X		
Buccal swab	7.9.2	X									
AML disease assessments[i]	7.6	X	X		X		X	X		X	
Bone marrow examination[j]	7.9.1	X			X[i]						
Immunophenotyping[k]	7.6.5	X			When confirming CR						
Provide reminder card	7.10.2	X	X	X	X	X	X	X			
Poststudy disease status	6.4.2									X	
[redacted]											

CR = complete remission.

[a] During the treatment phase, subjects should be evaluated at the clinic in 21-day cycles in conjunction with the continuous administration of INCB053914. Subjects who receive subsequent reinduction or consolidation cycles of I-DAC should correlate the cycle start with Day 1 of a 21-day cycle visit whenever possible, following the Cycle 1 visit schedule (except inclusion/exclusion criteria review, any PK samples, and AML disease assessment [unless clinically indicated]). For example, a subject who starts a reinduction or consolidation regimen at Cycle 5 should have Cycle 5 Day 1, Day 5, and Day 15 study visits.

[b] I-DAC will be administered as a 1 g/m^2 2-hour infusion on Days 1 through 5.

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[c] Reinduction with I-DAC is permitted at the discretion of the investigator in subjects who have residual disease per Day 15 bone marrow examination provided all drug-related toxicities have returned to ≤ Grade 1. Additionally, subjects who achieve CR or CRp may receive up to 2 cycles of I-DAC consolidation therapy at the discretion of the investigator.

[d] All study drug for Cycle 1 will be dispensed at Cycle 1 Day 1; subject will bring unused study drug to clinic for compliance check on Cycle 1 Days 5, and 14. Drug will only be dispensed at Day 1 of all subsequent cycles and will bring unused study drug to clinic for compliance check on Day 11.

[e] EOT visit - compliance check only.

[f] Height only assessed at screening. Weight is only required at screening, Day 1 of each cycle, EOT, and the follow-up visit

[g] During I-DAC infusions, vital signs and laboratory assessments may be performed per institution standard, however only preinfusion assessments on Day 1 and Day 5 are required to be entered into the eCRF.

[h] Subjects must be followed for AEs for 30 days (+ 5 days) after the EOT visit (or after the last dose of study drug if the EOT visit was not performed.)

[i] Bone marrow biopsy and/or aspirates performed as clinically indicated or at Cycle 1 Day 15 (+ 2 weeks, depending upon chemotherapy recovery), Day 15 (+ 2 weeks) of any cycle where I-DAC is administered, and every other month as clinically indicated, or upon circulating blood cell recovery to assess antileukemic activity (cytogenetic testing is not required if CR is not presented). Note: For subjects who have a significant blast count reduction (as determined by the investigator) but have not completely cleared circulating blasts, the bone marrow during Cycle 2 is still strongly encouraged to be performed to assess the impact of treatment on the bone marrow blast content. See Section 7.6 for additional details.

[j] If a biopsy is not possible or contraindicated, or if the tissue requirement cannot be satisfied, then this requirement may be waived with approval from the medical monitor. Subjects with a history of allogenic hematopoietic stem cell transplantation should have tissue collected and analyzed locally for the purposes of determining disease status (where applicable); however, their sample does not need to be processed for sequencing due to chimeric potential.

[k] Immunophenotyping appropriate to AML will be conducted by flow cytometry at screening and when confirming CR.

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Table 10: Laboratory Assessments for I-DAC Combination Cohorts

Visit Day / Evaluation/Window	Section	Screening: Day -28 to Day -1	Cycle 1: D1	Cycle 1: D5 ± 1 Day	Cycle 1: D15 ± 1 Day	Subsequent Cycles[a]: D1	Subsequent Cycles[a]: D11 ± 4 Days	EOT: + 3 Days	Safety Follow-Up: EOT + 30-35 Days
Overnight fast before assessments	Table 11			X	X				
Comprehensive blood chemistries	Table 21	X[b]	X[b]	X	X	X	X	X	X
Hematology with differential	Table 21	X[b]	X[b]	X	X	X	X	X	X
LFT panel[c]	Table 21	X[b]	X[b]	X	X	X	X	X	X
Coagulation panel[c]	Table 21	X[b]	X[b]		X	X		X	X
Urinalysis	Table 21	X				X[d]		X	X
Lipid panel	Table 21	X				X[d]			
Hepatitis screening	Table 21	X							
Serum pregnancy test	7.5.5.2	X	X[e]						X
PK – plasma[f]	7.8.1			X	X				
[redacted]									

[a] The Cycle 1 laboratory assessment schedule, with the exception of the overnight fast and PK sample collection, should be followed whenever I-DAC is administered during a cycle for reinduction or consolidation. Urinalysis and lipid panels should also be collected on Day 1 of cycles where I-DAC reinduction or consolidation treatment aligns with a cycle where these are scheduled (eg, Cycle 4).

[b] Blood chemistry (including LFTs) and hematology screening assessments used to determine eligibility must be collected within 14 days before Cycle 1 Day 1. Cycle 1 Day 1 blood chemistry, hematology, LFT panel, and coagulation panel assessments may be omitted if the screening assessments were performed within 3 days before Cycle 1 Day 1.

[c] Additional LFT and coagulation monitoring may be required as per Table 5 and Appendix S.

[d] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles there after (eg, Cycle 10, Cycle 13, etc).

[e] If screening serum pregnancy testing is performed within 7 days of treatment initiation, it does not need to be repeated at Cycle 1 Day 1.

[f] See Table 11 for sample collection details.

[redacted]

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Table 11: Pharmacokinetic Assessments for I-DAC Combination Cohorts

Visit	Assessment	Fasting Requirement	HOLD AM Dose	Predose	INCB053914 Dose[a]	Time Postdose				
						1 h ± 15 min		2 h ± 15 min	4 h ± 15 min	8 h ± 30 min
C1D5	PK plasma	Fast overnight	X	X	♦	X	Snack/meal	X	X	X
C1D15	PK plasma	Fast overnight	X	X	♦	X	Snack/meal	X	X	X

[a] INCB053914 dose should be administered just before the start of the cytarabine infusion.

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Table 12: Schedule of Assessments for Azacitidine Combination Cohorts

Visit Day / Evaluation/Window	Section	Screening: Day -28 to Day -1	Treatment: 28-Day Cycles (Anchored to Azacitidine Schedule)[a] D1	D8	D15	D22[b]	D29-D42[c]	EOT: +3 Days	Follow-Up: Safety 30-35 Days After EOT	Disease Status Every 9 Weeks	Survival Every 12 Weeks
			± 2 Days								
Informed consent	7.1	X									
Inclusion/exclusion criteria	3	X	X								
Contact IRT	7.2	X	X					X			
Medical and cancer history	7.3.1	X									
Prior/concomitant medications	7.4	X	X	X	X	X	X	X	X		
Administer azacitidine in clinic[d]	5.1.5		X	X							
Administer INCB053914 in clinic	Table 14		X	X	X						
Drug dispense/compliance check[e]	5.1.7		X		X[f]		X[g]	X[f]			
Comprehensive physical exam	7.5.2.1	X						X	X		
Targeted physical exam	7.5.2.2		X	X	X	X	X				
ECOG performance status	7.7.1	X	X					X	X		
Vital signs/height/weight[h]	7.5.3	X[h]	X[h]	X	X	X	X	X[h]	X[h]		
12-lead ECG	7.5.4	X	X					X	X		
AE assessment[i]	7.5.1	X	X	X	X	X	X	X	X		
Laboratory assessments	Table 13	X	X	X	X	X	X	X	X		
Buccal swab	7.9.2	X									
AML disease assessment[j]	7.6	X	X					X		X	
Bone marrow examination[k]	7.9.1	X	X[j]								
Immunophenotyping[l]	7.6.5	X	When confirming CR								
Provide reminder cards	7.10.2	X	X	X	X	X	X	X			
Poststudy disease status	6.4.2									X	

CR = complete remission.

[a] From Cycle 4 onward, subjects are only required to receive azacitidine at the investigative site on Day 1 of each cycle. All other azacitidine doses and study assessments may be performed at a local clinic. Day 8 assessments are not required beginning with Cycle 4. Data from local clinic assessments do not need to be entered into the CRF.

[b] Day 22 assessments are performed in Cycle 1 only.

[c] If subjects have not sufficiently recovered from chemotherapy-related toxicities after 28 days, they should be seen weekly until such time that a subsequent cycle can be started. These visits should be entered as unscheduled visits in the eCRF. If subjects cannot start a subsequent cycle within 42 days, the site should contact the medical monitor.

[d] Azacitidine will be administered as 75 mg/m^2 SC or IV for 7 days during 9-day or less period (ie, a 2-day break allowed on weekend, if needed) of 28-day cycle.

[e] All study drug for Cycle 1 will be dispensed at Cycle 1 Day 1; subject will bring unused study drug to clinic for compliance check on Cycle 1 Day 15. Drug will only be dispensed at Day 1 of all subsequent cycles and compliance will be checked at the start of the next subsequent cycle.

[f] Compliance check only.

[g] If needed.

[h] Height measured at screening only. Weight required at screening, Day 1 of each cycle, EOT, and the follow-up visit.

[i] Subjects must be followed for AEs for 30 days (+ 5 days) after the EOT visit (or after the last dose of study drug if the EOT visit was not performed).

[j] Bone marrow biopsy and/or aspirates for response is to be performed at Cycle 4 Day 1 or earlier as clinically indicated, followed by every other month as clinically indicated, or upon circulating blood cell recovery to assess antileukemic activity (cytogenetic testing is not required if CR is not presented). Note: For subjects who have a significant blast count reduction (as determined by the investigator) but have not completely cleared circulating blasts, the Cycle 4 Day 1 bone marrow is still strongly encouraged to be performed to assess the impact of treatment on the bone marrow blast content. See Section 7.6 for additional details.

[k] If a biopsy is not possible or contraindicated, or the tissue requirement cannot be satisfied, this requirement may be waived with approval from the medical monitor. Subjects with a history of allogenic hematopoietic stem cell transplantation should have tissue collected and analyzed locally for the purposes of determining disease status (where applicable), however their sample does not need to be processed for sequencing due to chimeric potential.

[l] Immunophenotyping appropriate to AML will be conducted by flow cytometry at screening and when confirming CR.

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Table 13: Laboratory Assessments for Azacitidine Combination Cohorts

Visit Day	Section	Screening	28-Day Cycles (Anchor to Azacitidine Schedule)					EOT	Safety Follow-Up
			D1	D8[a]	D15	D22[a]	D29-D42[b]		
Evaluation/Window		Day -28 to Day -1		± 2 Days				+ 3 Days	EOT + 30-35 Days
Overnight fast before assessments[c]	Table 14			X	X				
Comprehensive blood chemistries	Table 21	X[d]	X[d]	X	X	X	X	X	X
Hematology with differential	Table 21	X[d]	X[d]	X	X	X	X	X	X
LFT panel[e]	Table 21	X[d]	X[d]	X	X	X	X[f]	X	X
Coagulation panel[e]	Table 21	X[d]	X[d]	X	X		X[f]	X	X
Urinalysis	Table 21	X	X[g]					X	
Lipid panel	Table 21	X	X[g]						
Hepatitis screening	Table 21	X							
Serum pregnancy test	7.5.5.2	X	X[h]					X	
PK – plasma[i]	7.8.1			X[i]	X[i]				
[redacted]									

[a] Day 8 assessments are not required beginning with Cycle 4. Day 22 assessments are performed in Cycle 1 only.
[b] If subjects have not sufficiently recovered from chemotherapy related toxicities after 28 days, they should be seen weekly until such time that a subsequent cycle can be started. These visits should be entered as unscheduled visits in the eCRF. If subjects cannot start a subsequent cycle within 42 days, the site should contact the medical monitor.
[c] Cycle 1 only.
[d] Blood chemistry (including LFTs) and hematology screening assessments used to determine eligibility must be collected within 14 days before Cycle 1 Day 1. Cycle 1 Day 1 blood chemistry, hematology, LFT panel, and coagulation panel assessments may be omitted if the screening assessments were performed within 3 days before Cycle 1 Day 1.
[e] Additional LFT and coagulation monitoring may be required as per Table 5 and Appendix S.
[f] Only if clinically indicated.
[g] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles there after (eg, Cycle 10, Cycle 13, etc).
[h] If screening serum pregnancy testing is performed within 7 days of treatment initiation, it does not need to be repeated at Cycle 1 Day 1.
[i] Cycle 1 only. See Table 14 for sample collection details. The visit window for the D8 PK sample (± 2 days) should be applied to collect samples on a cycle day when both azacitidine and INCB053914 are given.
[redacted]

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Table 14: Pharmacokinetic Assessments for Azacitidine Combination Cohorts

Visit	Assessment	Fasting Requirement	HOLD AM Dose	Predose	INCB053914 Dose	Azacitidine Dose	Time Postdose				
							1 h ± 15 min		2 h ± 15 min	4 h ± 15 min	8 h ± 30 min
C1D8[a]	PK plasma	Fast overnight	X	X	♦[b]	♦	X	Snack/meal	X	X	X
C1D15	PK plasma	Fast overnight	X	X	♦	n/a	X	Snack/meal	X	X	X

[a] Use the ± 2-day window to ensure that these samples are collected on a day when both INCB053914 and azacitidine are administered.
[b] INCB053914 dose should be administered just before the daily dose of azacitidine.

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Table 15: Schedule of Assessments for Ruxolitinib Combination Cohorts

		Screening	Treatment Phase[a]							EOT	Follow-up Phase	
Visit Day (Range)	**Section**	**Day -28 to Day -1**	**Day 1**	**Weeks 1, 2, 3[b]**	**Weeks 4, 8 ± 5 Days**	**Week 12 ± 5 Days**	**Weeks 16, 20 ± 5 Days**	**Week 24 ± 5 Days**	**Extension Visits (Q12W After Week 24) ± 7 Days**	**+3 Days**	**Safety Follow-Up + 30-35 Days After EOT**	**Survival Follow-Up Every 12 Weeks**
Informed consent	7.1	X										
Inclusion/exclusion criteria	3	X	X									
Contact IRT	7.2	X	X		X	X	X	X	X	X		
Medical and cancer history	7.3.1	X										
Prior/concomitant medication	7.4	X	X	X	X	X	X	X	X	X	X	
Transfusion history/status	7.3.2	X	X		X	X	X	X	X	X	X	
Screening Symptom Form	7.3.3	X										
Administer INCB053914 in clinic	Table 17		X	X	X	X	X	X				
Administer ruxolitinib in clinic	Table 17		X	X	X	X	X	X	X			
Drug dispense/compliance check	5.1.7		X		X	X	X	X	X	X[c]		
Comprehensive physical examination	7.5.2.1	X						X		X	X	
Targeted physical examination	7.5.2.2		X	X	X	X	X		X	X		
[redacted]												
ECOG performance status	7.7.1	X	X		X	X	X	X	X	X	X	
Vital signs/height/weight[d]	7.5.3	X[d]	X		X	X	X	X	X	X	X	
12-lead ECG	7.5.4	X	X					X		X	X	
AE assessment[e]	7.5.1	X	X	X	X	X	X	X	X	X	X	
Laboratory assessments	Table 16	X	X	X	X	X	X	X	X	X	X	
Buccal swab	7.9.2	X										
[redacted]												
Provide reminder card	7.10.1	X	X	X	X	X	X	X	X	X		
[redacted]												

CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging, PGIC = Patient Global Impression of Change.
[a] See Table 16 for scheduled visits where only lab assessments are collected (lab-only visits).
[b] Week 1 and Week 3 visits only pertain to Part 3 subjects.
[c] Compliance check only.

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[d] Height is only assessed at screening.
[e] Subjects must be followed for AEs for 30 days (+ 5 days) after the EOT visit (or after the last dose of study drug if the EOT visit was not performed).

[redacted]

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Table 16: Laboratory Assessments for Ruxolitinib Combination Cohorts

Visit	Section	Screening	Day 1	Weeks 1, 3 Part 3 ONLY	Weeks 2, 6, 10, 14, 18, 22, then Q4W	Weeks 4, 8, 12, 16, 20, 24, then Q12W	EOT	Follow-Up 30-35 Days After Last Dose of INCB053914
Evaluation/Window				The window for laboratory visits is ± 3 days				
Overnight fast before assessments	Table 17		X		X[a]	X[a]		
Comprehensive blood chemistries	Table 21	X[b]	X[b]	X		X	X	X
Hematology with differential	Table 21	X[b]	X[b]	X	X	X	X	X
LFT panel[c]	Table 21	X[b]	X[b]	X	X	X	X	X
Coagulation panel[c]	Table 21	X[b]	X[b]	X		X	X	X
Urinalysis	Table 21	X				X[d]	X	X
Lipid panel (requires overnight fast)	Table 21	X				X[d]	X	X
Hepatitis screening	Table 21	X						
Serum pregnancy	7.5.5.2	X	X[e]					X
PK – plasma	7.8.1		X		X[f]	X[f]		
[redacted]								

[a] At Week 2 and Week 4 only.
[b] Blood chemistry (including LFTs) and hematology screening assessments used to determine eligibility must be collected within 14 days before Cycle 1 Day 1. Cycle 1 Day 1 blood chemistry, hematology, LFT panel, and coagulation panel assessments may be omitted if the screening assessments were performed within 3 days before Cycle 1 Day 1.
[c] Additional LFT and coagulation monitoring may be required as per Table 5 and Appendix S
[d] Required Weeks 12 and 24 and Q12W.
[e] If screening serum pregnancy testing is performed within 7 days of treatment initiation, it does not need to be repeated at Cycle 1 Day 1.
[f] Pharmacokinetic sampling will occur on Day 1, Week 2, and Week 4 only. See Table 17.
[redacted]

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Table 17: Pharmacokinetic Assessments for Ruxolitinib Combination Cohorts

Visit	Assessment	Fasting Requirement	HOLD AM Doses	Predose	Drug Administration	Time Postdose				Drug Administration
						1 h ± 15 min		2 h ± 15 min	4 h ± 15 min	
Day 1	PK plasma	Fast overnight	N/A	X	Ruxolitinib	X	Snack/meal	X	X	INCB053914
Week 2	PK plasma	Fast overnight	X	X	INCB053914	X	Snack/meal	X	X	Ruxolitinib
Week 4	PK plasma	Fast overnight	X	X	INCB053914 + Ruxolitinib	X	Snack/meal	X	X	N/A

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Table 18: Schedule of Assessments for L-DAC Combination Cohorts

		Screening	Treatment								EOT	Follow–Up		
			28-Day Cycles (Anchored to L-DAC Schedule)											
			Cycle 1[a]				Cycle 2 and Beyond[a,b]					Safety	Disease	Survival
Visit Day		Day -28	D1	D10	D15/D22	D29-D42[c]	D1	D10	D15	D29-D42[c]				
Evaluation/Window	Section	to Day -1			± 1 Days				± 1 Days		+ 3 Days	30-35 Days After EOT	Every 9 Weeks	Every 12 Weeks
Informed consent	7.1	X												
Inclusion/exclusion criteria	3	X	X											
Contact IRT	7.2	X	X				X				X			
Medical and cancer history	7.3.1	X												
Prior/concomitant medications	7.4	X	X	X	X	X	X	X	X	X	X	X		
Administer cytarabine in clinic	5.1.4		X	X										
Administer INCB053914 in clinic	Table 20		X	X	X[d]									
Drug dispense/compliance check[e]	5.1.4		X	X			X	X		X	X[f]			
Comprehensive physical exam	7.5.2.1	X									X	X		
Targeted physical exam	7.5.2.2		X	X	X	X	X	X	X	X				
ECOG performance status	7.7	X	X				X				X	X		
Vital signs/height/weight[g]	7.5.3	X[g]	X[g]	X	X	X	X	X	X	X	X[g]	X[g]		
[redacted]														
12-lead ECG	7.5.4	X	X		X[d]		X				X	X		
AE assessment[h]	7.5.1	X	X	X	X	X	X	X	X	X	X	X		
Laboratory assessments	Table 19	X	X	X	X	X	X	X	X	X	X	X		
Buccal swab	7.9.2	X												
AML disease assessments[i]	7.6	X	X				X				X		X	
Bone marrow examination[j]	7.9.1	X					X[i]							
Immunophenotyping[k]	7.6.5	X	When confirming CR											
Provide reminder card	7.10.1	X	X	X	X	X	X	X	X	X	X			
Poststudy disease status	6.4.2												X	
[redacted]														

[a] When possible, L-DAC cytarabine cycles should be started on a Monday, Tuesday, or Wednesday to limit weekend dose administration.
[b] Subsequent cycles of L-DAC may begin every 4 to 6 weeks, provided all drug-related toxicities have returned to ≤ Grade 1 or baseline.
[c] If subjects have not sufficiently recovered from chemotherapy-related toxicities after 28 days, they should be seen weekly until such time that a subsequent cycle can be started. These visits should be entered as unscheduled visits in the eCRF. If subjects cannot start a subsequent cycle within 42 days, the site should contact the medical monitor.
[d] Day 15 only.
[e] All study drug for Cycle 1 will be dispensed at Cycle 1 Day 1; subject will bring unused study drug to clinic for compliance check on Cycle 1 Day 10. Drug will only be dispensed at Day 1 of all subsequent cycles.

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[f] EOT visit - compliance check only.
[g] Height measured at screening only. Weight required at screening, Day 1 of each cycle, EOT, and the follow-up visit.
[h] Subjects must be followed for AEs for 30 days (+ 5 days) after the EOT visit (or after the last dose of study drug if the EOT visit was not performed).
[i] Bone marrow biopsy and/or aspirates for response is to be performed at Cycle 2 Day 1 or earlier as clinically indicated, followed by every other month as clinically indicated, or upon circulating blood cell recovery to assess antileukemic activity (cytogenetic testing is not required if CR is not presented). Note, for subjects who have a significant blast count reduction (as determined by the investigator) but have not completely cleared circulating blasts, the Cycle 2 Day 1 bone marrow is still strongly encouraged to be performed to assess the impact of treatment on the bone marrow blast content. See Section 7.6 for additional details.
[j] If a biopsy is not possible or contraindicated, or the tissue requirement cannot be satisfied, this requirement may be waived with approval from the medical monitor. Subjects with a history of allogenic hematopoietic stem cell transplantation should have tissue collected and analyzed locally for the purposes of determining disease status (where applicable); however, their sample does not need to be processed for sequencing due to chimeric potential.
[k] Immunophenotyping appropriate to AML will be conducted by flow cytometry at screening and when confirming CR.

