Statistical Analysis Plan (SAP)

Protocol Title:	A Phase 2 Study to Evaluate the Safety and Tolerability of IMR-687 in Subjects with Beta Thalassemia
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1.0 Approvals

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2.0 Change History

Version/Date	Change Log
0.1/18-Feb-2020	Created as new
1.0/14-Oct-2021	Final

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Imara Protocol IMR-BTL-201.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Endpoints to be Analyzed and the Analysis sets
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol and case report form (CRF). Any further changes to the protocol or CRF may necessitate updates to the SAP prior to database lock.

6.1 Changes from Protocol

In this SAP three analysis sets were added - the Intent-to-Treat (ITT) Analysis Set, which is defined in Section 11.2, the Modified Intent-to-Treat (mITT) Analysis Set, which is defined in Section 11.3, and the PK Evaluable Set, which is defined in Section 11.6. The ITT and mITT Analysis Sets were added to summarize the efficacy analysis. The ITT Analysis set will allow for an assessment of all randomized subjects. The mITT Analysis set allows for an assessment of all randomized subjects who received at least one dose of study drug, regardless of their compliance with or any deviations from the protocol. The Per Protocol (PP) Analysis Set definition in Section 11.4 has been clarified to include subjects with any post-baseline assessment and who did not discontinue prior to week 12 for reasons other than AEs.

The definition of the Safety Analysis Set was clarified to remove the requirement for the subject to give informed consent. This does not change the definition in practice as all subjects in the Safety Analysis Set are required to receive at least one dose of study drug which would only happen after the subject gave informed consent.

The definition of the PK analysis set was modified. As per protocol, the PK Analysis Set was defined as a subset of the Safety Analysis Set that included all subjects who were enrolled in the study, received at least 1 dose of IMR-687, and had sufficient IMR-687 concentration data to be used in the PK analyses. This has been further delineated with the addition of a PK Evaluable Set and for each of these PK population subsets, the definitions were updated as follows:

- The PK Analysis Set, will be defined as a subset of the Safety Analysis Set that includes all subjects who are enrolled in the study, have received at least 1 dose of IMR-687, and have any measurable post-dose IMR-687 concentration-time data. This set will be used to generate the corresponding PK concentration summaries and plots.
- The PK Evaluable Set will be defined as all subjects in the Safety Analysis Set who are randomized, have received at least 1 dose of IMR-687, and have at least 4 consecutive non-zero post-dose IMR-687 concentration-time data points. The PK Evaluable Set will be used to generate the corresponding PK parameter assessments.

An interim analysis was added (IA 0.5) for the NTDT population to be performed when approximately 15 NTDT subjects have completed 12 weeks of treatment.

Several secondary efficacy endpoints were added:

- Proportion of subjects with a ≥20% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) over any 12-week rolling time period – Day 2

to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).

- Proportion of subjects with a ≥20% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) over any 14-week rolling time period – Day 2 to 99, Day 3 to 100, etc. through Day 156 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).
- Proportion of subjects with a ≥33% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) over any 12-week rolling time period – Day 2 to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).
- Proportion of subjects with a ≥33% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) over any 14-week rolling time period – Day 2 to 99, Day 3 to 100, etc. through Day 156 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).
- Proportion of subjects with a ≥50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) from Week 12 to Week 24 and Week 24 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).
- Proportion of subjects with a ≥50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) from Week 12 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).
- Proportion of subjects with a ≥50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) over any 12-week rolling time period – Day 2 to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).
- Proportion of subjects with a ≥50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) over any 14-week rolling time period – Day 2 to 99, Day 3 to 100, etc. through Day 156 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).

Several exploratory efficacy endpoints were added:

- Change from Baseline in mean pre-transfusion Hb values at Weeks 12 to 24, Weeks 24 to 36, and Weeks 12 to 36 [using pre-transfusion Hb from the Historical Transfusion Burden and the Transfusion Burden CRFs]
- Proportion of subjects with an increase from Baseline of ≥1.0 g/dL in mean pre-transfusion Hb values or a Reduction in RBC Transfusion Burden (≥33% reduction) Endpoint at Weeks 12 to 24, Weeks 24 to 36, and Weeks 12 to 36 [using pre-transfusion Hb from the Historical Transfusion Burden and the Transfusion Burden CRFs]
- Time to first Hb increase (≥1.0 g/dL)

Two exploratory efficacy endpoints were modified:

- The mean change from Baseline in NTDT-PRO score over a continuous 12-week interval from Week 12 to Week 24 and Week 24 to Week 36 was modified to the mean change from Baseline NTDT-PRO total score and domain scores including tiredness/weakness and shortness of breath domains over a continuous 12-week interval from Week 12 to Week 24 and Week 24 to Week 36
- The mean change from Baseline in NTDT-PRO domain total score at Week 24 was changed to the mean change from Baseline in NTDT-PRO total score and domain scores including tiredness/weakness and shortness of breath domain scores at Week 24 and Week 36.

Per protocol, plasma concentrations of IMR-687 and metabolites could have been analyzed and used for PK analyses. The PK analyses for this study will only include IMR-687 plasma concentration-time data. No PK analysis of IMR-687 metabolites will be performed.

7.0 Study Objectives

7.1 Primary Objective

The primary objective of this study in both Population 1 (transfusion-dependent thalassemia; TDT) and Population 2 (non-transfusion-dependent thalassemia; NTDT) is to assess the safety and tolerability of IMR-687 in adult subjects with β-thalassemia.

7.2 Secondary Objectives

7.2.1 Population 1: Transfusion-dependent β-Thalassemia

The secondary objectives in TDT subjects are:

- To evaluate the effect of IMR-687 versus placebo on reduction in red blood cell (RBC) transfusion burden.
- To evaluate the effect of IMR-687 versus placebo on the change in iron overload.
- To characterize the pharmacokinetic (PK) profile of IMR-687 and collect data for population PK analysis.

7.2.2 Population 2: Non-transfusion-dependent β-Thalassemia

The secondary objectives in NTDT subjects are:

- To evaluate the effect of IMR-687 versus placebo on anemia (as defined by total hemoglobin).
- To evaluate the effect of IMR-687 versus placebo on fetal hemoglobin (HbF).
- To evaluate the effect of IMR-687 versus placebo on the change in iron overload.
- To characterize the PK profile of IMR-687 and collect data for population PK analysis.

7.3 Exploratory Objectives

7.3.1 Population 1: Transfusion-dependent β-Thalassemia

The exploratory objectives in TDT subjects are:

- To characterize the pharmacodynamic (PD) profile of IMR-687 versus placebo with respect to erythropoiesis, iron metabolism, and hemolysis.
- To evaluate the effect of IMR-687 versus placebo on the proportion of subjects who are transfusion independent.
- To evaluate the effect of IMR-687 versus placebo on time to and duration of reduction in RBC transfusion burden.
- To evaluate the effect of IMR-687 versus placebo on functional and health-related quality of life (QoL).
- To evaluate responses to IMR-687 per genotypes in subjects with TDT.

7.3.2 Population 2: Non-transfusion-dependent β-Thalassemia

The exploratory objectives in NTDT subjects are:

- To characterize the PD profile of IMR-687 versus placebo with respect to erythropoiesis, iron metabolism, and hemolysis.
- To evaluate the effect of IMR-687 versus placebo on functional and health-related QoL.
- To evaluate the effect of IMR-687 versus placebo on β-thalassemia-related symptoms and severity.
- To evaluate responses to IMR-687 per genotypes in subjects with NTDT.

8.0 Study Design

This is a phase 2 randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of IMR-687 (PDE9 inhibitor) administered QD for 36 weeks in 2 populations of adult subjects with β-thalassemia: Population 1 (TDT subjects) and Population 2 (NTDT subjects). A schematic of the study is provided in Figure 1.

This study will enroll approximately 120 subjects with β-thalassemia (60 subjects with TDT and 60 subject with NTDT), aged 18 through 65 years across approximately 50 sites in North America, the United Kingdom, European Union, Middle East, Asia-Pacific, and Africa. This study consists of a retrospective data collection period, a screening period, a double-blind treatment period, and safety follow-up period. The planned maximum duration of study participation is approximately 44 weeks. During the screening period of up to 28 days, subjects will provide informed consent and be evaluated on eligibility criteria as stated in Sections 8.1 and 8.2 of the study protocol.

Randomization will be stratified by TDT/NTDT status. Subjects will be randomly assigned in a 2:1 ratio to receive either IMR-687 lower dose or placebo. Prior to the introduction of IMR-687 higher dose, the Data Monitoring Committee (DMC) was to review safety data for at least 5 subjects who received IMR-687. If the DMC recommended inclusion of the higher dose, randomization was then to proceed in a 1:2:1 ratio (IMR-687 lower dose, IMR-687 higher dose, or placebo). The DMC could request additional data and/or meeting(s) in order to make the recommendation on whether to move forward with inclusion of the higher dose. During study conduct under Protocol Version 4.0, the DMC approved the opening of enrollment in the higher dose IMR-687 group, which went into effect on 01 February 2021. With approval of enrollment in the higher dose arm, subjects receive IMR-687 lower dose ([≥3.4 to ≤5.0 mg/kg], higher dose [>4.5 to ≤6.7 mg/kg] or placebo in a blinded fashion; the precise exposure ranges for different groups of subjects are dependent on the weight gate for tablet strength as summarized below).

IMR-687 will be supplied as 100, 150, or 200 mg white tablets. Subjects will be advised to take two IMR-687 tablets with food QD for 36 weeks. To maintain appropriate exposures, 60 kg will be used as the weight gate for tablet strength. Subjects in the lower dose group weighing <60 kg will be dispensed 100 mg tablets and those weighing ≥60 kg will be dispensed 150 mg tablets (daily dose 200 mg and 300 mg, respectively). Subjects in the higher dose group weighing <60 kg will be dispensed 150 mg tablets and those weighing ≥60 kg will be dispensed 200 mg tablets (daily dose 300 mg and 400 mg, respectively). The different doses of IMR-687 are visually identical in tablet form.

Placebo will consist of tablets containing matrix absent IMR-687 and will be identical in appearance to the IMR-687 tablets. Subjects will be advised to take two placebo tablets orally with food QD for 36 weeks.

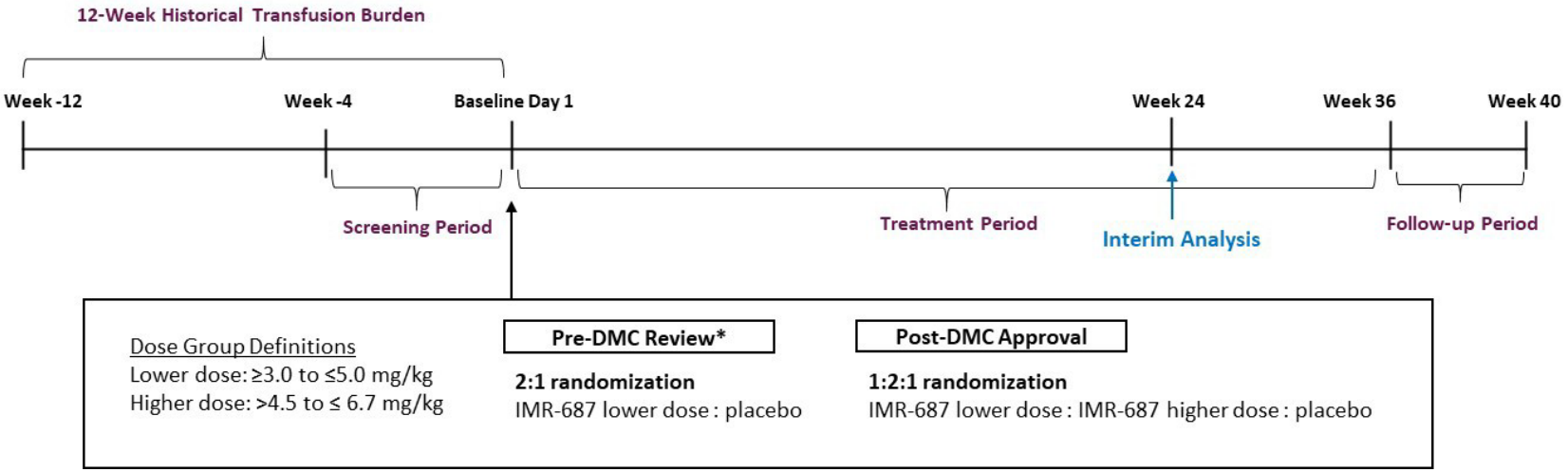
Subjects will be directed to take study drug (either IMR-687 or placebo) with food, but if a subject does not do so, it will not be considered a protocol deviation.

Interim analyses will be conducted at each of the following milestones:

- Approximately 15 subjects in the NTDT population have completed 12 weeks of treatment
- Approximately 30 subjects in the TDT population have completed 24 weeks of treatment
- Approximately 30 subjects in the NTDT population have completed 24 weeks of treatment
- Approximately 60 subjects in the TDT population have completed 24 weeks of treatment

- Approximately 60 subjects in the NTDT population have completed 24 weeks of treatment

Figure 1: Overview of Study Design and Dose Groups



* Prior to the introduction of IMR-687 higher dose, the DMC will review safety data for at least 5 subjects who received IMR-687 lower dose. If the DMC recommends inclusion of the higher dose, randomization across 3 dose groups will then proceed as shown. The DMC may request additional data and/or meeting(s) in order to make its recommendations. During study conduct under Protocol Version 4.0, the DMC approved the opening of enrollment in the higher dose IMR-687 group, which went into effect on 01 February 2021.
Refer to Protocol Section 5.1 for additional details on the dose groups.
Note: There will be an additional interim analysis (IA 0.5) for approximately 15 subjects in the NTDT population that have completed 12 weeks of treatment.

8.1 Sample Size Considerations

Both populations, TDT and NTDT have a primary objective of safety, therefore the population sample sizes are not based on statistical assumptions.

8.1.1 Population 1: Transfusion-dependent β-thalassemia

For the secondary efficacy endpoint of percentage of subjects with hematologic improvement (reduction in transfusion burden), 30 subjects in an active treatment arm and 20 subjects in the placebo arm will provide approximately 79% power to detect a difference of 10% of subjects improving in the placebo arm versus 50% of subjects improving in an active treatment arm, using a two-sided alpha level of 0.05. No multiple comparisons adjustments will be made as these are secondary analyses.

