A Phase III Multicenter, Randomized, Open Label Study of APR-246 in Combination with Azacitidine Versus Azacitidine Alone for the Treatment of *TP53* Mutant Myelodysplastic Syndromes

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CONFIDENTIAL

INVESTIGATOR'S STATEMENT

1. I have carefully read this protocol entitled "A Phase III Multicenter, Randomized, Open Label Study of APR-246 in Combination with Azacitidine Versus Azacitidine Alone for the Treatment of *TP53* Mutant Myelodysplastic Syndromes" and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.

2. I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee/Independent Ethics Committee (IRB/IEC), and that all administrative requirements of the governing body of the Institution will be complied with fully.

3. Informed written consent will be obtained from all participating patients in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013).

4. I will enroll patients who meet the protocol criteria for entry.

5. I understand that my signature on each completed Case Report Form (CRF) indicates that I have carefully reviewed the complete set of CRFs and accept full responsibility for the contents thereof.

6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration, a Competent Authority of the European Union or another Regulatory Authority.

Investigator:

Name: _____ Telephone: _____

Address: _____

_____

Signature: _____ Date: _____

Sponsor Representative:

Signature: ***REDACTED*** Date: JUN 24, 2016

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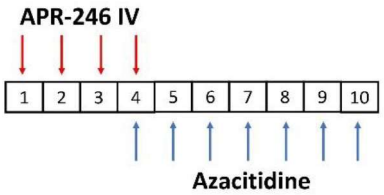
CLINICAL STUDY SYNOPSIS

Title	A Phase III Multicenter, Randomized, Open Label Study of APR-246 in Combination with Azacitidine Versus Azacitidine Alone for the Treatment of *TP53* Mutant Myelodysplastic Syndromes
Sponsor	Aprea Therapeutics AB
Monitor/CRO	Theradex Oncology
Lead Investigator	David Sallman, MD H. Lee Moffitt Cancer Center & Research Institute
Number of Study Centers	Multicenter
Clinical Phase	III
Investigational Agent	APR-246
Study Design	This study will be a multi-center, open-label, randomized, controlled Phase III trial to compare the efficacy of APR-246 in combination with azacitidine versus azacitidine alone for the treatment of *TP53* mutant myelodysplastic syndromes. Patients will be randomized (1:1) to one of two treatment arms and stratified by age (< 65 versus ≥ 65): 1) Experimental arm: APR-246 + azacitidine; or 2) Control arm: Azacitidine The Intent-to-Treat (ITT) population will be the primary analysis population for efficacy. All patients who are randomized on study will be considered eligible for the ITT population and will be used for demographics, baseline characteristics summaries. Patients may continue treatment as long as toxicity remains acceptable, progression has not occurred and the patient has not withdrawn consent. Response and progressive disease will be assessed based on the Guidelines for Implementation of International Working Group (IWG) response criteria after every two treatment cycles the first year, then every three cycles. Patients may remain on protocol therapy after relapse or progression if they are continuing to derive clinical benefit in the opinion of the Investigator. Investigators may choose to transition patients towards a stem cell transplantation (SCT) as appropriate after a response by the experimental or control treatment has been achieved. Patients who undergo SCT will be removed from study treatment and will be followed per the study calendar.
Study Objectives	Primary Objective: 1. To compare the complete response rate, defined as the proportion of patients who achieve complete remission (CR), and duration of CR with

	APR-246 + azacitidine treatment vs. azacitidine only. Secondary Objectives: To measure the following with APR-246 + azacitidine treatment vs. azacitidine alone: 1. Overall response rate (ORR) 2. Duration of response (DOR) 3. Rate and time to acute myeloid leukemia (AML) transformation 4. Overall survival (OS) 5. Relapse-free survival (RFS) 6. Transition rate to hematopoietic stem cell transplant (HSCT) 7. Safety profile 8. Rate of red blood cell (RBC) and/or platelet transfusion independence (TI) for 56 days (8 weeks) 9. Pharmacokinetics of APR-246 and azacitidine Exploratory Objectives: 1. Determine if biomarkers predictive for response to therapy can be derived from baseline molecular analyses of bone marrow or blood samples 2. Determine the depth of remission by IHC, PCR, and other techniques in serial bone marrow or blood samples 3. Investigate potential resistance mechanisms by molecular analysis of bone marrow or blood samples at disease progression VAF
Study Endpoints	Primary Endpoint: CR per the modified IWG (Cheson et al, 2006)[1] and time between achieving CR and relapse of disease. Secondary Endpoints: 1. ORR is the proportion of patients achieving hematological improvement (HI), partial remission (PR), CR, marrow CR by the IWG 2006 criteria 2. Response duration 3. AML transformation according to World Health Organization (WHO) criteria 4. OS 5. RFS 6. Proportion of patients who transition to HSCT 7. Safety endpoints can relate to adverse events, serious adverse events, dose adjustments or dose holds, lab parameter values, vital signs, ECGs 8. Patients who achieve RBC and/or platelet TI during the 56-day (8 week) period after randomization 9. Pharmacokinetic endpoints: C_{max} (maximum concentration), AUC (area under the curve), Vd and clearance (CL) of APR-246 and azacitidine Exploratory Endpoints: 1. Baseline molecular analyses may include, but are not limited to: TP53 VAF by NGS, p53 immunohistochemistry, mutations in other genes by NGS, RNA expression 2. Investigations of depth of remission may include, but are not limited to: PCR and p53 immunohistochemistry 3. Molecular analyses at disease progression may include, but are not limited to: TP53 VAF by NGS, p53 immunohistochemistry, mutations in other genes by NGS, RNA expression

Eligibility Criteria	**Inclusion Criteria**: 1. Patient has signed the Informed Consent (ICF) and is able to comply with protocol requirements 2. Documented diagnosis of MDS, according to WHO classification (<20% blasts), that meets IPSS-R classification of intermediate, high, or very high-risk disease 3. Patient has adequate organ function as defined by the following laboratory values: a) Creatinine clearance > 30 mL/min (by Cockcroft-Gault method; see Appendix IV) b) Total serum bilirubin < 1.5 × ULN unless due to Gilbert's Syndrome, underlying disease of MDS, hemolysis or considered an effect of regular blood transfusions c) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 × ULN, unless due to underlying disease of MDS 4. Age ≥18 years at the time of signing the informed consent form (ICF) 5. Having at least one TP53 mutation which is not benign or likely benign 6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 7. Females of childbearing potential: negative pre-treatment urine or serum pregnancy test 8. Females of childbearing potential and males with female partners of childbearing potential must be willing to use an effective form of contraception such as latex condom, hormonal birth control, intrauterine device or double barrier method during chemotherapy treatment and for at least six months thereafter **Exclusion Criteria:** 1. Patient has a known history of HIV or active hepatitis B or active hepatitis C infection (testing not mandatory). 2. Patient has any of the following cardiac abnormalities (as determined by treating MD): a) Myocardial infarction within six months prior to registration, b) New York Heart Association Class III or IV heart failure (see Appendix III) or known left ventricular ejection fraction (LVEF) < 40%, as assessed by echocardiogram or MUGA scan; c) A history of familial long QT syndrome, d) Symptomatic atrial or ventricular arrhythmias not controlled by medications, e) QTc ≥ 470 msec calculated from a mean of 3 ECG readings using Fridericia's correction ($QTcF = QT/RR^{0.33}$). *Note:* Patients with QTcF ≥ 470 msec and with bundle branch block and/or pacemaker rhythm may be enrolled after approval by Medical Monitor. 3. Concomitant malignancies or previous malignancies with less than a 1-year disease free interval at the time of signing consent. Patients with adequately resected basal or squamous cell carcinoma of the skin, or

	adequately resected carcinoma *in situ* (e.g. cervix) may enroll irrespective of the time of diagnosis. 4. Prior exposure to azacitidine, decitabine or investigational hypomethylating agent or induction chemotherapy for MDS or AML. *Note*: intensive chemotherapy for any other prior cancer is not exclusionary. 5. Use of cytotoxic chemotherapeutic agents, or experimental agents (agents that are not commercially available) for the treatment of MDS within 14 days of the first day of study drug treatment. 6. Concurrent use of erythroid stimulating agents, G-CSF, or GM-CSF within 14 days of the first day of study drug treatment. 7. History of allogeneic stem cell transplantation 8. Pregnancy: Pregnant women are excluded from this study because APR-246 has not been studied in pregnant patients. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with APR-246, breastfeeding should be discontinued if the mother is treated with APR-246. 9. Active uncontrolled infection.
Treatment plan	Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's disease. Patients will be randomized (1:1) to 1 of 2 arms and stratified by age (<65 versus ≥65): 1) Experimental: APR-246 + azacitidine; or 2) Control: azacitidine only **Treatment Schedule for Experimental Arm: APR-246 + Azacitidine**  APR-246 will be administered as a 6-hour intravenous (IV) infusion daily on days 1-4 of each 28-day cycle. APR-246 fixed dose is 4.5 g. One dose level reduction to 4.0 g is permitted. A second dose reduction could be permitted following discussion with the Sponsor and Medical Monitor. Azacitidine will be given at the standard dose of 75 mg/m^2 over 7 consecutive days **(Days 4-10)** as a subcutaneous injection or IV infusion, every 28 days. Control arm: Azacitidine (75 mg/m^2) only, on Days **4-10,** as a subcutaneous injection or IV infusion, every 28 days.
Dose delay / modifications	Dose delays/modifications are permitted per protocol. A single missed dose may be compensated by adding an additional dosing day for azacitidine, so that the patient

	receives the total 7 days of treatment per cycle (see Section 6.2.1).
Duration of Treatment	The projected Phase III duration is 30–36 months. Patients may continue treatment to the end of the trial while deriving clinical benefit, unless unacceptable toxicity, progression, death or patient withdrawal requires discontinuation. Patients may remain on protocol therapy after relapse or progression if they are continuing to derive clinical benefit in the opinion of the Investigator.
Duration of Follow-Up	Assuming there is no withdrawal of consent, patients who stop study treatment (APR-246 or azacitidine) for any reason (e.g. toxicity, transition to SCT, PD) will continue long term follow-up: 1. Patients who discontinue study treatment to receive SCT: a. Collect post SCT response assessments, transformation to AML and survival every month until relapse or death, whichever occurs first. b. After PD, collect data for survival and transformation to AML every 6 months until death. 2. Responders (CR, PR, mCR with HI, mCR without HI, HI) who discontinue study treatment for other reasons than progressive disease or SCT: a. Collect response assessments, transformation to AML and survival every month until relapse or death, whichever occurs first. b. After relapse/progression, continue collecting data for survival and transformation to AML every 6 months until death. 3. Non-Responders: patients who discontinue study treatment due to progressive disease: a. Collect data for survival and transformation to AML every 6 months until death. If a patient is removed from the study treatment due to unacceptable adverse events, the event(s) will be followed until resolution or stabilization. Criteria for Removal from Study Study drug treatment can continue for patients receiving clinical benefit, unless: one or more withdrawal criteria are met, or at the patient's discretion, or if the study is terminated. 1. Patient Completion A patient will be considered to have completed the study if the patient meets at least 1 of the following criteria: • The patient has progressive disease. • The patient died during the study. • The patient experienced a treatment related AE that led to withdrawal from the study. • The patient starts new treatment for their underlying disease (MDS). 2. Patient Withdrawal from Study Treatment: If the patient is permanently withdrawn from study treatment, but does not withdraw consent to be followed on study, the investigator must make every effort

	to have the patient complete all withdrawal assessments at the time of withdrawal, and complete all scheduled follow-up visits. 3. Patient Withdrawal from Study: A patient may voluntarily withdraw from study treatment or withdraw consent from the study at any time. The investigator may also, at his or her discretion, discontinue a patient from participating in the study at any time. The investigator and/or designated staff will record the date and the reason for patient withdrawal from the study. Study treatment must be discontinued if: - Evidence of disease progression according to IWG 2006 criteria. - A patient becomes pregnant. - A patient is significantly non-compliant with the requirements of the protocol. - A patient has an adverse experience that would, in the Investigator's judgment, make continued participation in the study an unacceptable risk. - A patient withdraws consent. - A patient receives HSCT.
Follow-Up on study	See **Schedule of Study Evaluations**.
Statistics	This study will be a multi-center, open-label, randomized, controlled Phase III trial to compare the efficacy of APR-246 in combination with azacitidine versus azacitidine alone for the treatment of TP53 mutant MDS. **Analysis Populations** Intent-to-treat (ITT): All patients who are randomized on study will be considered eligible for the ITT population and will be used for demographics, baseline characteristics summaries. The ITT population will be the primary analysis population for efficacy. Efficacy evaluable (EE): All patients who complete at least one treatment cycle of APR-246 and azacitidine and who have at least one post-treatment clinical response assessment. Patients who fail to complete one treatment cycle will also be considered EE if they show clear evidence of clinically significant disease progression. The EE population will be the secondary analysis population for efficacy. Safety population: Patients will be evaluable for safety if they receive at least one dose of APR-246 or azacitidine. The safety population will be used to summarize exposure and safety parameters. Pharmacokinetics (PK): Patients will be evaluable for pharmacokinetics if at least one sample for PK evaluation has been obtained. **Determination of Sample Size** This trial assumes a sample size of 154 patients with 77 patients randomized in a 1:1 ratio to one of the two treatment arms (APR-246 + azacitidine treatment versus

azacitidine treatment alone). If the true CR rate is 50% for the treatment arm and 25% for the control arm, the trial will have 90% power to detect a statistically significant effect in favor of the APR-246 treatment combination at a 2-sided alpha = 0.05 significance level.

Efficacy Analyses

Primary endpoint CR will be summarized for all randomized patients (ITT) as the proportion of patients (%) with CR. CR will be compared between arms using a Cochran-Mantel-Haenszel (CMH) test stratified by age (< 65 years versus ≥ 65 years). In addition to presenting the CR rate and associated exact 95% confidence intervals (CI) for each treatment arm, the treatment effect will be described using the CMH estimate of the common odds ratio together with its associated 95% CI.

Duration of response (DOR) is defined as the time from the date when criteria for response are met to the date of progressive disease or death due to any cause, whichever occurs first. Patients alive with no progressive disease will have their DOR censored at the date of the last clinical assessment. The duration of CR will be summarized in each treatment arm by providing the median DOR together with associated 95% (CI), using Kaplan-Meier methodology.

Overall response will be summarized in number (%) of patients in each category of responses (CR, PR, mCR with HI, mCR without HI, HI). ORR will be analyzed by using the similar method as primary endpoint CR. DOR, as defined above, will also be evaluated in regard to ORR. Time to AML is calculated from first day of study treatment to first onset of AML. Kaplan-Meier methodology will be utilized. Rate of AML transformation will be analyzed by using the similar method as primary endpoint CR.

Survival data are collected at treatment and follow-up periods. Patients will be followed until death. Overall survival (OS) is defined as the number of days from the date of randomization to the date of death. Kaplan-Meier methodology will be utilized.

Relapse-free survival (RFS) is defined as the time from the date of randomization to disease relapse or death from MDS, whichever occurs first. If neither event occurs, RFS will be censored at the date of the last clinical assessment. Kaplan-Meier methodology will be utilized.