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Table 19: Laboratory Assessments for L-DAC Combination Cohorts

Visit Day	Section	Screening	28-Day Cycles (Anchored to L-DAC Schedule)							EOT	Safety Follow-Up
			Cycle 1				Cycle 2 and Beyond				
Evaluation/Window		Day -28 to Day -1	D1	D10	D15/D22	D29-D42[a]	D1	D10/D15	D29-D42[a]	+ 3 Days	EOT + 30-35 Days
					± 1 Day			± 1 Day			
Overnight fast before assessments	Table 20			X	X[b]						
Comprehensive blood chemistries	Table 21	X[c]	X[c]	X	X	X	X	X	X	X	X
Hematology with differential	Table 21	X[c]	X[c]	X	X	X	X	X	X	X	X
LFT panel[d]	Table 21	X[c]	X[c]	X	X	X	X	X	X[e]	X	X
Coagulation panel[d]	Table 21	X[c]	X[c]	X	X[b]		X		X[e]	X	X
Urinalysis	Table 21	X					X[f]			X	X
Lipid panel	Table 21	X					X[f]				
Hepatitis screening	Table 21	X									
Serum pregnancy test	7.5.5.2	X	X[g]								X
PK – plasma[h]	7.8.1			X	X[b]						
[redacted]											

[a] If subjects have not sufficiently recovered from chemotherapy-related toxicities after 28-days, they should be seen weekly until such time that a subsequent cycle can be started. These visits should be entered as unscheduled visits in the eCRF. If subjects cannot start a subsequent cycle within 42 days, the site should contact the medical monitor.
[b] Day 15 only.
[c] Blood chemistry (including LFTs) and hematology screening assessments used to determine eligibility must be collected within 14 days before Cycle 1 Day 1. Cycle 1 Day 1 blood chemistry, hematology, LFT panel, and coagulation panel assessments may be omitted if the screening assessments were performed within 3 days before Cycle 1 Day 1.
[d] Additional LFT and coagulation monitoring may be required as per Table 5 and Appendix S.
[e] Only if clinically indicated.
[f] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles there after (eg, Cycle 10, Cycle 13, etc).
[g] If screening serum pregnancy testing is performed within 7 days of treatment initiation, it does not need to be repeated at Cycle 1 Day 1.
[h] See Table 20 for sample collection details.
[redacted]

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Table 20: Pharmacokinetic Assessments for L-DAC Combination Cohorts

Visit	Assessment	Fasting Requirement	HOLD AM Dose	Predose	INCB053914 Dose	L-DAC Dose	Time Postdose				
							1 h ± 15 min		2 h ± 15 min	4 h ± 15 min	8 h ± 30 min
C1D10	PK plasma	Fast overnight	X	X	♦[a]	♦	X	Snack/meal	X	X	X
C1D15	PK plasma	Fast overnight	X	X	♦	n/a	X	Snack/meal	X	X	X

[a] INCB053914 dose should be administered just before the morning dose of L-DAC.

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Table 21: Clinical Laboratory Analytes

Blood Chemistries	Hematology	Hepatitis Screening
Albumin Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose HbA1c[a] Lactate dehydrogenase Magnesium Phosphate Potassium Sodium Total protein Uric acid	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes[b] • Monocytes • Neutrophils[b] • Blasts[c]	Hepatitis B surface antibody Hepatitis B surface antigen Hepatitis B core antibody HBV-DNA[d] HCV antibody HCV-RNA[d]
		Pregnancy
		Female subjects of childbearing potential require a serum test at screening. Pregnancy tests (serum or urine) should be repeated during the study as required by local regulations.
		Coagulation Panel
		PT aPTT INR
LFT Panel	**Lipids**	**Urinalysis With Microscopic Examination**
Alkaline phosphatase ALT AST Total bilirubin Direct bilirubin[e]	Total cholesterol Triglycerides LDL HDL	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen

aPTT = activated partial thromboplastin time; HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; PT = prothrombin time.

[a] HbA1c to be performed on all Part 1 and Part 3 subjects at screening only.

[b] Absolute values must be provided for lymphocytes and neutrophils.

[c] Required at intervals specified in Table 6, Table 9, Table 12, Table 15, and Table 18 for diseases where peripheral blast count is part of disease assessments such as AML, MDS, MDS/MPN, and MF.

[d] Screening hepatitis B and C viral loads by PCR assay are required for all ruxolitinib combination subjects (C-TGC). For all other subjects, hepatitis B and C viral loads by PCR assay only need to be assessed when respective serology results are positive. Hepatitis B virus DNA does not need to be performed if the HBV surface antibody is the only positive result (indicating immunity due to vaccination).

[e] Direct bilirubin should only be performed when total bilirubin is > ULN and subject does not have Gilbert's syndrome.

6.1. Screening

The screening phase is the interval between signing the ICF and the day the subject is enrolled in the study (Day 1). The screening phase may not exceed 28 days. Informed consent must be obtained before performing any study-specific procedures not considered SOC.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging studies) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study.

Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this phase. Blood chemistry and hematology screening laboratory assessments used to determine subject eligibility must be collected within 14 days before Day 1. Results from the screening visit evaluations will be reviewed by the investigator to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before study drug administration will be used to determine subject eligibility. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection).

Additionally, the screening phase will be used to determine the baseline assessments of clinical condition and disease status. Tumor assessments appropriate to the type of malignancy will be performed and recorded in the eCRF.

6.2. Treatment

6.2.1. Day 1

The treatment phase begins on the day the subject receives the first dose of study drug; this is defined as **Day 1** (or Cycle 1 Day 1) and continues until a decision is made to permanently

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discontinue the study drug. At Day 1 (Cycle 1 Day 1), results from screening phase should be reviewed to determine if the subject continues to meet the eligibility requirements as specified in the Protocol. See Table 7, Table 8, Table 10, Table 11, Table 13, Table 14, Table 16, Table 17, Table 19, and Table 20 for discussion of details regarding the laboratory assessments performed at Day 1 (Cycle Day 1). Day 1 (Cycle 1 Day 1) blood chemistry and hematology assessments may be omitted if the screening laboratory samples are collected are within 3 days before Day 1 (Cycle 1 Day 1). If Day 1 (Cycle 1 Day 1) laboratory samples are collected, the blood draws should be performed before administration of first dose of study drug.

6.2.2. Visit Scheduling

Dates for subsequent study visits will be determined based on Day 1 (Cycle 1 Day 1) and should occur within the allotted visit window unless delayed for safety reasons. If study drug or SOC regimen administration must be interrupted at the beginning of a new planned cycle, the cycle will be delayed until the study drug or SOC regimen can be restarted as noted below. All planned assessments are shown in Table 6, Table 9, Table 12, Table 15, and Table 18.

- Visit schedules for Part 3 and Part 4 C-TGA subjects receiving I-DAC will be based on 21-day cycles anchored to the INCB053914 administration. If I-DAC is given as reinduction or consolidation, the regimen start should align with a Day 1 of the 21-day cycle whenever possible.
- Visit schedules for Part 3 and Part 4 C-TGB subjects will be based on the start of subsequent cycles of azacitidine. Should a cycle start be delayed, subjects should continue to receive INCB053914 if appropriate.
- Part 3 and Part 4 C-TGC subjects will be seen every 4 weeks through Week 24 and every 12 weeks thereafter irrespective of whether INCB053914 and/or ruxolitinib are on hold. The study visits (Week 1, Week 2, etc) were named to align with the completion of a week's worth of study drug (ie, Week 1 is planned to occur on Study Day 8, or the end of 1 week of study drug).
- If the optional C-TGA E2 (L-DAC combination) is conducted, visit schedules for these subjects will be based on the start of subsequent cycles of L-DAC. Should a cycle start be delayed, subjects should continue to receive INCB053914 if appropriate.

During the treatment phase, regular study visits (physician visits) and laboratory-only visits will occur as denoted on the respective Schedules of Assessment and Laboratory Assessment tables.

6.3. End of Treatment

When the subject permanently discontinues study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the follow-up visit.

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6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up phase is the interval between the EOT visit and the scheduled safety follow-up visit. Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the safety follow-up visit, or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the subject return for this follow-up visit and report any AEs that may occur during this period.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up phase and should be assessed at the intervals specified in Table 6, Table 9, Table 12, and Table 18, using the appropriate disease assessment criteria (Section 7.6) to monitor disease status. Every effort should be made to collect information regarding disease status until 1 of the following:

- Start of new antineoplastic therapy
- Disease progression
- Death
- Withdrawal of consent
- End of the study

[redacted]

6.5. Unscheduled Visits

Clinic visits or diagnostic laboratory visits not prescribed in the Protocol may be performed at any time clinically indicated. Results of assessments performed at these visits should be entered as "unscheduled" visits in the eCRF. The sponsor may also request additional visits to be performed, if needed, based on emerging safety data.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation. Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study (see Appendix A).

7.2. Interactive Response Technology Procedure

The interactive response technology (IRT) will be contacted to obtain a subject ID number when a subject enters the screening phase. Additionally, the IRT will be contacted at each visit at which study drug is dispensed to update the study drug supply and upon the decision to discontinue treatment. Refer to the IRT manual for detailed instructions.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and a complete medical and medication history will be collected at screening. This will include date of birth, race, ethnicity, and medical and surgical history for the disease under study. Details regarding the disease for which the subject has enrolled in this study (eg, date of diagnosis, primary tumor histology, prior systemic therapies, surgeries, radiation therapy, and stage of cancer) will be recorded separately and not listed in medical history.

7.3.2. Transfusion History Status (Ruxolitinib Combination Cohorts Only)

All transfusions of red blood cell products or platelets from at least 16 weeks before the screening visit will be recorded. The product(s) delivered, date of transfusion, and units delivered will be recorded on the CRF.

7.3.3. Screening Symptom Form (Ruxolitinib Combination Cohorts Only)

In order to satisfy inclusion criteria for Part 3 C-TGC and Part 4 C-TGC E1, active symptoms of MF at the screening visit as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form (Appendix O) will be recorded on the CRF.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedures performed within 30 days before the first dose and through

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the safety follow-up period will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

7.5. Safety Assessments

7.5.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

If a subject experiences a treatment-emergent rash, photographic images of the rash should be collected and retained as part of the subject's medical record. De-identified copies of the images should be submitted to the sponsor at its request so the character of the rash can be better evaluated.

7.5.2. Physical Examinations

7.5.2.1. Comprehensive Physical Examination

Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

7.5.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation conducted by the investigator or a medically qualified designee. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings.

7.5.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, height (at screening), and body weight. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

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7.5.4. Electrocardiograms

7.5.4.1. Twelve-Lead Electrocardiograms

A central ECG vendor will be used. The 12-lead ECGs will be interpreted by the investigator at the site for immediate subject management. The trace will also be transmitted to the central ECG vendor for analysis by a central reader, and data archiving. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Any treatment-emergent ECG finding occurring on study that is abnormal and clinically significant in the judgment of the investigator should be reported as an AE.

7.5.4.2. Electrocardiogram Procedures

All 12-lead ECGs will be performed with the subject in a recumbent position after 5 minutes of rest and should not be performed within 15 minutes after a blood collection.

7.5.4.3. Additional Instruction for Timed Electrocardiograms

Timed ECGs will be conducted before the clinic administration of study drug (predose) and using the schedule shown in Electrocardiograms conducted before administration (establishing the baseline for the day) should be performed in triplicate (Table 8). The ECGs should be conducted before, but within 15 minutes of, the PK blood collection at the corresponding timepoint. The specified postdose timepoints may be adjusted based on emerging PK data.

7.5.5. Laboratory Assessments

7.5.5.1. Chemistry, Hematology, Urinalysis, Liver Function Panel, Coagulation Panel, and Hepatitis Screening

Chemistry, hematology, liver function panel, coagulation panel, and hepatitis screening will all be analyzed by the local site laboratory. The investigative site will enter the local laboratory results and laboratory normal ranges into the eCRF. All local laboratory assessments (ie, blood chemistries, hematology assessments, LFTs, coagulation tests, lipid testing, and urinalysis) should be performed using standard procedures on the days indicated in Table 7, Table 10, Table 13, Table 16, and Table 19. Table 5 lists additional timepoints for increased frequency of LFT panel and coagulation panel assessments should subjects experience treatment-emergent liver enzyme elevations. Table 21 lists the required laboratory tests in each category; additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Blood chemistry (including LFTs) and hematology screening assessments used to determine subject eligibility must be collected within 14 days before Cycle 1 Day 1. On Day 1, laboratory data from the screening evaluations must be reviewed to confirm eligibility. Cycle 1 Day 1 blood chemistry, hematology, LFT, and coagulation assessments may be omitted if the screening laboratory samples are collected within 3 days before Cycle 1 Day 1. If Cycle 1 Day 1 laboratory samples are needed, they must be collected before administration of the first dose of study drug. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours

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before study drug administration (within the 3-day study window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

7.5.5.2. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential before first dose of study drug as shown in Table 7, Table 10, Table 13, Table 16, and Table 19. Subsequently, pregnancy tests (either serum or urine) may be conducted as medically indicated or as required per local guidelines.

7.5.5.3. Hepatitis Screening Tests

Testing for hepatitis (detailed in Table 21) is required at screening, and results should be reviewed before Day 1 to confirm eligibility. Due to the risk of seroconversion with ruxolitinib treatment, hepatitis B and C viral loads by PCR assay will be required for all ruxolitinib combination cohort subjects. However, for all other subjects, additional testing for HBV-DNA and HCV-RNA by PCR assay to further assess hepatitis status will only be required if hepatitis B and/or C serology are positive. Additionally, HBV-DNA does not need to be performed if the HBV surface antibody is the only positive result (indicating immunity due to vaccination).

The eligibility of any subject with positive viremia (eg, PCR assay targets detected) must be discussed with the medical monitor before subject enrollment.

Generally hepatitis serology tests should be submitted early in the screening process because of the length of time frequently needed to obtain the results.

7.6. Efficacy Assessments

The following disease response criteria will be used for each of the malignancies included in this study:

- Acute myeloid leukemia: International Working Group Response Criteria for Acute Myeloid Leukemia (Cheson et al 2003; Appendix D)

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[redacted]

Treatment cycles may be delayed; therefore, disease response assessments may be delayed as well to synchronize with treatment cycles. A disease assessment may be performed as an unscheduled procedure if clinically indicated. For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status until start of new anticancer therapy, documented disease progression, death, or the end of the study, whichever occurs first.

[redacted]

[redacted]

7.6.3. AML, [redacted] Bone Marrow Examination

Bone marrow examination (aspirate and biopsy) is required at screening for subjects with diseases that are typically monitored though bone marrow examination, including AML, [redacted] (bone marrow examination may be omitted with approval of the medical monitor).

[redacted]

In the combination cohorts (Parts [redacted] 4), if disease status requires assessment with bone marrow aspirate or biopsy, subjects with AML, [redacted] should have a bone marrow aspirate and/or biopsy performed after 1 cycle of therapy (or earlier if clinically indicated), Month 2, and then approximately every 2 months thereafter. Specific requirements for bone marrow examination of each combination cohort are included in the footnotes of each respective table (Section 6). Subjects without circulating blasts at the screening hematology assessment may use a historical biopsy obtained within 60 days before Cycle 1 Day 1 (Day 1), and all data and reports are available for investigator's review.

[redacted]

Samples of bone marrow biopsy and aspirate will be set to Incyte or its designee for additional immune and molecular profiling.

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Data from the pathology report result from the bone marrow examination will be captured in the eCRF. All bone marrow examinations should include a unilateral aspiration and biopsy with FISH and cytogenetic testing, when feasible. Subjects may be enrolled based on a biopsy only when a "packed marrow" precludes aspiration at the decision of the medical monitor. Results of assessments performed under SOC before the signing of informed consent may be used as the baseline disease assessment in lieu of a study-specific procedure if performed within 60 days of the first dose of study drug (Cycle 1 Day 1) and if adequate archive material is available and there has been no anticancer therapy in the interim.

Reference Section 7.9.1 for more information on tissue collection.

7.6.4. AML, [redacted]: Peripheral Blood Myeloid Blast Percentage

For disease assessment timepoints in AML, [redacted] that do not correspond to a bone marrow examination, peripheral blood myeloid blast percentage will be evaluated by microscopic evaluation or other appropriate methodology and will be used as appropriate in conjunction with other parameters (eg, cytopenias) in determining disease status.

7.6.5. [redacted] AML[redacted]: Immunophenotyping

For subjects with relevant hematologic malignancies (eg, [redacted] AML[redacted]), immunophenotyping appropriate to the underlying pathology will be conducted by flow cytometry at the local laboratory at screening and at subsequent times only as part of confirmation of CR. Results of flow cytometry performed under SOC before the signing of informed consent may be used as the baseline disease assessment in lieu of a study-specific procedure. See Section 7.6.3 for the timing and requirements of using the preconsent SOC tissue analysis as the study baseline assessment. Results will be captured in the eCRF.

[redacted]

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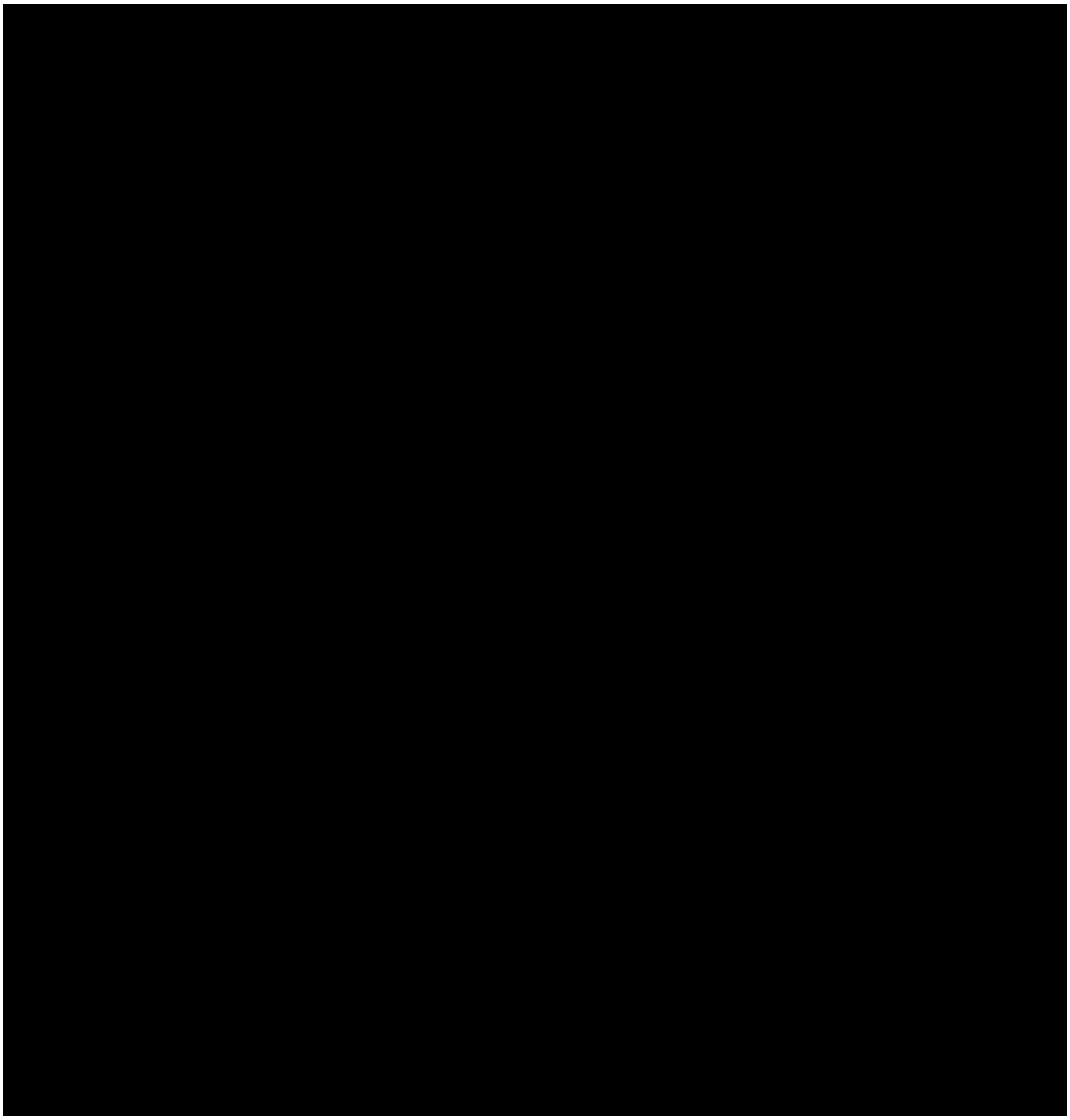
7.7. Performance and Quality-of-Life Assessments

7.7.1. Eastern Cooperative Oncology Group

Performance status will be assessed on all subjects using the ECOG performance status scale (Appendix C), according to the study schedule (Table 6, Table 9, Table 12, Table 15, and Table 18).



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7.8. Pharmacokinetic Assessments

7.8.1. Blood Sample Collection

Pharmacokinetic samples will be obtained at the visits indicated in the respective tables of PK, PD, and ECG assessments (see Table 8, Table 11, Table 14, Table 17, and Table 20) to evaluate plasma PK parameters as described in Appendix B. The study drug(s) will be administered in clinic with approximately 240 mL of water. Subjects should remain fasting from food or water for at least 1 hour postdose, after which a meal or snack may be consumed. For PK sample collection, the following will be recorded:

- The exact date and time of the blood sample.
- The date and time of the last dose of study drug before blood collection (if applicable).
- The date, time, and type of the most recent meal.

Subjects will receive reminder cards in advance of the study visit providing instructions to prepare for the visit (see Section 7.10.2). Instructions for plasma preparation and sample shipping will be provided in the Laboratory Manual. The specified postdose timepoints may be adjusted based on emerging PK data.