8.1.2 Population 2: Non-transfusion-dependent β-thalassemia

For the secondary efficacy endpoints of proportion of subjects with increase from Baseline of ≥1.0 g/dL in mean Hb values at Weeks 12 to 24 or Weeks 24 to 36, 30 subjects in an active arm and 15 subjects in the placebo arm will provide approximately 67% power to detect a difference of 10% of subjects improving in the placebo arm versus 50% of subjects improving in an active treatment arm, using a two-sided alpha level of 0.05. No multiple comparisons adjustments will be made as these are secondary analyses.

8.2 Randomization

All subjects who are screened (including screen failures) will be assigned a unique subject identification number.

On Day 1, eligible subjects in Population 1 (TDT Population) and Population 2 (NTDT Population) will be assigned another unique number (randomization number) in sequential order. The randomization number codes the subject's initial treatment assignment according to the randomization schedule generated prior to the study. Initially, subjects will be randomly assigned in a 2:1 ratio to receive either IMR-687 lower dose or placebo. If the DMC recommends inclusion of the higher dose, randomization will then proceed in a 1:2:1 ratio (IMR-687 lower dose, IMR-687 higher dose, or placebo).

Randomization schedules will be generated by Cytel, a subcontractor of the IXRS vendor Suvoda.

Subject randomization will be stratified by TDT/NTDT status.

Randomization number will not be reused once assigned. If a subject discontinues or is discontinued at the discretion of the investigator or DMC up to and including the Week 12 visit, the subject may be replaced with another subject, from the same TDT/NTDT stratum, meeting the eligibility criteria. In the event that a subject is replaced, the replacement subject will receive the same treatment as the replaced subject, and a different leading number will be used for the replacement randomization. Subjects who are replaced, or who are replacement subjects, will be included in the analyses sets according to the same criteria used for all other subjects, as described in Section 11.0.

9.0 Study Endpoints, Variables and Covariates

Primary Endpoints	TDT	NTDT
IMR-687 safety and tolerability assessed using: • Incidence and severity of adverse events and serious adverse events • Incidence of subjects with a post-Baseline clinically significant worsening in the CTCAE laboratory grade for a lab parameter	X	X

• Incidence of subjects with a post-Baseline clinically significant change in a vital signs parameter • Incidence of subjects meeting the clinically significant criteria for an electrocardiogram (ECG) parameter • Changes from Baseline in 12-lead ECG clinical laboratory test (chemistry, hematology, coagulation, and urinalysis), and vital signs parameters (continuous parameters only) • Changes in physical examination findings relative to the Baseline physical examination		
Secondary Endpoints	**TDT**	**NTDT**
Proportion of subjects with a ≥20% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for Week 12 to Week 24 and Week 24 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥20% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for Week 12 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥20% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for any 12-week rolling time period – Day 2 to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥20% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for any 14-week rolling time period – Day 2 to 99, Day 3 to 100, etc. through Day 156 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥33% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for Week 12 to Week 24 and Week 24 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥33% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for Week 12 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥33% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for any 12-week rolling time period – Day 2 to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥33% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for any 14-week rolling time period – Day 2 to 99, Day 3 to 100, etc. through Day 156 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).	X	

Proportion of subjects with a ≥50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for Week 12 to Week 24 and Week 24 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for Week 12 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for any 12-week rolling time period – Day 2 to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).	X	
Proportion of subjects with a ≥50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) for any 14-week rolling time period – Day 2 to 99, Day 3 to 100, etc. through Day 156 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1).	X	
Mean number of transfusion events from Baseline to Week 36.	X	
The plasma PK profile of IMR-687 after administration to subjects will be evaluated by determination of PK parameters, as appropriate, for Study Day 1 and Week 3/Week 4 and population PK, based on drug concentration levels in plasma obtained over time.	X	X
Mean change from Baseline to Week 36 for iron chelation therapy daily dose and serum ferritin.	X	X
Proportion of subjects with an increase from Baseline of ≥1.0 g/dL in mean Hb values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions.		X
Mean change from Baseline in mean Hb values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions.		X
Mean change from Baseline in mean HbF values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions.		X
Proportion of subjects with an increase from Baseline of ≥3% in mean HbF values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions.		X
Exploratory Endpoints	**TDT**	**NTDT**
The PD effects of IMR-687 from Baseline to Week 36, as measured by the mean change from Baseline in serum PD markers of erythropoiesis, iron metabolism, and hemolysis.	X	X
Mean change in transfusion burden expressed as units of RBCs as a continuous variable during Week 12 to Week 24, Week 24 to Week 36, and Week 12 to Week 36, compared to the 12 weeks prior to Baseline (Day 1).	X	

The proportion of subjects who are transfusion independent for ≥8 weeks during treatment.	X	
Mean change from Baseline in TranQOL quality of life tool at Weeks 12, 24, and 36.	X	
Mean change from Baseline in SF-36 quality of life tool at Weeks 12, 24, and 36.	X	X
Pharmacogenomic analyses of genes that may affect treatment response (including α-globin, gamma-globin *XmnI* polymorphism, and BCL11A).	X	X
Proportion of subjects who have an Hb increase of ≥1.0 g/dL from Baseline for ≥14 days in the absence of RBC transfusions.		X
Proportion of subjects who are RBC transfusion-free over 36 weeks and other variables of transfusion burden.		X
Duration of the mean Hb increase from Baseline of ≥1.0 g/dL over 36 weeks.		X
Proportion of subjects who have an increase from Baseline ≥1.5 g/dL in mean of Hb values at Week 24 and Week 36 compared to Baseline in the absence of transfusions.		X
Mean number of transfusion events from Baseline to Week 24.	X	
Mean change from Baseline in NTDT-PRO tiredness/weakness (T/W) domain score over a continuous 12-week interval from Week 12 to Week 24 and Week 24 to Week 36.		X
Mean change from Baseline in NTDT-PRO total score and T/W domain score at Week 24 and Week 36.		X
Mean change in biomarkers from Baseline to Week 36, stratified by genotype.[a]	X	X
Time to first Hb increase (≥1.0 g/dL)		X

ECG = electrocardiogram; Hb = hemoglobin; HbF = fetal hemoglobin; LDH = lactate dehydrogenase; NTDT = non-transfusion dependent β-thalassemia; NTDT-PRO = non-transfusion dependent β-thalassemia patient reported outcome; PD = pharmacodynamics; PK = pharmacokinetics; pRBC = packed red blood cells; PRO = patient-reported outcome; RBC = red blood cell; SF-36 = Short Form (36) Health Survey; t_{max} = time to maximum plasma concentration; TDT = transfusion dependent β-thalassemia; TranQOL = transfusion-dependent quality of life.

[a] See Section 13.6.8 for list of biomarkers.

10.0 Conventions and Derivations

10.1.1 Method for Handling Missing Data

There will be no imputation of incomplete or missing data unless otherwise specified in this SAP.

Please refer to Appendix 3 for specific data handling rules, including missing last dose date for the interim analysis, missing severity/relationship of adverse events, incomplete/missing dates for adverse events and prior/concomitant medications, interpretation of non-numeric results (e.g. "< BLQ", ">x.xx") from PK and laboratory measures, etc.

10.1.2 Definition of Baseline and Change from Baseline Values

Unless otherwise specified, Baseline is defined as the last non-missing measurements prior to the first dose of study drug.

The ECG Baseline and post-Baseline values are averages of the triplicate assessments. The change from Baseline is the difference between the post-Baseline and Baseline averages.

In analyses of pharmacodynamics (PD), including specialty hematology parameters, Baseline is defined as the average of non-missing values from the screening and Baseline visits. PD assessments include laboratory measurements based on blood samples as listed in sections 13.6.7 and 13.6.8.

10.1.3 Definition of Study Days

Study Day 1 is defined as the date on which subjects are administered their first dose of study drug. For visits (or events) that occur on or after the date of the first dose of study drug, study day is defined as (date of visit [event] – date of first dose of study drug + 1). For visits (or events) that occur prior to Study Day 1, study day is defined as (date of visit [event] – date of first dose of study drug). There is no Study Day 0.

10.1.4 Definition of Treatment-Emergence

A treatment-emergent adverse event (TEAE) is defined as an AE that starts after initiation of study drug, or an AE that existed pre-treatment and worsened in severity after initiation of study drug, through 30 days after the last dose of study drug.

10.1.5 Red Blood Cell Transfusion Reduction: 12-Week Fixed Interval

Transfusion burden will be measured using a "fixed" 12-week time interval. The 12-week intervals used for analysis are defined as:

Pre-treatment 12-week interval: from Day -83 to Day 1;

Week 13–24 interval: from Day 86 to Day 169;

Week 25–36 interval: from Day 170 to Day 253.

10.1.6 Red Blood Cell Transfusion Reduction: 24-Week Fixed Interval

Transfusion burden will also be measured using a "fixed" 24-week time interval. The 24-week intervals used for analysis are defined as below.

Pre-treatment 12-week interval: from Day -83 to Day 1;

Week 13–36 interval: from Day 86 to Day 253.

10.1.7 Red Blood Cell Transfusion Reduction: 12-Week Rolling Interval

Transfusion reduction will also be measured using any consecutive "rolling" 12-week time intervals during the study, e.g., Days 2 to 85, Day 3 to 86 and so on, compared to the pre-treatment 12-week interval (from Day-83 to Day 1). A transfusion occurring on Day 1 belongs to the pre-treatment period.

10.1.8 Red Blood Cell Transfusion Reduction: 14-Week Rolling Interval

Transfusion reduction will also be measured using any consecutive “rolling” 14-week time intervals during the study, e.g., Days 2 to 99, Day 3 to 100 and so on. Day 1 transfusion belongs to baseline.

10.1.9 Quality of Life Assessments

Quality of life will be assessed using the TranQOL and SF-36 QoL tools in the TDT population and the NTDT-PRO and SF-36 QoL tools in the NTDT population.

The TranQOL (Klaassen 2013; Klaassen 2014. See protocol section 16.) is a disease-specific QoL measure for children and adults with thalassemia major. It has four versions: (i) a child self-report; (ii) an adult self-report; (iii) a parent self-report (measuring the impact of the disease on the parent), and (iv) a parent proxy report (measuring the child’s QoL). The questionnaire length ranges from 29 items (child) to 39 items (parent). The questions are grouped into 4 domains: physical health, emotional health, family functioning, and school and career functioning. The adult and parent self-report questionnaires include a fifth category on sexual activity which is only one item. For this study, only the adult self-report will be used which includes 36 items and an open-ended question: “Was there anything else that bothered you?”. The mean TranQOL score for each domain ranges from 0 to 100 with higher scores indicating higher QoL. Derivations for domain scores are specified in Section 13.6.6.1. A within-patient clinically meaningful change from baseline was defined as a ≥ 4-point change for the TranQol total score (Cappellini 2020). The criteria may be modified based on further research.

The SF-36 (Hays 2004. See protocol section 16.) is a 36-item, patient reported survey of patient health. The SF-36 consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 to 100 scale based on each scale having equal weight. The lower the score the more disability and the higher the score the less disability (i.e., a score of 0 is equivalent to a maximum disability and a score of 100 is equivalent to no disability). The 8 sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Derivations for the scales and component scores are specified in Section 13.6.6.1. A within-patient clinically meaningful change from baseline was defined as 3.8–7.0-point improvement, based on the prespecified domain-specific cutoff values for the domains of the SF-36 questionnaire (Cappellini 2020).

The NTDT-PRO (Taher 2019. See protocol section 16.) is a new disease-specific health-related QoL tool for patients with NTDT. The NTDT-PRO was designed as a daily diary with recall of thalassemia-related symptoms over the previous 24 hours. The relatively short recall period is used due to the high level of day-to-day variation in symptoms experienced by patients with NTDT. The 6 NTDT-PRO items assess the presence or severity of specific symptoms using a numerical ration scale ranging from 0 (“absent/minimal”) to 10 (“extreme/high”): tiredness with or without physical activity, weakness with or without physical activity, and shortness of breath (SOB) with or without physical activity. NTDT-PRO items are grouped into 2 domains: tiredness/weakness (T/W) (tiredness with physical activity, tiredness without physical activity, weakness with physical activity, and weakness without physical activity) and shortness of breath (shortness of breath with physical activity, shortness of breath without physical activity). The total score is an average of the responses to questions 1-6. For this study, the NTDT-PRO will not be used as a daily diary; data will be collected at Baseline and at Weeks 12, 24, and 36. Derivations for domain scores and the total score are specified in Section 13.6.6.3.

10.1.10 Windowing Conventions

All scheduled study visits are defined relative to Study Day 1, the date of first dose. Scheduled visit windows are defined in Appendix 3. A windowing convention will be used to determine the analysis visit value for a given measurement and will be applicable for all by-visit summaries and analyses for efficacy and safety data. Refer to Table 1 (TDT) and Table 2 (NTDT) for specific visit windows.