Time to AML, OS and RFS will be analyzed using the similar methods as DOR.

Transition rate to HSCT will be analyzed using the similar methods as primary endpoint CR.

Safety Analyses

Safety data including adverse events, vital signs, laboratory data, ECG, physical exam will be tabulated for the safety population. Adverse events will be tabulated by body system, preferred term, severity, and relationship to treatments. The tabulation of laboratory parameters will include the normal ranges for each parameter. Each value will be classified as falling above, below, or within the normal range. Laboratory parameters will also be tabulated by maximum NCI-

	CTCAE v5.0 severity grade. **Pharmacokinetic Analysis** In Experimental Arm, sparse PK sampling for APR-246 will be done at all sites in cycles 1-3, on Days 1, 2 and 4. In both Arms, azacitidine PK will be performed at selected sites in cycle 1, on Day 4. The pharmacokinetics of APR-246 and azacitidine will be summarized using descriptive statistics. For APR-246, a population PK model will be used to estimate individual C_{max}, AUC and CL for each patient. APR-246 AUC and C_{max} will then be tested for association with signs of efficacy and safety. If an observable trend exists, a PK/PD model will be developed to evaluate the exposure-response relationship between APR-246 plasma exposure and outcome measures. Demographic and clinical data (ethnicity, current age, body weight, sex, disease status, etc.) will be utilized to assess interpatient variability in the PK and PK/PD relationships. For azacitidine non-compartmental methods will be used to derive PK parameters (C_{max}, T_{max}, AUC, V and CL).

LIST OF ABBREVIATIONS

ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
CBC	Complete Blood Count
CL	Clearance
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
C_{max}	Maximum Concentration
CMH	Cochran-Mantel-Haenszel
CMML	Chronic Myelomonocytic Leukemia
CNS	Central Nervous System
CR	Complete Remission
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Drug Accountability Record
ddPCR	Digital Droplet Polymerase Chain Reaction
DILI	Drug-Induced Liver Injury
DL	Dose Level
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DNMT	DNA Methyltransferase
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable
E_{max}	Maximal Effect
EOI	End of Infusion
ESA	Erythropoietic Stimulating Agent
EU	European Union
FAB	French–American–British Classification System
GCP	Good Clinical Practices
G-CSF	Granulocyte-Colony Stimulating Factor
GLP	Good Laboratory Practices
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GMP	Good Manufacturing Practices
hERG	Human Ether-a-Go-Go Gene
HFD	Highest Feasible Dose

Hgb	Hemoglobin
HGSOC	High Grade Serous Ovarian Cancer
HMA	Hypomethylating Agent
HI	Hematologic Improvement
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HR	Hazard Ratio
HSCT	Hematopoietic Stem Cell Transplant
IB	Investigator's Brochure
IEC/IRB	Independent Ethics Committee/Institutional Review Board
ICF	Informed Consent Form
IM	Intramuscular
IMP	Investigational Medicinal Product
IPSS/IPSS-R	International Prognostic Scoring System/ Revised IPSS
ITT	Intent-to-Treat
IV	Intravenous
IWG	International Working Group
IWRS	Interactive Web Response System
LBM	Lean Body Mass
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
mCR	Marrow Complete Remission
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MQ	2-Methylene-Quinuclidin-3-One
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NGS	Next Generation Sequencing
NHL	Non-Hodgkin's Lymphoma
NOAEL	No Observed Adverse Effect Level
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PLD	Pegylated Liposomal Doxorubicin
PR	Partial Remission
RA	Refractory Anemia
RAEB	Refractory Anemia with Excess Blasts
RAEB-T	Refractory Anemia with Excess Blasts in Transformation

RBC	Red Blood Cell
RFS	Relapse-Free Survival
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SC	Subcutaneous
SCT	Stem Cell Transplant
TEAE	Treatment Emergent Adverse Event
TI	Transfusion Independence
TID	Three Times a Day (*Ter in Die*)
T_{max}	Time of Maximum Concentration
TrxR1	Thioredoxin Reductase
ULN	Upper Limit Normal
US	United States
VAF	Variant Allele Frequency
V_d	Volume of Distribution
WHO	World Health Organization

1.0 GENERAL INFORMATION

1.1 Protocol Number and Title of the Study

Protocol Number: A18-15331
A Phase III Multicenter, Randomized, Open Label Study of APR-246 in Combination with Azacitidine Versus Azacitidine Alone for the Treatment of TP53 Mutant Myelodysplastic Syndromes

1.2 Sponsor

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1.3 Monitor/CRO

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1.4 Signature Authorization

Theradex Oncology will act as the Sponsor Representative.

1.5 Investigators and Institutions

Principal Investigator:
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This study will be performed at multiple institutions.

2.0 BACKGROUND INFORMATION

2.1 MDS

Myelodysplastic syndrome (MDS) represents a group of clonal hematopoietic stem cell disorders predominating in the elderly, characterized by ineffective hematopoiesis leading to blood cytopenias. In 2015, the estimated incidence of MDS in the US was 4 cases per 100,000 persons/year[2]. This syndrome shows variable clinical courses, from indolent to life-threatening conditions related to severe cytopenia or progression to acute myeloid leukemia (AML). Progression to AML, a diagnosis with very dismal prognosis, occurs in approximately 10% and 70% of lower- and higher-risk patients, respectively. MDS development is associated with accumulation of cytogenetic changes and/or gene mutations. At advanced stages widespread gene hypermethylation is seen, and hypomethylating agents (HMAs) azacitidine or decitabine are the cornerstone treatment.

The overall prognosis is largely based on factors such as the marrow blast percentage, number and extent of cytopenias and cytogenetic abnormalities, which are grouped in a recently revised International Prognostic Scoring System (IPSS/IPSS-R)[3]. Although the division is schematic, it is customary to separate MDS into 'higher risk' MDS (corresponding to IPSS high or intermediate-2) and 'lower risk' (corresponding to IPSS low or intermediate-1)[4], and this separation is often the base for treatment recommendations.

Current treatment options for patients with higher risk MDS include chemotherapy, HMAs, and allogeneic hematopoietic stem cell transplantation (allo-HSCT, which is the only potentially curative treatment, but limited by morbidity in the patient population)[5]. The following agents have been approved for the treatment of MDS by the US Food and Drug Administration:

- Azacitidine: May 2004, for both low- and high-risk patients with all sub-types of MDS, including refractory anemia with excess blasts in transformation (RAEB-T; now defined as AML with 20-30% blasts)
- Lenalidomide: December 2005, or transfusion-dependent MDS patients with isolated del(5q) and with a low or intermediate-1 risk IPSS score
- Decitabine: May 2006, same indication as azacitidine

AML-like intensive chemotherapy has limited indication in higher risk MDS patients. In particular, patients with unfavorable karyotype show few complete remissions/responses (CRs) and shorter CR duration[6]. Low-dose cytarabine was found to be significantly inferior to azacitidine (in terms of response and survival) in a randomized Phase III study[7], especially in patients with unfavorable cytogenetics. However, low-dose cytarabine may still be a treatment option in higher risk MDS patients with normal karyotype[8] who are not candidates for any intensive chemotherapy or allo-SCT, in particular when administration of azacitidine or decitabine is not possible[4]. Recent analyses also support the prognostic and predictive value of *TP53* mutations in MDS patients treated with HMAs (Section 2.2).

2.2 TP53 Mutated MDS

The advent of next generation sequencing (NGS) has provided a rapid and efficient platform for genome studies that has revolutionized the diagnostic, prognostic, and therapeutic realms of myeloid malignancies[9]. Current NGS myeloid panels incorporate 20-50 genes and can identify mutations in the vast majority of patients[10,11]. In MDS, mutations of ASXL1, ETV6, EZH2, RUNX1 and *TP53* were found to be independently associated with decreased survival[12]. Of these, recent investigations have suggested that the mutational status of *TP53* is the most important negative prognostic factor in MDS patients. To date, the only disease modifying agents in MDS include lenalidomide in patients with isolated deletion of 5q (del(5q)) and azacitidine (a DNA methyltransferase (DNMT) inhibitor/HMA) in MDS patients with higher risk disease (i.e., intermediate 2/high risk by IPSS and high/very-high by IPSS-R). Lenalidomide was approved based on the MDS-003 trial with 67% of del (5q) patients achieving transfusion independence and 45% of patients with complete cytogenetic response[13]. However, primary resistance to lenalidomide has been directly linked to *TP53* mutation which occurs in 20% of patients[14]. Whereas partial cytogenetic responses occur in up to 73% of patients, *TP53* mutated del(5q) patients only have cytogenetic responses in 0-11% of cases[15,16,17]. For higher risk MDS patients, azacitidine represents the standard of care based on the AZA-001 trial that demonstrated a survival advantage for azacitidine when compared with induction chemotherapy, low dose cytarabine, or best supportive care (24.5 months versus 15 months, $p<0.0001$)[18]. A recent study in MDS showed strong association of *TP53* mutation with poor outcome in azacitidine treated patients[19]. In addition, Bejar and colleagues recently confirmed decreased OS in *TP53* mutated MDS patients treated with HMA without effect on response rates[20]. Lastly, mutations of *TP53* strongly predict for lack of benefit to allogeneic bone marrow transplantation, which represents the only curative option for patients with MDS[21]. This study highlights the prognostic importance of TP53 mutations as patients with complex karyotype without TP53 mutation had similar survival to patients with normal karyotype.

As shown in Table 1, a range of ORR and CR rates within recent years, specifically among *TP53* mutant MDS/AML patients treated with HMA, has been reported. Bally and colleagues reported 22% CR (Takahashi reported as high as 34% but that combined CR among different regimens). Sallman *et al.* (Moffitt Cancer Center) performed an internal analysis (see below) and reported 19% CR. Therefore, a conservative historical rate on the usage of standard azacitidine regimen would be approximately 20%.

Table 1. Outcomes of Patients with AML and MDS Treated with HMA in Four Studies, According to *TP53* Mutation Status

Study	No. of patients	Patients with Mutated *TP53*	Overall Response			Complete Response			Overall Survival		
			Mutated *TP53*	Wild-Type *TP53*	P Value	Mutated *TP53*	Wild-Type *TP53*	P Value	Mutated *TP53*	Wild-Type *TP53*	P Value
Bally et al.†	62 (44 MDS)	23 (37)	10 (43)	20 (51)	0.60	5 (22)	15 (38)	0.26	Median of 12.4 mo	Median of 23.7 mo	< 0.001
Bejar et al.‡	213 MDS	39 (18)	20 (51)	80 (46)	NS	NA	NA	NA	Hazard ratio for death, 2.01 (95% CI, 1.29-3.14)		0.002
Takahashi et al.∫	168 MDS	38 (23)	15 (39)	41 (32)	0.13	13 (34)	35 (27)	0.38	Median of 9.4 mo	Median of 20.7 mo	< 0.001
Jung et al.	107 MDS	13 (12)	10 (77)	47 (50)	0.88	NA	NA	NA	31% at 2 yr.	67% at 2 yr.	0.003

† In the study by Bally *et al*., the regimen for all the patients was 75 mg of azacitidine per square meter of body-surface area per day for 7 days. The median duration of response was 7 months among patients with mutated *TP53* and 8 months among those with wild-type *TP53* (P=0.38).

‡ In the study by Bejar A al., 42 patients (20%) received azacitidine, 144 (68%) received decitabine, and 27 (13%) received decitabine plus another medication.

∫ In the study by Takahashi A *et al*., 38 patients (23%) received azacitidine at a dose of 75 mg per square meter per day for 5 to 7 days, 40 (24%) received 20 mg of decitabine per square meter per day for 5 days, 79 (47%) received azacitidine or decitabine plus another medication, and 11 (7%) received 60 mg of guadecitabine per square meter per day for 5 days. The median duration of response was 5.7 months among patients with mutated TP53 and 28.5 months among those with wild-type TP53 (P=0.003).

¶ In the study by Jung *et al*., 66 patients (62%) received azacitidine and 41 (38%) received decitabine.

Source: N Engl J Med 2017; 376:796-798 [22]

Sallman *et al.* performed an internal analysis of molecularly profiled patients at Moffitt Cancer Center and also identified that the clonal burden, or variant allele frequency (VAF), had significant impact on clinical phenotype and more importantly further stratified prognosis over binary mutational analysis alone and/or clinical prognostic models[23]. Specifically, MDS patients with a *TP53* VAF > 40% had a median overall survival (OS) of 124 days versus an OS that was not reached in patients with VAF < 20% (hazard ratio (HR), 3.52; P = 0.01) with validation in an independent cohort (HR, 4.94, P = 0.01). Overall, *TP53* mutant MDS and AML patients have a median OS ranging from 5-9 months with 8 months representing the best estimate when restricting to MDS and oligoblastic AML (20-30% blasts) (Figure 1) [20,23.24;25,26].

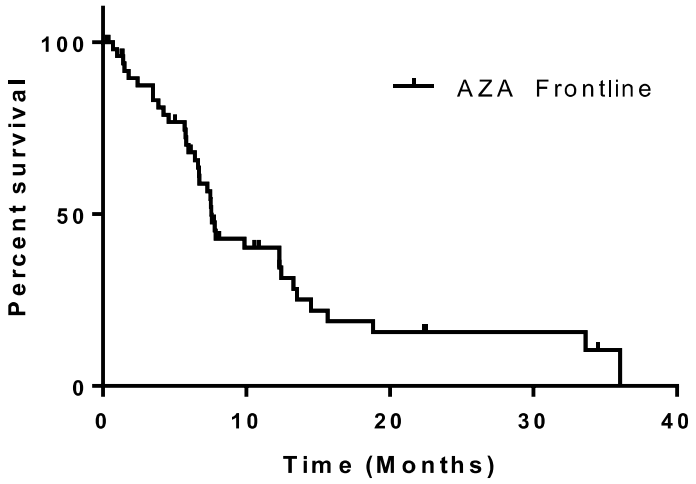

Figure 1. Historical Overall Survival for *TP53* Mutant MDS/AML (≤30% blasts) Treated with Frontline Azacitidine (Source: Moffitt Cancer Center Database).

Median OS of 7.6 Months in MDS/AML patients treated with frontline AZA (n=51).

Together, these data highlight the dismal outcomes of *TP53* mutant patients and the dire need for the development of novel therapeutic strategies, particularly in this patient population.

2.3 The Investigational Product

APR-246, 2-hydroxymethyl-2-methoxymethyl-1-azabicyclo [2,2,2] octan-3-one is also called PRIMA-1^{Met} in the literature, where PRIMA is an acronym for p53 reactivation and induction of massive apoptosis (see IB).

The APR-246 compound has a molecular weight of 199.24 g/mol, is a racemic mixture and is isolated as a white powder. The structure of APR-246 can be seen in Figure 2 below.

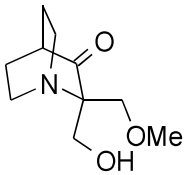

Figure 2. Structure of APR-246

2.4 Azacitidine

Azacitidine is a nucleoside metabolic inhibitor indicated by the U.S. FDA for the treatment of patients with the following French-American-British (FAB) MDS subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia

or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology laboratory values, is 75 mg/m^2 subcutaneously or intravenously, daily for 7 days. Patients are to be premedicated for nausea and vomiting. Repeat cycles every 28 days. Treatment may be continued as long as the patient continues to benefit.