7.8.2. Urine Sample Collection

Urine will be collected from each subject in a monotherapy cohort at Cycle 1 Day 8 after administration of INCB053914 and a predose void. Total urine will be collected over an 8-hour interval following study drug administration. Urine containers should be kept at reduced temperature (refrigerated or ice bath) during collection. After the interval, the total urine volume and the pH should be measured and recorded in the individual eCRF. Urine will be mixed thoroughly, and a 200 mL aliquot will be collected into a prelabeled, polypropylene storage bottle and frozen at or below -20°C. Shipping and handling instructions will be provided in the Laboratory Manual; samples will be analyzed by the sponsor or its designee for parameters described in Appendix B.

7.8.3. Bioanalytical Methodology and Analysis

Plasma samples will be analyzed by the sponsor, or designee, using a validated assay. Additionally, residual samples may be used for exploratory analyses to identify metabolites. Pharmacokinetic parameters that will be analyzed are shown in Appendix B, and the analysis methodology is described in Section 9.4.4.5.

7.8.4. Food-Effect Pharmacokinetic Testing

Pharmacokinetic testing for food effect on drug exposure will be performed in at least 12 and up to 18 subjects enrolled in all monotherapy expansion cohorts who are able to participate in the food study. Subjects may be excused from the food-effect portion of the study if they are unable to consume the meal.

Subjects will have been fasted from food (not including water) overnight for at least 8 hours. A standardized high-fat, high-calorie breakfast will be given to these subjects approximately

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30 minutes before administration of study drug. Subjects must consume the entire breakfast within 25 minutes, and study drug administration will begin 5 minutes after completing breakfast.

The high-fat, high-calorie breakfast (50% kcal from fat) will consist of:

- 2 eggs fried in butter
- 2 strips of bacon
- 1 English muffin with butter
- 4 oz hash brown potatoes
- 8 oz whole milk

Alternative menus with the same caloric and fat content may be substituted with the prior approval of the study sponsor.

7.9. Pharmacodynamic and Biomarker Assessments

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7.9.2. Buccal Swab

A buccal swab will be performed at screening on all subjects as a source of nontumor genetic material. Details of collection and shipping will be provided in the Laboratory Manual.

[redacted]

7.9.4. Whole Blood Pharmacodynamics (Monotherapy Cohorts Only)

Whole blood PD samples will be generally collected in conjunction with the timed PK samples (see Table 7 and Table 8) for the measurement of drug effect (phosphoprotein analysis in whole blood). These samples must be shipped directly (unfrozen) to the sponsor, **on the day of collection**, for processing and analysis. Refer to the Laboratory Manual for detailed collection, handling, and shipping instructions.

[redacted]

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[redacted]

7.10. Other Study Procedures

7.10.1. Administration of Study Drug in the Clinic

Study drug will be administered in the study clinic on days when it is necessary to collect a trough (predose) sample and when timed post-dose samples are collected.

7.10.2. Distribution of Subject Reminder Cards

Subjects will be provided with subject reminder cards at each visit. The subject reminder cards will indicate the date and time of the next visit. The reminder cards will have a field for the subject to enter the date and time of the last dose taken before the visit and to record the time of the last meal before applicable visits as per Table 8, Table 11, Table 14, Table 17, and Table 20. Reminder cards will include instructions specific for the study visits, including for visits where the subject will refrain from taking the study drug at home in the morning before the clinic visit. All necessary instructions, such as those for study drug administration, concomitant medications, and laboratory tests should be provided to the subject in writing on this reminder card or on accompanying written materials.

[redacted]

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8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (AE) is defined as the appearance of or worsening of any pre-existing undesirable sign, symptom, or medical condition that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 30 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

"Disease progression" should not be recorded as an AE itself unless there are no other identifiable AEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

Adverse events will be assessed according to the CTCAE v4.03. The CTCAE Grade 5 severity (death) will not be used in this study; rather, AEs with an outcome of death will be reported as CTCAE Grade 4, with an outcome of "fatal." Adverse events leading to death will be recorded with the outcome of the event as "fatal." If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.

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The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine the following:

- The severity grade (CTCAE Grade 1 to 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per SAE definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. Concomitant medication or nondrug therapy used to treat an AE should be recorded on the Adverse Event form as well as the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, which lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved. For analysis purposes, this will be considered 1 AE for this subject and the maximum severity will be used.

8.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal

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laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose modification for the laboratory abnormality may be required (see Section 5.2.3.1) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening (ie, immediate risk of dying).
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
  - Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, or where there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.
- Results in persistent or significant disability or incapacity.
- Constitutes a congenital anomaly or birth defect.
- Is clinically meaningful (ie, defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent 1 of the outcomes listed above).
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

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8.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the ICF and up to the last study visit, or up to 30 days after the subject has stopped study treatment, whichever is later, must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence. Any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor, or its designee, only if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as a follow-up to the original episode within 24 hours of the investigator receiving the information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported SAE should be reported separately as a new event. Previously planned (ie, before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment.

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives are listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

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8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be following in order to ensure subject safety:

- The investigator must notify the sponsor or its designee immediately.
- The study drug must be discontinued immediately (female subjects only; see Section 5.2.5 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

8.6. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the INCB053914 IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). Any important new safety information should be discussed with the subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

A formal Data Monitoring Committee will not be used for this study. The sponsor will continuously monitor safety through frequent contact with the treating investigators, review of the clinical data, and formal study meetings. Routine (weekly or biweekly) teleconferences will be held during the dose escalation and expansion phases among participating study sites to provide subject-by-subject updates on current study status, interim toxicities reported, and any other pertinent information. Adverse event and laboratory data entered into the clinical database will be reviewed periodically for trends and evolving safety signals. Lastly, formal review

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meetings will be conducted with investigators during the study to establish consensus on the safety and tolerability of a given dose, based on the collective experience of the group.

8.8. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint and any associated AEs via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.1.2 of this Protocol.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9. STATISTICS

9.1. Study Populations

The populations to be analyzed include the following:

The safety population is defined as all subjects who are enrolled and received at least 1 dose of study drug. All safety analyses will be based on the safety population.

The full analysis set (FAS) includes all subjects enrolled in the study who received at least 1 dose of study medication and have at least 1 postbaseline assessment or who discontinued treatment. All efficacy analyses will be based on FAS.

The PK/PD-evaluable population includes the safety population who has at least 1 valid PK/PD measurement.

9.2. Selection of Sample Size

9.2.1. Sample Size in Part 1

A 3 + 3 dose escalation design will be used in 2 disease-specific treatment groups. Dose escalation for TGA and TGB will proceed independently. Based on 3 + 3 algorithm, a minimum of 3 and up to 6 subjects will be enrolled at each dose level. The total sample size in Part 1 will depend on the frequency of DLTs and the number of dose levels tested before the MTD or PAD is reached. The details of the 2 dose-escalation groups are in Section 4.1.1.

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9.2.2. Sample Size in Part 2

Part 2 will include up to 5 expansion cohorts to further evaluate the safety, tolerability, efficacy, PK and PD of RP2Ds selected from Part 1. Within each cohort, at least 5 and up to approximately 15 subjects will be enrolled and treated at the RP2D identified in the corresponding treatment group. With 5 subjects enrolled, there is an 83% probability of observing at least 1 responder if the true underlying response rate is 30%. The details of 5 expansion cohorts are in Section 4.1.2.

9.2.3. Sample Size in Part 3

Part 3 will use a 3 + 3 design to evaluate different doses of INCB053914 in combination with cytarabine, azacitidine, or ruxolitinib in 3 treatment groups. Dose escalation for 3 treatment groups will proceed independently. Approximately 3 to 6 subjects will be enrolled in each dose cohort. The total number of subjects will depend on the frequency of DLTs and the number of dose levels tested before the MTD or PAD is reached. The details of 3 combination groups are in Section 4.1.3.

9.2.4. Sample Size in Part 4

In Part 4, up to 4 expansion cohorts will be included to further evaluate the safety, tolerability, efficacy, PK, and PD of RP2Ds selected from Part 3. A Simon 2-stage design (Simon 1989) will be used for combination expansion cohorts C-TGA E1 and C-TGB E1 and the optional C-TGA E2. The response rates for the historical control (p_0), desired response rates for the combination (p_1), number of subjects needed in Stage 1 (n_1) and Stage 2 (n_2), total number of subjects in both stages (n), first stage threshold declaring cohort undesirable (r_1), the upper limit of the number of responses in n patients such that futility of the drug is concluded (r), and probability of early termination under p_0 (PET[p_0]) are provided for each expansion cohort (Table 23). The calculation is based on a 1-sided Type I error of 0.05 and power of 80%.

Table 23: Simon 2-Stage Design

Cohort	p_0	p_1	n_1	n_2	n	r_1	r	PET(p_0)
C-TGA E1	20%	40%	13	30	43	3	12	0.7473
C-TGB E1	20%	40%	13	30	43	3	12	0.7473
C-TGA E2 (optional)	20%	40%	13	30	43	3	12	0.7473

Up to 16 subjects will be enrolled in the C-TGC E1 cohort. [redacted]

9.3. Level of Significance

For the primary efficacy endpoints, the 1-sided Type I error will be controlled at 0.05 for each individual cohort expansion. For other endpoints, CIs will be reported at a 95% confidence level.

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9.4. Statistical Analyses

9.4.1. Primary Analysis

- The clinical safety data (vital signs, ECGs, routine laboratory tests, and AEs) will be summarized using descriptive statistics (eg, mean, frequency) using the safety population.
- Part 4 only: Simon 2-stage design will be used to evaluate ORR, defined as the proportion of subjects who achieve CR or CRi, in C-TGA E1, C-TGB E1, and optional C-TGA E2. The interim analysis will be conducted once the first postbaseline bone marrow biopsies for Stage 1 subjects available. If fewer than or equal to a prespecified number of response is observed, the cohort will be discontinued. Otherwise, additional subjects will be enrolled for further evaluation.

9.4.2. Secondary Analyses

The secondary analysis includes the following:

- The clinical PK data (C_{max}, T_{max}, C_{min}, AUC_{0-t}, Cl/F) will be summarized using descriptive statistics (eg, mean, frequency) using the PK-evaluable population.
- Pharmacodynamic profile of INCB053914 defined by phosphorylation of Bcl-2–associated death promoter protein will be explored.

[redacted]

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9.4.4. Safety Analyses

9.4.4.1. Adverse Events

Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the CTCAE v4.03.

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.4.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into CTC grades for AEs (CTCAE v4.03). The following summaries will be produced for the laboratory data:

- Tables showing number and percentage of subjects with worst postbaseline CTC grade (regardless of baseline value) will be produced. Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables using CTC grades to compare baseline with the worst postbaseline value will be produced with CTC grade.
- For laboratory parameters where CTC grades are not defined, shift tables to the worst postbaseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

9.4.4.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, heart rate, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 24), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 24: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38ºC	< 35.5ºC
Respiratory rate	> 24/min	< 8/min

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9.4.4.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (Table 25). Subjects exhibiting clinically notable ECG abnormalities will be listed. Adverse events will be reported for clinically notable abnormalities that are considered clinically significant in the judgment of the investigator.

Table 25: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

9.4.4.5. Adverse Events of Special Interest

Adverse events of special interest include treatment-emergent ALT and AST elevations and treatment-emergent AEs related to liver toxicities.

Number (%) of subjects reporting any treatment-emergent ALT and AST will be summarized by grade. Any AEs related to liver toxicity will be identified using standard MedDRA queries.

9.4.5. Pharmacokinetic Analysis

The following PK parameters, C_{max}, T_{max}, C_{min}, AUC_t, and Cl/F (see Appendix B) will be calculated from the blood plasma concentrations of INCB053914 using standard noncompartmental (model-independent) PK methods. Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin (Pharsight Corporation, Mountain View, CA). Nominal times will be used in all cases, except when the difference between the actual time and nominal time is greater than 15 minutes for samples collected up to 4 hours after administration and greater than 30 minutes for samples collected more than 4 hours after administration; in these cases, actual time will be used for PK analysis. Additional details of analyses will be described in the data analysis plan.

If there is a sufficient amount of plasma concentration data from this study, the data will be analyzed by standard population PK methods, using appropriate software (eg, NONMEM).

9.5. Interim Analysis

In Part 4, there are up to 3 planned interim analyses for futility in C-TGA E1, C-TGB E1, and an optional C-TGA E2. The Simon 2-stage design will be applied to each expansion cohort independently. During Stage 1, 13 subjects will be enrolled into each expansion cohort. If 3 or fewer of the first 13 evaluable subjects achieve an objective response, the cohort will be terminated for futility. In any cohort that exceeds this number of responders, additional subjects will be enrolled for Stage 2 evaluation.

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Based on this early termination rule, the probability of early termination is 0.7473 under the assumption of historical control response rate; the probability of early termination is 0.1686 under the assumption of desired response rate.

The interim analysis for each expansion cohort will be conducted once the first postbaseline bone marrow biopsies for Stage 1 subjects within the cohort are available. Enrollment will be held at that time unless a sufficient number of responders (> 3 responders) have been observed before that time.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted.

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  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.

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- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors, and as designated by the sponsor, will have their own data flow management plans, or study charters, or biomarker plans, as applicable.

The sponsor (or designee) will be responsible for:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF 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.
- Managing and reconciling the data generated, and/or collected including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (e.g., laboratory data, imaging data, biomarker data, photographs, diary data), or as otherwise specified in the Protocol.
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current applicable medical records must be available.
- May have responsibility for sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

10.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor, or its designee, must adhere to applicable data privacy laws and regulations. The investigator and the sponsor, or its designee, are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials will be recorded in the eCRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

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10.6. Publication Policy

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
Source: CTFG 2014.

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APPENDIX B. PHARMACOKINETIC ANALYTICAL PARAMETERS

C_{ave}	Average steady-state plasma concentration (AUC_{0-12h}/12h or AUC_{0-24h}/24h)
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration during the dosing interval
T_{max}	Time to maximum plasma concentration
AUC_{0-t}	Area under the single-dose plasma concentration-time curve from Hour 0 to the last quantifiable measurable plasma concentration, calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
$AUC_{0-\tau}$ (ie, AUC_{0-12h} or AUC_{0-24h})	Area under the steady-state plasma concentration-time curve over 1 dosing interval (ie, from Hour 0 to 12 for BID administration or from Hour 0 to 24 for QD administration), calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
λ_z	Apparent terminal phase disposition rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{½}$	Apparent plasma terminal phase disposition half-life (whenever possible), where $t_{½} = (\ln 2) / \lambda_z$
Cl/F	Oral dose clearance
V_z/F	Apparent oral dose volume of distribution
Fluctuation	Steady-state fluctuation ($[C_{max} – C_{min}]/C_{ave}$)

In addition, the following PK parameters may be calculated, whenever possible, for each subject based on the urine INCB053914 concentrations:

A_e	Amount of drug excreted in the urine over sampling interval
Cl_r	Renal clearance, where $Cl_r = A_e/AUC$
% Excreted or f_e	percent excreted in the urine, where % Excreted = 100 (A_e/dose)

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin (Pharsight Corporation, Cary, NC). Additional details of analyses will be described in the Statistical Analysis Plan.

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APPENDIX C. EASTERN COOPERATIVE ONCOLOGYGROUP (ECOG) PEFORMANCE STATUS

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al 1982.

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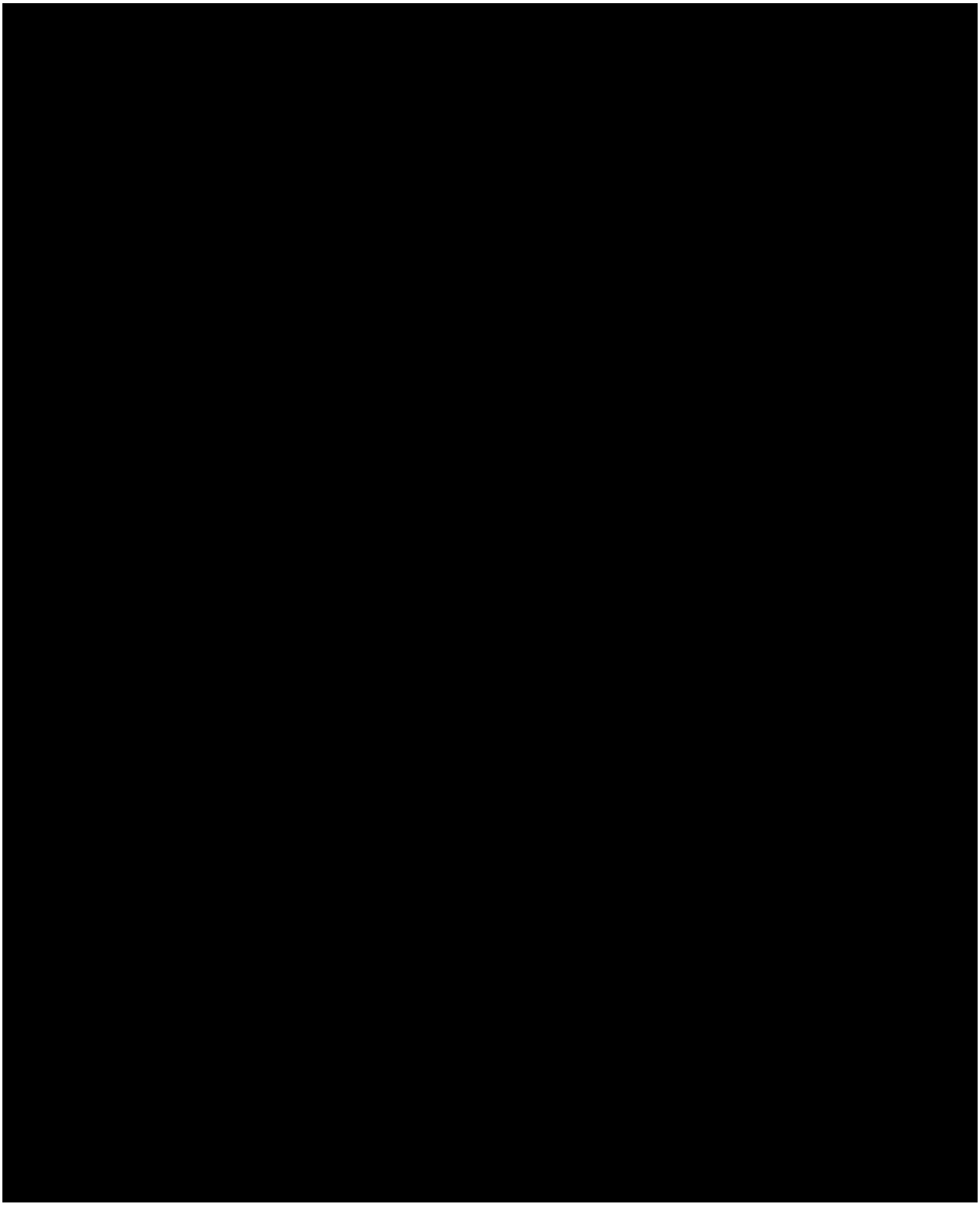
APPENDIX D. INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA

Response Category	Response Definition
Complete remission (CR)[1]	Bone marrow blasts < 5 percent; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0×10^9/L (1000/μL); platelet count >100×10^9/L (100,000/μL); independence of red cell transfusions
CR with incomplete recovery (CRi)	All CR criteria except for residual neutropenia (< 1.0×10^9/L [1000/μL]) or thrombocytopenia (< 100×10^9/L [100,000/μL])
Morphologic leukemia-free state	Bone marrow blasts < 5 percent; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent; and decrease of pretreatment bone marrow blast percentage by at least 50 percent
Cytogenetic CR (CRC)	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)	No standard definition; depends on molecular target
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi or PR (Phase 1 trials); only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse[2]	Bone marrow blasts ≥ 5 percent; or reappearance of blasts in the blood; or development of extramedullary disease

[1] All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

[2] In cases with low blast percentages (5 to 10 percent), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

Source: Cheson et al 2003.