Table 1: Visit Windows for Efficacy and Safety Analyses – TDT Population

Safety Analyses – Vital Signs and Weight	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 1 (Day 7 ± 2)	2 to 15
Week 3 (Day 21 ± 7)	16 to 32
Week 6 (Day 42 ± 7)	33 to 53
Week 9 (Day 63 ± 7)	54 to 74
Week 12 (Day 84 ± 7)	75 to 95
Week 15 (Day 105 ± 7)	96 to 116
Week 18 (Day 126 ± 7)	117 to 137
Week 21 (Day 147 ± 7)	138 to 158
Week 24 (Day 168 ± 7)	159 to 179
Week 27 (Day 189 ± 7)	180 to 200
Week 30 (Day 210 ± 7)	201 to 221
Week 33 (Day 231 ± 7)	222 to 242
Week 36 (Day 252 ± 7)	243 to 267
Week 40 (Day 280 ± 7)	≥ 268
Safety Analyses – 12-Lead ECG, Hematology (Except Specialty Hematology) and Chemistry	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 1 (Day 7 ± 2)	2 to 15
Week 3 (Day 21 ± 7)	16 to 32
Week 6 (Day 42 ± 7)	33 to 64
Week 12 (Day 84 ± 7)	65 to 106
Week 18 (Day 126 ± 7)	107 to 148
Week 24 (Day 168 ± 7)	149 to 190
Week 30 (Day 210 ± 7)	191 to 232
Week 36 (Day 252 ± 7)	233 to 267
Week 40 (Day 280 ± 7)	≥ 268
Safety Analyses – Urinalysis	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1

Week 3 (Day 21 ± 7)	2 to 53
Week 12 (Day 84 ± 7)	54 to 127
Week 24 (Day 168 ± 7)	128 to 211
Week 36 (Day 252 ± 7)	≥212
Safety Analyses – Coagulation	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 12 (Day 84 ± 7)	2 to 127
Week 24 (Day 168 ± 7)	128 to 211
Week 36 (Day 252 ± 7)	≥212
Efficacy Analyses – Specialty Hematology	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 3 (Day 21 ± 7)	2 to 53
Week 12 (Day 84 ± 7)	54 to 106
Week 18 (Day 126 ± 7)	107 to 148
Week 24 (Day 168 ± 7)	149 to 190
Week 30 (Day 210 ± 7)	191 to 232
Week 36 (Day 252 ± 7)	≥233
Efficacy Analyses- PD Biomarkers	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 3 (Day 21 ± 7)	2 to 53
Week 12 (Day 84 ± 7)	54 to 106
Week 18 (Day 126 ± 7)	107 to 148
Week 24 (Day 168 ± 7)	149 to 211
Week 36 (Day 252 ± 7)	≥212
QoL	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 12 (Day 84 ± 5)	2 to 127
Week 24 (Day 168 ± 7)	128 to 211
Week 36 (Day 252 ± 7)	≥212

Table 2: Visit Windows for Efficacy and Safety Analyses – NTDT Population

Safety Analyses – Vital Signs, Weight, 12-Lead ECG, Hematology (Except Specialty Hematology) and Chemistry	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 1 (Day 7 ± 2)	2 to 18
Week 4 (Day 28 ± 5)	19 to 43
Week 8 (Day 56 ± 7)	44 to 71
Week 12 (Day 84 ± 7)	72 to 99
Week 16 (Day 112 ± 7)	100 to 127
Week 20 (Day 140 ± 7)	128 to 155
Week 24 (Day 168 ± 7)	156 to 183
Week 28 (Day 196 ± 7)	184 to 211
Week 32 (Day 224 ± 7)	212 to 239
Week 36 (Day 252 ± 7)	240 to 267
Week 40 (Day 280 ± 7)	≥ 268
Safety Analyses – Urinalysis	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 4 (Day 28 ± 5)	2 to 57
Week 12 (Day 84 ± 7)	58 to 127
Week 24 (Day 168 ± 7)	128 to 211
Week 36 (Day 252 ± 7)	≥212
Safety Analyses – Coagulation	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 12 (Day 84 ± 7)	2 to 127
Week 24 (Day 168 ± 7)	128 to 211
Week 36 (Day 252 ± 7)	≥212
Efficacy Analyses – Specialty Hematology	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 4 (Day 28 ± 5)	2 to 57

Week 12 (Day 84 ± 7)	58 to 127
Week 24 (Day 168 ± 7)	128 to 211
Week 36 (Day 252 ± 7)	≥212
Efficacy Analyses- PD Biomarkers	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 4 (Day 28 ± 5)	2 to 57
Week 12 (Day 84 ± 7)	58 to 127
Week 24 (Day 168 ± 7)	128 to 211
Week 36 (Day 252 ± 7)	≥212
QoL	
Scheduled Study Visit (Protocol Scheduled Day)	**Analysis Visit Window (Study Day)**
Baseline	≤ 1
Week 12 (Day 84 ± 5)	2 to 127
Week 24 (Day 168 ± 7)	128 to 211
Week 36 (Day 252 ± 7)	≥212

Windowing will be applied prior to any missing data calculations. The last non-missing measurement taken prior to the date of first dose (including unscheduled assessments) will be labeled as “Baseline”. Screening visits that occurred before the Baseline visit will not be assigned an analysis visit. The early discontinuation visit will be eligible for allocation to an analysis visit.

If one or more results for a variable are assigned to the same analysis visit, the result with the date closest to the protocol scheduled day will be used in the analysis. If 2 measurements in the same analysis visit window are equidistant from the protocol scheduled study day, the earliest measurement will be used in the analysis. If multiple assessments are available on the same day (for the same time point), then the average of the assessment will be used in the analysis. If both central and local assessments of the same lab test are available for the same visit, the central result will take precedence over the local result if baseline is collected centrally. If a scheduled assessment is missing, due to clotting for example, and an unscheduled retest assessment is available in the visit window for the scheduled visit, the unscheduled retest assessment may be used in place of the missing scheduled assessment.

11.0 Analysis Sets

Analysis Set	Definition	Use	How Analyzed
Safety	All subjects who received at least one dose of study drug.	Safety and tolerability	According to actual treatment received
ITT	All subjects who are randomized.	PD and Efficacy	According to randomized treatment assigned

Analysis Set	Definition	Use	How Analyzed
mITT	All subjects who are randomized and received at least one dose of study drug. If all randomized subjects are dosed, the mITT Analysis Set will not be created and the ITT Analysis Set will be used.	PD and Efficacy	According to randomized treatment assigned
PP	All subjects in the Safety Analysis Set who have provided sufficient data without major protocol deviations or events that would be expected to affect the analysis. Sufficient data is defined as any post-baseline assessment and subject did not discontinue prior to Week 12 for reasons other than AEs.	PD and Efficacy	According to actual treatment received
PK (Analysis)	All subjects in the Safety Analysis Set who have received at least 1 dose of IMR-687 and have any measurable postdose IMR-687 concentration-time data.	PK concentrations	According to actual treatment received
PK (Evaluable)	All subjects in the Safety Analysis Set who have received at least 1 dose of IMR-687 and have at least 4 consecutive non-zero postdose IMR-687 concentration-time data points.	PK parameters	According to actual treatment received

11.1 Safety Analysis Set

The Safety Analysis Set will include all subjects who have received at least one dose of study drug and will be used to summarize all safety and tolerability data. In safety summaries, subjects will be analyzed according to the actual treatment they received.

11.2 Intent-to-Treat Analysis Set

The ITT Analysis Set will include all subjects who are randomized. Subjects will be analyzed according to their randomized treatment. The ITT Analysis Set will be used for PD and efficacy analyses.

11.3 Modified Intent-to-Treat Analysis Set

In the event that any subjects are randomized but not dosed, a mITT Analysis Set will be created that will include all subjects who are randomized and receive at least one dose of study drug. Subjects will be analyzed according to their randomized treatment. The mITT Analysis Set will be used for PD and efficacy analyses.

11.4 Per Protocol Analysis Set

The Per Protocol Analysis Set will include all subjects in the Safety Analysis Set who have provided sufficient data without major protocol deviations or events that would be expected to affect the analysis. Sufficient data is defined as any post-baseline assessment and subject did not discontinue prior to week 12 for reasons other than AEs. The PP Analysis Set will be identified based on blinded data prior to unblinding the final analysis dataset, and the TDT and NTDT populations may have their PP Analysis Set components defined at different times. The PP Analysis Set will be the primary analysis set used for PD and efficacy analyses. Subjects will be analyzed according to their randomized treatment.

11.5 PK Analysis Set

The PK Analysis Set will be defined as all subjects in the Safety Analysis Set who are randomized, have received at least 1 dose of IMR-687, and have any measurable postdose IMR-687 concentration data. The PK Analysis Set will be used to generate the corresponding PK concentration summaries and plots.

11.6 PK Evaluable Set

The PK Evaluable Set will be defined as all subjects in the Safety Analysis Set who are randomized, have received at least 1 dose of IMR-687, and have at least 4 consecutive non-zero postdose IMR-687 concentration-time data points. The PK Evaluable Set will be used to generate the corresponding PK parameter assessments.

12.0 Interim Analyses

There will be five unblinded interim analyses (IA) conducted at each of the following milestones:

- IA 0.5: Approximately 15 subjects in the NTDT population have completed 12 weeks of treatment
- IA 1.0:
    - Approximately 30 subjects in the TDT population have completed 24 weeks of treatment
    - Approximately 30 subjects in the NTDT population have completed 24 weeks of treatment
- IA 2.0:
    - Approximately 60 subjects in the TDT population have completed 24 weeks of treatment
    - Approximately 60 subjects in the NTDT population have completed 24 weeks of treatment

To facilitate the IAs, certain Sponsor representatives and designees may be unblinded to individual treatment assignments prior to and during the IA (including the unblinded clinical research organization (CRO) biostatistician and external groups for bioanalytical, PK, PK/PD analyses, and QoL analyses). Details are provided in the study unblinding plan. The blinded Sponsor and CRO study team members may be unblinded to the group analysis results (but not individual subject results) at the conclusion of the IA(s).

The IA(s) will include the primary endpoint analyses, selected secondary/ exploratory endpoint analyses and baseline summaries. The IA analyses will be performed by an unblinded statistical and programming team. No alpha spending will be used.

The following is a summary of the key IA tables and figures that will be provided at each IA. Additional IA analyses may be added/provided per Imara request/decision. More detailed analyses information will be provided in section 13.0 of the SAP.

No minimum and maximum values will be populated on tables and no scattered values will be populated on the boxplots, in order to ensure that group blinding is maintained. Further, to avoid unblinding, at IA's 0.5 and 1.0, adverse event tables will only present Placebo and pooled IMR-687 dose columns. In the Overall Summary of Treatment-Emergent Adverse Events tables, only AE categories with 10% or higher in the pooled IMR-687 dose column will be presented. In the remaining Adverse Events tables, only preferred terms with 10% or higher in the pooled IMR-687 dose column will be presented. Imara Blinded team members will only be group unblinded and cannot be exposed to that information as it could be potentially unblinding.

Table 3: Interim Analysis Tables – TDT Population

Outputs	Analysis Number	Timepoints	Analysis Set(s)
Tables			
Subject Disposition	IA 1.0, 2.0 FA	N/A	All Screened Subjects
Demographics and Baseline Characteristics	IA 1.0, 2.0 FA	N/A	Safety Analysis Set
Disease History	IA 1.0, 2.0 FA	N/A	Safety Analysis Set
Proportion of subjects with ≥20%, 33%, and 50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) – fixed time periods	IA 1.0	Week 12 to 24	Per Protocol Analysis Set
	IA 2.0	Week 12 to 24	Per protocol analysis set/ ITT analysis set
	FA	Week 12 to 24, Week 24 to 36, Week 12 to 36	Per protocol analysis set/ ITT (mITT) Analysis Set
Proportion of subjects with ≥20%, 33%, and 50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement) – rolling time periods	IA 1.0	Rolling time periods – Days 2 to 85, Day 3 to 86 and so on through Day 86 to 169, compared to the 12-week interval prior to Baseline (Day 1)	Per Protocol Analysis Set
	IA 2.0	Rolling time periods – Days 2 to 85, Day 3 to 86 and so on through Day 86 to 169, compared to the 12-week interval prior to Baseline (Day 1)	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Rolling time periods – Days 2 to 85, Day 3 to 86 and so on through Day 170 to 253 (Week 36), compared to the 12-week interval prior to Baseline (Day 1)	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Change and Percent Change from Baseline in mean Hb, Specialty Hematology, and PD parameters (listed in Sections 13.6.7 and 13.6.8)	IA 1.0	1.Week 12 to 24 Mean 2.Descriptive statistics by visit	Per Protocol Analysis Set

Outputs	Analysis Number	Timepoints	Analysis Set(s)
	IA 2.0	1.Week 12 to 24 Mean 2.Descriptive statistics by visit 3.MMRM of all visits up to Week 24 (Change only)	Per Protocol Analysis Set/ ITT Analysis Set
	FA	1.Week 12 to 24 Mean, Week 24 to 36 Mean 2.Descriptive statistics by visit 3.MMRM of all visits up to Week 36 (Change only)	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Mean number of transfusion events	IA 2.0	Through Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Through Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Mean change in transfusion burden	IA 2.0	Week 12 to Week 24, compared to the 12-week prior to Baseline (Day 1)	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 12 to Week 24, Week 24 to Week 36, and Week 12 to Week 36, compared to the 12-week prior to Baseline (Day 1)	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Proportion of subjects who are transfusion-free (independent) for ≥8 weeks during treatment	IA 2.0	Through Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Through Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Proportion of subjects who are RBC transfusion-free (independent)	IA 2.0	Over 24 Weeks	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Over 36 Weeks	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Average number of days between transfusions	IA 2.0	Through Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Over 36 weeks	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Change from Baseline in mean pre-transfusion Hb values at Weeks 12 to 24 [using pre-transfusion Hb from the Historical Transfusion Burden and the Transfusion Burden CRFs]	IA 2.0	Baseline to Week 12 to Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Baseline to Week 12 to Week 24, Week 24 to Week 36, and Week 12 to Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Proportion of subjects with an increase from Baseline of ≥1.0 g/dL in mean pre-transfusion Hb	IA 2.0	Week 12 to Week 24	Per Protocol Analysis Set/ ITT Analysis Set

Outputs	Analysis Number	Timepoints	Analysis Set(s)
values or a Reduction in RBC Transfusion Burden (≥33% reduction) Endpoint [using pre-transfusion Hb from the Historical Transfusion Burden and the Transfusion Burden CRFs]	FA	Week 24 to Week 36, Week 12 to Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Mean change from Baseline for Serum ferritin	IA 1.0	Week 24	Per Protocol Analysis Set
	IA 2.0	Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 24, 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Mean change from Baseline for Iron chelation therapy daily dose	IA 2.0	Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 24, 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Mean change from Baseline in TranQOL quality of life tool	IA 2.0	Weeks 12, 24	ITT Analysis Set
	FA	Weeks 12, 24, and 36	ITT (mITT) Analysis Set
Mean change from Baseline in SF-36 quality of life	IA 2.0	Weeks 12, 24	ITT analysis set
	FA	Weeks 12, 24, and 36	ITT (mITT) Analysis Set
Summary of exposure	IA 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
Overall summary of TEAEs	IA 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
TEAEs by SOC & PT	IA 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
TEAEs by PT	IA 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
Drug-related TEAEs by SOC & PT	IA 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
Drug-related TEAEs by PT	IA 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
TEAEs by SOC, PT & severity	IA 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set

Outputs	Analysis Number	Timepoints	Analysis Set(s)
Mean pharmacokinetic parameters for IMR-687 by dose and by study visit	IA 1.0	All available data up to Week 24	PK Evaluable Set
	FA	All available data	PK Evaluable Set
Figures			
Bar plot of proportion of subjects with reduction in RBC transfusion burden (hematological improvement) by treatment arm	IA 1.0	Week 12 to 24	Per Protocol Analysis Set
	IA 2.0	Week 12 to 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 12 to 24, Week 24 to 36, Week 12 to 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Arithmetic mean (± SD) plasma concentration of IMR-687 by dose and by study visit (linear and semi-logarithmic scale)	1.0	All available data up to Week 3	PK Analysis Set
	FA	All available data	PK Analysis Set