Azacitidine is rapidly absorbed after subcutaneous or IV administration with a V_d of 76 ± 26 L and a half-life of 41 ± 8 minutes. C_{max} is reached after about 30 minutes. Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Urinary excretion is the primary route of elimination; the cumulated urinary excretion is 85% of radioactive dose with less than 1% recovered in feces over 3 days.

Azacitidine undergoes spontaneous hydrolysis in aqueous solution and is deaminated by cytidine deamidases, whereas APR-246 is glucuronidated. Although both compounds and their degradation products and metabolites are primarily eliminated by urinary excretion drug-drug interaction is not likely, but will be investigated as part of the current trial.

2.5 APR-246 Preclinical Studies

2.5.1 Pharmacology and Mode of Action

APR-246 is a novel small molecule anti-cancer compound that reactivates non-functional p53 and targets the cellular redox balance, resulting in induction of apoptosis in tumor cells. APR-246 is sometimes denoted PRIMA-1^{Met} in the literature.

APR-246 is a chemically synthesized prodrug, which spontaneously decays into the active moiety MQ (2-methylene-quinuclidin-3-one) that binds covalently to cysteines in mutant p53. Transfer of MQ-modified mutant p53 protein into tumor cells lacking p53 induced massive apoptosis, indicating that covalent binding of MQ per se is sufficient to activate mutant p53 and induce a p53 dependent biological response. These and other experiments directly looking at the conformational state of p53 protein have confirmed that binding of MQ pushes unfolded mutant or wild type p53 towards a functional wild type conformation.

MQ is a 'soft' electrophile, hence strongly preferring 'soft' nucleophiles such as thiols. Two other cellular targets that have been identified are thioredoxin reductase 1 (TrxR1) and glutathione. TrxR1 was identified as a target of MQ, potentially contributing to the anti-cancer effect. MQ converts this enzyme from a reductase to an oxidase that can produce reactive oxygen species (ROS). Inhibition of TrxR1 has also been shown to cause endoplasmic reticulum stress, which is one observed effect of APR-246 treatment. Further

in vitro experiments have shown that MQ also readily reacts with glutathione, a central molecule in the cellular redox system. Thus, APR-246 via MQ has effects that lead to impairment of the tumor cells' capacity to handle oxidative stress, including depletion of glutathione. The enhanced oxidative stress in tumor cells pushes the redox system to the limit of its capacity, compared with normal cells, making the redox system an Achilles' heel of tumor cells, which may be utilized to selectively kill tumor cells.

APR-246 has been investigated for potency and efficacy in various *in vitro*, *ex vivo*, and *in vivo* cancer models, both as single substance and in combination with different conventional chemotherapeutics. In many of these models APR-246 has shown good potency and efficacy and unique pharmacological profile in comparison with conventional chemotherapeutic drugs. The effect of combination treatment with APR-246 and azacitidine in MDS cells has been investigated in preclinical models. A synergistic effect was shown with an MDS cell line carrying a TP53 mutation. In a colony growth assay with primary MDS cells there was a significantly larger effect of combination treatment than azacitidine alone, particularly in TP53-mutated patients. In a xenograft model, treatment resulted in a significant inhibition of tumor growth.

In conclusion, the preclinical results show that in addition to its own apoptotic effect, APR-246 acts synergistically with DNA damaging agents and other established anti-cancer compounds. This is accordance with the proposed mechanism of action of APR-246, activating mutant p53 and increasing the oxidative stress of tumor cells.

2.5.2 Safety Pharmacology

REDACTED

REDACTED

2.5.3 Pharmacokinetics and Metabolism in Animals

REDACTED

2.5.4 Toxicology

REDACTED

REDACTED

REDACTED

2.6 APR-246 Clinical Studies

Table 2. Overview of Clinical Studies with APR-246.

NCT number Study ID	Indication	Treatment/ Combination	Status
NCT00900614 APR-246-01	hematologic malignancies, prostate carcinoma	APR-246	Completed (Lehmann *et al.* 2012)[27]
NCT00900614 APR-246-01 Amendment 6	hematologic malignancies	APR-246	Completed (Deneberg *et al.* 2016)[28]
NCT03072043 MCC-18973 NCT03588078 GFM-APR246	TP53 Mutant Myeloid Neoplasms (MDS/AML)	APR-246 with azacitidine (Phase Ib also has APR-246 monotherapy lead-in days -14 to -11)	Phase Ib: enrolment completed Phase II: ongoing
NCT02098343 APR-407 (PiSARRO)	*TP53*-mutated high grade serous ovarian cancer, sensitive or partially sensitive to platinum	Phase Ib: APR-246 with carboplatin/PLD Phase II: APR-246 with carboplatin/PLD *vs*. carboplatin/PLD alone	Phase Ib: completed Phase II: ongoing
NCT03268382 APR-486 (PiSARRO-R)	*TP53*-mutated high grade serous ovarian cancer, platinum resistant	APR-246 with PLD	Ongoing
NCT03391050 APR-633	BRAF V600 mutant melanoma resistant to	APR-246 with dabrafenib	Ongoing

NCT number Study ID	Indication	Treatment/ Combination	Status
(EMERA)	dabrafenib/ trametinib		
NCT02999893 16/012 (APROC)	esophageal or gastro-esophageal junction cancers	APR-246 with cisplatin and 5-FU	Ongoing

2.6.1 Phase Ib/II MDS (Moffitt) Trial

This is an Investigator-led Phase Ib/II trial (MCC-18973), in which APR-246 (50, 75, and 100 mg/kg lean body mass (LBM), via 6-hour daily IV infusion × 4 consecutive days) is given in combination with azacitidine (75 mg/m^2 SC or IV for 7 days, first dose following the final APR-246 infusion on Day 4) every 28 days to patients with TP53 mutant myeloid neoplasms (MDS/AML). The first cycle also included a lead in phase with APR-246 in monotherapy days -14 to -11.

The Phase Ib portion (safety/dose limiting toxicities (DLT) endpoint) has completed enrollment (N=12). No DLTs or serious adverse events (SAE) attributable to the study treatment have been reported to date. Myelosuppression has been the most common drug-related treatment-emergent adverse event (TEAE) reported to date.

The Phase II part of the study completed enrollment in 2019. Patients received 4.5 g (equivalent to 100 mg/kg LBM) APR-246 with azacitidine.

In the Phase Ib portion, 100% of response evaluable patients had CR, mCR, PR or had hematological improvement at the 3-month assessment. Response rate and duration remains under investigation in the Phase 1b and II portions of the study. In addition, exploratory endpoints including p53 immunohistochemistry and TP53 variant allele frequency analysis, are planned.

2.6.2 Ongoing Phase I/II in TP53 Mutated Advanced Ovarian Cancer

APR-407 (PiSARRO) is a 2-part study in women with advanced high grade serous ovarian cancer (HGSOC) given APR-246 in combination with carboplatin and pegylated liposomal doxorubicin (PLD). This is based on the fact that >90% of HGSOC are *TP53* mutant and *in vitro* and *in vivo* data suggesting synergism with platinum agents[28]. The APR-407 Phase Ib portion was completed in the European Union (EU) and the recommended Phase II dose of 67.5 mg/kg (corresponding to 100 mg/kg LBM) was confirmed as safe to be administered in combination with carboplatin/PLD based upon assessment of cumulative safety data from

the Phase Ib. The APR-407 Phase II portion has completed accrual in the EU and US and is currently in blinded follow up. Final analysis is expected mid2019.

2.6.3 Completed Study APR-246-01: First in Human APR-246 in Solid and Hematological Malignancies

This first in human study was a multicenter, open label, non-comparative, Phase I/II dose escalating study of APR-246 infusions in patients with refractory hematological malignancies or prostate cancer (APR-246-01)[27]. The study assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple escalating doses of APR-246. An extension of this clinical trial has been conducted with the main objective to evaluate safety at an optimal dose in a more homogenous patient population (see below). The patients received APR-246 on 4 consecutive days as a 2-hour daily IV infusion. Dosing was conducted with three patients at each dose level. The first dose level was 2 mg/kg and was followed by 3, 10, 30, 60 and 90 mg/kg. The treatment phase was followed by a 17 days follow-up phase to reveal any late adverse effects. The highest feasible dose (HFD) was defined as the dose expected to result in maximal plasma concentration (C_{max}) close to but not exceeding 110 µg/mL in any single patient without showing signs of DLT, or the dose level below the dose where DLT occurred, whichever came first. In total 22 patients, 4 (18.2 %) female and 18 (81.8 %) male with an average age of 67.0 years were enrolled into the study. The indications for the 22 included patients were AML (7 patients), prostate carcinoma (7 patients), non-Hodgkin´s lymphoma (NHL) (4 patients), chronic lymphocytic leukemia (CLL) (3 patients) and multiple myeloma (MM) (1 patient). Eighteen (18) patients completed the study, i.e., completed the day 21 visit and 4 patients were prematurely discontinued.

In regards to activity, the apoptosis pattern in patients with hematological malignancies showed cell cycle changes compatible with cell cycle arrest in all patients with non T-cell malignancy[33]. Also, other apoptosis markers were affected such as increased staining for Annexin-V, up regulation of BAX (Bcl-2 associated X protein), NOXA and PUMA expression and up regulation of DcR2 (decoy receptor 2, a marker considered to be associated with senescence). The one responding patient in the initial Phase I clinical trial was the only *TP53* mutant AML patient. Specifically, this patient had a reduction of blast cell count from 46% to 26% and showed activation of p53 targets supporting *in vivo* activity.

2.6.4 Completed Phase I/Ib Study APR-246-01 (Amendment 6)

This was a multi-center, open label, non-comparative, Phase I, dose de-escalating study of APR-246 infusions in patients with refractory hematologic malignancies. In this study (Amendment No. 6) a longer infusion time was applied resulting in an increased exposure of APR-246[28]. In Amendment No. 6, the objective was to increase the knowledge of the optimal way to administer APR-246 and study the safety and tolerability as well as the pharmacokinetic (PK) profile of APR-246. Ten patients with AML or CLL were planned for

enrolment. The treatment schedule was 4 consecutive days with APR-246 with the modified dosing regimen of a start boosting infusion of 50 mg/kg during 45 min, followed by an 85 mg/kg infusion for 5.15 hours. If toxicity was shown, the dose was to be decreased to Dose level 2 (45 mg/kg for 45 min [infusion rate 60 mg/kg/h], followed by 60 mg/kg [infusion rate 10 mg/kg/h] for 5.15 hours), on the discretion of the investigator and/or the Study Board. Out of the 2 AML patients with *TP53* mutation, both had a blast reduction, one constituting a response according to the response criterion[28]. On the lower dose of 67.5mg/kg, there were no DLTs or SAEs. Overall in this study there were 6/10 patients treated at 67.5 mg/kg or higher with no or only mild side effects supporting the 67.5mg/kg dose as the HFD and recommended for further development.

PK was studied at selected time points during the treatment and the data showed that no accumulation of APR-246 was observed after four daily doses or after 3 cycles. Plasma clearance and volume of distribution were comparable between Day 1 and Day 4, suggesting time-independent kinetics. The PK parameters obtained in this study, were also in line with the previous single dose study (2-90 mg/kg, 2 h infusion) and linear kinetics could be concluded for APR-246 up to 135 mg/kg. Several patients tolerated the mid-dose, 105 mg/kg treatment, where the C_{max} was in the range of 45-85 µg/mL with an exposure up to 860 µg*h/mL ($AUC_{0\text{-}24h}$), whereas one patient withdrew having the highest exposure (1060 µg*h/mL) in the whole study. In the patients, plasma concentrations consistently above those associated with effects in both *ex vivo* and *in vivo* pre-clinical models have been achieved. Four patients showed signs of response and 2 of them were responders according to the definition in the protocol. A response was observed in 4 of the 5 patients carrying mutant *TP53*. The effect of APR-246 on tumor burden and apoptosis markers indicates beneficial effects.

2.6.5 APR-246 CNS Safety Overview

CNS adverse events have been observed following APR-246 treatment in the clinical studies. These symptoms typically have an onset during or in direct connection with the drug infusion and include nausea/vomiting, dizziness/vertigo, psychiatric disorders and motor disturbances. They are fully reversible and usually mild and non-serious. However, cases with severe intensity have occurred, including events defined as a dose-limiting toxicity.

To describe the observed clinical scope of these effects, potentially CNS events that have been reported in the following clinical studies are tabulated below:

- APR-246-01 (N=22)
- APR-246-01-Amd6 (N=10)
- APR-407 phase 1b (N=35)

Table 3 is an overview of all reported AEs without differentiation on severity or temporal relation to drug administration. Two columns are shown for study APR-407, one with drug-related events only and one with all AEs reported in at least 10% of patients. The table shows the number of patients who reported at least one event (not number of events); a patient could report several events. The number of SAEs and DLTs in each category is given in parentheses. To capture potential CNS effects, all AEs in the following Medical Dictionary for Drug Regulatory Activities (MedDRA) System Organ classes are listed:

- Nervous system
- Ear and labyrinth
- Psychiatric
- General (not all shown, see below)

Table 3. CNS–Related Adverse Events in Clinical Studies (Number of Patients)

	APR-246-01 All AEs	**APR-246-01 Amd 6 All AEs**	**APR-407 Phase Ib Related AEs only**	**APR-407 Phase Ib All AEs in ≥10%**
Administration	2 h infusion	6 h infusion	6 h infusion	6 h infusion
Co-treatment			+carboplatin/PLD	+carboplatin/PLD
Dosing regimen	one 4-day course	one 4-day course	six 4-day courses in 28-day cycles	six 4-day courses in 28-day cycles
	N=22	N=10	N=35	N=35
Ear and labyrinth				
Vertigo	2	2	1	
Nervous system				
Dizziness	4 [1 SAE] [1 DLT]	5	22 [1 SAE]	24 [1 SAE]
Balance disorder	1			
Ageusia	1			
Dysgeusia	1		9	12
Headache	3 [1 DLT]	2	9	16
Lethargy		1		
Ataxia		1		
Dyskinesia		1 [1 SAE]	2	
Somnolence	[1 DLT]	2	2	
Muscle contractions	1 [1 SAE]			
Sensory disturbance	1 [1 DLT]			

	APR-246-01 All AEs	APR-246-01 Amd 6 All AEs	APR-407 Phase Ib Related AEs only	APR-407 Phase Ib All AEs in ≥10%
Dysarthria	[1 DLT]			
Disturbance in attention			1	
Hyperesthesia			1	
Neuropathy peripheral			1	4
Restless legs syndrome			1	
Tremor		3	5	5
Cerebral hemorrhage	1 [1 SAE]			
Psychiatric				
Confusional state	2 [1 SAE] [1 DLT]	1	1	
Dysphemia	[1 DLT]			
Hallucination	[1 DLT]			
Bradyphrenia			1	
Disorientation		1		
General				
Fatigue	5	4	22	29
Gait disturbance			1	

Nausea and vomiting may also be triggered from the CNS, but are not listed in this overview. From the category General disorders and administration site conditions, only fatigue and gait disturbance are listed, being potentially CNS-related. Other AEs reported in this category were pyrexia, edema, mucosal inflammation, malaise, death and disease progression.