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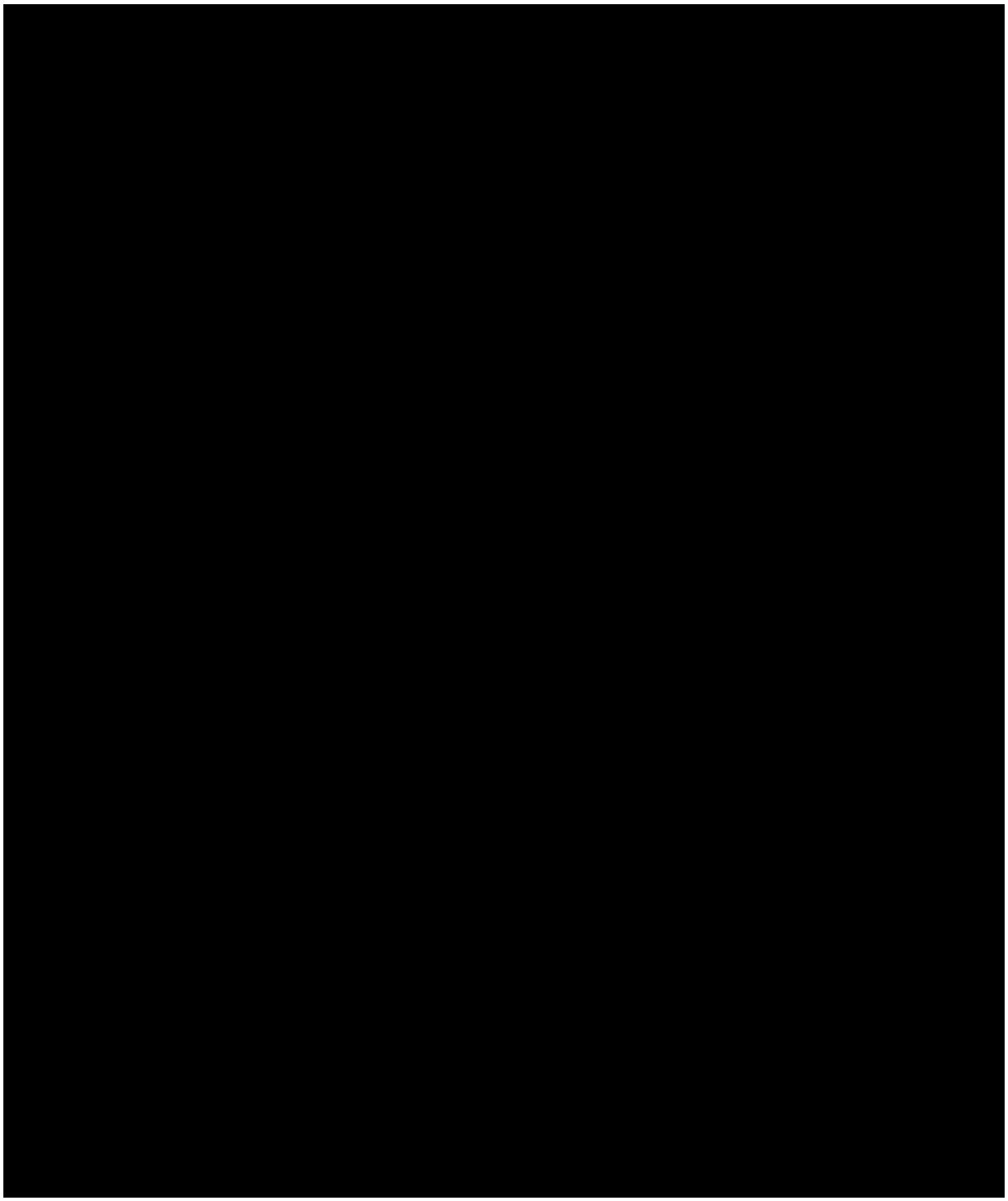

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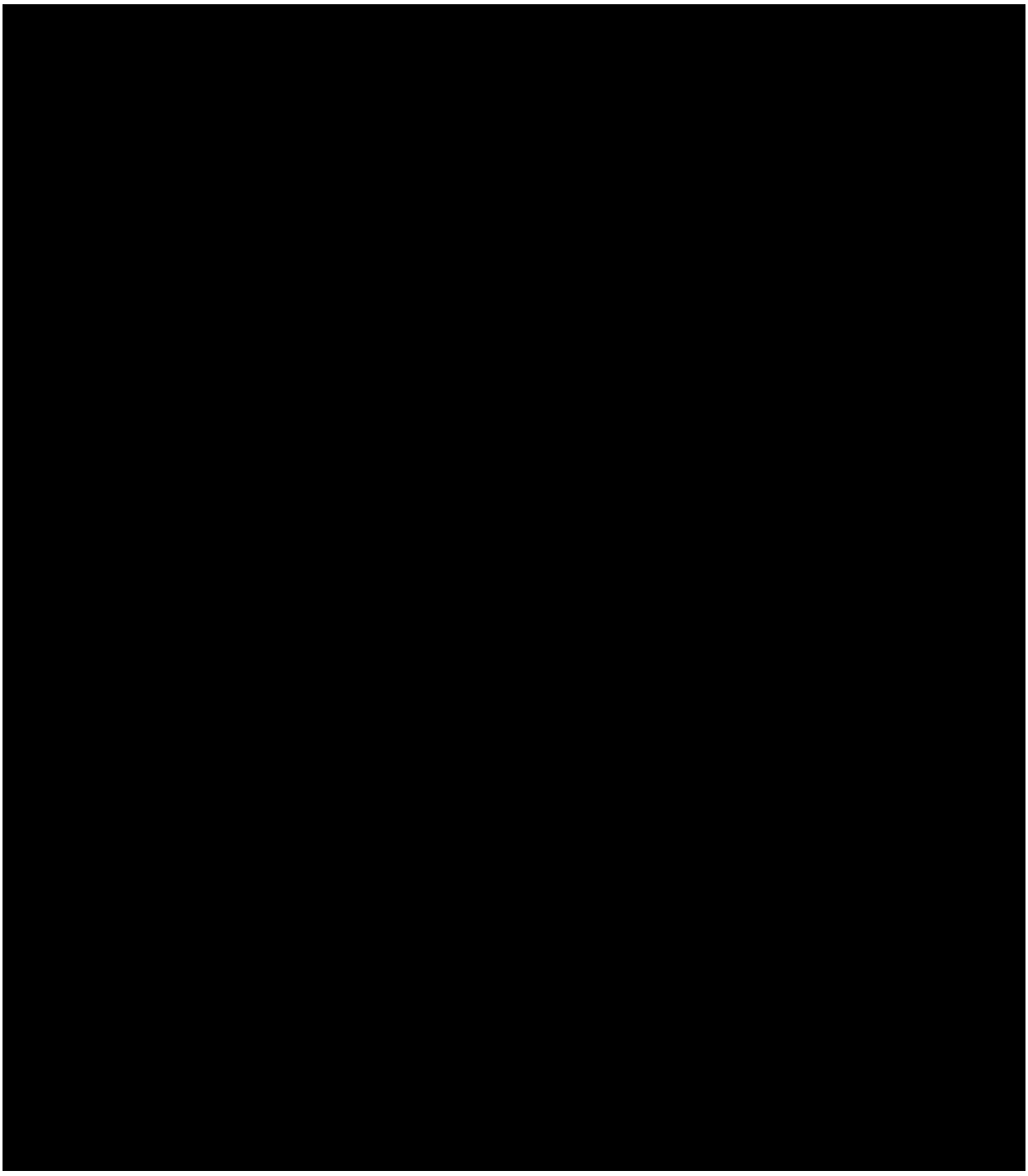

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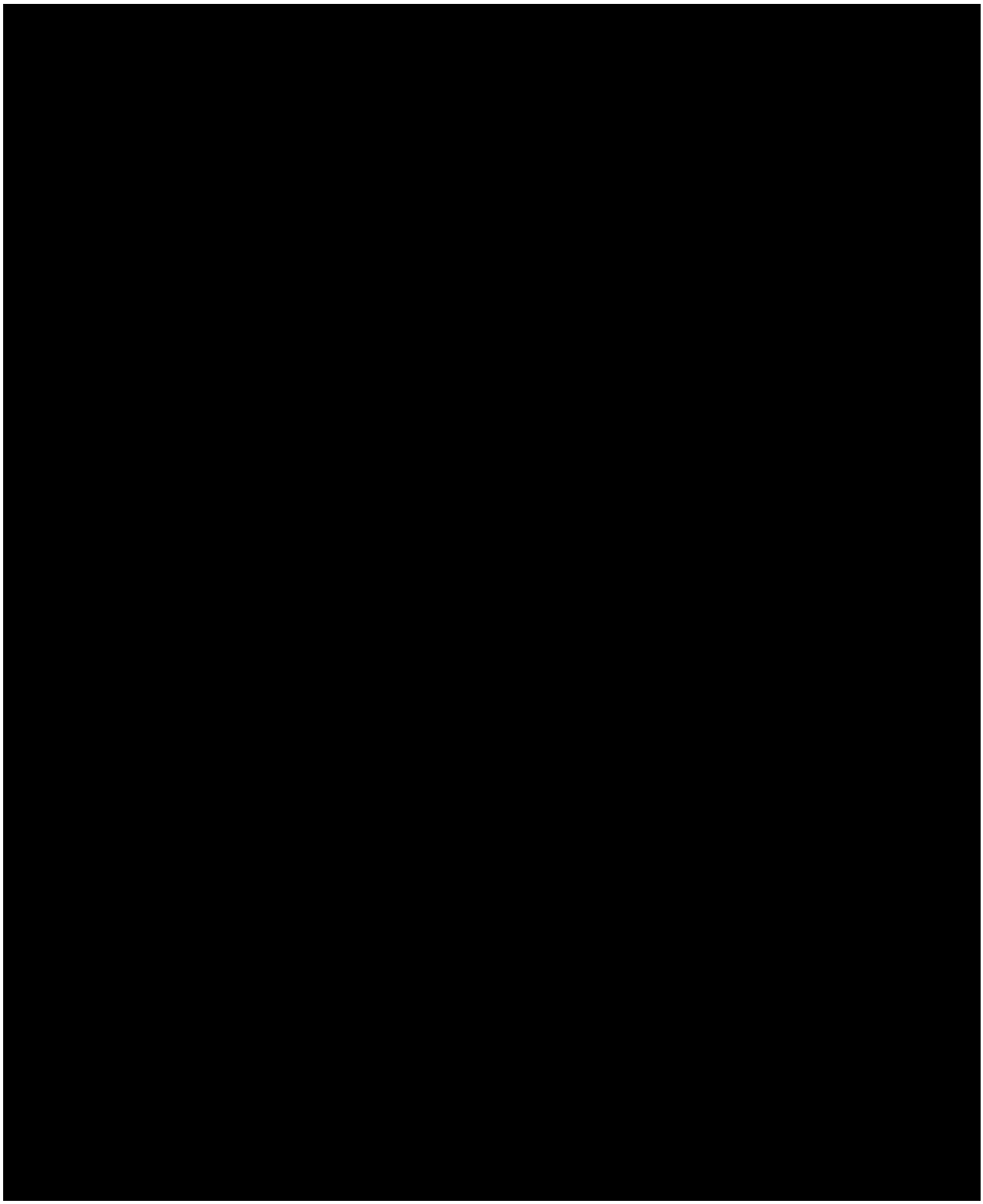

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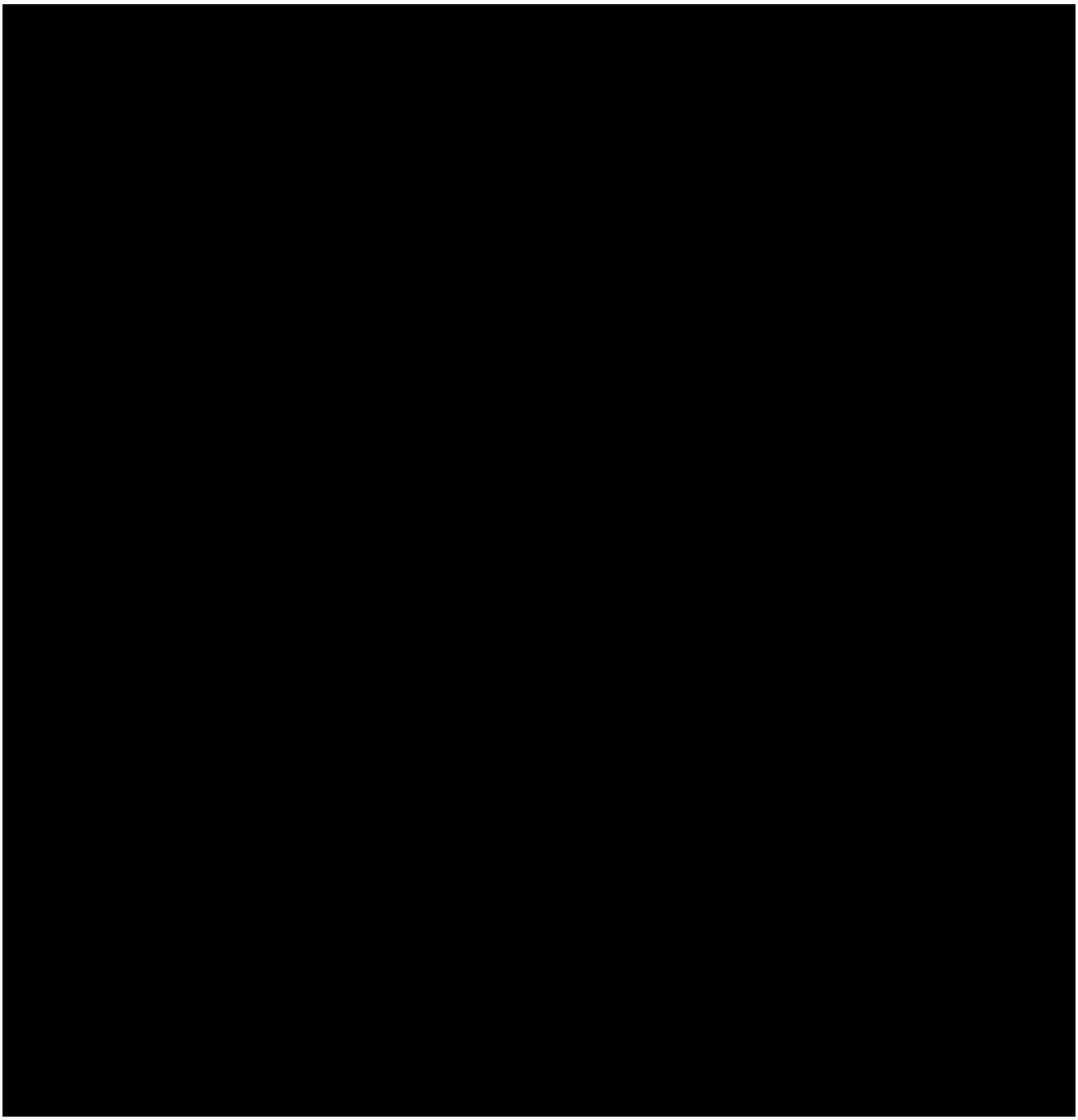

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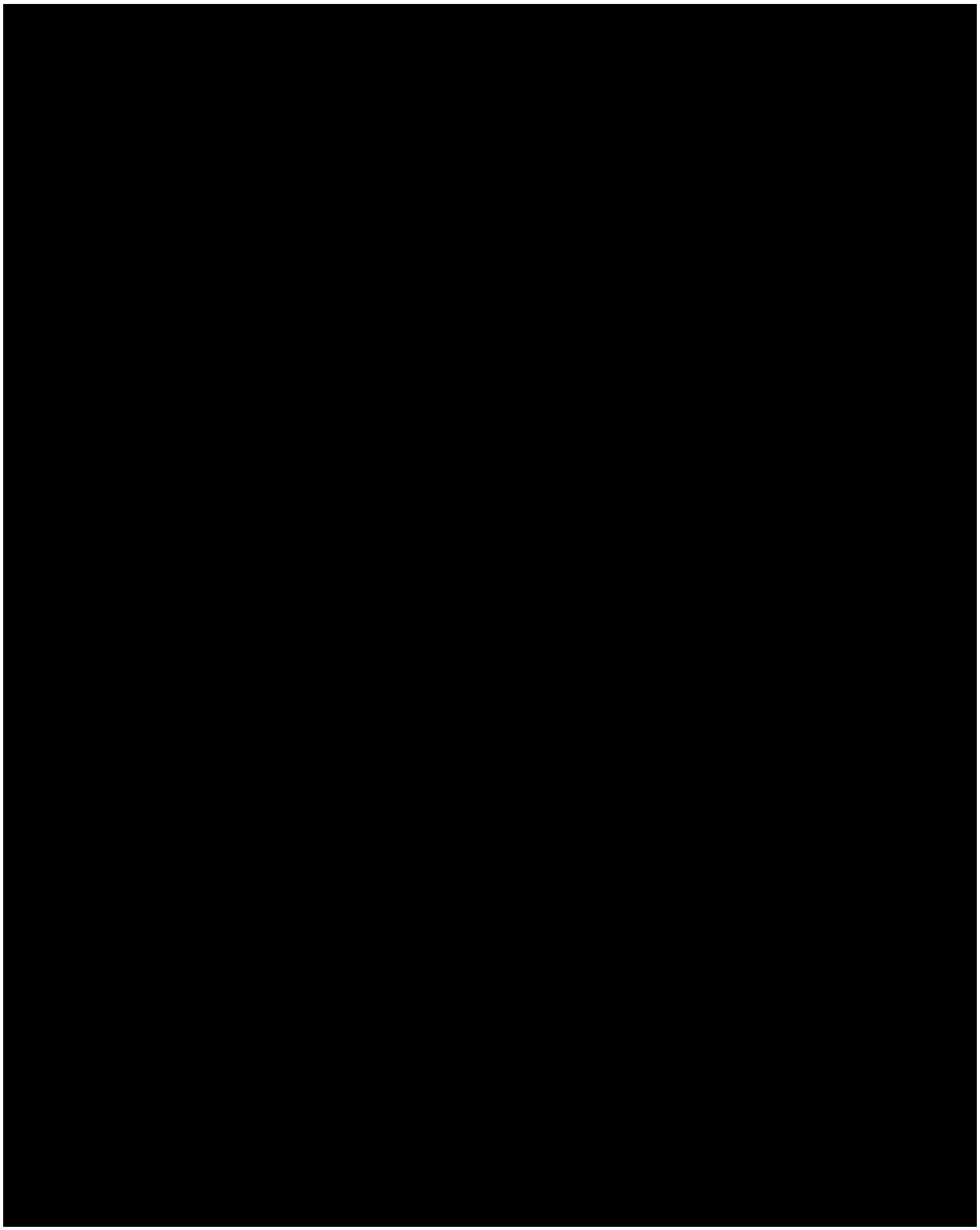

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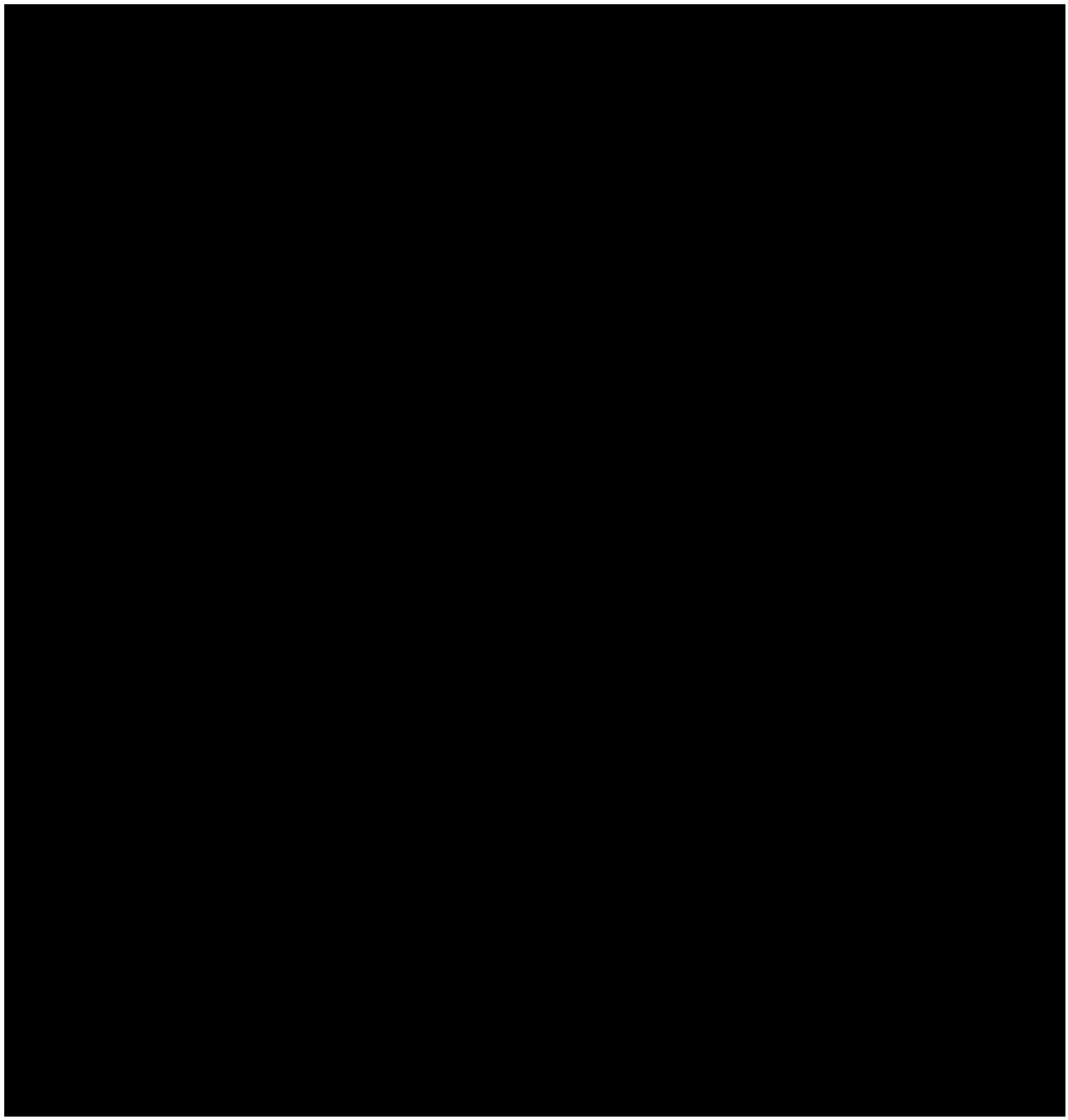