Table 4: Interim Analysis Tables – NTDT Population

Outputs	Analysis Number	Timepoints	Analysis Set(s)
Tables			
Subject Disposition	IA 0.5, 1.0, 2.0 FA	N/A	All Screened Subjects
Demographics and Baseline Characteristics	IA 0.5, 1.0, 2.0 FA	N/A	Safety Analysis Set
Disease History	IA 0.5, 1.0, 2.0 FA	N/A	Safety Analysis Set
Responder analysis - Analysis of proportion of subjects with ≥3% increase from baseline in mean HbF in the absence of transfusions	IA 0.5, 1.0	Week 12 to Week 24	Per Protocol Analysis Set
	IA 2.0	Week 12 to Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 12 to Week 24, and Week 24 to Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Responder analysis - Analysis of proportion of subjects with ≥3% increase from baseline in HbF in the absence of transfusions [sensitivity analysis]	IA 1.0, 2.0	Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 24, Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Responder analysis - Analysis of proportion of subjects with ≥1.0 g/dL increase from baseline in mean Hb in the absence of transfusions	IA 0.5, 1.0	Week 12 to Week 24	Per Protocol Analysis Set
	IA 2.0	Week 12 to Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 12 to Week 24, and Week 24 to Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Responder analysis - Analysis of proportion of subjects with ≥1.0 g/dL increase from baseline	IA 1.0, 2.0	Week 24	Per Protocol Analysis Set/ ITT Analysis Set

Outputs	Analysis Number	Timepoints	Analysis Set(s)
in Hb in the absence of transfusions [sensitivity analysis]	FA	Week 24, Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Responder analysis - Analysis of proportion of subjects with ≥1.5 g/dL increase from baseline in mean Hb in the absence of transfusions	IA 0.5, 1.0	Week 12 to Week 24	Per Protocol Analysis Set
	IA 2.0	Week 12 to Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 12 to Week 24, and Week 24 to Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Responder analysis - Analysis of proportion of subjects with ≥1.5 g/dL increase from baseline in Hb in the absence of transfusions [sensitivity analysis]	IA 1.0, 2.0	Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 24, Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Proportion of subjects who have an Hb increase of ≥1.0 g/dL from Baseline for ≥14 days in the absence of RBC transfusions	IA 2.0	14-day periods through Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	14-day periods through Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Change and Percent Change from Baseline in mean Hb, Specialty Hematology, and PD parameters (listed in Sections 13.6.7 and 13.6.8)	IA 0.5, 1.0	1.Week 12 to 24 Mean 2.Descriptive statistics by visit	Per Protocol Analysis Set
	IA 2.0	1.Week 12 to 24 Mean 2.Descriptive statistics by visit 3.MMRM of all visits up to Week 24 (Change only)	Per Protocol Analysis Set/ ITT Analysis Set
	FA	1.Week 12 to 24 Mean, Week 24 to 36 Mean 2.Descriptive statistics by visit 3.MMRM of all visits up to Week 36 (Change only)	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Duration of the mean Hb increase from Baseline of ≥1.0 g/dL	IA 2.0	Over 24 weeks from Baseline	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Over 36 weeks from Baseline	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Proportion of subjects who are transfusion-free (independent) for ≥8 weeks during treatment	IA 2.0	Through Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Through Week 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Proportion of subjects who are RBC transfusion-free (independent)	IA 2.0	Over 24 weeks	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Over 36 weeks	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Mean change from Baseline for Serum ferritin	IA 0.5	Week 24	Per Protocol Analysis Set

Outputs	Analysis Number	Timepoints	Analysis Set(s)
	IA 1.0	Week 24	Per Protocol Analysis Set
	IA 2.0	Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 24, 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Mean change from Baseline for Iron chelation therapy daily dose	IA 2.0	Week 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 24, 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Change from Baseline in SF-36 quality of life	IA 2.0	Weeks 12, 24	ITT Analysis Set
	FA	Weeks 12, 24, 36	ITT (mITT) Analysis set
Change from Baseline in mean NTDT-PRO total score and domain scores including tiredness/weakness domain over a continuous 12-week interval	IA 2.0	Week 12 to Week 24	ITT Analysis Set
	FA	Week 12 to Week 24, Week 24 to Week 36	ITT (mITT) Analysis Set
Change from Baseline in NTDT-PRO total score and domain score including tiredness/weakness domain	IA 2.0	Week 24	ITT Analysis Set
	FA	Weeks 24, 36	ITT (mITT) Analysis Set
Summary of exposure	IA 0.5, 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
Overall summary of TEAEs	IA 0.5, 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
TEAEs by SOC & PT	IA 0.5, 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
TEAEs by PT	IA 0.5, 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
Drug-related TEAEs by SOC & PT	IA 0.5, 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
Drug-related TEAEs by PT	IA 0.5, 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set
TEAEs by SOC, PT & severity	IA 0.5, 1.0, 2.0	All available data up to Week 24 at the time of IA	Safety Analysis Set
	FA	All available data	Safety Analysis Set

Outputs	Analysis Number	Timepoints	Analysis Set(s)
Mean pharmacokinetic parameters for IMR-687 by dose and by study visit	1.0	All available data up to Week 12	PK Evaluable Set
	FA	All available data	PK Evaluable Set
Figures			
Line plot of mean change from Baseline in Hb & HbF by treatment arm	IA 1.0 [arithmetic]	Week 12 to 24	Per Protocol Analysis Set
	2.0 [lsmeans]	Week 12 to 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA [lsmeans]	Week 12 to 24, Week 24 to 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Bar plot of proportion of subjects with ≥1.0 g/dL increase from baseline in mean Hb in the absence of transfusions	IA 1.0	Week 12 to 24	Per Protocol Analysis Set
	IA 2.0	Week 12 to 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 12 to 24, Week 24 to 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Bar plot of proportion of subjects with ≥3% increase from baseline in mean HbF in the absence of transfusions	IA 1.0	Week 12 to 24	Per Protocol Analysis Set
	IA 2.0	Week 12 to 24	Per Protocol Analysis Set/ ITT Analysis Set
	FA	Week 12 to 24, Week 24 to 36	Per Protocol Analysis Set/ ITT (mITT) Analysis Set
Arithmetic mean (± SD) plasma concentration of IMR-687 by dose and by study visit (linear and semi-logarithmic scale)	1.0	All available data up to Week 4	PK Analysis Set
	FA	All available data	PK Analysis Set

12.1 Data Monitoring Committee

The specific activities of the DMC will be governed by a charter which will define the DMC's membership, meeting frequency, procedures/conduct, and requirements for reporting its observations to the sponsor.

To ensure safety oversight throughout the trial, the DMC will review safety and preliminary efficacy data and provide recommendations to the Sponsor as described below.

The DMC will convene at the following times and for the following activities during the trial:

- Review safety data for at least 5 subjects who received IMR-687 at the lower dose and make recommendation as to the inclusion of the higher dose.
- Review safety data to confirm acceptable safety and tolerability of the higher dose of IMR-687. Make recommendation as to whether the dose level(s) could be modified; the proposed modification would occur only after a substantial protocol amendment was submitted to and approved by any applicable regulatory authorities.
- At any time during the trial—upon request by the Sponsor, medical monitor, or DMC—should a concern arise from emerging safety data for which DMC review and assessment is desired. This includes the emergence of a frequency or pattern of AEs or serious adverse events (SAEs) that suggest an unexpected or otherwise concerning safety signal.

The DMC may review the following subject data, depending on the scope of the meeting, and may recommend to continue the study as planned, modify the study, or terminate the study for safety or lack of efficacy concerns:

- Unblinded safety, preliminary efficacy, and PK data, which may include TEAEs, SAEs, clinical laboratory test results, vital signs, and other relevant data for all subjects randomized.
- Additionally, the DMC chairperson will receive copies of all SAE reports for ongoing review during the trial. The DMC chairperson may forward the SAE reports to the full DMC if he/she feels that their immediate input on, or awareness of the SAE would be helpful.

All assessments and decisions by the DMC will be documented in writing as noted in the DMC charter and prior to any resultant changes to the study unless their immediate implementation is considered necessary for subject safety. The composition of the DMC will be detailed in the DMC charter.

13.0 Statistical Methods

All statistical analyses will be conducted using SAS Version 9.4.

Descriptive summary statistics will be provided for demographics, disposition, and IMR-687 exposure. The number and percentage of subjects who discontinue from the study, along with reasons for discontinuation will be tabulated.

Continuous data will be summarized using descriptive statistics (number of subjects, mean, SD, median, first quartile (Q1), third quartile (Q3), minimum, and maximum, %CV). Frequencies and percentages will be used for summarizing categorical (discrete) data. For summaries of categorical variables, counts and percentages are based on the number of subjects in the analysis set unless otherwise specified.

All statistical tests and resulting p-values will be reported as 2-sided. Confidence intervals, when presented, will be constructed at the two-sided 95% level, unless noted otherwise.

P-values will be presented to 4 decimal places with values less than 0.0001 presented as “<0.0001” and p-values greater than 0.9999 presented as “>0.9999”.

Means, medians, Q1s, and Q3s will be presented to 1 or more decimal places than the recorded data. The SDs will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate, minimums, and maximums will be presented using the same number of decimal places as the parameter estimate. Percentages will be presented to 1 decimal place.

A month is operationally defined to be 30.4375 days. A year is defined to be 365.25 days. A week is defined to be 7 days.

Where specified, there will be pair-wise comparisons between IMR-687 lower dose vs. placebo, IMR-687 higher dose vs. placebo and IMR-687 pooled dose vs. placebo.

Separate table and figure outputs will be produced for each TDT/NTDT population. The TDT population may be unblinded and reported at a separate time from the NTDT population depending on enrollment. If this occurs the blind of the unfinished population will be preserved. Listings will include both the TDT and NTDT populations with the TDT population presented first in the listing

13.1 Subject Disposition

The number of subjects screened, screen failed, randomized, and treated in the study will be presented, together with the number and percentage of subjects who completed 24 weeks of treatment, completed 36 weeks of treatment, discontinued study drug, and discontinued from the study will be tabulated. The primary reason for screen failure, study drug discontinuation, and study discontinuation will also be tabulated.

Subjects who completed 24 weeks of treatment are defined as either 1) answered “Yes” to the “Did the subject take study drug dose during clinic visit?” question at the Week 24 visit, or later, on the Study Drug Administration eCRF, or 2) have a non-missing “Start Date of Dose From This Bottle“ or “Date of Last

Dose for this Bottle" on the Study Drug Accountability eCRF that is on or after the Week 24 visit. Subjects who completed 36 weeks of treatment are defined similarly relative to the week 36 visit.

Percentages for screen failed, primary reason for screen failure, and randomized will be based on all subjects screened. Percentages for number of subjects treated in the study will be based on all randomized subjects. Percentages for number of subjects who completed 24 weeks of treatment, number of subjects who completed 36 weeks of treatment, number of subjects who discontinued study drug, primary reason for study drug discontinuation, number of subjects discontinued from the study, and the primary reason for study discontinuation will be based on all treated subjects.

Summaries will be based on all subjects screened and tabulated for each treatment arm and the total and will be reported separately for TDT and NTDT subjects.

Tabulation of the number and percentage of subjects included in each analysis set will be provided. All percentages will be based on all randomized subjects, for each treatment arm and the total, and will be reported separately for TDT and NTDT subjects.

Details regarding randomization assignments, replacement of randomized subjects, subjects who discontinued study drug and/or study, and subject analysis sets will be reported in by-subject listings.

13.2 Important Protocol Deviations

Prior to the database lock for the primary analysis, the Sponsor or designee medical and statistics personnel will identify and review any deviations from the study protocol. Any protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being will be classified as important protocol deviations (FDA, ICH, 2013, January).

Tabulation of the number and percentage of subjects with important protocol deviations by center and category within each treatment arm will be presented on the Safety Analysis Set separately for each population. Categories will be sorted alphabetically, and deviations within each category will be sorted alphabetically. Categories will include:

- Deviations related to study inclusion or exclusion criteria
- Receipt of any prohibited therapies as defined in the protocol
- Significant deviations in study drug administration
- Subjects were not withdrawn after developing withdrawal criteria during the study

Details for protocol deviations for subjects in the Safety Analysis Set will be provided in protocol deviation and important protocol deviation data listings.

13.3 Treatment

13.3.1 Extent of Study Drug Exposure and Drug Accountability

A summary of exposure and compliance, to be reported on the Safety Analysis Set, will include the total number of tablets taken, compliance (%), total exposure (mg), average daily dose (mg/day), duration of exposure (in weeks), and incidence and duration of dose interruption. These parameters will be calculated as follows:

- Duration of exposure (in weeks) will be calculated as [(date of last dose of study medication – date of first dose of study medication + 1)/7]. The date of first dose of study medication will be collected from the Study Drug Administration CRF page and the date of last dose of study medication will be collected from the End of Treatment CRF page. If there is no date for end of treatment on the End of Treatment CRF page, the last available dose date will be used. See Appendix 3 for a complete set of data handling rules.
- Total number of tablets taken = total number of tablets dispensed – total number of tablets returned. The total number of tablets dispensed and returned will be collected from Study Drug

Accountability CRF Page. They are to be collected at study visits and will be summed over the whole study treatment period.

- Total exposure (mg) of IMR-687 = Total number of tablets taken * tablet dose level (100/150/200 mg). IMR-687 will be supplied as 100, 150, or 200 mg white tablets in the study. In the lower dose group (≥3.0 to ≤5.0 mg/kg), subjects weighing <60 kg will be dispensed 100 mg tablets and those weighing ≥60 kg will be dispensed 150 mg tablets. In the higher dose group (>4.5 to ≤6.7 mg/kg), subjects weighing <60 kg will be dispensed 150 mg tablets and those weighing ≥60 kg will be dispensed 200 mg tablets. The dose regimen for all subjects is 2 tablets once daily. The weight at the baseline will be used to establish the dose level and the same dose level will be used throughout the trial.
- Incidence and duration of dose interruption: as collected from the IP Interruptions CRF page.
- Overall compliance (%) = [(total number of tablets dispensed – total number of tablets returned) / duration of exposure (days)] x 100.
- Average daily dose (mg/day) = total exposure (mg) / duration of therapy (days).