2.6.6 APR-246 Cardiac Safety Overview

REDACTED

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2.7 Dose Rationale for APR-246 in Combination with Azacitidine

REDACTED

2.7.1 Rationale for Fixed APR-246 Dosing

REDACTED

2.8 Potential Risks and Benefits

2.8.1 Potential Risks

Potential risks identified with APR-246 include transient CNS-related adverse events, bone marrow suppression, QTc prolongation, glucuronidation of acetaminophen.

CNS adverse events:
Non-clinical data have shown APR-246 induced CNS adverse effects at high concentration levels in mice and dogs. The effects were transient and occurred during or in direct connection with dosing (related to high C_{max}). They are fully reversible, usually mild and non-severe, and may be managed by supportive medication (see Section 6.2.2) and/or dose reductions. However, cases with severe intensity have occurred, including events defined as a dose-limiting toxicity. Please consult with the Medical Monitor if you are unfamiliar with these events.

Bone marrow suppression:
No hematological toxicity was detected in nonclinical and clinical studies nor when APR/246 has been dosed alone, but when combined with carboplatin and pegylated liposomal doxorubicin in the study in HGSOC performed under IND 124841, there have been events of agranulocytosis (×1), anemia (×3), febrile neutropenia (×6), leucopenia (×1) and thrombocytopenia (×8). To date there have been no clinical or non-clinical data to support or rule out a contribution from APR-246 to chemotherapy induced bone marrow suppression.

REDACTED

Glucuronidation of Acetaminophen:
Based on co-administration studies in mice, it cannot be excluded that APR-246 may have a negative influence on the glucuronidation of acetaminophen, and therefore potentially potentiating hepatotoxicity after an over-dose of acetaminophen. No hepatotoxicity caused by acetaminophen has been identified in the ongoing clinical studies.

The Investigator's Brochure (IB) may be updated during the course of this study with additional risks and benefits. Please see the current IB for further details about the potential risks and benefits associated with this study.

2.8.2 Potential Benefits

Based on the nonclinical safety profile, the emerging clinical safety profile in over 300 patients, the early evidence of activity in *TP53* mutated MDS patients, as well as the limited life expectancy and lack of effective treatments for these patients, the benefit/risk assessment supports the use of APR-246 for this trial.

2.9 Characteristics of a Well-Conducted Trial

The following characteristics of an adequate and well-conducted trial will be implemented:

1. The Investigators will be well qualified by scientific training and experience.

2. Detailed Case Report Forms (CRFs) will be completed for every patient.

3. Requirements for institutional ethics review as set forth by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC), Title 21 Code of Federal Regulations (CFR) Part 56, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Sections 3 and 4, and the terms of the Declaration of Helsinki (2013), will be followed.

4. Requirements for informed consent in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013), will be followed.

5. Safety data will be recorded and evaluated.

6. Routine monitoring visits will be conducted by the Sponsor's representative (Theradex Oncology) to ensure data accuracy.

7. Drug accountability will be strictly maintained.

8. This trial will be conducted according to Good Clinical Practice (GCP), the protocol and applicable regulatory requirements.

2.10 Patient Population

This study will enroll patients with documented diagnosis of MDS, according to WHO classification, and documented *TP53* mutation that meets IPSS-R classification of intermediate, high, or very high-risk disease, who also meet the eligibility requirements of this protocol.

3.0 TRIAL OBJECTIVES AND PURPOSE

3.1 Primary Objectives

1. To compare the complete response rate, defined as the proportion of patients who achieve CR, and duration of CR with APR-246 + azacitidine treatment vs. azacitidine only.

3.2 Secondary Objectives

To measure the following with APR-246 + azacitidine treatment vs. azacitidine alone:

1. Overall response rate (ORR)
2. DOR
3. Rate and time AML transformation
4. Overall survival (OS)
5. Relapse-free survival (RFS)
6. Transition rate to hematopoietic stem cell transplant (HSCT)
7. Safety profile
8. Rate of red blood cell (RBC) and/or platelet transfusion independence (TI) for 56 days (8 weeks)
9. Pharmacokinetics of APR-246 and azacitidine

3.3 Exploratory Objectives

1. Determine if biomarkers predictive for response to therapy can be derived from baseline molecular analyses of bone marrow or blood samples
2. Determine the depth of remission by IHC, PCR, and other techniques in serial bone marrow or blood samples
3. Investigate potential resistance mechanisms by molecular analysis of bone marrow or blood samples at disease progression

4.0 TRIAL DESIGN

4.1 Overview of Trial Design

This will be a Phase III, multicenter, randomized study to compare the rate of CR and duration of CR, in patients with *TP53*-mutated MDS who will receive APR-246 and azacitidine or azacitidine alone.

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's disease.

Patients will be randomized (1:1) to one of two arms, stratified by age (< 65 years versus ≥ 65):

1. Experimental arm: APR-246 + azacitidine; or
2. Control arm: Azacitidine

The ITT population will be the primary analysis population for efficacy. All patients who are randomized on study will be considered eligible for the ITT population and will be used for demographics, baseline characteristics summaries.

Patients may continue treatment to the end of the trial as long as toxicity remains acceptable, progression has not occurred and the patient has not withdrawn consent. Response and progressive disease will be assessed based on the Guidelines for Implementation of International Working Group (IWG) response criteria (see Appendix II) after every two treatment cycles the first year, then every three cycles.

Investigators may choose to transition patients towards a stem cell transplantation (SCT) as appropriate after a response (CR, PR, mCR with HI, mCR without HI, HI) by the experimental or control treatment has been achieved. Patients who undergo SCT will be removed from study treatment and will be followed per the study calendar.

4.2 End of Study

The end of the study is defined as the date of the last visit of the last patient participating in the trial. Long-term follow up will continue until the time of each patient's death.

4.3 Minimizing Bias

All eligible patients entering the clinical trial will be randomized to either the experimental or the control treatment arms at a 1:1 ratio and using the following stratification factors to ensure a balance of patients: by age (< 65 years and ≥ 65 years).

4.4 Drug Products

4.4.1 APR-246

Chemical Name: 2-hydroxymethyl-2-methoxymethyl-1-azabicyclo [2,2,2] octan-3-one)

Storage, preparation and stability: The IMP (investigational medicinal product) should be stored at 2-8°C (35.6-46.4°F). The IMP is formulated as a concentrate for solution for IV infusion, to be diluted with sterile 0.9% NaCl solution prior to administration.

The solution for infusion should be prepared with the prescribed dosage for each patient in accordance with the protocol and separate technical instruction. After preparation of the ready to use solution for infusion the pH of the solution will range from slightly above 4 up to approximately 4.8, depending on dosage. The infusion will be slightly hypertonic, with an osmolarity of maximum 413 mOsm/L. The infusion to the patient should be finalized within 24 h from the time of preparation.

4.4.2 Azacitidine

Chemical Name: 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one

Formulation, preparation, storage and stability: Please see commercial package insert approved by regulatory agencies [30,31]

Route of Administration: Subcutaneous injection preferred*; or intravenous infusion.
Azacitidine is administered SC or IV for 7 consecutive days (Days **4-10**).
* SC preferred but will allow for IV at the Investigator's discretion. However, the same route should be maintained over the 7-day treatment period (whichever route is used on Day **4**, the other days should follow the same route of administration**)**.

4.5 Duration of Therapy

The projected Phase III duration is 30**–**36 months. Patients may continue treatment to the end of the trial while deriving clinical benefit, unless unacceptable toxicity, progression, death or patient withdrawal requires discontinuation. Patients may remain on protocol therapy after relapse or progression if they are continuing to derive clinical benefit in the opinion of the Investigator.

4.6 Trial Discontinuation

For reasonable cause, the Sponsor may terminate this study prematurely. Written notification of the termination is required. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigators to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements (non-compliance).
- Lack of evaluable and/or complete data.
- Decision to modify the developmental plan of the drug.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

4.7 Post-Treatment/Long-Term Follow-up

After discontinuation from study treatment, every effort will be made to conduct a post-treatment follow-up visit within 28 days after the last dose of the study drug. All patients should be followed until death. Patients who discontinue any study treatment will be contacted by the study staff for survival status, and/or response assessments, transition to AML, until death as described in Section 7.6.

4.8 Investigational Drug Procurement/Drug Accountability/Disposition of Clinical Trial Supplies

APR-246 should be requested by the Principal Investigator (or his/her authorized designees) at each participating institution. Instructions for ordering APR-246 will be provided in the Pharmacy Binder APR-246 may not be used outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in the clinical study. Investigators may delegate the responsibility for drug ordering, storage, accountability, and preparation to their designees. Drug accountability records will be maintained for all clinical trial supplies. All drug received, dispensed, and returned by the patients must be recorded on a Drug Accountability Record (DAR).

All empty and partially used vials and clinical trial supplies will be destroyed in accordance with the institution's requirements for a cytotoxic agent. The pharmacy will maintain detailed documentation of the number and identification of vials which are destroyed, and copies of these documents will be provided to the Sponsor. Disposition of all unused boxes of study drug will be carried out according to instructions provided by the Sponsor at the end of the study after drug accountability is performed by the Theradex Oncology monitor.

4.9 Registration and Randomization

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-study evaluations (see Section 7.2). Patients must meet all of the eligibility requirements listed in Section 7.5. There will be no eligibility waivers granted for this study. Patients will be registered and randomized on the study by using the Theradex Oncology Interactive Web

Response System (IWRS) automated patient registration system (see the Study Operations Binder for specific instructions).

Sites will be asked to provide patient specific inclusion and exclusion criteria documentation for medical review (prior to randomization), including redacted NGS and bone marrow exam reports.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

Patients considered for enrollment on this study must have a diagnosis of MDS based on the WHO classification, documented *TP53* mutation, and meets IPSS-R classification of intermediate, high, or very high-risk disease. The patients must meet all inclusion and no exclusion criteria. Investigators must be listed on the FDA 1572 form in order to be authorized to obtain information consent. No study-specific procedures can be performed until the patient has signed an ICF that has been approved by the IRB or IEC. Procedures that are performed prior to patients signing ICFs can be used to satisfy protocol requirements if these procedures are performed as routine medical care for the patient's underlying disease or other illnesses.

The study will enroll patients with *TP53* mutations that are not benign or likely benign, as determined by local Next Generation Sequencing (NGS) and a study-specific variant interpretation algorithm. The *TP53* variant interpretation will be verified centrally prior to inclusion. Central NGS testing including *TP53* will subsequently be conducted on all patients after enrollment. If there is discordance between local and central testing patients will be allowed to remain on study.

5.1 Inclusion Criteria

Patients must fulfill all of the following criteria; there will be no eligibility waivers granted:

1. Patient has signed the Informed Consent (ICF) and is able to comply with protocol requirements.
2. Documented diagnosis of MDS, according to World Health Organization (WHO) classification (< 20% blasts), that meets IPSS-R classification of intermediate, high, or very high-risk disease.
3. Patient has adequate organ function as defined by the following laboratory values:
   a) Creatinine clearance > 30 mL/min (by Cockcroft-Gault method; see Appendix IV)
   b) Total serum bilirubin < 1.5 × ULN, unless due to Gilbert's Syndrome, underlying disease of MDS, hemolysis or considered an effect of regular blood transfusions
   c) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 × ULN, unless due to underlying disease of MDS
4. Age ≥18 years at the time of signing the informed consent form
5. Having at least one *TP53* mutation which is not benign or likely benign
6. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (Appendix I).
7. Females of childbearing potential, negative pre-treatment urine or serum pregnancy test.
8. Females of childbearing potential and males with female partners of childbearing potential must be willing to use an effective form of contraception such as latex condom, hormonal birth control, intrauterine device or double barrier method

during chemotherapy treatment and for at least six months thereafter.

5.2 Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

1. Patient has a known history of HIV or active hepatitis B or active hepatitis C infection (testing not mandatory)
2. Patient has any of the following cardiac abnormalities (as determined by treating MD):
    a. Myocardial infarction within six months prior to registration,
    b. New York Heart Association Class III or IV heart failure (Appendix III) or known left ventricular ejection fraction (LVEF) < 40%, as assessed by echocardiogram or MUGA scan;
    c. A history of familial long QT syndrome;
    d. Symptomatic atrial or ventricular arrhythmias not controlled by medications
    e. QTc ≥ 470 msec calculated from a mean of 3 ECG readings using Fridericia's correction ($QTcF = QT/RR^{0.33}$). *Note*: Patients with QTcF ≥ 470 msec and with bundle branch block and/or pacemaker rhythm may be enrolled after approval by Medical Monitor;
3. Concomitant malignancies or previous malignancies with less than a 1-year disease free interval at the time of signing consent. Patients with adequately resected basal or squamous cell carcinoma of the skin, or adequately resected carcinoma *in situ* (e.g. cervix) may enroll irrespective of the time of diagnosis
   Prior exposure to azacitidine, decitabine or investigational hypomethylating agent, or induction chemotherapy for MDS or AML. *Note*: intensive chemotherapy for any other prior cancer is *not* exclusionary.
4. Use of cytotoxic chemotherapeutic agents, or experimental agents (agents that are not commercially available) for the treatment of MDS within 14 days of the first day of study drug treatment
5. Concurrent use of erythroid stimulating agents, G-CSF, or GM-CSF within 14 days of the first day of study drug treatment.
6. History of allogeneic stem cell transplantation
7. Pregnancy: Pregnant women are excluded from this study because APR-246 has not been studied in pregnant patients. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with APR-246, breastfeeding should be discontinued if the mother is treated with APR-246.
8. Active uncontrolled infection.

5.3 Inclusion of Women, Minorities and Children

This study is open to both male and female patients of all ethnicities. This study excludes patients aged < 18 years.

5.4 Withdrawal Criteria

Protocol therapy will be discontinued at any time if any of the following situations occur:

1. Clinically significant progressive disease
2. The development of toxicity which, in the Investigator's judgment, precludes further therapy.
3. Patient refusal
4. A pattern of noncompliance with study medication or protocol-required evaluations and follow-up visits
5. Intercurrent illness: a condition, injury, or disease unrelated to cancer in the opinion of the investigator, that renders continuing treatment unsafe or regular follow-up impossible
6. At the discretion of the Investigator that it is in the best interest of the patient to withdraw
7. Pregnancy
8. Study termination by the sponsor

5.4.1 Withdrawn Subjects

When a patient is removed from the study, the Investigator will clearly document the reason in the medical record and complete the appropriate CRF page describing the reason for discontinuation. In addition, every effort should be made to complete the appropriate assessments listed in Section 7.5.

5.5 Noncompliance

All instances of noncompliance and all resulting protocol deviations will be entered in the CRF and/or documented in monitoring reports.

6.0 TREATMENT OF SUBJECTS

6.1 Drug Preparation and Administration

At the pharmacies, the IMP vials are to be stored at 2-8°C (35.6-46.4°F). At the pharmacies and at the study centers, the prepared APR-246 study product (diluted in sodium chloride solution) is to be stored at not more than 25°C. The infusion should be completed within 24 hours from the time of preparation (see Pharmacy Binder).