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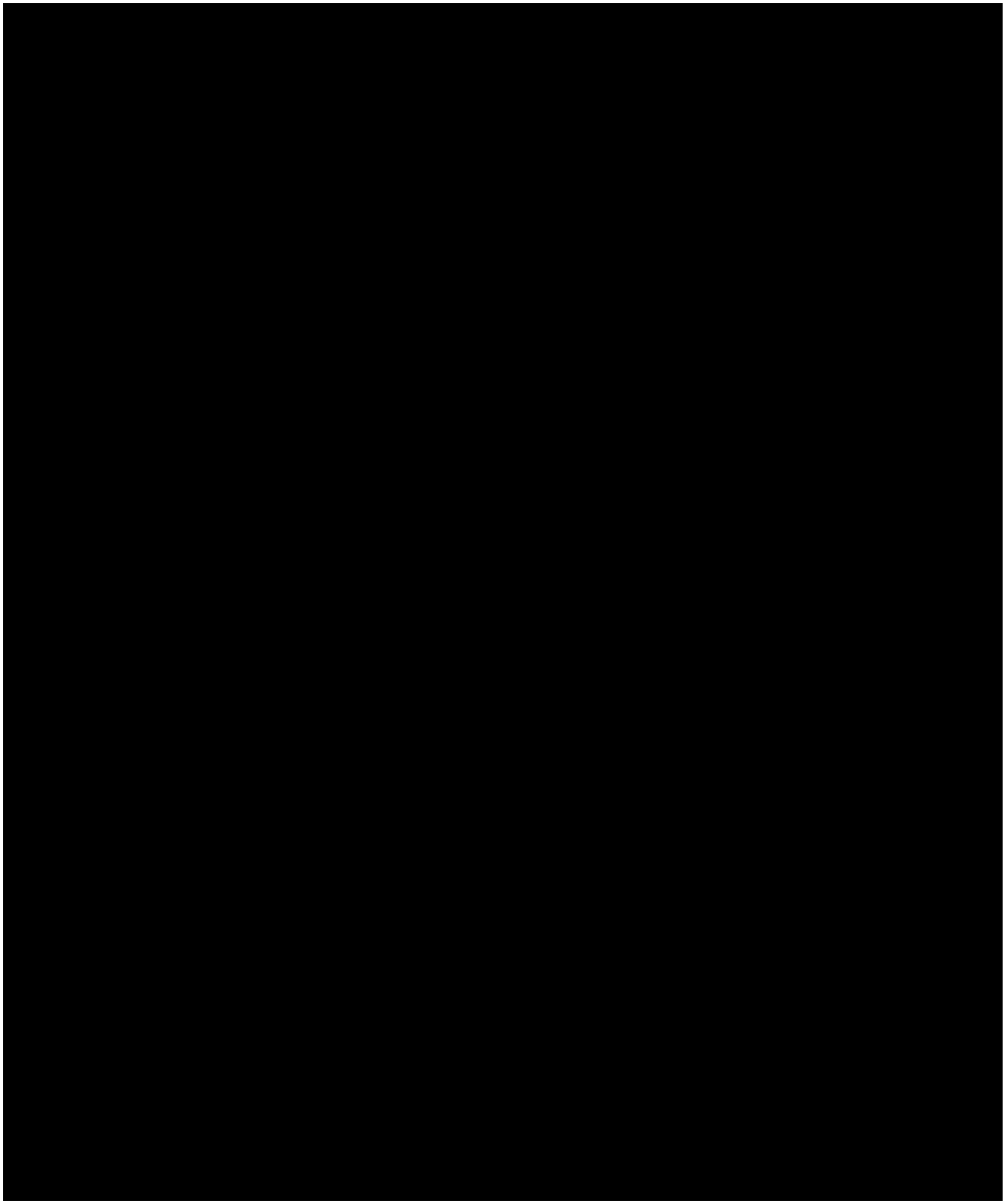

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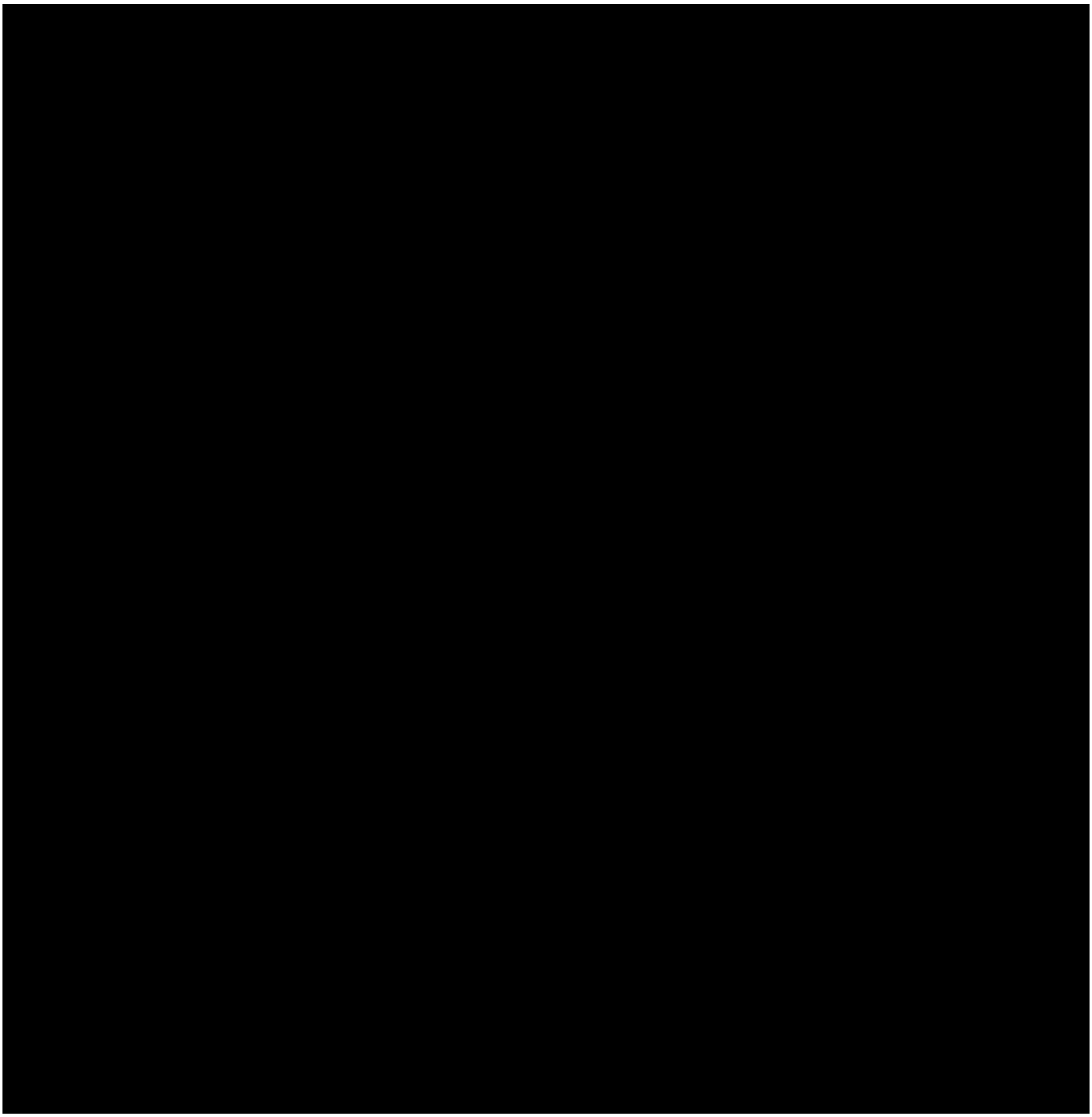

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APPENDIX M. CYTOCHROME P450 3A INHIBITORS AND INDUCERS

Source: University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed October 2016. Highlighted rows indicate recent additions to the lists at the time the database search was performed.

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In Vivo CYP3A Inhibitors

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUCr > 5)						
VIEKIRA PAK[2]	Antivirals	See note[2]	tacrolimus[2]	55.76	25708713	2015 May
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)	alfentanil	36.5	19225389	2009 Mar
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)	midazolam	26.91	20147896	2010 Jun
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h	midazolam	26.41	20002087	2009 Dec
cobicistat (GS-9350)	None	200 mg QD (14 days)	midazolam	19.03	20043009	2010 Mar
indinavir	Protease Inhibitors	800 mg TID (7 days)	vardenafil	16.25	NDA # 021400	2003 Aug
ketoconazole	Antifungals	400 mg QD (4 days)	midazolam	15.9	8181191	1994 May
troleandomycin	Antibiotics	500 mg single dose	midazolam	14.8	15536460	2004 Dec
telaprevir	Antivirals	750 mg TID (16 days)	midazolam	13.5	22162542	2012 Oct
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)	midazolam	13.42	23872824	2013 Nov
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)	midazolam	12.8	NDA # 203100	2012
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)	midazolam	12.48	19792991	2009 Oct
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)	alfentanil	11.47	24067429	2013 Dec
itraconazole	Antifungals	200 mg QD (4 days)	midazolam	10.8	8181191	1994 May
voriconazole	Antifungals	200 mg BID (9 days)	midazolam	9.63	21937987	2011 Nov
mibefradil	Calcium Channel Blockers	100 mg single dose	midazolam	8.86	14517191	2003 Oct
LCL161	Cancer Treatments	600 mg single dose	midazolam	8.8	23585187	2013 Jun
clarithromycin	Antibiotics	500 mg BID (7 days)	midazolam	8.39	16432272	2006 Feb
posaconazole	Antifungals	400 mg BID (7 days)	midazolam	6.23	19302901	2009 Feb
telithromycin	Antibiotics	800 mg QD (6 days)	midazolam	6.2	NDA# 021144	2004
grapefruit juice DS[3]	Food Products	240 mL TID (2 days) and 90 min, 60 min, 30 min prior to midazolam	midazolam	5.95	12953340	2003 Aug
conivaptan	Diuretics	40 mg BID (5 days)	midazolam	5.76	NDA # 021697	2005
nefazodone	Antidepressants	100-200 mg BID (12 days)	midazolam	5.44	14551182	2003 Nov
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	midazolam	5.29	21406602	2011 Jun
saquinavir	Protease Inhibitors	1200 mg TID (5 days)	midazolam	5.18	10430107	1999 Jul
idelalisib	Kinase Inhibitors	150 mg BID (8 days)	midazolam	5.15	25760671	2015 Aug
boceprevir	Antivirals	800 mg TID (6 days)	midazolam	5.05	NDA # 202258	2011

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Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5)						
erythromycin	Antibiotics	1000 mg single dose	midazolam	**4.99**	25139487	2014 Dec
fluconazole	Antifungals	400 mg single dose	midazolam	**4.93**	16172184	2005 Oct
atazanavir / RIT	Protease Inhibitors	300/100 mg BID	maraviroc	**4.9**	18333863	2008 Apr
darunavir	Protease Inhibitors	1200 mg BID (14 days)	saquinavir	**4.9**	NDA # 021976	2006
diltiazem	Calcium Channel Blockers	60 mg TID (2 days)	midazolam	**4.06**	21209240	2011 Nov
darunavir / RIT	Protease Inhibitors	400/100 mg BID (8 days)	sildenafil	**4.0**	NDA # 021976	2006
dronedarone	Antiarrhythmics	400 mg BID (14 days)	simvastatin	**3.66**	NDA # 022425	2009
crizotinib	Kinase Inhibitors	250 mg BID (28 days)	midazolam	**3.65**	NDA # 202570	2011
atazanavir	Protease Inhibitors	400 mg QD (7 days)	maraviroc	**3.57**	18333863	2008 Apr
aprepitant	Antiemetics	80-125 mg QD (5 days)	midazolam	**3.29**	12891225	2003 Aug
casopitant	Antiemetics	120 mg QD (14 days)	midazolam	**3.13**	20840445	2010 Oct
amprenavir	Protease Inhibitors	1200 mg BID (10 days)	rifabutin	**2.93**	11158747	2001 Feb
faldaprevir	Antivirals	240 mg BID (14 days)	midazolam	**2.92**	25449227	2015 Apr
imatinib	Antineoplastic Agents	400 mg QD (7 days)	simvastatin	**2.92**	14612892	2003 Nov
verapamil	Calcium Channel Blockers	80 mg TID (2 days)	midazolam	**2.92**	8198928	1994 Mar
netupitant	Antiemetics	300 mg single dose	midazolam	**2.44**	23729226	2013 Oct
nilotinib	Kinase Inhibitors	400 mg BID (12 days)	midazolam	**2.4**	25418605	2015 Apr
grapefruit juice	Food Products	240 mL QD (4 days)	midazolam	**2.39**	10546919	1999 Oct
tofisopam	Benzodiazepines	100 mg TID (9 days)	midazolam	**2.36**	17989974	2008 Jan
cyclosporine	Immunosuppressants	Not provided (1-5 years)	midazolam	**2.21**	21753749	2011 Sep
ACT-178882	Renin Inhibitors	300 mg QD (14 days)	midazolam	**2.19**	22849770	2013 Dec
ciprofloxacin[4]	Antibiotics	500 mg single dose	sildenafil	**2.12**	16372380	2005 Dec
schisandra sphenanthera	Herbal Medications	3 capsules (= 11.25 mg deoxyschizandrin) BID (7 days)	midazolam	**2.05**	19552749	2009 May
isavuconazole	Antifungals	clinical dose (detail not provided)	midazolam	**2.03**	NDA # 207500	2015
cimetidine	H-2 Receptor Antagonists	200-400 mg QID (1.5 days)	midazolam	**2.02**	6152615	1984 Sep
FK1706	Central Nervous System Agents	60 mg QD (14 days)	midazolam	**2.01**	19889885	2010 Feb

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Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)						
tabimorelin	Hormone Replacement	2.86-3.21 mg QD (7 days)	midazolam	1.93	12610745	2003 Feb
ranolazine	Cardiovascular Drugs	1000 mg BID (7 days)	simvastatin	1.89	NDA # 021526	2006
amlodipine	Calcium Channel Blockers	10 mg QD (9 days)	simvastatin	1.8	23965645	2014 Apr
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	1.77	24734312	2014 Mar
fosaprepitant (IV)	Antiemetics	150 mg single 30-min infusion	midazolam	1.76	21209230	2011 Dec
Seville orange juice	Food Products	240 mL single dose	felodipine	1.76	11180034	2001 Jan
amiodarone	Antiarrhythmics	400 mg QD (4 days)	simvastatin acid	1.76	17301736	2007 May
chlorzoxazone	Muscle Relaxants	250 mg single dose (part of a 6-drug cocktail)	midazolam	1.68	11736864	2001 Nov
M100240	Antihypertensive Agents	50 mg single dose	midazolam	1.66	15051745	2004 Apr
fluvoxamine	Antidepressants	50-00 mg BID (12 days)	midazolam	1.66	14551182	2003 Nov
ranitidine	H-2 Receptor Antagonists	150 mg BID (1.5 days)	midazolam	1.66	6135440	1983 Jun
fostamatinib[5]	Anti-inflammatory Drugs	100 mg BID (7 days)	simvastatin	1.64	26748647	2016 Mar
goldenseal	Herbal Medications	1,323 mg (= 24.1 mg isoquinoline alkaloids) TID (14 days)	midazolam	1.63	17495878	2008 Jan
clotrimazole	Antifungals	10 mg TID (5 days)	midazolam	1.61	20233179	2010 Feb
tacrolimus	Immunosuppressants	Not provided (1-5 years)	midazolam	1.61	21753749	2011 Sep
palbociclib	Kinase Inhibitors	125 mg QD (8 days)	midazolam	1.58	NDA # 207103	2015
cilostazol	Antiplatelets	100 mg BID (7 days)	lovastatin	1.56	10702889	1999
ticagrelor	Antiplatelets	180 mg bid (7 days)	simvastatin	1.56	NDA # 022433	2011
peppermint oil	Food Products	600 mg (= 300 uL peppermint oil) single dose	felodipine	1.55	12235445	2002 Sep
ivacaftor	Cystic fibrosis treatments	150 mg BID (6 days)	midazolam	1.54	25103957	2015 Jan
GSK2248761	Transcriptase Inhibitors	100 mg QD (12 days)	midazolam	1.54	22288567	2012 Aug
Guan Mai Ning	Herbal Medications	3 tablets TID (7 days)	simvastatin	1.51	25801058	2015 Sep
AZD2327	Depression Treatments	15 mg QD (7 days)	midazolam	1.49	26081137	2015 Nov
resveratrol	Food Products	500 mg QD (10 days)	carbamazepine	1.48	25624269	2015 May
roxithromycin	Antibiotics	300 mg QD (6 days)	midazolam	1.47	7995324	1994
suvorexant	Hypnotics - Sedatives	80 mg QD (14 days)	midazolam	1.47	NDA # 204569	2014
propiverine	Anticholinergics	15 mg BID (7 days)	midazolam	1.46	16183781	2005 Dec
isoniazid	Antibiotics	90 mg BID (4 days)	triazolam	1.46	6140941	1983 Dec
berberine	Herbal Medications	300 mg TID (14 days)	midazolam	1.45	21870106	2012 Feb
oral contraceptives	Oral contraceptives	OC with low doses of estrogen (< 35 ug ethinylestradiol) (> 3 months)	triazolam	1.44	6149030	1984 Nov
delavirdine	NNRTIs	400 mg TID (9 days)	indinavir	1.44	9665503	1998 Jul
daclatasvir	Antivirals	60 mg QD (7 days)	simeprevir	1.44	NDA # 205123	2013
simeprevir	Protease Inhibitors	150 mg QD (11 days)	midazolam	1.43	NDA # 205123	2013
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	10-40 mg/day (chronic treatment)	midazolam IV	1.41	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	60 mg single dose	lovastatin	1.41	NDA # 022275	2009
almorexant	Hypnotics - Sedatives	200 mg QD (9 days)	midazolam	1.37	22990330	2013 Mar
GSK1292263	Other Antilipemics	300 mg BID (9 days)	simvastatin	1.36	23256625	2013 Jun
evacetrapid	CETP inhibitors	300 mg QD (15 days)	midazolam	1.35	26264702	2015 Dec
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	10 mg QD (6 days)	simvastatin	1.34	20497745	2010 Jun
grazoprevir *(ingredient of Zepatier)*	Antivirals	200 mg QD (7 days)	midazolam	1.34	NDA # 208261	2016
lacidipine	Calcium Channel Blockers	4 mg QD (8 days)	simvastatin	1.33	11259986	2001 Feb
cranberry juice	Food Products	240 mL double strength juice, 1 glass q 15 min x 3	midazolam	1.33	19114462	2009 Mar
pazopanib	Kinase Inhibitors	800 mg QD (17 days)	midazolam	1.32	20881954	2010 Nov
everolimus	Immunosuppressants	10 mg QD (5 days)	midazolam	1.31	23426978	2013 Apr
blueberry juice	Food Products	two doses of 300 mL, separated by 16 hours	buspirone	1.31	22943633	2013 Apr
flibanserin	Central Nervous System Agents	50 mg BID (4 days)	simvastatin	1.31	NDA # 022526	2015
AMD070	Fusion Inhibitors	200 mg BID (8 days)	midazolam	1.29	18362694	2008 Apr

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alprazolam	Benzodiazepines	1 mg TID (7 days)	buspirone	1.29	8300893	1993 Nov
Tong Xin Luo	Herbal Medications	4 capsules TID (7 days)	simvastatin	1.29	25801058	2015 Sep
bicalutamide	Antiandrogens	150 mg QD (>3 months)	midazolam	1.27	15509184	2004
sitaxentan	Endothelin Receptor Antagonists	100 mg QD (7 days)	sildenafil	1.27	20078609	2010 Jan
azithromycin	Antibiotics	500 mg QD (3 days)	midazolam	1.27	8720318	1996 Feb
ginkgo	Herbal Medications	120 mg TID (28 days)	midazolam	1.25	17050793	2006 Nov
teriflunomide	Other Immunomodulators	14-70 mg QD (14 days)	midazolam	1.25	NDA # 202992	2012

[1] To allow better comparability, DDI studies with the probe substrate midazolam were selected first.
When no study with midazolam was available, the AUCratio of another probe or sensitive substrate is presented.
[2] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days. Tacrolimus is also a substrate of OATP1B1/1B3 that can be inhibited by Viekira Pak.
[3] 240 mL GFJ double-strength administered TID for 3 days
[4] Of note, co-administration of ciprofloxacin (750 mg BID for 7 days) did not affect plasma concentrations of ivacaftor, which is also a sensitive substrate for CYP3A (KALYDECO Prescribing Information).
[5] Fostamatinib also inhibits BCRP, and BCRP inhibition likely participates to the increase in exposure of simvastatin

In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)	PMID or NDA #	Published
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))							
rifampin	Antibiotics	budesonide	99.7	36904.5	600 mg QD (7 days)	15726657	2005 Mar
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)	21220434	2011 Apr
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)	12766253	2003 Sep
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)	8917062	1996 Nov
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)	16390352	2006 Jan
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)	NDA # 203415	2012
St John's Wort extract	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)	16341856	2006 Jan
rifabutin	Antibiotics	delavirdine	Not Provided	458.0	300 mg QD (14 days)	9224961	1997 Jun
phenobarbital	Anticonvulsants	verapamil	76.6	400.9	100 mg QD (21 days)	3392664	1988 Jul
Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%))							
ritonavir and St. Johns wort	None	midazolam	77.2	Not Provided	ritonavir: 300 mg BID and SJW: 300 mg TID (14 days)	19924124	2010 Feb
semagacestat	Alzheimer's Treatments	midazolam	76.4	324.6	140 mg QD (10 days)	22789530	2012 Oct
efavirenz	NNRTIs	alfentanil	76	369.4	600 mg QD (20 days)	22398970	2012 Apr
tipranavir and ritonavir	Protease Inhibitors	saquinavir	75.6	Not Provided	tipranavir: 500 mg and ritonavir: 200 mg BID (14 days)	18176328	2008 Apr
bosentan	Endothelin Receptor Antagonists	sildenafil	69.0	239.8	62.5-125 mg BID (8 weeks)	15963102	2005 Jul
genistein	Food Products	midazolam	13.7	136.9	1000 mg QD (14 days)	21943317	2012 Feb
thioridazine	Antipsychotics	quetiapine	68.7	104.5	100-300 mg QD (15 days)	22569350	2012 Jun
nafcillin	Antibiotics	nifedipine	62.6	145.1	500 mg 4 times daily (5 days)	12814453	2003 Jun
talviraline	NNRTIs	indinavir	61.7	181.2	500 mg TID (14 days)	10516944	1999 Oct
lopinavir	Protease Inhibitors	amprenavir	59.7	Not Provided	400 mg BID (4 weeks)	15060509	2004 Apr
modafinil	Psychostimulants	triazolam	57.6	35.7	200-400 mg QD (28 days)	11823757	2002 Jan
etravirine	NNRTIs	sildenafil	56.7	Not Provided	800 mg BID (13.5 days)	NDA# 022187	2008
lersivirine	NNRTIs	midazolam	51.4	105.5	1000 mg BID (14 days)	22527351	2012 Nov