Additional considerations and data handling in exposure and drug accountabilities may be needed for the DMC, IA, and final analysis when some of drug dosing and accountability information is deemed incomplete. See Appendix 3 for a complete set of data handling rules for drug exposure and accountability.

The same tabulation will be generated for the PP Analysis set if it is not the same as the Safety Analysis Set.

Details of the administration of study drug, including randomized and actual treatment, start date and time of each dose, dose per administration, and date, time, and composition of last meal will be listed on the Safety Analysis Set.

Details of study drug accountability including date dispensed, date returned, amount returned, and compliance per dosing period (in %, as collected directly from CRF), overall compliance (in %, for the whole duration of study drug exposure, as calculated as above) will be listed based on the Safety Analysis Set.

13.4 Demographic and Baseline Characteristics

By-population tabulation summaries and by-subject listings of demographics, baseline characteristics, disease history, and historical transfusion burden will be presented in the Safety Analysis Set.

The demographic and baseline characteristics consist of:

- Age (years) –as numeric value
- Sex (Female, Male)
- Ethnicity (Categories as collected from CRF)
- Race (Categories as collected from CRF)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Baseline Eastern Cooperative Oncology Group (ECOG) Score (0, 1)
- Region (Europe/North America, Asia/Africa) (see Appendix 5 for countries included in each region)
- Beta Thalassemia Diagnosis (Major, Intermediate, E)
- Concomitant Alpha Gene Status (Deletion, Duplication/Triplication, No Alpha)

- Previous/Ongoing Cardiac and/or Hepatic Co-morbidities due to Iron Overload (TDT) (Yes, No)
- Baseline Transfusion Burden in Packed RBC Units (day -83 to 1) continuously and categorically categorized level: Low Transfusion Burden (≤ 5), Medium Transfusion Burden (> 5-< 7) and High Transfusion Burden (> 7)) [TDT]
- Pre-transfusion Hemoglobin Threshold, defined as mean of all documented pre-transfusion hemoglobin values during the 12 weeks prior to Dose 1 Day 1 (continuous and categorized level: < 9 g/dL and ≥ 9 g/dL) [TDT]
- Baseline Serum Ferritin –as numeric value
- Daily Iron Chelation Use (Yes, No)
- Splenectomy (Yes, No)
- Baseline Hemoglobin (≤8.5, >8.5) [NTDT]

13.4.1 Medical and Surgical History

Medical and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher and will be summarized for each population by treatment arm and total in the Safety Analysis Set, using System Organ Class (SOC) and MedDRA preferred term (PT). The table will include the number and percentage of subjects and will be sorted alphabetically by SOC and in decreasing frequency by PT and then alphabetically for ties (based on the total count in the analysis set). A subject will only be counted once within a class.

A by-subject listing for medical and surgical history generated on the Safety Analysis Set.

13.5 Prior and Concomitant Treatments and Procedures

13.5.1 Prior and Concomitant Beta-Thalassemia Treatment

A prior Beta-Thalassemia treatment is any medication taken prior to first dose of study drug that is reported on the Prior/Concomitant Medications eCRF and categorized as “Disease Under Study” under the “Primary Reason Medication was Taken/Therapy was Given”. A concomitant Beta-Thalassemia treatment is any medication ongoing at the time of the first dose of study drug, or that started after first dose and within 30 days of the last dose of study drug, that is reported on the Prior/Concomitant Medications eCRF and categorized as “Disease Under Study” under the “Primary Reason Medication was Taken/Therapy was Given”.

The number and percentage of subjects taking prior Beta-Thalassemia treatment will be tabulated for each population by treatment arm, the combined active arms, and the total using the World Health Organization Drug Dictionary (WHO-DD) (01MAR2020 or later) standardized medication name for the Safety Analysis Set. Medications will be classified by Anatomical Therapeutic Chemical (ATC) level 2 groups, then by preferred name within each ATC group. If the ATC level 2 group is missing, the next non-missing level will be used. Subjects will only be counted once within each ATC group and each preferred name. ATC groups will be sorted alphabetically and preferred name will be sorted in descending frequency, using the numbers in the combined active arms column, and then alphabetically in the event of any ties.

The number and percentage of subjects taking concomitant Beta-Thalassemia treatment will be tabulated for each population by treatment arm and the combined active arms using the World Health Organization Drug Dictionary (WHO-DD) (01MAR2020 or later) standardized medication name for the Safety Analysis Set. Medications will be classified by Anatomical Therapeutic Chemical (ATC) level 2 groups, then by preferred name within each ATC group. If the ATC level 2 group is missing, the next non-missing level will be used. Subjects will only be counted once within each ATC group and each preferred name. ATC groups will be sorted alphabetically and preferred name will be sorted in descending frequency, using the numbers in the combined active arms column, and then alphabetically in the event of any ties.

All prior and concomitant Beta-Thalassemia treatment data will be presented in a listing based on the Safety Analysis Set for TDT and NTDT subjects.

13.5.2 Prior and Concomitant Medications

Prior medications are medications that started before the first dose of study drug. Concomitant medications are medications ongoing at the time of the first dose of study drug, or that started after first dose and within 30 days of the last dose of study drug.

The number and percentage of subjects who took prior medications will be tabulated for each population by treatment arm, the combined active arms, and the total using the WHO-DD (01MAR2020 or later) standardized medication name for the Safety Analysis Set. Medications will be classified by ATC level 2 groups, then by preferred name within each ATC group. If the ATC level 2 group is missing, the next non-missing level will be used. Subjects will only be counted once within each ATC group and each preferred name. ATC groups will be sorted alphabetically and preferred name will be sorted in descending frequency, using the numbers in the combined active arms column, and then alphabetically in the event of any ties.

The number and percentage of subjects taking concomitant medications will be tabulated for each population by treatment arm and the combined active arms using the WHO-DD (01MAR2020 or later) standardized medication name for the Safety Analysis Set. Medications will be classified by ATC level 2 groups, then by preferred name within each ATC group. If the ATC level 2 group is missing, the next non-missing level will be used. Subjects will only be counted once within each ATC group and each preferred name. ATC groups will be sorted alphabetically and preferred name will be sorted in descending frequency, using the numbers in the combined active arms column, and then alphabetically in the event of any ties.

All prior and concomitant medications data will be presented in a listing based on the Safety Analysis Set for TDT and NTDT subjects.

13.5.3 Concomitant Procedures

Concomitant procedures are procedures ongoing at the time of the first dose of study drug, or that started after first dose and within 30 days of the last dose of study drug. The number and percentage of subjects having concomitant procedures will be tabulated for each population by treatment arm and the combined active arms using MedDRA (version 23.0 or later) for the Safety Analysis Set. Procedures will be classified by SOC, then by PT. Subjects will only be counted once within each SOC and PT. The SOCs and PTs will be sorted alphabetically by SOC and in decreasing frequency by PT using the numbers in the combined active arms column, and then alphabetically in the event of any ties (based on the total count in the analysis set).

All concomitant procedures data will be presented in a listing based on the Safety Analysis Set for TDT and NTDT subjects. In addition, a listing of concomitant procedures that are reported on the Concomitant Procedures eCRF and categorized as “Disease Under Study” under the “Primary Reason Procedure was Performed”, based on the Safety Analysis Set for TDT and NTDT subjects, will be provided.

13.5.4 Prior and Concomitant Iron Chelation Therapy

Prior iron chelation therapies are defined as therapies that were started before the first dose of study drug that are reported on the Iron Chelation Therapy eCRF. Concomitant iron chelation therapies are therapies ongoing at the time of the first dose of study drug, or that started after first dose and within 30 days of the last dose of study drug, that are reported on the Iron Chelation Therapy eCRF.

The number and percentage of subjects who took prior iron chelation therapies will be tabulated for each population by treatment arm, the combined active arms, and the total using the WHO-DD (01MAR2020 or later) standardized medication name for the Safety Analysis Set. Medications will be classified by ATC level 2 groups, then by preferred name within each ATC group. If the ATC level 2 group is missing, the next non-missing level will be used. Subjects will only be counted once within each ATC group and each

preferred name. ATC groups will be sorted alphabetically and preferred name will be sorted in descending frequency, using the numbers in the combined active arms column, and then alphabetically in the event of any ties.

The number and percentage of subjects taking concomitant iron chelation therapies will be tabulated for each population by treatment arm and the combined active arms using the World Health Organization WHO-DD (01MAR2020 or later) standardized medication name for the Safety Analysis Set. Medications will be classified by Anatomical Therapeutic Chemical (ATC) level 2 groups, then by preferred name within each ATC group. If the ATC level 2 group is missing, the next non-missing level will be used. Subjects will only be counted once within each ATC group and each preferred name. ATC groups will be sorted alphabetically and preferred name will be sorted in descending frequency, using the numbers in the combined active arms column, and then alphabetically in the event of any ties.
All prior and concomitant iron chelation therapies data will be presented in a listing based on the Safety Analysis Set for TDT and NTDT subjects.

13.6 Endpoint Analyses

Endpoint analyses for TDT and NTDT populations will be reported separately. All efficacy endpoints will be conducted using the PP Analysis Set and may be repeated for the mITT Analysis Set (if applicable), and the ITT Analysis Set (where applicable).

13.6.1 Hypothesis Testing Strategy and Multiplicity

There will be no adjustment for multiple testing.

13.6.2 Safety Analyses

The below information regarding safety analyses is relevant for both the TDT and NTDT populations. The two populations will be summarized separately.

IMR-687 safety and tolerability will be measured in both populations by:

- Incidence and severity of AEs and SAEs
- Incidence of subjects with a post-Baseline clinically significant worsening in the CTCAE laboratory grade for a lab parameter
- Incidence of subjects with a post-Baseline clinically significant change in a vital signs parameter
- Incidence of subjects meeting the clinically significant criteria for an electrocardiogram (ECG) parameter
- Changes from Baseline in clinical laboratory tests (hematology, coagulation chemistry, urinalysis), vital signs (continuous parameters only) for any timepoint and 12-lead ECG parameters
- Changes in physical examination findings relative to the Baseline physical examination

13.6.2.1 Adverse Events

MedDRA Coding

AEs will be coded using MedDRA (v23.0 or higher).

Treatment-emergent adverse event (TEAE)

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges on or after the initiation of study drug, or an AE that existed pre-treatment and worsened in severity on or after the initiation of study drug, through 30 days after the last dose of study drug. A pre-treatment adverse event is an AE that emerges before the date of initiation of study drug.

Refer to Appendix 3 for handling of partial dates for AEs for the purpose of assigning treatment-emergent flags. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as treatment emergent.

Severity

Severity is classified as Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life Threatening, Grade 5: Death Related to AE, using the Common Terminology Criteria for Adverse Events, v5.0 (CTCAE v5.0). For the AE summary by CTCAE severity grade, an AE with missing CTCAE severity grade will not be imputed. Imputed values will not be included in data listings.

Relationship to Study Treatment

Relationship is classified as “Unlikely/Not related”, “Possible”, “Probably/Likely”, or “Certain/Related” by the Investigator. A “treatment-related TEAE” for the purpose of this summary is defined as a TEAE with relationship to study drug of “Possible”, “Probably/Likely” or “Certain/Related”. For the AE summary by relationship, an AE with a missing relationship to study drug will not be imputed. Imputed values will not be included in data listings.

TEAEs Leading to Discontinuation of Study Treatment

TEAEs leading to discontinuation of study treatment will be identified by action taken with study treatment being recorded as “Drug withdrawn” on the Adverse events CRF.

Serious and Non-Serious TEAEs

Serious adverse events (SAEs) are those events recorded as “Yes” for the question “Was the adverse event serious?” on the Adverse Event CRF.

TEAEs Leading to Death

TEAEs leading to death are those events which are recorded as “Yes” for the question “Did the adverse event result in death?”, or recorded CTCAE Toxicity Grade 5, or with outcome = “Fatal” on the Adverse Events CRF.

TEAEs Leading to Study Discontinuation

TEAEs leading to study discontinuation are those events which are recorded as “Yes” for the question “Did the adverse event cause the subject to be discontinued from the study?” on the Adverse events CRF.

TEAEs Leading to Dose Reduction

TEAEs leading to dose reduction will be identified by action taken with study treatment being recorded as “Dose Reduced” on the Adverse events CRF.

A summary of TEAEs will be presented by treatment arm and the combined IMR-687 treatment arms for TDT and NTDT subjects. The number and percentage of subjects reporting any of the following categories will be provided:

- Any pre-treatment adverse event
- Any TEAE
- Grade 3 or higher TEAEs
- Treatment-related TEAEs
- Treatment-related grade 3 or higher TEAEs
- TEAEs with outcome of death
- SAEs
- Treatment-related SAEs

- Treatment-related grade 3 or higher SAEs
- Treatment-related grade 2 or higher TEAEs
- TEAEs leading to discontinuation of study drug
- Treatment-related TEAEs leading to discontinuation of study drug
- TEAEs leading to study discontinuation
- Treatment-related TEAEs leading to study discontinuation
- TEAEs leading to dose reduction
- Treatment-related TEAEs leading to dose reduction

The following AE tables will be summarized by treatment arm and the combined IMR-687 treatment arms, SOC and PT (according to the MedDRA dictionary version 23.0 or higher) for TDT and NTDT subjects. SOCs will be sorted alphabetically and PTs will be sorted by descending frequency, by the combined IMR-687 treatment arm column, and then alphabetically for ties.

- The number and percentage of subjects reporting each TEAE. The AE count will be by subject, not event, and subjects are only counted once within each SOC or PT
- The number and percentage of subjects reporting treatment-related TEAEs. Subjects with multiple events within a particular SOC or PT will be counted under the category of their most drug-related event within that SOC or PT. AEs will be considered related to study drug if they are reported as certain/related, probably/likely related, and possibly related.
- The number and percentage of subjects reporting TEAEs, by severity (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, all defined in Section 12.1.2.2.1 of the study protocol), will also be provided. Subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT. AE severity (intensity) will be graded using NCI CTCAE, version 5.0
- The number and percentage of subjects reporting treatment-related TEAEs, by severity
- The number and percentage of subjects reporting Grade 3 or higher TEAEs
- The number and percentage of subjects reporting treatment-related Grade 3 or higher TEAEs
- The number and percentage of subjects reporting treatment-related Grade 2 or higher TEAEs
- The number and percentage of subjects reporting AEs leading to discontinuation of study drug
- The number and percentage of subjects reporting treatment-related TEAEs, by relationship
- SAEs
- TEAEs leading to death

The following AE tables will be summarized by treatment arm and the combined IMR-687 treatment arms, and PT for TDT and NTDT subjects. PTs will be sorted by descending frequency, by the combined IMR-687 treatment arm column, and then alphabetically for ties.