APR-246 treatment (Experimental Arm only) will be administered on Days 1-4, and azacitidine on Days **4-10** (Figure 4). Treatment may be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's disease.

Patients will be randomized (1:1) to 1 of 2 arms, Experimental or Control arm.

6.1.1 Experimental Arm (APR-246 + Azacitidine)

APR-246 will be administered as a 6-hour intravenous infusion daily on days 1–4 of each 28-day cycle. APR-246 fixed dose is 4.5 g. APR-246 is administered in a 2-step infusion:

Step 1: Loading dose of 1.5 g for the first 45 minutes (± 2 min)

Step 2: Maintenance dose of 3 g over 5 hours 15 minutes (± 30 min)

Detailed instructions on vial concentration, preparation and dispensing can be found in the Pharmacy Binder. The infusion timing, including start/stop times and the time of rate change, must be recorded.

Azacitidine will be given at the standard dose of 75 mg/m^2 SC or IV over 7 consecutive days, Days **4-10**. On **Day 4** azacitidine is administered immediately after the APR-246 infusion. SC method is preferred but IV is allowed at the Investigator's discretion. However, the same route should be maintained over the 7-day treatment period (whichever route is used on Day **4**, the other days should follow the same route of administration). Detailed instructions on preparation and administration can be found in the Pharmacy Binder, current package insert, and in Section 6.1.2, below.

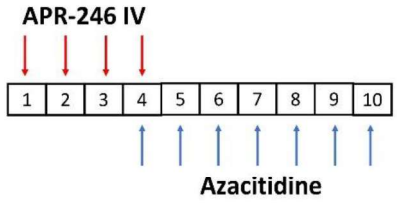

Figure 4. Drug Administration Schema for Experimental Arm: APR-246 and Azacitidine

6.1.2 Control Arm (Azacitidine Only)

Azacitidine will be given at the standard dose of 75 mg/m^2 SC or IV over 7 consecutive days, Days **4-10**, every 28 days. SC method is preferred but IV is allowed at the Investigator's discretion. However, the same route should be maintained over the 7-day treatment period (whichever route is used on Day 4, the other days should follow the same route of administration).

Detailed instructions on preparation and administration can be found in the Pharmacy Binder, and current package insert.

Control Arm: Azacitidine only

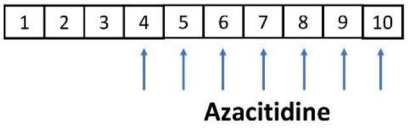

Figure 5. Drug Administration Schema for Control Arm: Azacitidine Only

6.2 Criteria for Treatment, Retreatment and Dose Modifications

6.2.1 APR-246

This section outlines the requirements for proceeding with treatment with APR-246, and the protocol rules for APR-246 dose modification due to toxicity.

The

Table **4** describes the routine ECG requirements from screening through Cycle 4 for patients in Experimental Arm:

Table 4. ECG Requirements in Experimental Arm

Time Point	ECG, n	Timing
Baseline/Screening	Triplicate	Within 28 days of Cycle 1 Day 1
Cycle 1, Days 1-4	Triplicate	Pre-dose; Post dose (6 hrs. after start of infusion; ± 30 min)
Cycles 2+, Day 1	Triplicate	Pre-dose

At screening (baseline), 12-lead ECGs should be collected in triplicate to confirm QT interval does not exceed 470 msec. QT interval must be calculated from a mean of all three ECG readings using Fridericia's correction ($QTcF = QT/RR^{0.33}$).

During Cycle 1 ECG should be collected in triplicate prior to infusion of APR-246 and at the end of infusion of APR-246 (6 hours after start of infusion, ± 30 min) on Days 1 - 4. QTcF must be calculated from a mean of all three ECG readings to confirm it does not exceed 470 msec.

If a pre-dose ECG shows QTcF ≥ 470 msec, the QTc reading should be confirmed by manual assessment using Fridericia's correction ($QTcF = QT/RR^{0.33}$). Serum concentrations of electrolytes should be monitored and corrected, if necessary. Additionally, concomitant medication should be reviewed and adjusted, if necessary. ECG may be repeated at any time, including the same day. APR-246 may only be administered when QTcF has returned to < 470 msec. If APR-246 is given on the same day, procedures outlined in the Schedule of Study Evaluations (Table 8) must be followed. If APR-246 cannot be administered on the same day, that dose must be omitted from the cycle.

If there is a significant change in QTcF, defined as either: a) increase > 60 msec from baseline (or pre-dose), or b) increase to an absolute value ≥ 501 msec, i.e. consistent with NCI CTCAE Grade 3 QTc prolongation, QTc prolongation must be confirmed by a manual assessment of the ECG, and using Fridericia's correction ($QTcF = QT/RR^{0.33}$). If confirmed, the therapy should be interrupted until a cause (electrolyte disorders or an effect of a concomitant medication) has been identified and addressed, and QTcF has returned to < 470 msec. If all other causes for clinically significant QT interval prolongation are excluded, APR-246 must be permanently discontinued.

During subsequent cycles ECG should be collected in triplicate prior to infusion of APR-246 on Day 1 of each cycle. QTcF must be calculated from a mean of all three ECG readings to confirm it does not exceed 449 msec. If pre-dose QTcF is 450-469 msec, APR-246 may be administered, and additional triplicate ECG should be performed at the end of infusion (6 hours after start of infusion, ± 30 min). If post-dose ECG shows a significant change in QTcF, defined as either: a) increase > 60 msec from baseline (or pre-dose), or b) increase to an absolute value ≥ 501 msec, i.e. consistent with NCI CTCAE Grade 3 QTc prolongation, QTc prolongation must be confirmed by a manual assessment of the ECG, and using Fridericia's correction ($QTcF = QT/RR^{0.33}$). If confirmed, the therapy should be interrupted until a cause

(electrolyte disorders or an effect of a concomitant medication) has been identified and addressed, and QTcF has returned to < 470 msec. If all other causes for clinically significant QT interval prolongation are excluded, APR-246 must be permanently discontinued. If QTcF is unchanged or there is no significant change, additional ECG is not required during that cycle.

If repeated QTcF measurements show a stable QTcF < 450 msec, or if QTcF remains stable within the interval of 450 – 469 msec with no significant change at the end of infusion during several cycles of treatment, reducing the number of ECGs performed in the study may be discussed with the Medical Monitor.

If a patient starts treatment with another medication known to prolong QT interval at any time during the study therapy, an additional pre- and post-dose (6 hours after start of infusion, ± 30 min) ECG should be performed on the next treatment day. For patients who do not tolerate the protocol-specified dosing schedule, one dose level reduction is permitted (Table 5) in order to allow the patient to continue the study treatment. A second dose reduction could be permitted following discussion with the Sponsor and Medical Monitor.

Table 5. APR-246 Dose Levels

Dose Modification	APR-246 Dose
Starting Dose Level (DL)	APR-246 4.5 g/day 1.5 g (for first 45 minutes) + 3.0 g (for 5 hours 15 minutes)
One dose level reduction (DL-1)	APR-246 4.0 g/day 1.33 g (for first 45 minutes) + 2.67 g (for 5 hours 15 minutes)
Second dose level reduction (DL-2)*	APR-246 3.5 g/day 1.16 g (for first 45 minutes) + 2.34 g (for 5 hours 15 minutes)

* Discuss with Sponsor and Medical Monitor before implementing second dose level reduction.
The rationale behind this dose reduction scheme is the steep relation between C_{max} and dose, e.g. the suggested 11% and 22% reductions in dose result in 19% and 33% lowering of the average C_{max}, respectively

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 5). Once a dose has been reduced during a treatment cycle, re-escalation during subsequent cycles may be permitted following discussion with the Medical Monitor. If the administration of

APR-246 is interrupted for reasons other than toxicity, then treatment with APR-246 may be resumed at the same dose. The same provision applies if the patient experienced an unacceptable toxicity not specifically described in Table 6, provided that this toxicity resolved to ≤ Grade 1, unless otherwise specified.

Following 4 cycles of therapy for responding patients (i.e. CR, PR, HI, mCR with HI, mCR without HI) treatment with APR-246 and azacitidine can be delayed for up to 14 days to allow for count recovery at Investigator discretion pending discussion with the Sponsor and Medical Monitor.

Non-hematologic Grade 4 treatment related adverse events will lead to permanent discontinuation, irrespective of recovery time, unless otherwise specified. Exceptions would include nausea/vomiting/diarrhea which can be controlled by medications and/or asymptomatic electrolyte imbalances which can be corrected. In addition, in most instances, patients that experience a prolonged treatment interruption because of an adverse event and/or a Grade 3 adverse event will decrease the dose of study drug after their recovery (see specific tables for dose adjustment guidelines).

If any drug-related Grade 3 or 4 toxicity that is not clearly related to azacitidine is observed, APR-246 dose must be reduced for the next and subsequent cycles.

Patients requiring >2 dose reductions for APR-246 will be permanently discontinued from study drug. Patients who permanently discontinue APR-246 or azacitidine should have follow-up within 28 days after discontinuation of all study treatment or resolution of the AE to ≤ Grade 1, whichever occurs first, that includes all study assessments appropriate to monitor the event.

Table 6. Recommendations for APR-246 Dose Modifications and Criteria for Treatment Interruption and Re-Initiation with Treatment-Related Adverse Events

Any changes in dose must be recorded on the Dosage Administration Record CRF.

Renal Toxicities

Parameter	Worst toxicity[†]	Dose Modifications for APR-246
Serum Creatinine	Grade 1 (< 1.5 × baseline)	Maintain dose level
	Grade 2 (> 1.5 to 3.0 × baseline)	Omit dose until resolved to ≤ Grade 1, then: If first occurrence, then maintain dose level If second or more consecutive occurrence, then ↓ 1 dose level
	Grade 3 (> 3.0 – 6.0 × baseline)	Omit dose until resolved to ≤ Grade 1, then: ↓ 1 dose level If not resolved or resolved in > 7 days, evaluate if other contributing factors are present. If none, or after consideration of best interest of the patient, discontinue patient from APR-246. If other factors present, consider continuing after ↓ 1 dose level
	Grade 4 (> 6.0 × baseline)	Permanently discontinue patient from APR-246
[†] Common Terminology Criteria for Adverse Events (CTCAE) version 5.		

Hepatic Toxicities[◊]

Parameter	Worst toxicity	Dose Modifications for APR-246
Bilirubin[‡]	Grade 1 (> ULN - 1.5 × ULN)	Maintain dose level with LFTs[≠] monitored as per protocol
	Grade 2 (> 1.5 - 3.0 × ULN) with ALT or AST ≤ 3.0 × ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, if first occurrence, then maintain dose level If second or more consecutive occurrence or if resolved in > 7 days, then ↓ 1 dose level
	Grade 3 (> 3.0 - 10.0 × ULN) with ALT or AST ≤ 3.0 × ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level. If no subsequent event, consider re-escalation to original dose level. Omit dose until resolved to ≤ Grade 1, then: ↓ 1 dose level. If second or more consecutive occurrence or if not resolved or resolved in > 7 days, evaluate if other contributing factors are present. If none, or after consideration of best interest of the patient, discontinue patient from APR-246. If other factors present, consider continuing after ↓ 1 dose level.
	Grade 4 (> 10.0 × ULN)	Permanently discontinue patient from APR-246

Parameter	Worst toxicity	Dose Modifications for APR-246
AST or ALT	Grade 1 (> ULN - 3.0 × ULN if baseline was normal; 1.5 - 3.0 × baseline if baseline was abnormal)	Maintain dose level with LFTs[≠] monitored per protocol
	Grade 2 (> 3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal) in the absence of total bilirubin elevation to > 2.0 × ULN	Omit dose until resolved to ≤ Grade 1, then If resolved in ≤ 7 days, if first consecutive occurrence, then maintain dose level If second or more consecutive occurrence or if resolved in > 7 days, then ↓ 1 dose level
	Grade 3 (> 5.0 - 20.0 × ULN if baseline was normal; > 5.0 – 20.0 x baseline if baseline was abnormal) in the absence of total bilirubin elevation to > 2.0 × ULN	Omit dose until resolved to ≤ Grade 1, then If resolved in ≤ 7 days, if first consecutive occurrence, then maintain dose level. If second or more consecutive occurrence or if not resolved or resolved in > 7 days, evaluate if other contributing factors are present. If none, or after consideration of best interest of the patient, discontinue patient from APR-246. If other factors present consider continuing after ↓ 1 dose level
	Grade 4 (> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal)	Permanently discontinue patient from APR-246

[◊] Please note that the Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study. Hy's law identifies patients at risk for severe drug-induced liver injury, DILI, and is defined as AST or ALT ≥ 3× ULN together with Total Bilirubin Level ≥2×ULN, where no other reason, other than the suspected drug, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.
[†] Common Terminology Criteria for Adverse Events (CTCAE) version 5.
[‡] For patients with Gilbert's syndrome, these dose modifications apply to changes in direct bilirubin only.
[≠] LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 × ULN), alkaline phosphatase.

Hematological Toxicities[†]

Parameter	Worst toxicity	Dose Modifications for APR-246
Febrile neutropenia	ANC < 0.5 × 10^9/L, temperature of ≥ 38 °C or a sustained temperature of ≥ 38°C for more than 1hour	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Thrombocytopenia	Grade 4 (PLT < 25 × 10^9/L)[‡] and major bleeding event	Permanently discontinue patient from APR-246

[†] Only applicable for patients with normal baseline absolute neutrophil count (ANC) and platelets. For patients with low (abnormal) baseline ANC and/or platelets that do not return to baseline (pre-cycle) after a clinically significant decrease following treatment, please contact the Medical Monitor.
[‡] Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Other Non-Hematological Toxicities

Parameter	Worst toxicity	Dose Modifications for APR-246
CNS – dizziness, dyskinesia and ataxia	Grade 1	Maintain dose level
	Grade 2	If resolved (to ≤ Grade 1) with medical therapy, continue same dose level If not resolved despite treatment interruption and maximal medical therapy, stop infusion and ↓ 1 dose level for subsequent dose
	Grade 3	Stop infusion and give medical therapy. If resolved (to ≤ Grade 1) with medical therapy, infusion may continue at the investigator's discretion. ↓ 1 dose level for subsequent dose
	Grade 4	Permanently discontinue patient from APR-246.
Infusion Related Reaction	Grade 1	Maintain dose level.
	Grade 2	Maintain dose level; Symptomatic management (e.g., antihistamines, corticosteroids, narcotics, IV fluids)
	Grade 3	If resolved (to ≤ Grade 1) in < 4 hours with treatment interruption and medical therapy (e.g., antihistamines, corticosteroids, narcotics, IV fluids), continue same dose level and rate. If not resolved in < 4 hours despite treatment interruption and maximal medical therapy, stop infusion and ↓ 1 dose level for subsequent dose
	Grade 4	Permanently discontinue patient from APR-246.
Nausea/Vomiting/ Diarrhea	Grade 1	Maintain dose level
	Grade 2	If resolved (to ≤ Grade 1), then maintain dose level If not resolved despite maximal medical therapy, then ↓ 1 dose level
	Grade 3	If resolved (to ≤ Grade 1), then maintain dose level If not resolved despite maximal medical therapy, then ↓ 1 dose level
	Grade 4	Permanently discontinue patient from APR-246
Any Other Toxicity	Grade 3 or 4	Delay dose until resolution to ≤ Grade1, then ↓ 1 dose level
† Common Terminology Criteria for Adverse Events (CTCAE) version 5.		