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Weak Inducers (AUC decreased by 20-50% or CL increased by 20-100% (less than 2 fold))							
eslicarbazepine	Anticonvulsants	simvastatin	**49.4**	**98.4**	800 mg QD (14 days)	23726291	2013 Sep
telaprevir	Antivirals	darunavir	**48.4**	Not Provided	1125 mg BID (4 days)	NDA# 201917	2011
garlic	Food Products	saquinavir	**44.7**	Not Provided	caplet of GarliPure BID (20 days)	11740713	2002 Jan
bexarotene	Other Antineoplastics	atorvastatin	**45.3**	Not Provided	400 mg/m2 QD (at least two 4-week cycles)	22057855	2012 Feb
artesunate and mefloquine	Antimalarials	lopinavir	**43.1**	**75.4**	4 mg/kg QD artesunate on Days 1-3 + 750 mg mefloquine on Day 1 and 500 m	26452725	2015
amprenavir (fosamprenavir)	Protease Inhibitors	lopinavir	**43.0**	Not Provided	700 mg BID (2-4 weeks)	15668539	2005 Jan
raltegravir	HIV-Integrase Strand Transfer Inhibitors	darunavir	**42.0**	Not Provided	400 mg BID	21958880	2012 Feb
lesinurad	Antigout and Uricosuric Agents	amlodipine	**41.9**	**72.5**	400 mg QD (24 days)	NDA # 207988	2015
vemurafenib	Kinase Inhibitors	midazolam	**39.4**	Not Provided	960 mg BID (15 days)	NDA # 202429	2011
troglitazone	Thiazolidinediones	simvastatin	**37.7**	Not Provided	400 mg QD (24 days)	11361054	2001 May
sorafenib	Kinase Inhibitors	sirolimus	**36.9**	Not Provided	200 mg BID (11 days)	21045832	2010 Nov
rufinamide	Anticonvulsants	triazolam	**36.7**	**53.4**	400 mg BID (11.5 days)	NDA # 021911	2008
sirukumab* **	Immunomodulators Biologics	midazolam	**35.7**	Not Provided	300 mg single dose subcutaneously	26054042	2015 Dec
pleconaril	Antivirals	midazolam	**34.6**	**52.8**	400 mg TID (6 days)	16467135	2006 May
ginseng	Herbal Medications	midazolam	**34.2**	**50.7**	500 mg BID (28 days)	21646440	2012 Jun
boceprevir	Antivirals	darunavir	**34.2**	**41.0**	800 mg every 8 hrs (6 days)	23155151	2013 Mar
sulfinpyrazone	Antigout and Uricosuric Agents	cyclosporine	**33.9** (change in C_{avg})		200 mg/day	11124491	2000 Dec
ginkgo	Herbal Medications	midazolam	**33.7**	**52.6**	120 mg BID (28 days)	18205997	2008 Feb
vinblastine	Vinca Alkaloids	midazolam IV	**33.2**	**48.8**	not provided (4 cycles)	20959500	2010 Nov
nevirapine	NNRTIs	indinavir	**32.5**	Not Provided	200 mg QD (14 days), then BID (19 days)	10191212	1999 May
armodafinil (R-modafinil)	Psychostimulants	midazolam	**32.2**	**54.7**	100-250 mg/day (31 days)	18076219	2008
ticagrelor	Anticoagulants and Antiplatelets	midazolam	**31.7**	**46.5**	400 mg QD (6 days)	23870610	2013 Jul
LCL161	Cancer Treatments	midazolam	**29.8**	**34.0**	600 mg single dose	23585187	2013 Jun

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vicriviroc and ritonavir	Treatments of AIDS	ethinyl estradiol	**29.4**	Not Provided	30 mg vicriviroc and 100 mg ritonavir QD (10 days)	22015327	2011 Oct
ritonavir	Protease Inhibitors	ethinyl estradiol	**29.2**	Not Provided	100 mg QD (10 days)	22015327	2011 Oct
prednisone	Corticosteroids	tacrolimus	**29.0**	Not Provided	1.5 mg/kg/day	15787787	2005 Apr
oxcarbazepine	Anticonvulsants	felodipine	**28.1**	Not Provided	450 mg BID (7 days)	8451779	1993 Feb
danshen	Herbal Medications	midazolam	**27.9**	**32.8**	4 g TID (14 days)	20565457	2010 Jun
clobazam	Benzodiazepines	midazolam	**27.7**	Not Provided	40 mg QD (15 days)	22422635	2012 Apr
echinacea	Herbal Medications	midazolam	**27.3**	**37.5**	500 mg TID (28 days)	20653355	2010 Aug
ticlopidine	Anticoagulants and Antiplatelets	alfentanil	**27.0**	**50.0**	250 mg BID (4 days)	23361846	2013 Mar
isavuconazole	Antifungals	lopinavir	**27.0**	Not Provided	not provided (clinical dose)	NDA # 207500	2015
brivaracetam	Anticonvulsants	ethinyl estradiol	**26.8**	**37.3**	200 mg BID (21 days)	24386664	2013 Dec
Stribild*	Treatments of AIDS	ethinyl estradiol	**26.2**	**31.3**	150 mg ELV + 150 mg COB + 200 mg EMT+ 300 mg TEN	NDA # 203100	2012
pioglitazone	Thiazolidinediones	midazolam	**26.0**	Not Provided	45 mg QD 7 days	Actos® Product Label	2004 Aug
VIEKIRA PAK**	Antivirals	darunavir	**25.7**	Not Provided	See note**	NDA # 206619	2014
dexamethasone	Corticosteroids	aprepitant	**25.0**	Not Provided	8 mg/day (5 days)	NDA # 021549	2003
terbinafine	Antifungals	midazolam	**24.5**	Not Provided	250 mg QD (4 days)	8527290	1995 Sep
quercetin	Food Products	midazolam	**23.6**	Not Provided	500 mg QD (13 days)	21680781	2012 Jun
glycyrrhizin	Herbal Medications	midazolam	**23.0**	Not Provided	150 mg BID (15 days)	20393696	2010 Aug
aprepitant	Neurokinin-1 Receptor Antagonists	midazolam IV	**22.1**	**28.5**	125/80 mg QD (3 days)	14973304	2004 Mar
pretomanib (PA-824)	Antibiotics	midazolam	**22.1**	**20.7**	400 mg QD (14 days)	23689718	2013 Aug
oritavancin	Antibiotics	midazolam	**18.7**	**23.9**	1200 mg IV single infusion	NDA # 206334	2014
AZD 7325	Anxiolytics	midazolam	**18.7**	**22.6**	10 mg QD (12 days)	22122233	2012 Jul
methylprednisolone	Corticosteroids	cyclosporine	**15.8**	**35.0**	16 mg/day (12 days) then 8 mg/day (6 months)	12164891	2002 Sep
topiramate	Anticonvulsants	ethinyl estradiol	**12.0**	**20.2**	50 mg/day (21 days)	12681003	2003 Apr

1- Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity.
2- All the substrates presented in the table are sensitive CYP3A substrates (see definition in FDA guidance) except verapamil, cyclosporine, ethinyl estradiol, and delavirdine.

* **Stribild** is a combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF
** VIEKIRA PAK = paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD + dasabuvir 250 mg BID for 14 days
*** Sirukumab is not a CYP inducer per se. It reverses the IL-6 mediated suppression of CYP3A activity in patients with active rheumatoid arthritis

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APPENDIX N. P-GLYCOPROTEIN SUBSTRATES

Co-administration with INCB053914 not recommended	
• cyclosporin	• saquinavir
• everolimus	• sirolimus
• itraconazole	• tacrolimus
• ritonavir	• tenofovir
Potential for increased oral absorption with these drugs cannot be ruled out and therefore caution should be exercised when used in combination with INCB053914	
• aliskiren	• mirabegron
• ambrisentan	• morphine
• apixaban	• nadolol
• *atorvastatin*	• naloxegol
• azithromycin	• nevirapine
• buprenorphine	• paroxetine
• celiprolol	• pilsicainide
• cerivastatin	• prednisolone
• cetirizine	• prednisone
• dabigatran etexilate	• proguanil
• dicloxacillin	• quinidine
• digoxin	• ranitidine
• domperidone	• ranolazine
• edoxaban	• risperidone
• erythromycin	• simvastatin
• ezetimibe	• sotrastaurin
• fexofenadine	• tedisamil
• lapatinib	• teneligliptin
• ledipasvir	• ticagrelor
• linezolid	• umeclidinium
• loperamide	• verapamil
• maraviroc	• voclosporin
• methylprednisolone	• ximelagatran

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APPENDIX O. SCREENING SYMPTOM FORM

Instructions to Subjects: Please answer all questions to the best of your ability, based on your memory **over the past 7 days (1 week)**. There is no right or wrong answer.

1. During the past 7 days, how severe were your worst night sweats (or feeling hot or flushed) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2. During the past 7 days, how severe was your worst itchiness due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3. During the past 7 days, how severe was your worst abdominal discomfort (feel uncomfortable, pressure or bloating) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
4. During the past 7 days, how severe was your worst pain under the ribs on the left side due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
5. During the past 7 days, what was the worst feeling of fullness (early satiety) you had after beginning to eat, due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
6. During the past 7 days, how severe was your worst bone or muscle pain due to MF (diffuse, not joint or arthritis pain)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
7. During the past 7 days, what was the worst degree of inactivity (including work and social activities) you had due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Investigators/Site Staff:

Please complete the table below to confirm the criterion used to confirm the subject's eligibility in the trial based on an assessment of his/her active symptoms of myelofibrosis.

ELIGIBILITY CRITERION	CONFIRMATION
A symptom score of at least 5 on at least 1 of the symptoms	□ Yes □ No
A symptom score of 3 or greater on at least 2 of the symptoms	□ Yes □ No

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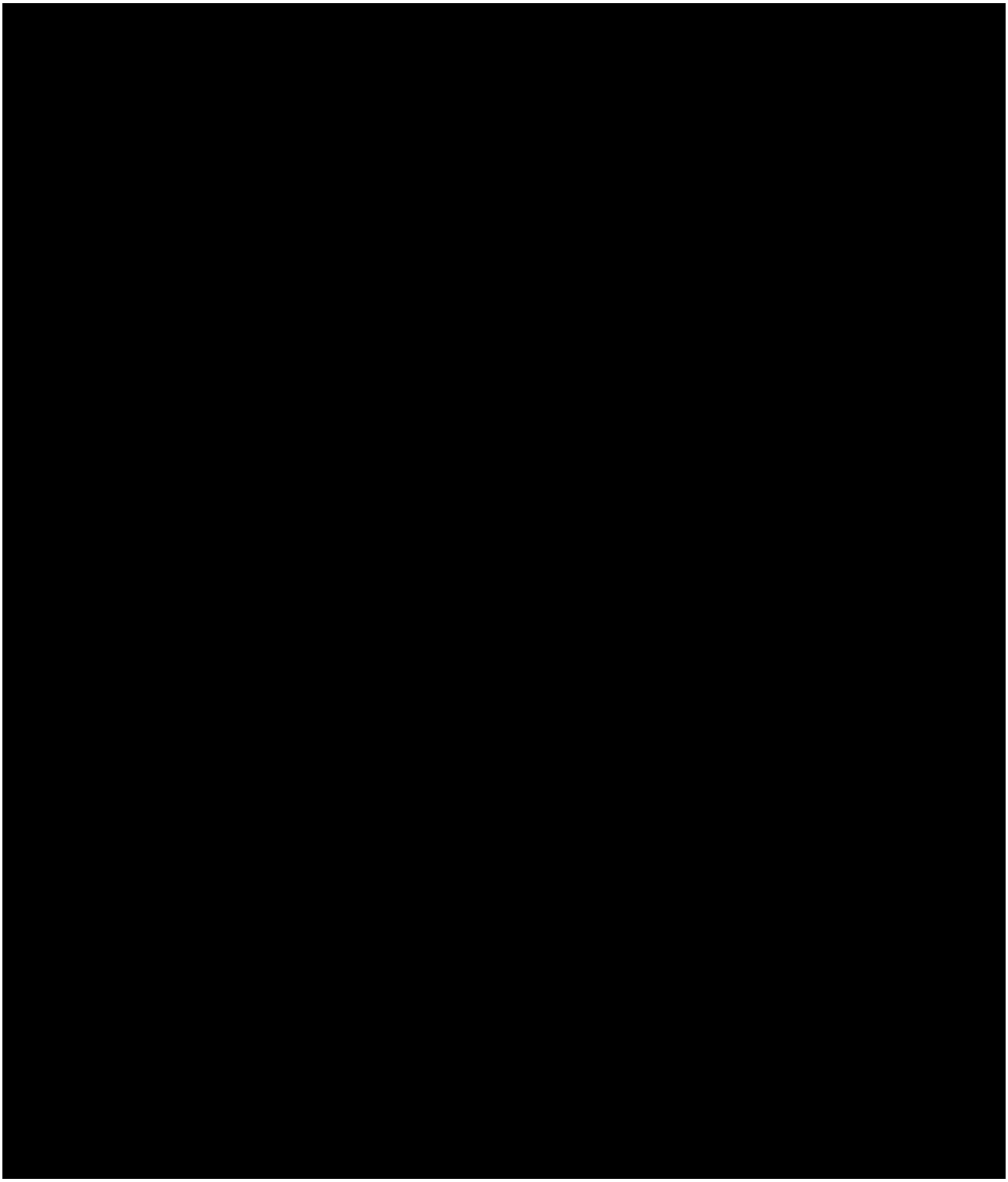

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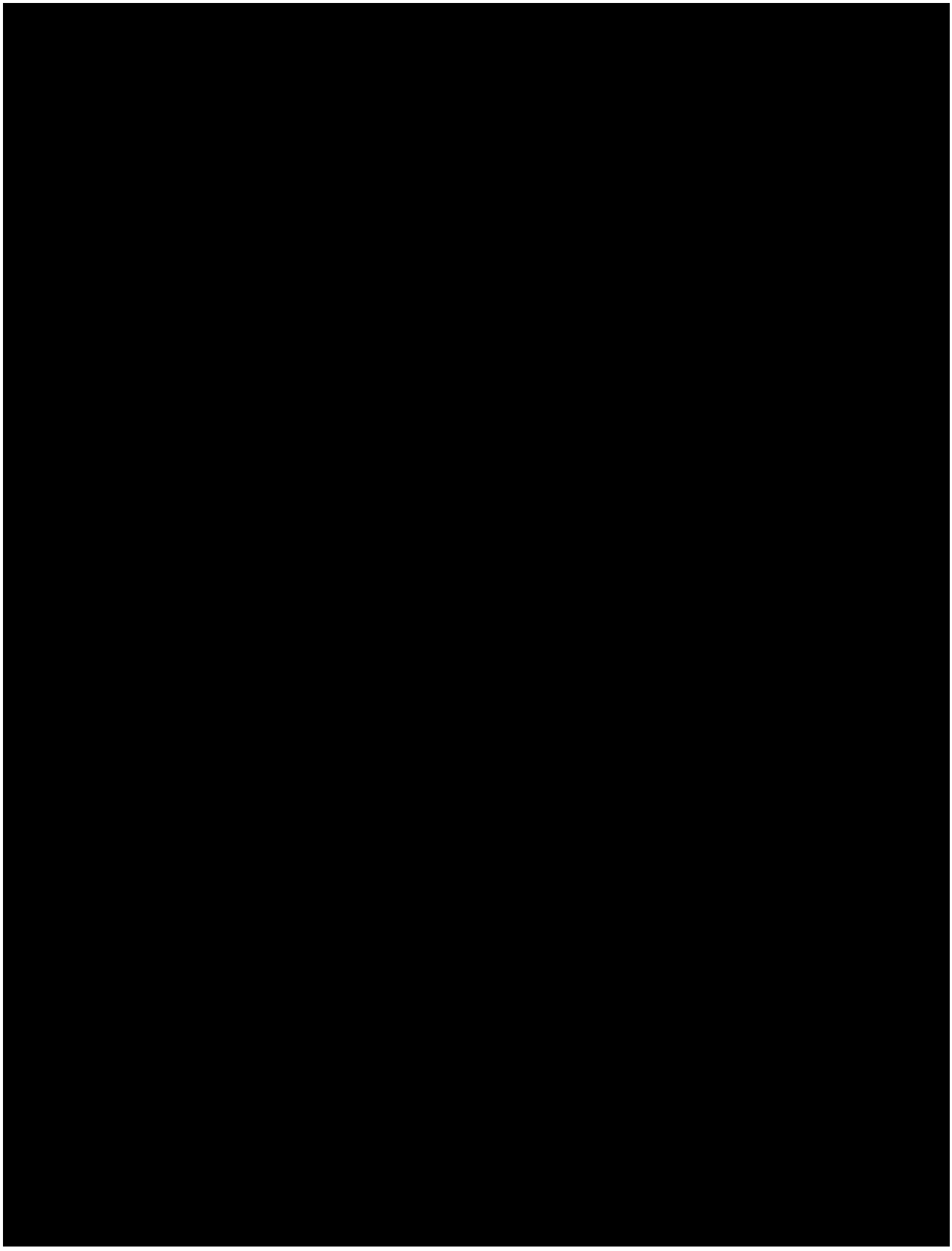