- The number and percentage of subjects reporting each TEAE.
- The number and percentage of subjects reporting treatment-related TEAEs
- The number and percentage of subjects reporting each TEAE with frequency ≥10%
- The number and percentage of subjects reporting treatment-related TEAEs with frequency ≥10%

All AEs (including non-treatment-emergent events) recorded on the CRF, all SAEs, and all deaths that occur following the first dose of study drug will be listed. All AE tables and listings will be reported using the Safety Analysis Set.

13.6.2.2 Clinical Laboratory Evaluation

Clinical laboratory tests (serum chemistry, central laboratory hematology, local laboratory hematology, and specialty hematology) will be summarized using the Safety Analysis Set and will be evaluated and presented using International System of Units (SI) unless otherwise stated. Clinical laboratory values will be graded from Grade 1 to Grade 4 using the NCI CTCAE, version 5.0. Post-Baseline laboratory values will only be compared to Baseline values from the same source. For example, local laboratory post-Baseline results can only be compared to local laboratory Baseline results.

Hematology assessments include: RBC count (mean corpuscular volume [MCV], RDW, mean corpuscular Hb, and mean corpuscular Hb concentration), hematocrit, Hb, platelets, WBC count (with differential: basophils, eosinophils, neutrophils, monocytes, and lymphocytes), erythrocyte count, and reticulocyte count and reticulocyte percentage. Some of these assessments are also considered PD endpoints, further detailed in the exploratory endpoint section below.

Specialty hematology assessments include: HbF and F-cells (%).

Coagulation assessments include: PT, aPTT, and international normalized ratio (INR).

Serum chemistry assessments include: alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), chloride, calcium, creatinine, glucose, lactate dehydrogenase (LDH), sodium, potassium, magnesium, phosphate, bilirubin (total, direct, and indirect), creatine kinase, total protein, glomerular filtration rate (GFR), and gamma-glutamyl transferase (GGT). Follicle stimulating hormone (FSH) will be included as well, but this is only collected for post-menopausal women at screening. Some of these assessments are also considered PD endpoints, further detailed in the exploratory endpoint section below.

Descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, and maximum) for the observed, change from Baseline, and percent change from Baseline values will be summarized by visit, treatment arm, and the combined IMR-687 treatment arms, and presented separately for chemistry and hematology and for each population. Study Baseline defined in Section 10.1.2 will be used for change from baseline. Note that character urinalysis tests will only be listed.

Urinalysis assessments include: appearance, color, pH, specific gravity, ketones, protein, glucose, bilirubin, and urobilinogen, including occult blood and microscopic examination of sediment (only if occult blood is detected).

Shift tables will be used to summarize the shift from Baseline grade to maximum CTCAE grade (Grade 1 to 4 and Missing) for selected hematology and chemistry parameters listed in Appendix 4, by treatment arm and the combined IMR-687 treatment arms and presented separately for each population. Any subject with a post-Baseline result meeting the criteria, including those collected at unscheduled visits, will be included in the tabulation.

Potentially clinically significant (PCS) Criteria for hepatic function and renal function are shown in Table 5 below. The number and percentage of subjects meeting these PCS criteria will be summarized for hepatic function parameters (ALT, AST, ALP, and total bilirubin), the renal function parameter (serum creatinine), and platelet count separately. Any subject with any post-baseline result (including “unscheduled” visits) meeting the criteria will be included in the tabulation.

Table 5 PCS Criteria for Hepatic Function, Renal Function, and Platelet Count

Hepatic Function	Renal Function	Platelet Count
○ Post-baseline Alanine Aminotransferase (ALT) ≥ 3 x upper limit of normal (ULN) ○ Post-baseline Aspartate Aminotransferase (AST) ≥ 3 x ULN ○ Post-baseline Direct Bilirubin (BILDIR) ≥ 2 x ULN ○ Post-baseline ALT/AST and BILDIR (ALT≥ 3 x ULN or AST≥ 3x ULN) and BILDIR≥ 2 x ULN (Hy's Law)	○ Post-baseline Creatinine Clearance (CREATCLR) < 0.5 x baseline ○ Post-baseline Serum Creatinine (CREAT) > 2 x baseline	○ Post-baseline Platelet Count >1000 x 10^9/L

The following figures will be provided for the following hematology, chemistry, and coagulation results: MCV, platelets, neutrophils, reticulocyte (absolute and percent), GGT, LDH, creatinine, AST, ALT, indirect bilirubin, ACR.

- Shift plot from baseline to post-baseline maximum value for each parameter by treatment arm and for the combined IMR-687 treatment arms;
- Box and whisker plot for each lab parameter by visit for each treatment arm and the combined IMR-687 treatment arms.

All laboratory parameters (serum chemistry, central laboratory hematology, local laboratory hematology, specialty hematology, coagulation, and urinalysis) will be displayed in individual subject data listings. In addition, a listing of only abnormal laboratory values will be provided. All lab tables and listings will be reported on the Safety Analysis Set.

13.6.2.3 Vital Signs

Descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, and maximum) will be used to summarize vital sign parameters (body temperature, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate) at Baseline, each post-Baseline visit, and change from Baseline to each post-Baseline visit, by treatment arm and the combined IMR-687 treatment arms, for both populations. Study Baseline as defined in Section 10.1.2 will be used.

Potentially clinically significant (PCS) post-baseline vital signs can be identified using the criteria shown in the table below. The number and percentage of subjects with any post-baseline treatment-emergent potentially clinically significant vital sign value will be tabulated by treatment group for each criterion. Any subject with a post-baseline result meeting the criteria, including those collected at unscheduled visits, will be counted.

Potentially clinically significant (PCS) post-baseline vital signs can be identified using the criteria shown Table 6 below. The number and percentage of subjects with any post-baseline treatment-emergent potentially clinically significant vital sign value will be tabulated by treatment arm and the combined IMR-687 treatment arms and will be provided separately for each population for each criterion. Any subject with a post-baseline result meeting the criteria, including those collected at unscheduled visits, will be counted.

Table 6 PCS Criteria for Vital Signs

Vital Signs	
Parameter	Criteria
Heart Rate	• ≤ 50 and decrease ≥ 15 bpm • ≥ 100 bpm and increase ≥ 15 bpm • ≥ 120 and increase ≥ 15 bpm
SBP	• ≤ 90 and decrease ≥ 20 mm Hg • < 140 mmHg and increase ≥ 20 mmHg • ≥ 140 mmHg and increase ≥ 20 mmHg • ≥ 160 and increase ≥ 20 mm Hg
DBP	• ≤50 and decrease ≥15 mm Hg • < 100 mmHg and Increase ≥ 20 mmHg • ≥ 100 mmHg and Increase ≥ 20 mmHg • ≥100 mmHg and increase ≥15 mm Hg

A plot will be presented to show the pattern of the SBP and DBP values over time by treatment arm and the combined IMR-687 treatment arms. Mean and SE will be presented in the plot. Additionally, spaghetti plots for SBP and DBP values over time will be provided for 1) individual subjects with maximum post-baseline SBP increased ≥ 20 mmHg and SBP ≥ 150 mmHg and 2) maximum post-baseline DBP increased ≥ 20 mmHg and DBP ≥ 100 mmHg. A shift plot displaying shifts from Baseline heart rate ≤ 100 to maximum heart rate >100 post-Baseline will be provided for each population.

All vital signs will be listed in a data listing. All vital sign tables and listings will be reported on the Safety Analysis Set.

13.6.2.4 12-lead ECGs

The average of triplicate 12-lead ECGs will be performed to evaluate the change from Baseline in ECG parameters (heart rate, PR interval, RR interval, QRS duration, QT interval, and QTcF interval). Descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, and maximum) of ECG parameters will be presented for Baseline, each post-Baseline visit, and change from Baseline to each post-Baseline visit by treatment arm, and the combined IMR-687 treatment arms, for both populations. Study Baseline defined in Section 10.1.2 will be used. At Baseline and Week 3 (TDT Population)/Week 4 (NTDT Population), descriptive statistics will also be presented for change from pre-dose to post-dose. All measurements, including those during unscheduled visits, will be provided in data listings, but only the scheduled measurements will be included in the summary.

The average of the ECG results by visit and parameter will be calculated if two or more of the triplicate ECG values are reported at the visit for baseline or post-baseline visits.

The number of subjects whose baseline or post-baseline QTcF values have exceeded the selected Criteria below, will be summarized with the number and percentage of subjects meeting each criterion, by treatment arm, and the combined IMR-687 treatment arms, and visit (baseline, post-baseline), separately for each population. Subjects with baseline or post-baseline (including unscheduled visits) results meeting any criteria will be counted.

Table 7 PCS Criteria for ECGs

ECGs	
Parameter	Criteria
QTcF Interval	• > 450 msec (males only) • > 470 msec (females only) • > 500 msec
QTcF Interval Increase from Baseline	• ≥ 30 msec • ≥ 60 msec

All ECG parameters will be listed in a data listing. All ECG tables and listings will be reported using the Safety Analysis Set.

13.6.2.5 Physical Examinations

All physical examination findings will be listed in by-subject listings on the Safety Analysis Set. No tabulation summaries will be provided.

13.6.3 Imputation Methods for Endpoints

Unless otherwise specified, no imputation of data relating to the primary endpoint of safety and tolerability, or for secondary or exploratory efficacy endpoints, will be performed.

13.6.3.1 Pooling of Sites

There will be no pooling of sites.

13.6.4 Efficacy Analyses (Secondary Endpoints)

The PP Analysis Set will be used for all efficacy endpoint analyses. Selected analyses will be repeated on the mITT and/or ITT Analysis Sets as sensitivity analyses, with mITT only used if different than the ITT. The TDT and NTDT populations will be summarized separately for all analyses.

Table 8 Secondary Endpoints – TDT Population

Secondary Endpoints	Time Points	Secondary Endpoint Analysis
Proportion of subjects with a ≥20% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement)	Fixed time periods of Week 12 to Week 24, Week 24 to Week 36, and Week 12 to Week 36, compared to the 12-week interval prior to Baseline (Day 1)	• Cochran-Mantel Haenszel (CMH) analysis: Odds ratios (OR) (active arms vs. placebo), 2-sided 95% CI, p-value • Summary of number and percentage of responders with difference in proportions (active arm-Placebo) and corresponding 2-sided 95% CI • Forest plots of ORs, 2-sided 95% CIs, p-value – Higher dose vs. placebo, Lower dose vs. placebo
Proportion of subjects with a ≥33% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement)		
Proportion of subjects with a ≥50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement)		
Proportion of subjects with a ≥20% reduction in RBC transfusion burden with a	Rolling 12-week time periods –	

reduction of at least 2 units of RBCs (hematological improvement)	Day 2 to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36), compared to the 12-week interval prior to Baseline (Day 1) Rolling 14-week time periods – Day 2 to 99, Day 3 to 100, etc. through Day 156 to Day 253 (Week 36), compared to the 12-week interval prior to Baseline (Day 1)	
Proportion of subjects with a ≥33% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement)		
Proportion of subjects with a ≥50% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement)		
Number of transfusion events	Baseline to Week 24, Baseline to Week 36	• Summary statistics of the number of cumulative transfusions at every 3 weeks post-Baseline from Week 3 through Week 36. • Analysis of Covariance (ANCOVA) analysis with Baseline value as a covariate: LSMean (95% CI), LSMean difference (95% CI) between each active dose and placebo, and p-value. • Plots of the mean number of transfusions, mean number of units, and mean Hb by time periods (Weeks 1-12, Weeks 13-24, Weeks 25-36)
Change from Baseline for mean iron chelation therapy daily dose and mean serum ferritin	Baseline to Week 36	• Analysis of Covariance (ANCOVA) analysis with Baseline value as a covariate: LSMean (95% CI), LSMean difference (95% CI) between each active dose and placebo, and p-value.
The plasma PK profile of IMR-687after administration to subjects will be evaluated by determination of PK parameters (e.g., C_{max}, t_{max}, AUC_{0-24}) based on drug concentration levels in plasma obtained over time	Baseline and Week 3 (TDT) Baseline and Week 4 (NTDT)	Descriptive summary

Table 9 Secondary Endpoints – NTDT Population

Secondary Endpoints	Time Points	Secondary Endpoint Analysis
Change from Baseline for iron chelation therapy daily dose and serum ferritin	Baseline to Week 36	• Analysis of Covariance (ANCOVA) analysis with Baseline value as a covariate: LSMean (95% CI), LSMean difference (95% CI)

		between each active dose and placebo, and p-value.
Change from Baseline in mean Hb values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions [using Hb from Laboratory Hematology] Change from Baseline in mean HbF values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions	Baseline to Week 12-24, and Week 24-36	• Summary statistics for the Baseline, post-Baseline, and change from Baseline Hb and HbF by treatment arm • Scatter box-whisker plots for mean change over continuous 12-week intervals • ANCOVA analysis with Baseline value as a covariate: LSMean (95% CI), LSMean difference (95% CI), and p-value.
Proportion of subjects with an increase from Baseline of ≥3% in mean HbF values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions.	Week 12 to Week 24, and Week 24 to Week 36	• Cochran-Mantel Haenszel (CMH) analysis: Odds ratios (OR) (active arms vs. placebo), 2-sided 95% CI, p-value • Summary of number and percentage of responders with difference in proportions (active arm-Placebo) and corresponding 2-sided 95% CI • Forest plots of ORs, 2-sided 95% Cis, p-value – Higher dose vs. placebo, Lower dose vs. placebo
Proportion of subjects with an increase from Baseline of ≥1.0 g/dL in mean Hb values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions. [using Hb from Laboratory Hematology]	Week 12 to Week 24, and Week 24 to Week 36	• Cochran-Mantel Haenszel (CMH) analysis: Odds ratios (OR) (active arms vs. placebo), 2-sided 95% CI, p-value • Summary of number and percentage of responders with difference in proportions (active arm-Placebo) and corresponding 2-sided 95% CI • Forest plots of ORs, 2-sided 95% Cis, p-value – Higher dose vs. placebo, Lower dose vs. placebo
Proportion of subjects with an increase from Baseline of ≥1.5 g/dL in mean Hb values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions. [using Hb from Laboratory Hematology]	Week 12 to Week 24, and Week 24 to Week 36	• Cochran-Mantel Haenszel (CMH) analysis: Odds ratios (OR) (active arms vs. placebo), 2-sided 95% CI, p-value • Summary of number and percentage of responders with difference in proportions (active arm-Placebo) and corresponding 2-sided 95% CI • Forest plots of ORs, 2-sided 95% Cis, p-value – Higher dose vs. placebo, Lower dose vs. placebo
The plasma PK profile of IMR-687 after administration to subjects will be evaluated by determination of PK parameters (e.g., C_{max}, t_{max}, AUC_{0-24}) based on drug concentration levels in plasma obtained over time	Baseline and Week 3 (TDT) Baseline and Week 4 (NTDT)	Descriptive summary

13.6.4.1 TDT Population

Hematological Improvement Endpoints

Hematological improvement is defined as a ≥20%, ≥33%, or a ≥50% reduction in pRBC units transfused, with a reduction of at least 2 units of RBCs, measured over a fixed period of 12 weeks (from Week 12 to Week 24 and from Week 24 to Week 36) or over 24 weeks (from Week 12 to Week 36) as compared to the 12-week period prior to the Baseline (Day 1) visit. The pRBC units are defined as the sum all pRBCs units for the specific 12- or 24-week period.