Treating physicians should use clinical judgment and may consult the Medical Monitor for guidance with dose modifications.

6.2.2 Management of CNS Adverse Events

If a patient reports any clinical adverse event of any grade during the administration period of APR-246 that could be considered to originate from the CNS (e.g. dizziness, vertigo, nausea) then the patient will be given a rescue medication as per the institutional standard of care.

Dose modifications have been successfully used to manage potential CNS effects occurring during the infusion. For any clinical adverse event Grade ≥ 3, the infusion should immediately be stopped, and if all symptoms resolve to CTCAE ≤ Grade 1 within 2 hours, the infusion may be resumed at the same infusion rate. If the same symptoms do occur or increase in severity during re-challenge the infusion should be stopped.

If the event lasts longer than 2 hours, then the APR-246 infusion should be discontinued for that day, the remaining drug should be discarded, and toxicity should be managed according to recommendations in Table 6.

After an adverse event considered as related, a single level dose reduction of APR-246 is allowed. Dose reduction is recommended after any Grade ≥ 3 CNS AEs.

In prior studies, prochlorperazine 10 mg orally tid (three times daily) has been reported to be an effective treatment that may also be used prophylactically. When prochlorperazine is used prophylactically, start the day prior to the Day 1 and continue 10 mg tid to day 4 (as needed). The US label for prochlorperazine does not list QT prolongation as a known risk associated with use of this drug.

Re-escalation after dose reduction due to any APR-246-related toxicity may be permitted following discussion with the Medical Monitor.

6.2.3 Management of Nausea and Vomiting

Patients who experience nausea and vomiting in association with APR-246 infusion will be prescribed appropriate rescue treatment and prophylaxis (e.g., anti-nausea or anti-emetics medication) as per institutional guidelines. Patients who receive additional drugs that are known to cause QT prolongation (Section 6.3) must be monitored for any signs of QT prolongation via an ECG before and after the APR-246 infusion.

- If QTc > 501 msec is observed in a patient concomitantly treated with another QT interval prolonging drug, this drug should be stopped and treatment with APR-246 may be restarted when QTc < 470 msec (refer to section 6.2.1).

A list of suggested rescue medications is provided below in Table 7.

Table 7. Medications for Managements of Nausea and Vomiting

Drug	Dosage	QT Prolongation[1]
Ondansetron	8 mg PO administered 30 minutes before the start of infusion or per label	Yes
Dolasetron	100 mg PO administered within one hour before start of infusion or per label	Yes
Palonosetron	0.5 mg PO administered approximately one hour prior to the start of infusion or per label	No
Prochlorperazine	10 mg PO three times daily. Continue until the end of Day 4 of the cycle. When used prophylactically in subsequent cycles, start the day prior to Day 1 administration of APR-246	No

[1] Please refer to Section 6.2.1 for details on concurrent administration of medications known to cause QTc interval prolongation.

6.2.4 Management of Infusion Reactions

If a patient experiences an infusion reaction during the study, the infusion will be stopped and appropriate medical care (e.g., epinephrine, oxygen, H1 and H2 antagonists, and/or corticosteroids) will be administered.[32]

6.2.5 Azacitidine Dose Adjustments

Azacitidine dose modifications will follow the Prescribing Information[30,31] or institutional practice, supported by international recommendations. Azacitidine should be administered SC or IV over 7 consecutive days, Days **4-10,** every 28 days. A single missed dose (for any reason but toxicity) may, at the Investigator's decision, be compensated by adding an additional dosing day for azacitidine (e.g. Day **11**) so that the patient receives the total 7 days of treatment per cycle. If the azacitidine dose interruption is > 2 days, discuss with the Medical Monitor.

6.3 Concomitant Treatment

If patients experience prolonged myelosuppression they will be placed on infection prophylaxis per standard of care.

Patients may not receive any other drug to treat MDS while on study. Patients may continue their baseline medication(s) as long as they are not prohibited. Palliative and supportive care (e.g., anti-emetics, bisphosphonates) for disease related symptoms will be offered to all patients in the study per institutional practices. Adverse events will be treated

as clinically indicated. All concomitant medications that are currently in use or that become necessary during the study should be recorded.

Hydroxyurea may be administered before study start and up to the time of study randomization. At the investigator's discretion, for patients with significant leukocytosis during the early treatment cycles, hydroxyurea may be administered. The hydroxyurea should be discontinued as soon as clinically appropriate.

If the patient develops an acute infusion reaction (≥ Grade 2), the infusion must be stopped until the reaction is resolved to ≤ Grade 1. Premedication (e.g., dexamethasone) may be used after the first cycle.

The prophylactic use of G-CSF is prohibited. Supportive use of G-CSF for treatment of cytopenias may be allowed at the discretion of the investigator per institutional practices.

6.4 Monitoring Subject Compliance

All instances of protocol deviations will be entered into Monitor Express and will be reviewed by the Investigator, Sponsor and appropriate Theradex designee.

7.0 STUDY EVALUATIONS

7.1 Schedule of Study Evaluations

Table 8. Schedule of Study Evaluations (also described in Sections 7.2 through 7.5)

Study Calendar Evaluation [a]	Screening	Cycle 1								Cycle 2 and Subsequent Cycles								End of Odd Cycles	End of Even Cycles	Q3M After Month 12	End of Treat-ment [o]	Long-Term Follow-Up[p]
		D1	D2	D3	D4	D5-**10**	D 8	D15 [b]	D22 [b]	D1 [c]	D2	D3	D4	D5 -**10**	D8	D15 [b]	D22[b]					
Informed consent	×																					
TP53 confirmation [d]	×																					
Medical history [e]	×																					
Physical examination [f]	×	×								×											×	
Height	×																					
Weight	×	×								×											×	
Vital signs [f]	×	×	×	×	×	**×**	**×**			×	×	×	×	**×**	**×**						×	
ECOG PS	×	×								×											×	
APR-246 (experimental arm)[g]		×	×	×	×					×	×	×	×									
Azacitidine [h]					×	×	**×**						×	×	**×**							
Bone marrow collection[i]	×																		×	×	×	×
Response assessment[r]																		×	×			
Hematology [j]	×	×					×	×	×	×[j]					×	×	×			×	×	×
Blood chemistry [k]	×	×					×	×	×	×					×	×	×				×	
Creatinine clearance[k]	**×**																					
Pregnancy test [l]	×																					
ECG [m]	×	×[m]	×[m]	×[m]	×[m]					×												
APR-246 PK sample [n]		×	×		×					×	×		×									
Azacitidine PK sample [n]					×																	
Survival & transformation to AML																					×	×
Transfusion log		From 8 weeks prior to randomization to end of treatment/off treatment																				
Adverse events		Starting at the time of eligibility confirmation through 30 days after last dose[q]																				
Concomitant medications	×	Reviewed throughout study																				

Footnotes to Schedule of Study Evaluations

a. All screening/baseline evaluations will be performed within 28 days prior to the start of APR-246 and azacitidine treatment. In the event that a visit or test cannot be scheduled on the exact visit day, a window of ±3 days is allowable.

b. A window of ±3 days applies to this study visit.

c. After the first cycle, Day 1 evaluations of subsequent cycles are to be done within 3 days prior to next cycle drug administration.

d. Confirmation of TP53 status for eligibility will be performed centrally using the local lab report.

e. Full medical history will be obtained at baseline for safety and eligibility purposes; this will include any issues/clinically significant findings from 28 days prior to screening date.

f. Physical exam and vital signs (including blood pressure, heart rate, respiration rate and temperature) will be completed for safety purposes and clinically significant items will be recorded as AEs where appropriate. **In Experimental Arm, v**ital signs will be collected prior to APR-246, 2 hours into infusion and at end of infusion (EOI) (±30 min. at all time points). **Both arms: if azacitidine is given via IV infusion, vital signs will be taken before the infusion (within 0-2 hours) and at EOI (30-60 minutes); if azacitidine is given via SQ injection, vital signs will be taken before the injection (within 0-2hours). In the Control Arm, the physical exam and vital signs are not needed on each day prior to the first day of azacitidine administration; vital signs will be assessed on treatment days only.**

g. For Experimental Arm Only, APR-246 is administered IV on days 1-4 of each 28-day cycle.

h. Azacitidine is administered SC over 7 consecutive days, on Days **4-10** of each 28-day cycle. On **Day 4** azacitidine is administered immediately after the APR-246 infusion. SC route is preferred but site may give IV at the investigator's discretion. The same route should be maintained over the 7-day treatment period (whichever route is used on day **4,** the other days should follow the same route of administration).

i. **B**one marrow aspirate sample and biopsy core is collected at baseline and when bone marrow is sampled for disease assessment. If no aspirate is available, then peripheral blood is acceptable. Bone marrow assessment completed within 28 days of signing consent will be accepted to fulfill screening requirement, as long as it has been completed following the last MDS treatment (excluding ESAs (erythropoietic stimulating agent)).

j. Hematology including hemoglobin, hematocrit, MCV, platelet count, blasts, WBC and WBC differentials weekly. **The** peripheral blood sample collected on Day 1 of each cycle starting at Cycle 2 **will be** for disease assessment, if bone marrow aspirate is not available **(see footnote r).** For patients with documented CR at disease assessment following Cycle 2, hematology and blood chemistry assessments will be required for D1 of each subsequent cycle and more frequently per the discretion of the treating physician. Otherwise performed weekly until CR.

k. Blood chemistry including sodium, potassium, BUN, glucose, ALT/AST, alkaline phosphatase, total protein, total bilirubin, albumin, creatinine, calcium, chloride and magnesium weekly. At screening, the creatinine clearance may be calculated from the serum creatinine. A 24-hour urine for Creatinine Clearance may be performed at investigator's discretion. For patients with documented CR at disease assessment following Cycle 2, hematology and blood chemistry assessments will be required for D1 of each subsequent cycle and more frequently per the discretion of the treating physician. Otherwise perform weekly until CR.

l. Pregnancy test; for women of childbearing potential, a negative pregnancy test (urine or serum) must be documented between Screening and first day of treatment on study. Must be documented prior to 1st dose of treatment on study.

m. Standard 12-lead ECGs to be performed in triplicate at baseline/screening, on Days 1 - 4 of Cycle 1 (experimental arm only) and on Days 1 of each subsequent cycle (experimental arm only) with patient in a semi-recumbent position. Please consult Table 10 for ECG collection schedule.

n. Please consult section 8.3, Table 9 for PK collection schedule.

o. Patients discontinuing treatment early should complete their end of treatment visit within approximately 28 days of their last dose of investigational product. Physical exam, vital signs, adverse event reporting, CBC (complete blood count), and blood chemistry and BM aspirate and biopsy with NGS analysis should be performed if feasible.

   Off Treatment assessment includes best response, date of first response, date of loss of response, reason for discontinuation.

   Off study CRF: vital status, date of death/last contact, transformation to AML and the date of transformation to AML if applicable.

p. Long-term follow up can be done remotely (e.g. via telephone, via Local Practitioner or via review of medical records). Assuming there is no withdrawal of consent, patients who stop study treatment (APR-246 or azacitidine) for any reason (e.g. toxicity, transition to SCT, PD) will continue long-term follow-up (see Section 7.6).

   If a patient is removed from the study due to unacceptable adverse events, the event(s) will be followed until resolution or stabilization of the adverse event.

q. AE description, grade and start date and resolution date should be captured and documented.

r. Response assessment is performed at the end of each cycle (every 4 weeks), based on peripheral blood and bone marrow (at the end of even cycles), and peripheral blood alone (at the end of odd cycles).

7.2 Pre-Study Assessments (All Patients)

Prior to performing any procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to all patient candidates and written informed consent will be obtained. Patients who choose to participate will have to consent to the biobanking program and will be asked to sign the mandatory section in the main study consent form related to biobank samples. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study specific evaluations. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent.

7.2.1 Screening (All patients)

All pre-treatment evaluations are to be performed within 28 days of Day 1 unless otherwise noted.

- Informed Consent
- TP53 mutation confirmation – send local report to vendor (see lab manual for instructions)
- Medical history – must include a thorough assessment and documentation of all transfusions received beginning from 8 weeks prior to randomization to end of treatment/off treatment; record transfusions on transfusion log.
- Physical examination
- Height
- Weight
- ECOG performance status
- Creatinine clearance (Cockcroft-Gault method; see Appendix IV)
- Vital signs: including blood pressure, heart rate, respiration rate and temperature
- Hematology: hemoglobin, hematocrit, MCV, platelet count, blasts, WBC and WBC differentials.
- Blood chemistry including sodium, potassium, BUN, glucose, ALT/AST, alkaline phosphatase, total protein, total bilirubin, albumin, creatinine, calcium, chloride and magnesium.
- Serum pregnancy test: For patients with reproductive potential.
- ECG: Standard 12-lead ECGs to be performed with patient in a semi-recumbent position in triplicate.
- Concomitant medication
- Bone marrow aspirate and biopsy - Bone marrow assessment completed within 28 days of signing consent will be accepted to fulfill screening requirement as long as it has been completed following the last MDS treatment (excluding ESAs).
- Baseline bone marrow aspirate and biopsy core for exploratory objectives. If no aspirate is available, then peripheral blood is acceptable.
- Adverse Events: baseline, at the time of eligibility confirmation.

7.2.2 Randomization

Randomization will occur after screening, once a patient has had their eligibility confirmed, has agreed to participate and is ready to start on the study treatment.

Stratified randomization will be based on age group (< 65 years and ≥ 65 years). Patients will be assigned to one of two strata based on age group (< 65 years and ≥ 65 years), and then assigned to the particular treatment arm from the randomization list for that stratum. Randomization will be balanced within each stratum with patients randomly assigned with equal probability (1:1 allocation) to one of the two treatment arms (APR-246 + azacitidine or azacitidine). Permuted block randomization (random allocation within block) will be used to assign patients to treatments within each stratum.

7.3 Experimental Arm (APR-246 + Azacitidine)

In the event that a visit or test cannot be scheduled on the exact visit day, a window of ±3 days is allowable.

7.3.1 Cycle 1

7.3.1.1 Days 1-10

Day 1 examinations marked ***** do not need to be repeated if already performed within 3 days prior to day 1 cycle 1.