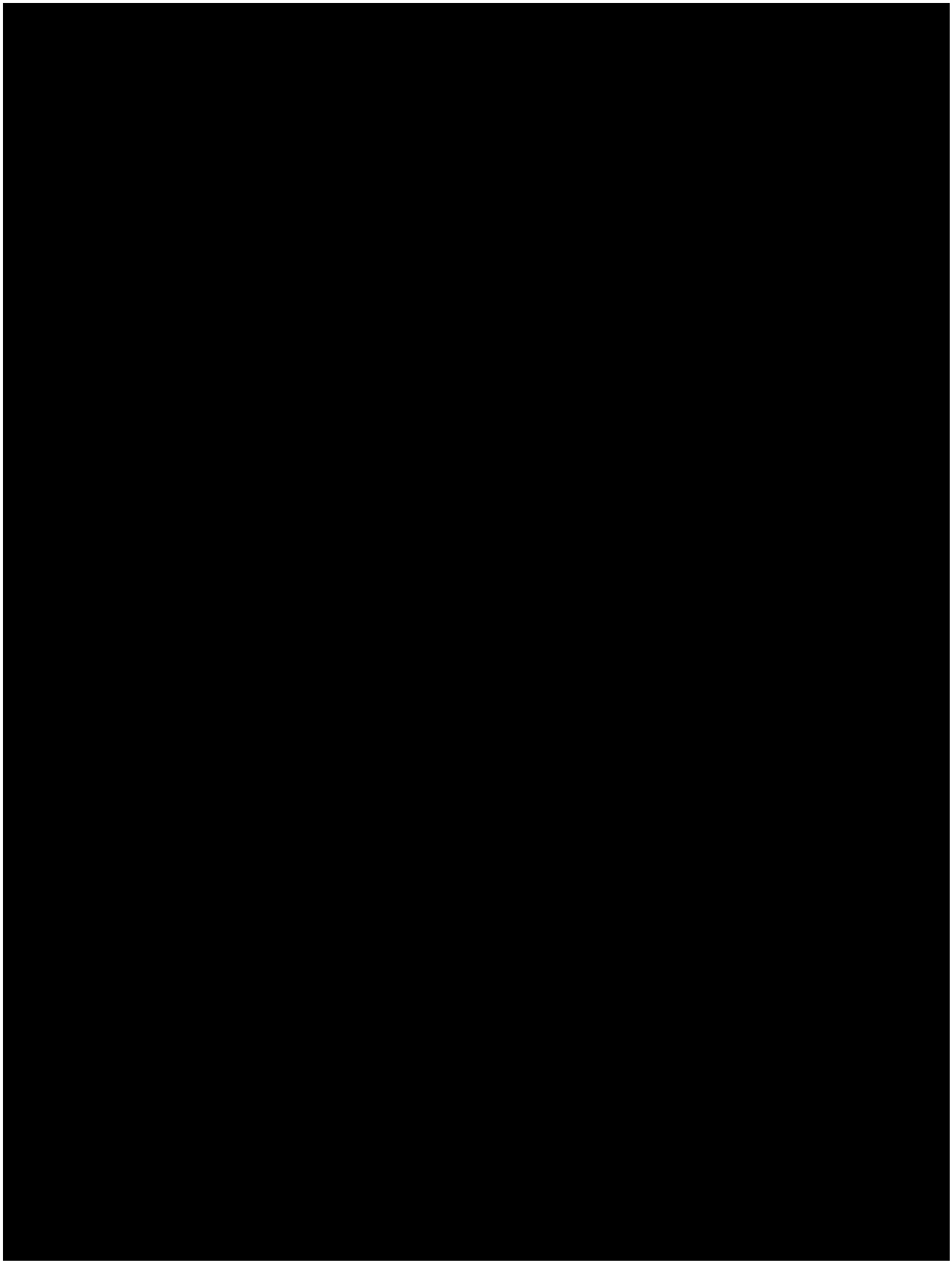

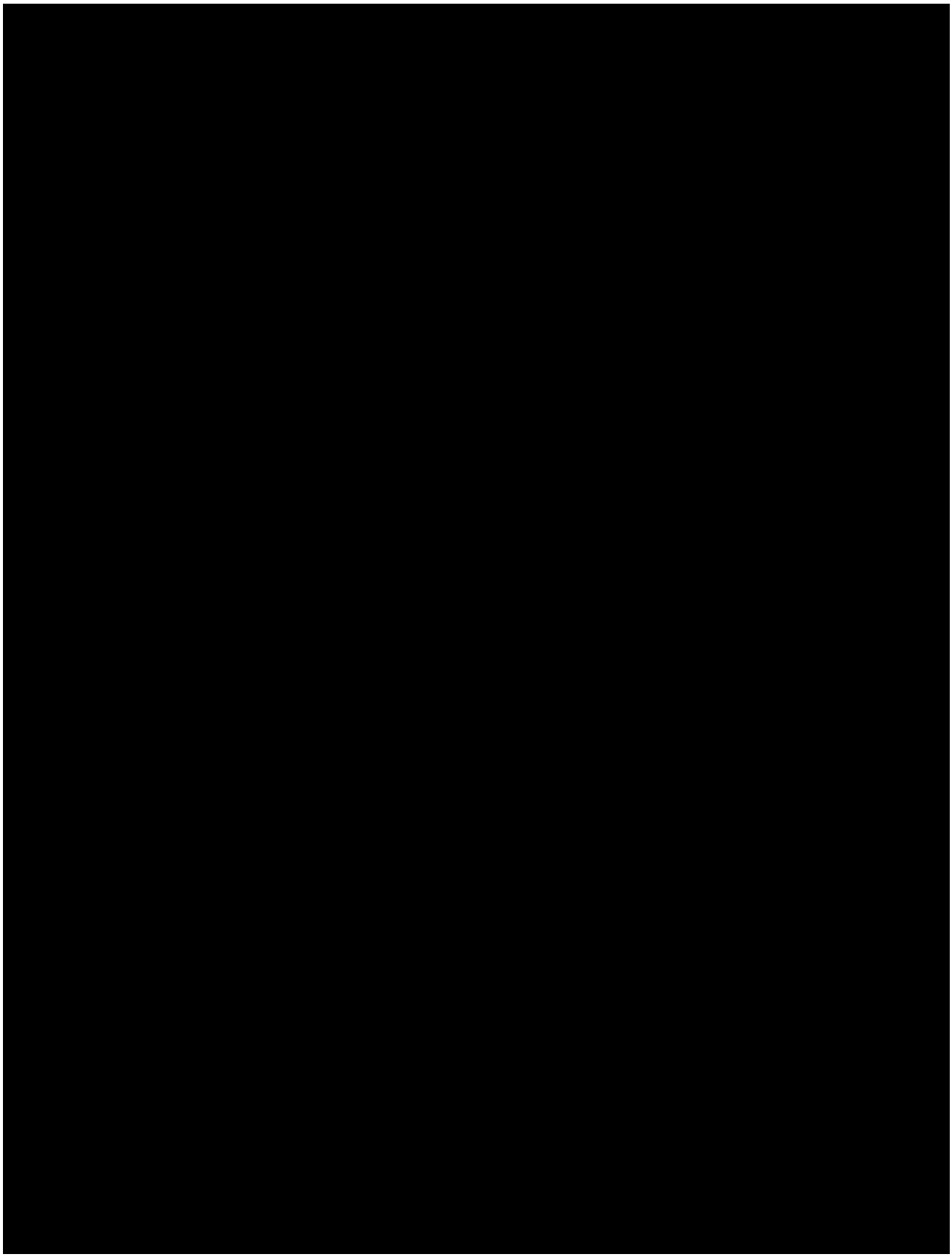

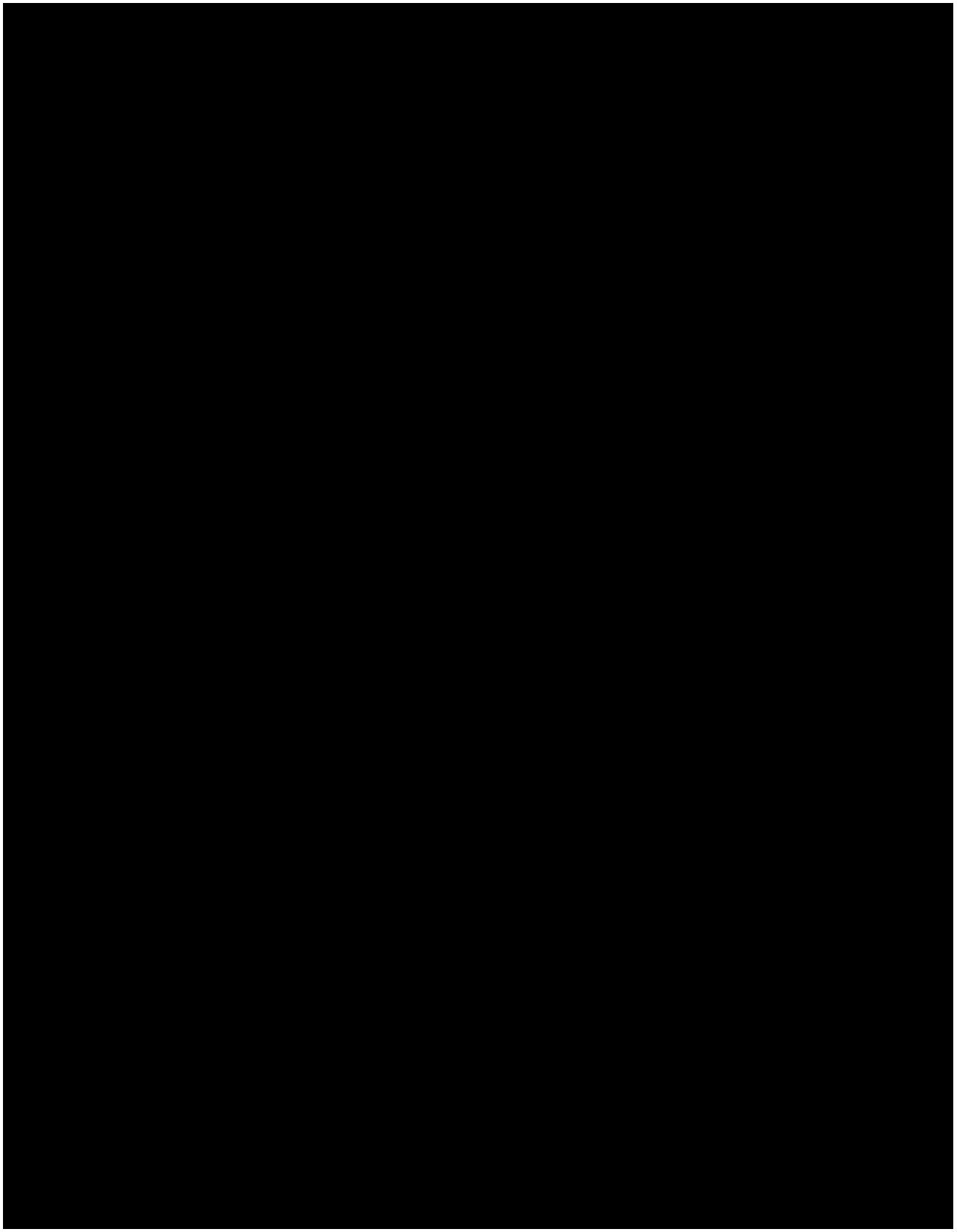

APPENDIX S. MANAGING POTENTIAL HY'S LAW CASES

INTRODUCTION

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's law (PHL) criteria at any point during the study.

The investigator participates, in conjunction with Incyte clinical project and pharmacovigilance representatives, in the review and assessment of cases fulfilling PHL criteria to ascertain whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug.

The investigator fulfils requirements for the recording of data pertaining to PHL or Hy's law cases and AE/SAE reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

For the purpose of this process definitions are as follows

Potential Hy's Law (PHL)

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN at any point during the study. The elevations do not have to be at the same time or within a specified time frame.

Hy's Law

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, where no other reason can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug.

ACTIONS REQUIRED IN CASES OF AST OR ALT > 3 × ULN OR TOTAL BILIRUBIN ≥ 2 × ULN

Identification and Determination of Potential Hy's Law

To identify cases of AST or ALT > 3 × ULN or total bilirubin > 2 × ULN and consequently determine whether the subject meets PHL criteria, please follow the instructions below:

- Review the laboratory report and if a subject has AST or ALT > 3 × ULN OR total bilirubin > 2 × ULN at any visit:
  - Determine without delay whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits.
  - Enter the laboratory data into the laboratory CRF as soon as possible.

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Potential Hy's Law Criteria Not Met

If the subject has NOT had AST or ALT > 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified time frame), irrespective of ALP, please follow the instruction below:

- Perform follow-up on subsequent laboratory results according to the guidance provided in Section 5.2.4 of the Protocol.

Potential Hy's Law Criteria Met

If the subject has had AST or ALT > 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified time frame), irrespective of ALP, please follow the instruction below:

- Have subject interrupt study drug.
- Notify Incyte study team without delay.
  - The investigator, or designee, should contact the medical monitor to discuss and agree upon an approach for the study subject's follow-up and the continuous review of data.
- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as medically indicated.
- Investigate the etiology of the event and perform any relevant diagnostic investigations as discussed with the medical monitor.
- Enter the laboratory data into the laboratory CRF as soon as possible.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality was initially detected and the criteria for PHL was met, the medical monitor, Incyte pharmacovigilance physician, and investigator will discuss and review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug. Subject matter experts will be included in the review as appropriate.

Evaluation of Alternative Causes

In order to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, the following alternative etiologies should be considered, including, but not limited to,

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis
- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder

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and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.

- Concomitant treatment
- Other causes such as systemic infections (bacterial, fungal, viral), nonalcoholic steatohepatitis (NASH), and cardiovascular diseases

Actions After Review and Assessment

According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the AST or ALT **and** total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the standard study processes.
- Have subject resume study drug as per Protocol guidelines.

If it is agreed that there is no explanation that would explain the AST or ALT and total bilirubin elevations:

- Have subject permanently discontinue study drug and perform EOT procedures.
- Report an SAE (report term "Hy's Law").
  - The 'medically important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's law case, a causality assessment of related should be assigned.
- If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's law case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. Report an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above.

ACTIONS REQUIRED FOR REPEAT EPISODES OF AST OR ALT > 3 × ULN AND/OR TOTAL BILIRUBIN > 2 × ULN

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

If the alternative cause for the previous occurrence of PHL was not chronic or progressing malignant disease, please follow the process for PHL review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of PHL was chronic or progressing malignant disease please follow the instructions below:

- Determine if there has been a significant change* in the subject's condition.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described for PHL review and assessment as described in this appendix.

* A 'significant' change in the subject's condition refers to a clinically relevant change in ALT, AST, or total bilirubin, or associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

REFERENCE

FDA Guidance for Industry (issued July 2009). Drug-induced liver injury: premarketing clinical evaluation. http://www.fda.gov/downloads/Drugs/Guidances/UCM174090.pdf.

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APPENDIX T. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	17 JUL 2015
Amendment (Version) 2:	30 OCT 2015
Amendment (Version) 3:	13 JUL 2016
Amendment (Version) 4:	26 AUG 2016
Amendment (Version) 5:	13 DEC 2016
Amendment (Version) 6:	15 MAR 2017
Amendment (Version) 7:	25 FEB 2019
Amendment (Version) 8:	18 DEC 2019

Amendment 8 (18 DEC 2019)

Overall Rationale for the Amendment: The primary objectives of this amendment are to extend the required duration of post-treatment contraception in male subjects and to include relevant updates from IB Edition 5.

1. **Synopsis; Section 3.1.2, Parts 3 and 4; Section 3.2, Subject Inclusion Criteria; Section 3.3, Subject Exclusion Criteria; Section 4.1.3, Part 3 Combination Therapy Dose-Finding; Section 4.1.4, Part 4 Combination Expansion Cohorts**

   Description of change: Inclusion criteria 2j, 2m, and 3e, as well as analogous language throughout the protocol were modified to clearly state that eligible subjects must be currently experiencing a suboptimal response to a current dose of ruxolitinib monotherapy. Inclusion criterion 7c was modified to extend the duration of post-treatment contraception for male subjects. Exclusion criterion 3 was modified to clearly state that C-TGC subjects should continue their ruxolitinib throughout the screening period. Exclusion criterion 14 was modified to redefine cardiac disease history window.

   Rationale for change: Inclusion criteria 2j, 2m, 3e, and exclusion criterion 3, along with relevant analogous language throughout the protocol were amended to prevent subject enrollment errors. Inclusion criterion 7c was modified as a precautionary response to results of the 3-month dog toxicology study. Exclusion criterion 14 was modified to align with current Incyte standards in this subject population.

2. **Section 1.4.1, Potential Risks of INCB053914 Based on Nonclinical Safety**

   Description of change: A summary of relevant results of the 3-month dog toxicity study was added.

   Rationale for change: To include updated nonclinical toxicology data.

3. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Amendment 7 (25 FEB 2019)

Overall Rationale for the Amendment: The primary objective of this amendment is to modify the eligibility criteria based on investigator feedback to better align with the nature of the disease under study (MF) in the INCB053914 + ruxolitinib combination treatment group (C-TGC).

[redacted]

2. **Synopsis; Section 3.2, Subject Inclusion Criteria**

   Description of change: Inclusion criterion 3e was modified to reduce the minimum prior treatment duration of ruxolitinib from 6 months to 8 weeks and to allow 1 ruxolitinib dose reduction due to toxicities before the start of the combination regimen.

   Rationale for change: To redefine the MF population who may benefit from the treatment of INCB053914 in combination with ruxolitinib.

3. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   Description of changes: Exclusion criteria 1, 2b, 2e, and 3e were modified. In criterion 1, the platelet and ANC level time frames for C-TGC were updated. Criteria 2b and 2e were updated to exclude subjects with AST or ALT > 1.5 × ULN. Criterion 3e was revised to prohibit concomitant hydroxyurea in subjects with MF within 8 weeks of Day 1.

   Rationale for changes: Exclusion criterion 1 was modified to better align with the modification made to inclusion criterion 3e. Exclusion criteria 2b and 2e were modified to account for the enrollment subjects with low level transaminitis at baseline, as this is often seen in patients with MF according to investigator feedback. Exclusion criterion 3e was clarified to indicate that concurrent hydroxyurea was not allowed in the C-TGC cohorts.

[redacted]

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5. **Section 5.2.8.2, Prohibited Medications**

   Description of change: Specific language prohibiting concomitant anticancer therapy was added.

   Rationale for change: To clarify that the study treatment should be the only therapy administered to treat the disease under study during the treatment period.

[redacted]

8. **Section 10.3, Data Management**

   Description of change: Updated language added.

   Rationale for change: Language was modified to align with current company standards.

9. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Amendment 6 (15 MAR 2017)

Overall Rationale for the Amendment: The primary objectives of this amendment are based upon emerging data from the current study and are to modify inclusion/exclusion criteria relevant to liver function; to modify Protocol guidelines for managing treatment-emergent liver function test (LFT) elevations and rashes [redacted] and to clarify the subject populations in the monotherapy expansion cohorts Treatment Group A Expansion Cohort 1 (TGA E1) and Treatment Group B Expansion Cohort 2 (TGB E2).

1. **Synopsis; Section 1.4.2.1, ALT/AST Elevations; Section 3, Subject Eligibility; Section 5.2.4, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 5: Guidelines for Interruption and Restarting of Study Drug); Section 5.2.8.1, Restricted Medications; Section 6, Study Assessments; Section 7.5.5.1, Chemistry, Hematology, Urinalysis, Liver Function Panel, Coagulation Panel, and Hepatitis Screening; Section 9.4.4.5, Adverse Events of Special Interest; Appendix S, Managing Potential Hy's Law Cases**

   Description of change:

   - The exclusion criteria were modified 1) to exclude subjects with total bilirubin, alanine transaminase (ALT), and aspartate transaminase (AST) level greater than the local laboratory's upper limit of normal at screening (criterion 2), and 2) to exclude subjects with excessive alcohol and chronic acetaminophen use (new criteria 27 and 28).
   - Section 1.4.2.1 was added to include AST/ALT elevation data as of 31 DEC 2016 from the current study.
   - Table 5 was updated to expand the management of LFT elevations.
   - In Section 5.2.8.1 (Restricted Medications), language was added regarding chronic acetaminophen use less than 2 g per day and restriction of hydroxyurea administration during or proximal to azacitidine administration.
   - In Section 6 the laboratory assessment tables for all treatment groups (Tables 7, 10, 13, 16, and 19) were updated with increased frequency of LFT and coagulation panel sample collection.
   - Section 7.5.5.1 was modified to reflect the change in sample collection of LFT and coagulation panel assessments.
   - Section 9.4.4.5 was added to document how treatment-emergent ALT and AST elevations, as well as treatment-emergent adverse events related to liver toxicities, would be analyzed.
   - Appendix S was added to provide investigators with a process to collect, review, and assess data relevant to potential Hy's law cases.

   Rationale: The above changes were made to the Protocol based emerging CTCAE v4.03 Grade 3 and Grade 4 ALT/AST elevations in the current study.

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2. **Section 1.4.2.2, Rash; Section 7.5.1, Adverse Events**

   Description of change: Section 1.4.2.2 was added to describe the treatment-emergent Grade 3 rashes experienced on study to date. Section 7.5.1 was modified to request that investigators obtain photographic documentation of any treatment-emergent rash and provide de-identified images to the sponsor at its request.

   Rationale: To inform investigators of the potential risk of treatment-emergent rash and to add a provision by which the nature and character of these adverse events may be better evaluated across all the investigative sites.

[redacted]

4. **Section 6, Study Assessments (Tables 12 and 13)**

   Description of change: The study cycle visit that is not required beginning with Cycle 4 was changed from the Day 15 visit to the Day 8 visit.

   Rationale: Making the Day 15 visit mandatory in all cycles allows for safety assessments midcycle.

5. [redacted]

[redacted]

7. **Synopsis; Section 3.2, Subject Inclusion Criteria; Section 4.1, Overall Study Design (Figure 1: Monotherapy Study Design); Section 4.1.2, Part 2 Monotherapy Dose Expansion**

   Description of change: Protocol section text and Figure 1 were updated to restrict TGA E1 and TGB E2 to subjects with AML and diffuse large B-cell lymphoma, respectively.

   Rationale: The subject populations in these cohorts were revised to ensure consistency of targeted subject populations between study Part 2 and Part 4.

8. **Section 1.2.4; Pharmacokinetics of INCB053914 in Study INCB 53914-101**

   Description of change: This section was updated with pharmacokinetic summary data inclusive of the 115 mg twice daily Part 1 TGA cohort.

   Rationale: To provide updated pharmacokinetic data.

9. **Section 1.4.2; Potential Risks of INCB053914 Based on Preliminary Clinical Experience**

   Description of change: This section was updated to include a preliminary, unaudited summary of safety data from the INCB 53914-101 study inclusive of the 3 dose-limiting toxicities observed in the study to date.

   Rationale: To provide updated summary of the adverse event data observed in this study.

10. **Synopsis; Section 3.3; Subject Exclusion Criteria**

    Description of change: In addition to the exclusion criteria changes referenced in item 1, the following exclusion criteria were edited or added:

    - Exclusion criterion 3e was modified to restrict hydroxyurea administration during or proximal to azacitidine administration.
    - Exclusion criterion 8 was clarified to ensure that all relevant subjects have HbA1c assessed at screening.
    - Exclusion criterion 29 was added to exclude subjects with comorbid Type 1 or uncontrolled Type 2 diabetes (Part 1 and Part 3 only).

    Rationale: To clarify the subject population in the Protocol eligibility criteria.

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11. **Section 6; Study Assessments (Table 7: Laboratory Assessments for INCB053914 Monotherapy Cohorts; Table 8: Pharmacokinetic, Pharmacodynamic, and Electrocardiogram Assessments for INCB053914 Monotherapy Cohorts); Section 7.9.3, Plasma Pharmacodynamics (Monotherapy Cohorts Only)**

    Description of change: Plasma pharmacodynamic sample collection and analysis was removed from the Protocol.

    Rationale: There is no further need to assess the plasma-based pharmacodynamic changes in pBAD.

12. **Incorporation of administrative changes:** Other minor, administrative changes have been incorporated throughout the Protocol, including the schedules of assessments, and are noted in the redline version of the amendment.

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Amendment 5 (13 DEC 2016)

Overall Rationale for the Amendment: The primary objectives of this amendment are to add dose-finding and expansion cohorts to evaluate INCB053914 in combination with select standard-of-care (SOC) treatment regimens in advanced malignancies and to update aspects of the monotherapy design based on emerging data from the current study.

This amendment includes changes to Protocol INCB 53914-101 Amendment 4 (26 AUG 2016) as summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 1, Introduction; Section 2, Study Objectives and Endpoints; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5, Treatment; Section 6, Study Assessments; Section 7, Conduct of Study Assessments and Procedures; Section 9, Statistics; Appendix O, Screening Symptom Form; Appendix P, Patient Global Impression of Change**

   Description of change: The study design was revised to include SOC combination dose-finding and expansion cohorts. All relevant Protocol sections, including tables and figures, were revised accordingly.

   Rationale: To provide the background, rationale, study design, study objectives/endpoints, inclusion/exclusion criteria, treatment details, study assessments, and statistical considerations in order to research INCB053914 in combination with SOC regimens in advanced malignancies.

2. **Synopsis; Section 3.3, Subject Exclusion Criteria (Criterion 3e); Section 5.2.8.1, Restricted Medications**

   Description of change: Added language to restrict concomitant intake of hydroxyurea within 48 hours before and on the day of a pharmacodynamic (PD) sample collection.

   Rationale: To avoid the effects of hydroxyurea on the levels of circulating, highly proliferative cells and INCB053914 PD data.

3. **Section 1.2.1, Pharmacology of INCB053914; Section 1.2.3, Projected Pharmacokinetics of INCB053914 in Humans**

   Description of change: Replaced language pertaining to the human dose projected to provide plasma concentrations to achieve IC_{50} pBAD inhibition in a whole blood assay with a reference to the Investigator's Brochure (IB).

   Rationale: To align Protocol text with the IB version 2 and update now that clinical data are available.

4. **Section 1.2.4; Pharmacokinetics of INCB053914 in Study INCB 53914-101**

   Description of change: This section was updated with pharmacokinetic summary data inclusive of the 80 mg BID Part 1 TGA cohort.

   Rationale: To provide updated pharmacokinetic data to support the Part 3 dose-finding cohort INCB053914 starting dose.

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5. **Section 1.4.2; Potential Risks of INCB053914 Based on Preliminary Clinical Experience**

   Description of change: This section was updated to include a preliminary, unaudited summary of safety data from the INCB 53914-101 study inclusive of the 80 mg BID Part 1 TGA Cohort initial evaluation period.

   Rationale: To provide updated summary of the adverse event data observed in this study.

6. **Section 5.2.4; Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 5: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: The management strategy for Grade 2 alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) elevations was updated.

   Rationale: To allow for more frequent liver enzyme monitoring and ensure investigators manage subjects' concomitant medications in the event of ALT/AST elevations.

7. **Section 6; Study Assessments (Table 7: Laboratory Assessments for INCB053914 Monotherapy Cohorts; Table 8: Pharmacokinetic, Pharmacodynamic, and Electrocardiogram Assessments for INCB053914 Monotherapy Cohorts); Section 7.9.4, Whole Blood Pharmacodynamics (Monotherapy Cohorts Only)**

   Description of change: The collection of whole blood samples for PD analysis, which were removed in Protocol Amendment 3 (13 JUL 2016), were added back into the study.

   Rationale: Assessments were added back into the study based on emerging data and to perform further phosphoprotein analysis.

8. **Incorporation of administrative changes:** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Amendment 4 (26 AUG 2016)

Overall Rationale for the Amendment: The primary objective of this amendment is to update inclusion criterion #3. With this amendment, inclusion criterion #3 is reverted back to the same exact wording as was in Amendment 2 (30 OCT 2015).