Hematological improvement will also be assessed using any 12-week rolling time period – Day 2 to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1) – and any 14-week rolling time period – Day 2 to 99, Day 3 to 100, etc. through Day 156 to Day 253 (Week 36) – compared to the 12 weeks prior to Baseline (Day 1). For the rolling time periods, a responder is defined as a subject who meets the hematological improvement criteria in at least one of the rolling time periods.

The proportion of subjects with a ≥20% hematological improvement (a 20% or more reduction in pRBC units transfused, with a reduction of at least 2 units of RBCs) during Week 12 to Week 24 and Week 24 to Week 36, compared to the 12-week prior to Baseline (Day 1) timeframe, will be assessed using a CMH test. The estimate of the odds ratios and the associated 95% confidence intervals (CIs) and p-values from the CMH tests will be presented for each active arm vs. placebo at each timepoint. The difference in proportions (each active arm-Placebo and the combined active arms-Placebo) and corresponding 95% CI will be also provided. An odds ratio exceeding 1 indicates that the proportion of improved subjects in the treated arm is higher than in the placebo arm.

The proportion of subjects with a ≥33% hematological improvement and the proportion of subjects with a ≥50% hematological improvement for the Week 12 to Week 24 and Week 24 to Week 36 time periods will be analyzed similarly as for the proportion of subjects with ≥20% hematological improvement.

The above analyses for the proportions of subjects with ≥20%, ≥33%, ≥50% hematological improvement will be repeated for the 24-week post-Baseline time period, Week 12 to Week 36.

The proportion of subjects with a ≥20%, ≥33%, and ≥50% hematological improvement for the 12-week rolling and 14 week rolling time periods will be analyzed similarly as for the fixed time periods above.

Bar plots will be provided. The proportion of subjects with a ≥20%, ≥33%, and ≥50% hematological improvement, odds ratios, 95% CIs, and p-values will be displayed by treatment arm for Week 12 to Week 24, Week 24 to Week 36, and Week 12 to Week 36, compared to the 12-week period prior to Baseline (Day 1). Separately, bar plots will be provided for the 12 week rolling time periods and for the 14 week rolling time periods.

Number of Transfusion Events Endpoint

The number of transfusion events in IMR-687 arms from Baseline to Week 36 compared to placebo will be assessed using an ANCOVA model with baseline value as a covariate and treatment as a factor. Summary statistics of the number of cumulative transfusions at every 12 weeks post-Baseline from Week 12 through Week 36 will be presented. All post-baseline assessments of number of transfusions will be cumulative from baseline. For example, the number of transfusions at Week 24 and Week 36 will include all transfusions from baseline through the Week 24 and Week 36 visits, respectively. The least squares mean (LSMean) estimates and 95% CIs will be presented for each active arm, the combined active arms, and placebo at Week 36. Additionally, the LSMean difference estimates and associated 95% CIs and p-values at Week 36 will also be reported for each active arm vs. placebo and the combined active arms vs. Placebo.

Box whisker plots of the mean number of transfusion events, mean number of units, and mean pre-transfusion Hb with outliers over time will be provided by time periods (Weeks 1-12, Weeks 13-24, and Weeks 25-36) by treatment arm.

Transfusion events data will be reported in a by-subject listing using the ITT Analysis Set.

Iron Chelation Therapy Endpoints

The mean changes from Baseline to Week 36 for iron chelation therapy daily (ICT) dose will be assessed using ANCOVA models with baseline value as a covariate on the Safety Analysis Set. The Baseline mean daily dose of ICT will be calculated during the 12 weeks prior to the first dose of study drug. The post-baseline (Week 36) mean values will be calculated during the last 12 weeks of the 36-week treatment period, or the last 12 weeks of study drug for subjects who are discontinued early. Summary statistics for observed values at Baseline and Week 36 and change from Baseline to Week 36 of ICT will be presented. The change from baseline in mean daily dose of ICT at Week 36 will be analyzed using an ANCOVA model with baseline ICT mean daily dose as a covariate, including only subjects who did not change their ICT drug from Baseline to post-baseline and used only one ICT drug. LSMean estimates and 95% CIs will be presented for each active arm and placebo at Week 36. The LSMean difference estimates and associated 95% CIs and p-values at Week 36 will also be reported for each active arm vs. placebo and the combined active arms vs. Placebo. The values at Week 24 will be analyzed in a similar manner. Line plots will be provided for mean change from Baseline with 95% CI to Week 36 for ICT daily dose by treatment arm.

The number and percentage of subjects who took monotherapy (i.e., only one ICT drug) vs. combo therapy (i.e., more than one ICT drug) will be summarized at Baseline and Week 36, by treatment arm. The percent change in mean daily dose of ICT from Baseline to Week 36 will be summarized with descriptive statistics, by treatment arm.

For subjects that are stable on the same ICT drug(s) throughout the study, the change in mean daily dose will be calculated. Subjects who switched drugs during the study will be excluded. For subjects on more than one drug, the change will be averaged for the drugs.

Serum Ferritin Endpoint

The mean changes from Baseline to Week 36 for serum ferritin will be assessed using ANCOVA models with baseline value as a covariate on the Safety Analysis Set. The Baseline mean serum ferritin will be calculated during the 12 weeks prior to the first dose of study drug. The post-baseline (Week 36) mean values will be calculated during the last 12 weeks of the 36-week treatment period, or the last 12 weeks of study drug for subjects who are discontinued early. Summary statistics for observed values at Baseline and Week 36 and change from Baseline to Week 36 of serum ferritin will be presented. The change from baseline in mean serum ferritin at Week 36 will be analyzed using an ANCOVA model with baseline serum ferritin mean as a covariate. LSMean estimates and 95% CIs will be presented for each active arm and placebo at Week 36. The LSMean difference estimates and associated 95% CIs and p-values at Week 36 will also be reported for each active arm vs. placebo and the combined active arms vs. Placebo. Line plots will be provided for mean change from Baseline with 95% CI to Week 36 for serum ferritin by treatment arm. The values at Week 24 will be analyzed in a similar manner.

13.6.4.2 Imputation Methods for the Hb and HbF Endpoints for the NTDT Population

The following imputation rules will be applied for the secondary efficacy endpoints related to Hb and HbF (Mean change from Baseline in mean Hb values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions. Mean change from Baseline in mean HbF values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions. Proportion of subjects with an increase from Baseline of ≥3% in mean HbF values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions, and Proportion of subjects with an increase from Baseline of ≥1.0 g/dL in mean Hb values at Weeks 12 to 24 and Weeks 24 to 36 in the absence of transfusions):

Hb :

1. Subject will be treated as a non-responder for the Week 12 to 24 endpoint time period if they received an RBC Transfusion within the prior 8 weeks (from Week 4 to 24) and a non-responder for the Week 24 to 36 endpoint time period if they received an RBC Transfusion within the prior 8 weeks (from Week 16 to 36). For the mean change from Baseline endpoints this means that the mean change from Baseline will be set to missing. For the proportion of subjects with an

increase from Baseline endpoints, this means that the subject will not be included in the proportion of subjects with an increase.

2. If some of the Hb values are missing during any of the time periods, the mean of the non-missing values during that time period will be used for the mean change from Baseline endpoints and the non- missing values during that time period will be used for the determination of the proportion of subjects with an increase from Baseline endpoints.

HbF :

1. If the subject received an RBC Transfusion during the time periods described above for Hb, regardless of the reason, the HbF will be imputed as the last assessment prior to transfusion
2. If some of the HbF values are missing during any of the time periods, the mean of the non-missing values during that time period will be used for the mean change from Baseline endpoints and the non- missing values during that time period will be used for the determination of the proportion of subjects with an increase from Baseline endpoints.

The number of subjects with imputed values for the secondary efficacy endpoints and the reason for imputation will also be summarized.

13.6.4.3 NTDT Population

Responder Analyses

Proportion of Subjects with an Increase from Baseline of ≥3% in Mean HbF Endpoint

The proportion of subjects with increase from Baseline of ≥3% in mean HbF values (at Weeks 12 to 24 and Weeks 24 to 36) will be assessed using a CMH test. The number and percentage of responders and non-responders at Weeks 12-24 and Weeks 24-36 will be presented for each treatment arm as well as ORs, 95% CIs, and p-values from the CMH tests. The difference in proportions (active arm-Placebo and and the combined active arms-Placebo) and corresponding 95% CI will be also provided. Bar plots will be provided. The proportion of subjects with response in HbF, where a responder has an increase of ≥3% at Weeks 12-24 and Weeks 24-36 compared to Baseline, Odds ratios, 95% CI, and p values will be displayed by treatment arm.

Proportion of Subjects with an Increase from Baseline of ≥1.0 g/dL in Mean Hb Endpoint

The proportion of subjects with increase from Baseline of ≥1.0 g/dL in mean Hb values (at Weeks 12 to 24 and Weeks 24 to 36) will be evaluated using a Cochran-Mantel-Haenzel (CMH) test to compare the proportion of subjects who achieved improvement between the placebo group and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose) and the combined active arms. The number and percentage of responders and non-responders, ORs, 95% CIs, p-values from the CMH tests and the difference in proportions and corresponding 95% CI will be provided similarly to the HbF above.

Mean Change Analyses

Change from Baseline in Mean Hb and HbF Endpoints

The Baseline value of Hb will be defined as the mean of the screening and baseline Hb values. The Baseline value of HbF will be defined in an analogous manner. Post-Baseline Hb is defined as the mean of all documented hemoglobin values collected during each 12-week interval. If there are any missing values at scheduled collected times, the mean will still be calculated from the remaining non-missing values. However, any Hb values collected within 8 weeks after a transfusion will not be included in the calculation of the mean. Post-Baseline HbF will be defined in an analogous manner. To estimate the change of Hb and HbF after dosing within each 12-week interval (Week 12-24, week 24-36), summary statistics for the Baseline, post-Baseline, and change from Baseline Hb and HbF will be provided by treatment arm.

The number and percentage of subjects meeting the following selected change in Hb categories will be tabulated by treatment arm:

- Increase ≥1 g/dL
- Increase ≥1.5 g/dL

The number and percentage of subjects meeting the following selected change in HbF categories will be tabulated by treatment arm:

- Increase ≥3%

Scatter box-whisker plots for the mean change in Hb and HbF concentrations over continuous 12-week intervals from Week 12 to Week 24 and Week 24 to Week 36 in the absence of transfusions will be provided by treatment arm.

In addition, the change in mean Hb and HbF concentrations over continuous 12-week intervals from Week 12 to Week 24, and Week 24 to Week 36 in the absence of transfusions will be assessed using ANCOVA models with Baseline value as a covariate. Summary statistics for observed values at Baseline, Weeks 12-24, and Weeks 24-36, and change from Baseline to Weeks 12-24 and 24-36 will be presented. LSMean estimates and 95% CIs will be presented for each active arm and placebo at Weeks 12-24 and Weeks 24-36. The LSMean difference estimates and associated 95% CIs and p-values at Weeks 12-24, and Weeks 24-36 will also be reported for each active arm compared to placebo and the combined active arms compared to Placebo.

Iron Chelation Therapy and Serum Ferritin Endpoints

The mean change from Baseline to Week 36 for iron chelation therapy daily (ICT) dose and serum ferritin will be assessed for the NTDT Population similar to above in section 13.6.4.1 for the TDT Population.

13.6.4.4 Sensitivity Analyses

All sensitivity analyses will be performed on the PP Analysis Set unless otherwise specified.

13.6.4.4.1 NTDT Population

Proportion of Subjects with an Increase from Baseline of ≥1.0 g/dL in Hb

The proportion of subjects with increase from Baseline of ≥1.0 g/dL in Hb values (at Weeks 24 and 36) will be evaluated using a CMH test to compare the proportion of subjects who achieved improvement between the placebo group and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose) and the combined active arms. The number and percentage of responders and non-responders, ORs, 95% CIs, p-values from the CMH tests and the difference in proportions and corresponding 95% CI will be provided similarly to the secondary endpoint – Proportion of subjects with an increase from Baseline of ≥1.0 g/dL in mean Hb values.

Proportion of Subjects with an Increase from Baseline of ≥3% in HbF

The proportion of subjects with increase from Baseline of ≥3% in HbF values (at Weeks 24 and 36) will be assessed using a CMH test. The number and percentage of responders and non-responders at Weeks 24 and 36 will be presented for each treatment group as well as ORs, 95% CIs, and p-values from the CMH tests. The difference in proportions (active arm-Placebo and the combined active arms-Placebo) and corresponding 95% CI will be also provided. The proportion of subjects with response in HbF, where a responder has an increase of ≥3% at Weeks 24 and 36 compared to Baseline, Odds ratios, 95% CI, and p values will be displayed by treatment arm.