- Transfusion log: must capture all transfusions beginning from 8 weeks prior to randomization to end of treatment/off treatment.
- Adverse Events: All adverse events since the last visit should be recorded. Even though pre-medicated, patients should be closely monitored.
- Concomitant medications.
- Physical examination: Day 1* weight, body surface area.
- ECOG performance status: Day 1.
- Vital signs. **Before infusion,** 2 hours into **each** infusion (± 30 min) and at EOI (± 30 min)
- Hematology: Day 1* hemoglobin, hematocrit, MCV, platelet count, blasts, WBC and WBC differentials.
- Blood chemistry: Day 1* sodium, potassium, BUN, glucose, ALT/AST, alkaline phosphatase, total protein, total bilirubin, albumin, creatinine, calcium, chloride and magnesium.
- ECG: Standard 12-lead ECG to be performed with patient in a semi-recumbent position; pre-dose (prior to the PK blood draw before the infusion) and at the end of infusion, per Table 10.
- Pharmacokinetics for APR-246: on Days 1, 2, 4, per Section 8.3

- APR-246 administration.
- Azacitidine administration. Administered daily for 7 consecutive days starting on Day **4** (Days **4** to **10** inclusive). The same route should be maintained over the 7-day treatment period (whichever route is used on Day **4,** the other days should follow the same method route of administration). On **Day 4** azacitidine is given immediately after APR-246 infusion.
- Pharmacokinetics for azacitidine: Day 4, per Section 8.3 (at selected sites only)

7.3.1.2 Week 2 (Day 8 ± 3 Day)

- Adverse events
- Concomitant medications
- Hematology
- Blood chemistry

7.3.1.3 Perform Weekly

- Adverse events
- Concomitant medications
- Hematology weekly
- Blood chemistry weekly

7.3.2 Cycle 2 Day 1 ± 3 Day (same as Cycle 1 Day 29)

Tests should be performed prior to first dose
Day 1 examinations marked ***** do not need to be repeated if already performed within 3 days prior to day 1 of cycle 2.

- Adverse Events: All adverse events since the last visit should be recorded. Even though pre-medicated, patients should be closely monitored.
- Concomitant medications.
- Physical examination: Day 1* weight, body surface area.
- ECOG performance status: Day 1.
- Vital signs.
- Hematology: Day 1* hemoglobin, hematocrit, MCV, platelet count, blasts, WBC and WBC differentials.
- Blood chemistry: Day 1* sodium, potassium, BUN, glucose, ALT/AST, alkaline phosphatase, total protein, total bilirubin, albumin, creatinine, calcium, chloride and magnesium.
- ECGs pre-dose. Standard 12-lead ECGs to be performed in triplicate on Day 1 with patient in a semi-recumbent position. Perform prior to the PK blood draw before infusion, per Table 10.

7.3.2.1 Days 1-10

- Adverse events: All adverse events since the last visit should be recorded. Even though pre-medicated, patients should be closely monitored.
- Concomitant medications.
- Vital signs. Before infusion, then 2 hours into each infusion (±30 min) and at EOI (± 30 min)
- APR-246 administration (Days 1 – 4).
- Azacitidine administration. Administered daily for 7 consecutive days starting on Day **4** (Days **4** to **10** inclusive). The same route should be maintained over the 7-day treatment period (whichever route is used on Day **4,** the other days should follow the same method route of administration). On **Day** 4 azacitidine is given immediately after APR-246 infusion.
- Pharmacokinetics for APR-246: Cycle 2 and 3: Days 1, 2, 4

7.3.2.2 Week 2 (Day 8 ± 3 Day)

- Adverse events
- Concomitant medications
- Hematology
- Blood chemistry

7.3.2.3 Week 3 (Day 15 ± 3 Day)

- Adverse events
- Concomitant medications
- Hematology
- Blood chemistry

7.3.2.4 Week 4 (Day 22 ± 3 Day) (Rest Period)

- Adverse events
- Concomitant medications
- Hematology
- Blood chemistry

7.3.2.5 End of Cycle 2

- Bone marrow/response assessment
- Bone marrow aspirate and biopsy core for exploratory objectives. If no aspirate is available, then peripheral blood is acceptable.

7.3.3 Cycle 3 Day 1 ±3 Day (same as Cycle 2 Day 29) and Onwards (Cycle 4+)

These tests should be performed prior to first dose

- Adverse Events: All adverse events since the last visit should be recorded. Even though pre-medicated, patients should be closely monitored.
- Concomitant medications.
- Physical examination: Day 1* weight, body surface area.
- ECOG performance status: Day 1.
- Vital signs.
- Hematology: Day 1* hemoglobin, hematocrit, MCV, platelet count, blasts, WBC and WBC differentials.
- Blood chemistry: Day 1* sodium, potassium, BUN, glucose, ALT/AST, alkaline phosphatase, total protein, total bilirubin, albumin, creatinine, calcium, chloride and magnesium.
- ECGs: see Table 10.

7.3.3.1 Days 1-10

- Adverse Events: All adverse events since the last visit should be recorded. Even though pre-medicated, patients should be closely monitored.
- Concomitant medications.
- Vital signs. Before infusion, then 2 hours into each infusion (± 30 min) and at EOI (± 30 min)
- APR-246 administration (Days 1 – 4).
- Azacitidine administration. Administered daily for 7 consecutive days starting on Day **4** (Days **4** to **10** inclusive). The same route should be maintained over the 7-day treatment period (whichever route is used on Day 1, the other days should follow the same method route of administration). On **Day 4** azacitidine is given immediately after APR-246 infusion
- ECG: Standard 12-lead ECGs to be performed with patient in semi-recumbent position:
    - Day 1 only: Perform prior to the PK blood draw before infusion, per Table 10.
- Cycle 3 Only: Pharmacokinetics APR-246 as per Section 8.3
- Hematology weekly
- Blood chemistries weekly

7.3.3.2 Week 2 (Day 8 ± 3 Day)

- Adverse events
- Concomitant medications
- Hematology. For patients with documented CR at disease assessment following cycle 2, hematology and blood chemistry assessments will be required for D1 of each subsequent cycle and more frequently per the discretion of the treating

physician.
- Blood chemistry. For patients with documented CR at disease assessment following cycle 2, hematology and blood chemistry assessments will be required for D1 of each subsequent cycle and more frequently per the discretion of the treating physician.

7.3.3.3 Week 3 (Day 15 ± 3 Day)

- Adverse events
- Concomitant medications
- Hematology weekly as needed (see above)
- Blood chemistry weekly as needed (see above)

7.3.3.4 Week 4 (Day 22 ± 3 Day) (Rest Period)

- Adverse events
- Concomitant medications
- Hematology weekly as needed (see above)
- Blood chemistry weekly as needed (see above)

7.3.4 End of Odd Numbered Cycles Up to Month 12

- Response assessment, based on peripheral blood

7.3.5 End of Even Numbered Cycles Up to and Including Month 12

- Bone marrow sample for response assessment
- Bone marrow aspirate and biopsy core for exploratory objectives. If no aspirate is available, then peripheral blood is acceptable.

7.3.6 After Month 12

Every 3 Month Visits:
- Adverse events
- Concomitant medications
- Bone marrow aspirate and biopsy / response assessment
- Bone marrow aspirate and biopsy core for exploratory objectives. If no aspirate is available, then peripheral blood is acceptable.
- CBCs as needed.

7.4 Control Arm (azacitidine)

In the event that a visit or test cannot be scheduled on the exact visit day, a window of ±3 days is allowable. After the first cycle, Day 1 of each subsequent cycle is the same as Day 29 of the previous cycle.

7.4.1 Each Cycle Day 1 ±3 Days (same as Day 29 of previous cycle) through Day 10

Tests should be performed prior to first dose
Day 1 examinations marked ***** do not need to be repeated if already performed within 3 days prior to day 1 cycle 1.

- Adverse Events: All adverse events since the last visit should be recorded. Even though pre-medicated, patients should be closely monitored.
- Concomitant medications.
- Physical examination: Day 1*. Weight, body surface area.
- ECOG performance status: Day 1.
- Vital signs**. If azacitidine is given IV:** before (within 0-2 hours) and EOI (30-60 minutes). **If azacitidine is given SC: before administration (within 0-2 hours).**
- Hematology: Day 1* hemoglobin, hematocrit, MCV, platelet count, blasts, WBC and WBC differentials.
- Blood chemistry: Day 1* sodium, potassium, BUN, glucose, ALT/AST, alkaline phosphatase, total protein, total bilirubin, albumin, creatinine, calcium, chloride and magnesium.
- Azacitidine will be administered daily for 7 consecutive days starting on Day **4** (Days **4** to **10** inclusive). SC preferred but will allow for IV at the discretion of the treating physician. If SC (or IV) is used on Day 4, the other days should follow the same method of administration.
- Pharmacokinetics for azacitidine: Only Cycle 1 Day 4, per Section 8.3.

7.4.2 Perform Weekly

- Adverse events
- Concomitant medications
- Hematology
- Blood chemistry

7.4.3 End of Odd Numbered Cycles Up to Month 12

- Response assessment, based on peripheral blood

7.4.4 End of Even Numbered Cycles Up to and Including Month 12

- Bone marrow sample for response assessment
- Bone marrow aspirate and biopsy core for exploratory objectives. If no aspirate is available, then peripheral blood is acceptable.

7.4.5 After Month 12

Every 3 Month Visits:

- Adverse events
- Concomitant medications
- Bone marrow aspirate and biopsy / Response assessment
- Bone marrow aspirate and biopsy core for exploratory objectives. If no aspirate is available, then peripheral blood is acceptable.
- CBCs as needed.

7.5 End of Treatment Visit (All Patients)

This visit should take place within 28 days of the last dose of APR-246 or azacitidine, if treatment is stopped early for any reasons.

- Physical examination: weight, body surface area.
- Vital Signs
- Disease Assessment
- Bone marrow aspirate and biopsy core for exploratory objectives. If no aspirate is available, then peripheral blood is acceptable.
- ECOG performance status
- Hematology
- Blood chemistry
- Safety: Adverse events must be collected up to 30 days after the last dose.

7.6 Long-Term Follow-Up

This can be done remotely (e.g. via telephone, via General Practitioner or via review of medical records).

Assuming there is no withdrawal of consent, patients who stop study treatment (APR-246 or azacitidine) for any reason (e.g. toxicity, transition to SCT, PD) will continue long-term follow-up:

1. Patients who discontinue study treatment to receive SCT:
    a. Collect post SCT response assessments, transformation to AML and survival every month until relapse or death, whichever occurs first.
    b. After PD, collect data for survival and transformation to AML every 6 months until death.
2. Responders (CR, PR, mCR with HI, mCR without HI, HI) who discontinue study treatment for other reasons than progressive disease or SCT:
    a. Collect response assessments, transformation to AML and survival monthly until relapse or death, whichever occurs first.

b. After relapse/progression, continue collecting data for survival and transformation to AML every 6 months until death.

3. Non-Responders: patients who discontinue study treatment due to progressive disease:
   a. Collect data for survival and transformation to AML every 6 months until death.

8.0 STUDY ASSESSMENTS

8.1 Safety Assessments

All randomized patients who received any amount of study medication will be evaluated for safety. Adverse events (AEs) are collected during the study, from the time of eligibility confirmation, until 30 days after the last dose of study treatment. AEs are graded according to NCI CTCAE version 5.0. Patients will be assessed at baseline and throughout the study according to the Schedule of Study Evaluations including AEs, laboratory abnormalities, vital signs, physical exam, ECG and performance status.

8.1.1 Safety Analysis

Safety data including AEs, vital signs, laboratory data, ECG, and physical exam will be tabulated for the safety population. Adverse events will be tabulated by body system, preferred term, severity, and relationship to treatments. The tabulation of laboratory parameters will include the normal ranges for each parameter. Each value will be classified as falling above, below, or within the normal range. Laboratory parameters will also be tabulated by maximum NCI-CTCAE severity grade.

8.1.2 Reporting of Adverse Events

8.1.2.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event includes abnormal laboratory values or test results, even when they do not induce clinical signs or symptoms or require therapy.

The adverse event reporting period begins at the time of eligibility confirmation and will continue up to 30 days after the last dose of study treatment.

At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms.

All adverse events (except Grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, are to be recorded in the case report form and source documentation. Adverse events are to be coded according to MedDRA version 21.1. The Investigator must determine the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (see

http://ctep.info.nih.gov) and their causal relationship. Those AEs not covered by these criteria will be graded as follows:

1. Mild: Discomfort noticed, but no disruption of normal daily activity. Prescription drug not ordinarily needed for relief of symptom but may be given because of personality of patient.

2. Moderate: Discomfort sufficient to reduce or affect normal daily activity. Patient is able to continue in study; treatment for symptom may be needed.

3. Severe: Incapacitating, severe discomfort with inability to work or to perform normal daily activity. Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or patient hospitalized.

4. Life-Threatening: Symptom(s) place the patient at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more serious from, might have caused death.

5. Fatal: Event caused the death of the patient.

Adverse events will be followed until resolution or stabilization while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization, unless, in the Investigator's opinion the event is unlikely to resolve due to the patient's underlying disease, or until the patient starts a new treatment.

Laboratory values are to be graded based on the NCI-CTCAE version 5.0 criteria.

8.1.2.2 Attribution Definitions

An adverse event is considered to be associated with the use of the Investigational agent if the attribution is determined as possible, probable or definite. Attribution of AEs will be recorded in the CRF as:

- Unrelated: The AE is clearly not related to the study treatment.
- Unlikely: The AE is doubtfully related to the study treatment.
- Possible: The AE may be related to the study treatment.
- Probable: The AE is likely related to the study treatment.
- Definite: The AE is clearly related to the study treatment.

8.1.2.3 Definition of an Unexpected Adverse Event

An unexpected adverse event is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current IB; or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in this protocol or in the regulatory agency study authorization application.

Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the IB) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

8.1.2.4 Serious Adverse Event (SAE)

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

1. Results in death,

2. Is life-threatening (i.e., the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe),

3. Requires in-patient hospitalization or prolongation of existing hospitalization excluding that for pain management, disease staging/re-staging procedures, or catheter placement unless associated with other serious events,

4. Results in persistent or significant disability/incapacity, or

5. Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.1.2.5 Pregnancy

Any pregnancy diagnosed during the study, or that occurs within 30 days after stopping study medication, must be reported immediately to the Investigator. Pregnancy, in and of itself, is not regarded as an adverse event, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication. If the patient becomes pregnant while on-study, the study drug should be immediately discontinued. Pregnancy information about a female patient or a female partner of a male patient should be reported immediately from the time the Investigator first becomes aware of a

pregnancy or its outcome. This will be performed by the Investigator completing a Pregnancy Form and forwarding it to Theradex Oncology fax number at ***REDACTED*** ***REDACTED***

Any pregnancy complication, spontaneous abortion, elective termination of a pregnancy for medical reasons, outcome of stillbirth, congenital anomaly/birth defect, or serious adverse event in the mother will be recorded as an SAE and will be reported as described in Section 8.1.2.6.

8.1.2.6 Reporting of Serious Adverse Events

Adverse events classified as serious require expeditious handling and reporting to Theradex Oncology to comply with regulatory requirements.

All SAEs, regardless of relationship to the study drug, which occur during the period of observation (from the time of eligibility confirmation to 30 days following the date of the last dose of study drug administration) must be immediately reported (within 1 business day of the initial observation of the event) by email, fax or telephone to the Theradex Oncology Safety Desk. Notification by email is preferred. After this period, only those SAEs assessed as possibly, probably or definitely related to the study drug should be reported.