1. **Synopsis; Section 3.2, Subject Inclusion Criteria**

   Description of change: Inclusion criterion 3 was updated to indicate that subjects must be unresponsive to currently available therapy, and there is no further standard-of-care therapy available in the judgment of the investigator.

   Rationale: Revised per FDA request.

2. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Amendment 3 (13 JUL 2016)

Overall Rationale for the Amendment: The primary objectives of this amendment are to update the study design, eligibility criteria, dose-limiting toxicity (DLT) criteria and dose interruption/reduction criteria as appropriate to the underlying pathology in the disease-specific treatment groups.

1. **Synopsis; Section 3, Subject Eligibility; Section 4.1, Overall Study Design; Section 5.2.3, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose (Table 1: Definition of Dose-Limiting Toxicity); Section 5.2.4, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 2: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: Treatment Group C (TGC; myelodysplastic/ myeloproliferative neoplasms [MDS/MPNs], myelofibrosis [MF][) has been removed from the Protocol. Subjects with MDS/MPN will be regrouped into Treatment Group A (TGA), and TGA eligibility and DLT criteria will apply to these subjects. Subjects with MF have been removed from Part 1 (dose escalation) of the study. Additionally, the original Part 2 expansion Cohort D (MDS/MPN or MF subjects) has been replaced with 2 distinct expansion cohorts (Cohorts B and C), and the MM and lymphoma cohorts were renamed accordingly as Cohorts D and E. All relevant Protocol sections have been updated accordingly.

   Rationale: Subjects with MDS/MPN and MF considered for this study are in the relapsed/refractory stage of disease and will usually present to the clinic with varying degrees of pancytopenias (Mughal 2015). This is consistent with screening experience to date in INCB 53914-101. These pre-existing pancytopenias make it difficult 1) for these subjects to meet TGC hematologic eligibility criteria detailed in Protocol Amendment 2, 2) to appropriately assess these subjects for hematologic DLTs according to the TGC DLT criteria, and 3) to appropriately manage on-study hematologic toxicities per the mitigating actions for TGC as listed in Table 2 of Protocol Amendment 2. As per routine practice and product labels of compounds (eg, azacitadine, decitabine) approved in indications characterized by pancytopenia, decreasing hematologic cell counts do not warrant interruption of standard treatments. Per the azacitidine package insert (Vidaza 2016), dose adjustments for subjects whose baseline counts are WBC $< 3.0 \times 10^9$/L, ANC $< 1.5 \times 10^9$/L, or platelets $< 75.0 \times 10^9$/L should be based on nadir counts and bone marrow cellularity at the time of the nadir. Including MDS/MPN subjects in TGA, along with AML and MDS subjects, is reasonable since clinically meaningful differences in treatment-emergent toxicities and their management are not expected.

   Given the low disease incidence, subjects with MF were removed from Part 1 (dose escalation) in order to accelerate identification of the recommended Phase 2 dose (RP2D) and minimize the number of subjects who would be exposed to potentially nonefficacious doses during this part of the study.

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2. **Synopsis; Section 3.1, Study Population; Section 4.1, Overall Study Design**

   Description of change: Specified that only subjects with acute leukemia and high-risk MDS would be eligible to enroll in this study.

   Rationale: Text was added to clarify the appropriate subject population for this study.

3. **Synopsis; Section 4.1.1, Part 1 Dose Escalation**

   Description of change: Text added to clarify that different RP2Ds could be identified among disease types during dose escalation.

   Rationale: To make it clear that multiple RP2Ds could be selected for the expansion cohorts based on the data from Part 1 of the study.

4. **Synopsis; Section 4.1, Overall Study Design (Figure 1); Section 4.1.2, Part 2 Dose Expansion**

   Description of change: Revised the expansion cohort enrollment to at least 5 and up to approximately 15 subjects.

   Rationale: This update provides flexibility with regard to the expansion cohort enrollment to allow for a more thorough evaluation of safety, tolerability, efficacy, PK, and PD of the selected dose in the defined cohorts.

5. **Synopsis; Section 3.2, Subject Inclusion Criteria**

   Description of changes:

   a. Inclusion criterion 3 was updated to indicate that there must be no further standard-of-care therapy available or that subjects must be intolerant to or refuse any further established therapy. Specific prior therapy requirements for subjects with MM, AML, and MF were added.
   b. Inclusion criterion 5 was updated to indicate that the baseline bone marrow biopsy and/or aspirate requirement may be waived with approval by the medical monitor if a biopsy is not possible or is contraindicated, or the tissue requirement cannot be satisfied.

   Rationales:

   a. Text added to further define the subject population appropriate for the study and to provide guidance to participating sites with regard to prior therapy requirements for select disease types.
   b. Text added so that subjects who were willing to have a baseline bone marrow aspirate performed but for whom the procedure is not feasible or is unsuccessful could still enroll in the study with medical monitor approval.

6. **Synopsis; Section 3.3, Subject Exclusion Criteria**

Description of changes:

a. Exclusion criterion 2 was updated to clarify how subjects' bilirubin and creatinine clearance levels should be gauged for study eligibility.
b. Exclusion criterion 3 was updated to specify the washout period for prior biologic or immunotherapies, and bullet "e" was added to provide some additional clarification with regard to allowed anticancer therapies.
c. Exclusion criterion 4 was updated to specify some immunosuppressive therapies that fall under this criterion.
d. Exclusion criterion 8 was modified to allow subjects with well-controlled diabetes into Part 1 of the study.
e. Exclusion criterion 11 was updated to reference the Protocol section regarding hepatitis screening.
f. Exclusion criterion 14 was amended to delineate more appropriate eligibility criteria relative to cardiac history.

Rationales:

a. The bilirubin criterion was reworded to better follow how sites are directed to report bilirubin results (eg, direct bilirubin is only tested if total bilirubin is > 1.5 × ULN). The creatinine clearance threshold for non-MM subjects in Part 1 was reduced slightly to more closely approximate values observed in the clinic in the subject population. Likewise, the option to measure the creatinine clearance via 24-hour urine collection was provided to investigators to allow them to exercise their clinical judgment when evaluating subjects during screening.
b. While most antibodies and biological therapies have long half-lives, the washout period for these therapies was reduced to 28 days to minimize gaps in anticancer therapy for subjects with advanced, rapidly progressing disease while allowing a safe washout period. Additionally, a washout period of 5 half-lives is not necessary since there should be a low risk of overlapping toxicities of INCB053914 and biologics and immunotherapies used in this setting.
c. Exclusion criterion 4 was amended to provide investigators with examples of prohibited immunosuppressive therapies.
d. Exclusion criterion 8 was revised to allow subjects with well-controlled diabetes to enroll in Part 1 of the study as there is no evidence of significant increase in risk of uncontrollable hyperglycemia and considering the high prevalence of comorbid diabetes in the defined subject population.
e. Because the risk of viral reactivation after exposure to INCB053914 is minimal based on the mechanism of action (MOA), the exclusion criteria was modified so that subjects who have negative hepatitis B and C serology do not need to have the HBV DNA and HCV RNA test, respectively, for which it often takes a long time to receive results, and therefore may enroll in the study and begin study treatment sooner, eg, for those aggressive diseases such as AML.
f. To modify the exclusion criteria to reflect the relative cardiac risk of the subject population.

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7. **Synopsis; Section 4.3.1, Planned Number of Subjects**

   Description of change: The planned number of subjects for Part 2 was revised to up to 75 subjects.

   Rationale: The planned number of subjects was modified to align with the updated expansion cohort enrollment estimates.

8. **Section 1.2.4, Pharmacokinetics of INCB053914 in Humans; Section 1.3.2, Potential Risks of INCB053914 Based on Preliminary Clinical Experience**

   Description of change: Preliminary INCB 53914-101 pharmacokinetic data and a summary of unaudited safety data were added to the Protocol.

   Rationale: New sections were added to update Protocol with data from the current study analyzed to date.

9. **Section 4.1.1, Part 1 Dose Escalation**

   Description of change: The definition of the pharmacologically active dose (PAD) is now based on PK projected pBAD inhibition levels.

   Rationale: The definition of the PAD was updated for clarification.

10. **Section 4.1.2, Part 2 Dose Expansion; Section 7.8.4 Food-Effect Pharmacokinetic Testing**

    Description of change: The number of potential subjects for the food-effect study was revised to include at least 12 and up to 18 subjects enrolled from all expansion cohorts.

    Rationale: The number of subjects and enrollment strategy for the food-effect study were corrected.

11. **Section 5.1.3.3, Storage; Section 5.1.3.4, Instructions to Subjects for Handling Study Drug**

    Description of change: The study drug storage conditions and instructions for subject storage of the study drug were updated.

    Rationale: To reflect that the conditions stipulated on the investigational product label should be followed, inclusive of the forthcoming ambient formulation.

12. **Section 5.2.4, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 2: Guidelines for Interruption and Restarting of Study Drug)**

    Description of change: The management of liver function test (LFT) elevations was modified to provide specific guidelines for each CTCAE grade of ALT or AST elevation, as well as to no longer mandate study drug interruptions for transient LFT elevations. The criteria for dose interruption for Grade 3 thrombocytopenia in TGB subjects was modified to specify that drug should be held if the AE is persistent or associated with a bleeding event.

    Rationale: The criteria to trigger actions taken with study drug interruptions, restarts, and dose reductions for LFT elevations and thrombocytopenia (in TGB) were modified to provide investigators with toxicity management plans with greater clarity and granularity, and that mirror clinical practice more closely. Specifically for LFT elevations, transient,

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isolated (not accompanied with bilirubin increase) low-grade increases (≤ Grade 2) can have various causes apart from exposure to study drug and often resolve without interruption of targeted agents. In the amended Protocol, subjects with LFT elevations ≥ Grade 2 will be monitored more closely (at least weekly) until resolved to baseline or ≤ Grade 1. The amended language allows for subjects who have a Grade 2 elevation to continue to receive study drug while LFTs are monitored at least weekly, and only interrupt if they do not resolve (≤ Grade 1 or baseline) within 14 days. If subjects are eligible to resume study medication after the first occurrence of a Grade 2 or Grade 3 LFT elevation requiring interruption resolves, they will be rechallenged at the same study drug dose in order to monitor whether LFT elevations will recur and also avoid unnecessary dose reductions.

13. **Section 5.2.8.1, Restricted Medications**

    Description of change: The use of corticosteroids during the study was expanded to allow for short-course dose regimens > 10 mg/day prednisone (or equivalent).

    Rationale: Clinical management of this subject population sometimes requires short courses of systemic corticosteroids in > 10 mg/day prednisone (or equivalent). As such, the medication restriction was clarified so these instances do not meet the definition of a Protocol deviation.

14. **Section 6, Study Assessments (Table 4: Laboratory Assessments, Table 6: Cycle 1 and Cycle 2 Pharmacokinetic, Pharmacodynamic, and Electrocardiogram Assessments); Section 7.9.4, Whole Blood Pharmacodynamics**

    Description of change: Section 7.9.4 was removed from the Protocol as were references to the PD-whole blood samples in Table 4 and Table 6. The collection of untimed PK samples at each cycle Day 1 was removed from Table 4. Cycle 2 Day 1 and Day 2 PD plasma samples were removed from the food-effect cohort in Table 6.

    Rationale: PD-whole blood samples, PK samples beyond Cycle 2, and PD plasma samples in the food-effect study subjects are not necessary.

15. **Section 6, Study Assessments (Table 4: Laboratory Assessments); Section 6.1, Screening; Section 6.1.1, Day 1; Section 7.5.5.1, Chemistry, Hematology, Urinalysis, Coagulation Panel, and Hepatitis Screening**

    Description of change: Section 6.1 was updated to allow for screening assessments that fail eligibility requirements to be repeated if the investigator believes the results were in error and allow for subjects who fail screening to repeat the screening process once if the investigator believes there has been a change in eligibility status. Section 6.1, Section 7.5.5.1, and Table 4 were updated to stipulate that blood chemistry and hematology screening assessment used to determine subject eligibility must be collected within 14 days prior to Cycle 1 Day1. Sections 6.1.1 and 7.5.5.1 was updated to clarify that results from the screening phase of the study should be reviewed on Cycle 1 Day 1 to confirm eligibility. Section 6.1.1, Section 7.5.5.1, and Table 4 were also updated to allow for Cycle 1 Day 1 blood chemistry and hematology screening assessments to be omitted if the blood chemistry and hematology screening evaluations are collected within 3 days

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before Cycle 1 Day 1, and to remind sites that if Cycle 1 Day 1 laboratory samples were needed, they should be collected before the first dose of study drug.

Rationale: The updates to Section 6.1 provide the investigator with the opportunities to repeat screening assessments or the screening process if they feel the results to be in error or that the eligibility of their subject may have changed. The updates to Sections 6.1.1, Section 7.5.5.1, and Table 4 clarify that subject eligibility is based on laboratory values obtained during screening and to reduce the phlebotomy burden on subjects who have screening assessments completed proximal to their enrollment date. The stipulation on the timing of the screening blood chemistry and hematology assessments being collected within 14 days before Cycle 1 Day 1 was added to Section 6.1 and Section 7.5.5.1 to ensure that the assessment of subjects' adequate bone marrow and organ functions are made closer to study enrollment.

16. **Section 6, Study Assessments (Table 5: Clinical Laboratory Analytes)**

Description of change: Hemoglobin A1c (HbA1c) was added as an analyte and blasts were added as a mandatory part of the CBC differential for subjects with diseases where peripheral blast measurements are a part of the disease assessments. "Serology" was modified to "Hepatitis Screening." Hepatitis B surface antibody was added as a required analyte for the hepatitis B screening. The HBV-DNA and HCV-RNA tests were clarified to only be performed if the serology returned positive results.

Rationale: HbA1c was added to allow investigators to document adequate glucose control of diabetic subjects as per the revised exclusion criterion #8. Blasts were added as an analyte to reiterate mandatory reporting in relevant disease types. "Serology" was amended to "Hepatitis Screening" to clarify that not all tests listed fall under serology and help distinguish between the mandatory serological evaluations and the optional PCR assays. The hepatitis B surface antibody analyte was added to the serology panel to help further gauge a subject's hepatitis status. As the risk of viral reactivation after exposure to INCB053914 is minimal due to the MOA and PCR assays usually take several days to report out in clinical laboratories, the HBV-DNA and HCV-RNA PCR assays were relegated from mandatory tests to only be performed if serology is positive. This will allow subjects with negative serology to proceed with enrollment and begin study therapy sooner.

17. **Section 7.5.5.3, Hepatitis Screening Tests**

Description of change: The language concerning the hepatitis screening was amended to support the changes made to exclusion criterion #11 and Table 5, as well as clarify when the HBV-DNA and HCV RNA tests should be performed and provide guidance to investigators on managing positive viremia results.

Rationale: As the risk of viral reactivation after exposure to INCB053914 is minimal due to the MOA and PCR assays usually take several days to report out in clinical laboratories, the HBV-DNA and HCV-RNA PCR assays were relegated from mandatory tests to reflex tests (performed only if serology is positive) to allow subjects with negative serology to proceed with enrollment and begin study therapy sooner. Additionally, language was added to clarify hepatitis statuses that would meet eligibility criteria.

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[redacted]

19. **Incorporation of administrative changes.** Changes delineated in Protocol Administrative Change 1 (06 APR 2016; addition of a 15 mg tablet strength in the Synopsis and Section 5.1.3.2, and updating language regarding collection of prior meal data in Section 7.8.1) as well as other minor, administrative changes and clarifications have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

REFERENCES

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Amendment 2 (30 OCT 2015)

Overall Rationale for the Amendment: The primary objectives of this amendment are to update the hematologic eligibility, dose-limiting toxicity (DLT), and dose interruption/reduction criteria appropriate to the underlying pathology in the disease-specific treatment groups.

1. **Synopsis; Section 3.2, Subject Inclusion Criteria; Section 7.9.1, Tumor Tissue Collection**

   Description of change: Inclusion criterion #5, pertaining to bone marrow collection requirement, and Section 7.9.1 were updated to indicate that bone marrow biopsy or aspirate may be performed as appropriate to disease.

   Rationale: To clarify that type of bone marrow sample collected (ie, biopsy or aspirate) and submitted to the sponsor should be relevant to the type of disease.

2. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   Description of change:

   a. Exclusion criterion #1, relating to bone marrow function (including platelet count, hemoglobin, and absolute neutrophil count), was eliminated for Part 1/Treatment Group A (TGA).
   b. The exclusion criterion for hemoglobin was changed from "< 10.0 g/dL" to "< 8.0 g/dL" for Part 1/Treatment Groups B and C.

   Rationale:

   a. To modify the exclusion criteria to match the clinical manifestation of the diseases under study. Treatment Group A comprises subjects with diseases of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), which are typically manifested by severe cytopenias; requiring specific parameters would be a significant barrier to recruitment and could significantly confound the assessment of toxicities associated with the investigational agent in AML and MDS.
   b. To modify the exclusion criteria to match clinical manifestation and management of the diseases under study. Treatment Groups B and C comprise a population that includes multiple myeloma, myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes, and myelofibrosis. Optimal management of patients with these diseases in the relapsed and refractory setting typically includes maintaining a hemoglobin level of $\geq$ 8.0 g/dL; thus the criterion is being updated accordingly.

3. **Section 3.3, Subject Exclusion Criteria**

   Description of change: Exclusion criterion #12, which pertains to current infection and use of systemic antibiotic, antifungal, or antiviral treatment, was clarified to specify "active and uncontrolled" infectious diseases requiring systemic antibiotic, antifungal, or antiviral treatment.

   Rationale: To provide clarification for the exclusion criterion. The intent of the criterion is to ensure that only subjects with active and uncontrolled infections are excluded; subjects with current infections that are adequately controlled by antimicrobrial agents or those on antimicrobrial agents for infection prophylaxis are not excluded.

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4. **Section 5.2.3, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose (Table 1: Dose-Limiting Toxicity Criteria)**

   Description of change: The dose-limiting toxicity criterion of febrile neutropenia was updated to include only subjects in Treatment Groups B and C.

   Rationale: Treatment Group A comprises subjects with relapsed and/or refractory AML and MDS, for whom fever (≥ 38.5°C) in the setting of severe neutropenia (ANC < 1.0×10^9/L) is a common and expected occurrence due to underlying disease pathology. Subjects are routinely monitored for fever, neutropenia, and infection for the duration of the study. Requiring a DLT criterion for febrile neutropenia for Treatment Group A does not enhance subject safety and will make AE causality assessment difficult when fever and neutropenia are common symptoms of the underlying diseases.

5. **Section 5.2.4, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 2: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: Guidelines for interruption and restarting of study drug for neutropenia and thrombocytopenia were updated for Part 1/TGA and Part 2 Cohorts A and D.

   Rationale: Because there are no hematologic eligibility criteria required for Part 1/TGA and Part 2 Cohorts A and D, specific degrees of cytopenia are no longer relevant. Guidelines for dose interruption and restart were updated to allow for management of cytopenias as per institutional standard and to require treatment hold and discussion with the sponsor in the setting of suspected causality.

6. **Section 8.1.2, Adverse Event Reporting**

   Description of change: Adverse event reporting guidelines for events associated with disease progression were updated.

   Rationale: To further specify how to report adverse events and serious adverse events that are associated with disease progression.

7. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the red-line/strike-out version of the amendment.

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Amendment 1 (17 JUL 2015)

Overall Rationale for the Amendment: The primary objectives of this amendment are to change the dose-escalation design in each treatment group from an accelerated titration to a conventional 3 + 3 approach, to refine the eligibility criteria to only include subjects with advanced hematological malignancies unresponsive to currently available therapy and for whom there is no standard of care available, and to update the dose-limiting toxicity criteria as appropriate to the diseases included in each dose-escalation treatment group.

1. **Synopsis; Section 4, Investigational Plan; Section 9.2, Selection of Sample Size**

   Description of change: The dose-escalation design in each treatment group was updated from an accelerated titration followed by a modified Toxicity Probability Interval design to a standard 3 + 3 design. Additionally, the estimated sample size was updated accordingly.

   Rationale: Change requested by FDA.

2. **Synopsis; Section 3, Subject Eligibility**

   Description of change: The eligibility criteria and description of the study population were updated to only include subjects with advanced hematological malignancies unresponsive to currently available therapy and for whom there is no standard-of-care therapy available.

   Rationale: Change requested by FDA.

3. **Section 5.2.3, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose**

   Description of change: Dose-limiting toxicity criteria in Part 1 were modified, consistent with FDA requests, for Treatment Group A, Treatment Group B, and Treatment Group C (added in current amendment) and were applied as appropriate to the diseases included in each group.

   Rationale: Change requested by FDA.

4. **Synopsis; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5.2, Treatment of Subjects; Section 7.8.4, Food-Effect Pharmacokinetic Testing**

   Description of change: Treatment Group A and Expansion Cohort A were updated to include only subjects with leukemia and MDS; MDS/MPN (including atypical chronic myeloid leukemia [aCML], chronic myelomonocytic leukemia [CMML], myelodysplastic/ myeloproliferative neoplasm unclassifiable [MDS/MPN-U], and refractory anemia with ring sideroblasts and thrombocytosis [RARS-T]) and MF were removed from these groups. Treatment Group C and Expansion Cohort D, which include only subjects with MDS/MPN and MF, were added to Part 1 and Part 2, respectively. Accordingly, appropriate detail was added to all of the relevant Protocol sections, including study design and investigational plan, subject eligibility and number of subjects, dose-limiting toxicity and dose interruption/ adjustment criteria, and pharmacokinetic assessments, consistent with the newly defined treatment group.

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Rationale for change: Per FDA request, Treatment Group B dose-limiting toxicity criteria were applied to subjects with MDS/MPN and MF. To optimally assess the safety and tolerability of INCB053914 in subjects with these diseases, separate dose-escalation and expansion groups that include only MDS/MPN and MF were added to the study Protocol.

5. **Synopsis; Section 2.2.2, Secondary Endpoints**

   Description of change: Secondary endpoint pertaining to pharmacokinetic assessment time point at Day 15 was changed to Day 8.

   Rationale for change: Endpoint was updated to reflect correct visit day at which steady-state and serial PK sampling is performed.

6. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the red-line/strike-out version of the amendment.

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