SAEs will be reported to: Theradex Oncology Safety Desk
REDACTED

8.1.2.7 Safety Monitoring Plan

The medical monitor will be responsible for ongoing safety monitoring for the study per the detailed safety plan. This monitoring will include a review of all serious adverse events as they are reported by the study site. The medical monitor will also be in contact with site monitors and will be available to discuss any issues concerning safety with site staff. Safety data will be reviewed periodically by Theradex Medical Monitor and the Sponsor Medical Officer.

8.1.3 Independent Data Monitoring Committee (IDMC)

The Independent Data Monitoring Committee (IDMC) will be formed to, at pre-specified data-points, review and evaluate the study progress and safety, and to assess reports on cumulated serious adverse events (SAEs). Based on these reviews the IDMC will provide recommendations to the sponsor Aprea regarding the scientific and ethical integrity, the progress and possible modifications of the study.

8.2 Efficacy Assessments

The primary endpoint is CR per the modified IWG (Cheson et al, 2006; see Appendix II) and time between achieving CR and relapse of disease.

8.2.1 Duration of Response

Duration of response (DOR) is measured from the time of initial response to disease **relapse/**progression or death.

8.2.2 Overall Survival

Overall survival is defined for all randomized patients, as measured from the date of randomization until the date of death.

8.2.3 Stem Cell Transplant

Patients may go on to receive SCT and this is likely to be a reflection of a positive outcome to treatment with the randomized therapies. The primary approach will be to use a treatment policy strategy (ICH E9 (R1) addendum)[33] where patients who receive SCT will continue to be followed for OS and relapse from any response with their date of death/relapse used in the analysis. If for any reason a patient receives SCT prior to a documented CR they will not be counted as a response. The inverse probability of censoring weights (IPCW)[34] method will be used adjusting for baseline predictors of outcome and time-dependent covariates such as blast, platelet and neutrophil counts. For patients who receive SCT, this method effectively replaces their outcome with patients who most resemble them and who do not receive SCT, in terms of response treatment and baseline attributes. The IPCW approach is preferred to censoring patients who receive SCT, as receipt of SCT is associated with a good response to therapy and would introduce informative censoring and underestimate the true DOR.

8.3 Pharmacokinetics

Experimental arm: Sparse PK sampling for APR-246 will be done at all sites in cycles 1-3, on Days 1, 2 and 4.

For both arms, azacitidine PK will be done at selected sites in cycle 1, on Day 4.

Due to the instability of both drugs a strict routine for serum preparation and handling must be followed, as outlined in the Laboratory manual.

Table 9. Sparse PK Blood Sampling Time Points for APR-246 (first 3 cycles) and azacitidine (first cycle only)

Experimental Arm: PK for APR-246 (Cycles 1 – 3) at all sites, all patients[1]

APR-246 Sample Time Points	D1	D2	D4
Prior to APR-246 infusion	×	×	×
At the end of APR-246 infusion	×		×
30 – 60 min after APR-246 infusion	×		×[1]

[1] Selected Sites Only: the sampling on Day 4 of the APR-246 infusion is coordinated with azacitidine sampling. Please see Laboratory Manual for sites participating in azacitidine PK sample collection: Section 1.2.3, Figure 4 (part C), and page 44 (PK Blood Sampling and Collection Form).

Experimental and Control Arms: PK for azacitidine (Cycle 1)

Azacitidine Sample Time Point	C1D4
Prior to azacitidine administration	×
At the end of azacitidine administration	×
0.25 hour after administration	×
0.5 hour after administration	×
1 hour after administration	×
2 hours after administration	×
4 hours after administration	×

8.4 ECG in Experimental Arm: ECG for APR-246

Table 10 describes the routine ECG requirements from screening through cycle 4:

Table 10. ECG Requirements in Experimental Arm

Time Point	ECG, number	Timing
Baseline/Screening	Triplicate	Must be within 28 days of C1D1
Cycle 1, Days 1-4	Triplicate	Pre-dose; Post dose (6 hrs. after start of infusion; ± 30 min)
Cycles 2+, Day 1	Triplicate	Pre-dose

If repeated QTcF measurements show a stable QTcF < 450 msec, or if QTcF remains stable within the interval of 450 – 469 msec with no significant change at the end of infusion during several cycles of treatment, reducing the number of ECGs performed in the study may be discussed with the Medical Monitor.

If a patient starts treatment with another medication known to prolong QT interval at any time during the study therapy, an additional pre- and post-dose (6 hours after start of infusion, ± 30 min) ECG should be performed on the next treatment day.

Please consult Section 6.2.1 for additional requirements for proceeding with treatment with APR-246.

8.5 TP53 Testing

Patients are enrolled based on central interpretation of local NGS *TP53* sequencing results confirming at least one *TP53* mutation not defined as benign or likely benign (see Laboratory Manual). Next-generation sequencing data report (de-identified, with only the patient's assigned screening number) must be sent to the central laboratory for evaluation of *TP53* data.

9.0 STATISTICS

9.1 Sample Size

This trial will include 154 patients with 77 patients randomized in a 1:1 ratio to each of the two treatment arms (APR-246 + azacitidine treatment versus azacitidine treatment alone).

If the true CR rate is 50% for the treatment arm and 25% for the control arm, the trial will have 90% power to detect a statistically significant effect in favor of the APR-246 at a 2-sided alpha = 0.05 significance level.

9.2 Analysis Populations

Intent-to-Treat (ITT) population: All patients who are randomized on study will be considered eligible for the ITT population and will be used for demographics, baseline characteristics summaries. The ITT population will be the primary analysis population for efficacy.

Efficacy-Evaluable (EE) population: All patients who complete at least one treatment cycle of APR-246 and azacitidine and who have at least one post-treatment clinical response assessment. Patients who fail to complete one post-treatment clinical response assessment will also be considered EE if they show clear evidence of clinically significant disease progression. The EE population will be the secondary analysis population for efficacy.

Safety population: Patients will be evaluable for safety if they receive at least one dose of APR-246 or azacitidine. The safety population will be used to summarize exposure and safety parameters.

Pharmacokinetics: Patients will be evaluable for pharmacokinetics if at least one sample for PK evaluation has been obtained.

9.3 Statistical Methods

9.3.1 Efficacy Analyses

Primary endpoint CR will be summarized for all randomized patients (ITT) as the proportion of patients (%) with CR. CR will be compared between treatment arms using a Cochran-Mantel-Haenszel (CMH) test stratified by age (< 65 years versus ≥ 65 years). In addition to presenting the CR rate and associated exact 95% CI for each treatment arm, the treatment effect will be described using the CMH estimate of the common odds ratio together with its associated 95% CI.

Duration of response (DOR) is defined as the time from the date when criteria for

response) are met to the date of relapse, progression, or death due to any cause, whichever occurs first. Patients alive without relapse or progression will have their DOR censored at the date of the last clinical assessment. The duration of CR will be summarized in each treatment arm by providing the median DOR together with associated 95% CI, using Kaplan-Meier methodology.

Overall response will be summarized in number (%) of patients in each category of responses (CR, PR, mCR with HI, mCR without HI, HI). ORR will be analyzed by using the similar method as primary endpoint CR. DOR, as defined above, will also be evaluated in regards to ORR.

Time to AML is calculated from first day of study treatment to first onset of AML. Kaplan-Meier methodology will be utilized. Rate of AML transformation will be analyzed by using the same method as primary endpoint CR.

Survival data are collected at treatment and follow-up periods. Patients will be followed until death. Overall Survival (OS) is defined as the number of days from the date of randomization to the date of death. Kaplan-Meier methodology will be utilized.

Relapse-free survival (RFS) is defined as the time from the date of randomization to disease relapse, progression or death from MDS, whichever occurs first. If neither event occurs, RFS will be censored at the date of the last assessment. Kaplan-Meier methodology will be utilized.

Time to AML, OS and RFS will be analyzed using the similar methods as DOR.

Transition rate to SCT will be analyzed using the similar methods as complete response rate.
Important subgroup analyses will be detailed in the Statistical Analysis Plan.

9.3.2 Exploratory Analyses

Descriptive statistics/results from the assays (DNA mutation panel, RNA expression profile, p53 IHC, TP53 VAF by NGS, PCR) will be written. Not all analyses listed may be performed.

9.3.3 Safety Analysis

Safety data will be summarized for the safety population. These data will include adverse events and laboratory parameters. Adverse event terms will be coded using the MedDRA®, version 21.1 or higher. Adverse events will be summarized by body system, preferred term, severity, and relationship to treatment. Serious adverse events, deaths, and AEs leading to early discontinuation of study drug will be summarized. Laboratory parameters will be summarized by maximum NCI-CTCAE v5.0 severity grade and also by change from pre-treatment to scheduled time points using descriptive statistics. Laboratory parameter listings will include the normal ranges for each parameter. Each value will be classified as falling above, below, or within the normal range.

Data summaries will include only treatment-emergent adverse events (TEAEs), defined as events occurring at the start of infusion on Day 1, Cycle 1 up to and including 30 days after last dose.

9.3.4 Pharmacokinetic Analysis

APR-246 concentrations will be determined by a validated high-performance liquid chromatography (HPLC) tandem mass spectrometry (LC/MS/MS) method. A population PK model will be used to estimate individual C_{max}, AUC and CL for each patient. APR-246 AUC and C_{max} will then be tested for association with signs of efficacy and safety. If an observable trend exists, a PK/PD model will be developed to evaluate the exposure-response relationship between APR-246 plasma exposure and outcome measures. Demographic and clinical data (ethnicity, current age, body weight, sex, disease status, etc.) will be utilized to assess interpatient variability in the PK and PK/PD relationships.

Azacitidine concentrations will be determined. The PK parameters will be derived using non-compartmental methods. C_{max} and $AUC_{0\text{-}4h}$ will be compared between treatment arms on Day 4 (azacitidine with and without APR-246) to determine the impact of APR-246 on azacitidine PK.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

10.1 Monitoring of the Study and Regulatory Compliance

The project manager, or designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the course of the study, the monitor will make regular site visits in order to review protocol compliance, examine CRFs and individual subject's medical records and assure that the study is being conducted according to pertinent regulatory requirements. All CRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

10.2 Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 and a financial disclosure statement to Theradex Oncology. All Sub-investigators will be required to provide a current curriculum vitae and a financial disclosure statement to Theradex Oncology.

10.3 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative (Theradex Oncology). Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (e.g. change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/IEC by the Principal Investigator.

10.4 Publication Policy

The publication of the results of the study will be subject to the terms and conditions of the clinical trial agreement between the Sponsor and Investigators. Sponsor approval is required for publication of any data from this trial.

11.0 ETHICAL CONSIDERATIONS

11.1 Informed Consent

The Investigator will obtain written informed consent from each patient, or the patient's authorized representative, participating in the study. The form must be signed and dated. The ICF will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2008). Copies of the signed document should be given to the patient and filed in the patient's medical record if in conformance with the institution's Standard Operating Procedures.

In cases incapacitated subjects are to be included, two sets of information sheets might be needed according to national regulations. In addition to the information given to the patient's legal representative, the patient should be given information according to his/her capacity to understand. This information should include, where appropriate, a statement that the patient's decision not to participate or to withdraw from a trial will be respected, even if consent is given by the parent/legal representative.

11.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The study will not be initiated without approval of the appropriate IRB/IEC and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be approved by the IRB/IEC in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH/GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/IEC will be kept informed by the Investigator, Theradex Oncology or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected adverse events.

11.3 Patient Privacy

In order to maintain patient confidentiality, all CRFs, study reports and communications relating to the study will identify patients by initials and assigned patient numbers; patients should not be identified by name. In accordance with local, national or federal regulations, the Investigator will allow the Sponsor or designee personnel access to all pertinent medical records in order to verify the data gathered on the CRFs and to audit the data collection process. Regulatory agencies such as the US Food and Drug Administration (FDA) may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the patient as outlined in the patient consent form.

12.0 DATA HANDLING AND RECORD KEEPING

12.1 Data to be Entered Directly in the CRF

The CRF will be the source record for the following data: None

12.2 Recording of Data

Data collected during the study will be recorded in the patient's CRF by the investigational site staff. The staff will keep records of the patient's visit in the files considered as source documents for the site, e.g., hospital chart, patient medical records. The Investigator will be responsible for the recording of all data on the CRF and for submitting the data to the Sponsor or their designee in a timely manner. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the CRF.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data. To facilitate photocopying, entries must be recorded legibly in black ink only. Erroneous entries will be crossed out with a single line, so as to remain legible. The correct value will be entered above the error and then initialed and dated by the person authorized to make the correction.

12.3 Study Records

U.S. Federal laws require that an Investigator maintain all study records for the indication under investigation for two years following the date a Product Licensing Application is approved or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

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APPENDIX I – ECOG PERFORMANCE STATUS

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light 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.

APPENDIX II – PROPOSED MODIFIED INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR ALTERING NATURAL HISTORY OF MDS

(from Cheson et al, Blood 2006)

Category	Definition
Complete remission (CR)	Bone marrow blasts ≤5% myeloblasts with normal maturation of all cell lines[*] Persistent dysplasia will be noted [*≠] Peripheral blood [◊] Hemoglobin (Hgb) ≥ 11 g/dL Platelets ≥ 100 × 10^9/L Neutrophils ≥ 1.0 × 10^9/L [≠] Blasts 0%
Partial remission (PR)	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR ≠	Bone marrow: ≤ 5%, myeloblasts and decrease by ≥ 50% over pretreatment [≠] Peripheral blood: if HI responses, they will be noted in addition to marrow CR [≠]
Stable disease	Failure to achieve at least PR< but no evidence of progression for > 8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥ 15

	g/dL or transfusion dependence
Cytogenic response	Complete = Disappearance of the chromosomal abnormality without appearance of new ones Partial = at least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts; 5-10% blasts: ≥ 50% increase to > 10% blasts; 10-20% blasts: ≥ 50% increase to > 20% blasts; 20-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 2 g/dL Transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free failure or death from any cause PFS: disease progression or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

* Dysplastic changes should consider the normal ranges of dysplastic changes (modification) [35]

≠ Modification to IWG response criteria.

◊ In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Proposed modified IWG response criteria for hematologic improvement

Hematologic improvement	Response criteria (responses must last at least 8 weeks)[†]
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBD transfusion response evaluation [†]
Platelet response (pretreatment, < 100 × 10^9L)	Absolute increase of ≥ 30 × 10^9/L for patients starting with > 20 × 10^9/L and by at least 100% [†]
Neutrophil response (pretreatment, < 1.0 × 10^9/L	At least 100% increase and an absolute increase > 0.5 × 10^9/L [†]
Progression or relapse after HI [‡]	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence

Deletions to the IWG response criteria are not shown.
To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.
[*]Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) 1 week apart (modification). [35]
[†]Modification to IWG response criteria.

‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

APPENDIX III – NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

NYHA grading		**MET***
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnea or palpitations (asymptomatic LV dysfunction)	>7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pectoris (mild CHF).	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF)	2 – 3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).	1.6

*MET (metabolic equivalent) is defined as the resting VO_2 for a 40-year-old 70kg man. 1 MET = 3.5mL O_2/min/kg body weight.

APPENDIX IV – COCKCROFT–GAULT EQUATION

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$