Mean Change from Baseline in Hb

The mean change in Hb concentration at Week 24 in the absence of transfusions will be assessed using an ANCOVA model with Baseline value as a covariate. Summary statistics for observed values at Baseline and Week 24, and change from Baseline to Week 24 will be presented. LSMean estimates and 95% CIs will be presented for each active arm and placebo at Week 24. The LSMean difference estimates and associated 95% CIs and p-values at Week 24 will also be reported for each active arm compared to placebo and the combined active arms-Placebo.

13.6.4.5 Subgroup Analyses

Subgroup analyses will be performed for the secondary endpoints listed below using the categories listed below. All analyses performed on the secondary endpoints will be repeated for each subgroup level. Descriptive statistics will be provided. No inferential statistics will be performed. Summary tables and a forest plot will display descriptive statistics for each level of a subgroup for a population.

Subgroup analyses will be performed for all secondary endpoints using the categories listed below. All analyses performed on the secondary endpoints will be repeated for each subgroup level for the following efficacy endpoints:

- TDT: Transfusion burden proportion analyses –33% fixed and rolling
- TDT: Transfusion burden – mean change from pre-treatment
- NTDT: Mean change from baseline in Hb, HbF, and PRO scores (NTDT-PRO T/W domain and total score; SF-36 PCS and MCS)

Subgroup analyses will also be performed for the following endpoints for the polymorphism genes (listed below – BCL11A and XMN1):

- TDT: Transfusion burden proportion analyses –20% and 50% fixed and rolling
- NTDT: Proportion of subjects with ≥1.0 g/dL increase from baseline in mean Hb in the absence of transfusions
- NTDT: Proportion of subjects with 3% increase from baseline in mean HbF in the absence of transfusions

Subgroups for the TDT population:

- Region (Europe/North America, Asia/Africa)
- Age (≤ median, > median)
- Sex (male, female)
- Mutation (β^0/β^0, non-β^0/β^0)
- Pre-treatment transfusion burden (≤ median, > median)
- Pre-treatment transfusion burden (units/12 weeks):
    - Low transfusion burden (≤ 5 units/12 weeks)
    - Medium transfusion burden (> 5 - ≤7 units/12 weeks)
    - High transfusion burden (> 7 units/12 weeks)
- Splenectomy (yes, no)
- Diagnosis (Major, Intermedia, BE/B+, BE/BO) (disease under history page)
- Baseline serum ferritin (≤ median, > median of the total TDT population)
- Pre-transfusion Hb (≤ median, > median of the total TDT population)
- Baseline BCL11A
- Baseline XMN1

Subgroups for the NTDT population:

- Age (≤ median, > median of the total population)
- Sex (male, female)

- Region (Europe/North America, Asia/Africa)
- Diagnosis (Major, Intermedia, BE/B+, BE/BO) (disease under history page)
- Splenectomy (yes, no)
- Baseline serum ferritin (≤ median, > median of the total NTDT population)
- Baseline Hb (≤ median, > median of the total NTDT population)
- Baseline HbF (≤ median, > median of the total NTDT population)
- Baseline NTDT-PRO T/W domain (≤3, >3)
- Baseline BCL11A
- Baseline XMN1

13.6.5 Pharmacokinetic Analyses

Data from subjects who experience emesis within the PK sampling duration of IMR-687 at Study Day 1 or Week 3 (TDT) or Week 4 (NTDT) visits, will be evaluated on a case-by-case basis for exclusion from concentration-time data and PK analysis descriptive summaries. The individual subject data will be listed.

If a quantifiable pre-dose concentration of IMR-687 is detected at Baseline (Study Day 1) and this concentration is greater than 5% of the corresponding C_{max}, all subject data will be excluded from all concentration-time and PK analysis descriptive summaries but will be included in the subject data listings.

All plasma concentration-time data will be reported to the same number of significant figures as displayed in the bioanalytical data. $Lambda_z$ will be reported up to 4 decimal places and time-related PK parameters ($T_{1/2}$, T_{max}, and T_{last} will be reported up to 3 decimal places. All other PK parameters will be reported to the same number of significant figures as displayed in the bioanalytical data.

The concentration-time data from subjects with sparse PK sampling collected using the sampling schedule reflected in protocol version 5.0 (15 Mar2021) will be summarized descriptively and included in subject listings and analyzed for population PK. Noncompartmental analysis will not be performed with the PK data collected from these subjects. The concentration-time data from subjects with PK samples collected using the sampling schedule reflected in the prior protocol versions (up to version 4.0; 15 Jan 2020) will be summarized descriptively and listed. The PK data from these subjects will be used for the estimation of PK parameters using noncompartmental analysis. All available PK data from this study will also be used to explore any relationship between IMR-687 exposure and clinical response, PD endpoints, or AEs, as data permit. These data will be analyzed together with PK data from other clinical studies for a population PK analysis, as appropriate. Population PK analysis and other exploratory PK/PD analyses are not within the scope of this SAP and will be detailed in a separate population PK analysis plan.

No analysis visit windows will be applied for reporting of plasma concentration-time data and PK analysis, nominal visit times will be used (i.e., Study Day 1, Week 3 or Week 4).

13.6.5.1 Plasma Concentrations

Plasma concentrations of IMR-687 BLQ will be set to 0.01 ng/mL in the computation of mean concentration values. Descriptive statistics (number of subjects, mean, geometric mean, SD, coefficient of variation (%CV), geometric %CV, median, minimum, and maximum) will be used to summarize the plasma concentrations by treatment and by study visit (i.e., Study Day 1 and Week 3/Week 4) for each disease state (TDT and NTDT) at each scheduled timepoint.

Linear and semi-logarithmic plots of the arithmetic mean (±SD) and geometric mean (±SD) plasma concentration by scheduled sampling time will be provided by dose, by study visit, and by disease state.

These plots will show time in hours. The plots will present all calculated means and will include a reference line for the lower limit of quantification (LLOQ).

Linear and semi-logarithmic plots of the individual plasma concentration by scheduled sampling time will be provided by dose, by subject (one subject per page), and by study visit for each disease state. These plots will show time in hours. Individual plots will use the BLQ handling procedure described below for "Plasma Pharmacokinetic Parameters".

13.6.5.2 Plasma Pharmacokinetic Parameters Analyses

Plasma PK parameters for IMR-687 will be estimated using non-compartmental methods with Phoenix® WinNonlin® Version 8.1 (Certara, USA). The PK parameters will be estimated from the concentration-time profiles, and all AUCs will be calculated using a linear up/log down method using actual sampling times.

The apparent terminal elimination half-life, $T_{1/2}$, where determinable, will be calculated as the natural log of 2 divided by the terminal phase rate constant, $lambda_z$. The number of data points included in the regression will be determined by visual inspection, but a minimum of 3 data points in the terminal phase, excluding C_{max}, is required to estimate $lambda_z$. In order for $lambda_z$ and $lambda_z$ derived parameters (AUC_{inf}, $T_{1/2}$, V_z/F, CL/F, and V_z/F (steady state) to be reported, the adjusted r^2 value reported in Phoenix® WinNonlin® must be ≥0.80.

For the purposes of estimating the PK parameters, BLQ values will be set to zero prior to the first quantifiable concentration and set to missing thereafter, including embedded BLQs. Scheduled sampling times will be used for the interim analyses and actual sampling times will be used for the final analysis.

Missing concentration-time data will be treated as missing except for the pre-dose plasma concentrations where a value of 0 will be imputed for Baseline for the purposes of PK parameter estimation. Similarly for the Week 3/4 visit, missing concentration-time data will be treated as missing except for the pre-dose concentration following steady state dosing where the lowest concentration value over the dosing interval (C_{min}) will be used for imputation purposes.

For the final analysis, if the actual time is missing, the scheduled time will be substituted and flagged. Subjects must have at least 4 consecutive non-zero post-dose plasma concentrations to be considered evaluable. Profiles that do not meet this criterion will be flagged for exclusion.

Descriptive statistics (number of subjects, mean, geometric mean, SD, %CV, geometric %CV, median, minimum, and maximum) will be used to summarize the PK parameters by dose and by study visit for each disease state. Additional PK evaluations may be performed as needed.

C_{trough} concentrations for Study Day 1 and Week 3/4 will be summarized along with C_{trough} concentrations at Week 1, Week 24, and Week 36.

All individual subject PK parameters will be listed.

The following PK parameters for IMR-687 may be computed, where feasible. Additional PK parameters may be determined:

Table 10 PK Parameters

Parameter	Description
Study Day 1 (Single Dose)	
C_{max}	Maximum plasma concentration postdose. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units.
T_{max}	Time to maximum plasma concentration postdose. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.
T_{last}	Time of last measurable plasma concentration.
C_{trough}	Concentration at the end of the dosing interval
AUC_{last}	Area under the concentration-time curve from time 0 to the last measurable concentration postdose
AUC_{inf}	Area under the concentration-time curve from time 0 to infinity, calculated as AUC_{last} + (C_{last}/$Lambda_z$)
$Lambda_z$	Apparent terminal elimination phase rate constant
$T_{1/2}$	Apparent terminal elimination half-life
CL/F	Apparent total body clearance from oral administration, calculated as Dose/AUC_{inf}
V_z/F	Apparent volume of distribution from oral administration, calculated as Dose/$lambda_z$ × AUC_{inf}
Week 3/4 (Steady State)	
$C_{max,ss}$	Maximum plasma concentration postdose at steady state. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units.
$T_{max,ss}$	Time to maximum plasma concentration postdose at steady state. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.
T_{last}	Time of last measurable plasma concentration.
C_{trough}	Concentration at the end of the dosing interval
AUC_{0-24}	Area under the concentration-time curve from time 0 to 24 hours postdose.
$Lambda_z$	Apparent terminal elimination phase rate constant
CL_{ss}/F	Apparent total body clearance from oral administration at steady state, calculated as Dose/AUC_{0-24}
V_z/F	Apparent volume of distribution from oral administration at steady state, calculated as Dose/$lambda_z$ × AUC_{0-24}
R_{AUC}	Accumulation ratio, calculated as AUC_{0-24} (Week 3/4)/AUC_{last} (Study Day 1; AUClast = 24 hour)

C_{last} = last observed measurable plasma concentration

13.6.6 Exploratory Efficacy Analyses

The PP Analysis Set will be used for all exploratory efficacy endpoint analyses. Selected analyses will be repeated on the ITT and/or mITT Analysis Sets as sensitivity analyses.

Table 11 Exploratory Endpoints – TDT Population

Exploratory Endpoints	Time Points	Exploratory Endpoint Analysis
The PD effects as measured by the mean change from Baseline in serum PD markers of erythropoiesis, iron metabolism, and hemolysis.	Baseline to week 36 (including all visits in between)	Mixed Model Repeated Measures (MMRM) analysis: Mean (95% CI), Mean difference (95% CI), and p-value will be provided.
Mean change in transfusion burden (pRBC units) as a continuous variable	Week 12 to Week 24, Week 24 to Week 36, and Week 12 to Week 36, compared to the 12-week prior to Baseline (Day 1)	Descriptive summary
Proportion of subjects who are transfusion-free (independent) for ≥8 weeks during treatment	Over treatment time	CMH analysis: Odds ratios (active arm vs. placebo), 95% CI, p-value, difference in proportions (active arm-Placebo) and corresponding 95% CI will be provided
Proportion of subjects who are RBC transfusion-free (independent) over 36 weeks and other variables of transfusion burden	Over 36 weeks	CMH analysis: Odds ratios (active arm vs. placebo), 95% CI, p-value, difference in proportions (active arm-Placebo) and corresponding 95% CI will be provided
Mean number of transfusion events	Baseline to Week 36	• Summary statistics of the number of cumulative transfusions at every 3 weeks post-Baseline from Week 3 through Week 36. • Analysis of Covariance (ANCOVA) analysis with Baseline value as a covariate: LSMean (95% CI), LSMean difference (95% CI) between each active dose and placebo, and p-value. • Plots of the mean number of transfusions, mean number of units, and pre-transfusion mean Hb over time
Change from Baseline in mean pre-transfusion Hb values at Weeks 12 to 24, Weeks 24 to 36, and Weeks 12 to 36 [using pre-transfusion Hb from the Historical Transfusion Burden and the Transfusion Burden CRFs]	Baseline to Week 12 to Week 24, Week 24 to Week 36, and Week 12 to Week 36	• Summary statistics for the Baseline, post-Baseline, and change from Baseline Hb by treatment arm • Scatter box-whisker plots for mean change over continuous 12-week and 24-week intervals • ANCOVA analysis with Baseline value as a covariate: LSMean (95% CI), LSMean difference (95% CI), and p-value.
Proportion of subjects with an increase from Baseline of ≥1.0 g/dL in mean pre-transfusion Hb values or a Reduction in RBC	Week 12 to Week 24, Week 24 to Week 36, and Week 12 to Week 36	• Cochran-Mantel Haenszel (CMH) analysis: Odds ratios (OR) (active arms vs.

Transfusion Burden (≥33% reduction) Endpoint at Weeks 12 to 24, Weeks 24 to 36, and Weeks 12 to 36 [using pre-transfusion Hb from the Historical Transfusion Burden and the Transfusion Burden CRFs]		placebo), 2-sided 95% CI, p-value • Summary of number and percentage of responders with difference in proportions (active arm-Placebo) and corresponding 2-sided 95% CI • Forest plots of ORs, 2-sided 95% Cis, p-value – Higher dose vs. placebo, Lower dose vs. placebo
Mean change from Baseline in TranQOL quality of life tool	Weeks, 12, 24, and 36	Descriptive Summary
Mean change from Baseline in SF-36 quality of life (PCS and MCS domains and 8 sections)	Weeks, 12, 24, and 36	Descriptive Summary
Pharmacogenomic analyses of genes that may affect treatment response (including α-globin, gamma-globin *XmnI* polymorphism, and BLC11A)	NA	Descriptive Summary
Average number of days between transfusions	Over 36 weeks	Descriptive Summary

Table 12 Exploratory Endpoints – NTDT Population

Exploratory Endpoints	Time Points	Exploratory Endpoint Analysis
Proportion of subjects who are transfusion-free (independent) for ≥8 weeks during treatment	Over treatment time	CMH analysis: Odds ratios (active arm vs. placebo), 95% CI, p-value, difference in proportions (active arm-Placebo) and corresponding 95% CI will be provided
Proportion of subjects who are RBC transfusion-free (independent) over 36 weeks and other variables of transfusion burden	Over 36 weeks	CMH analysis: Odds ratios (active arm vs. placebo), 95% CI, p-value, difference in proportions (active arm-Placebo) and corresponding 95% CI will be provided
Mean change from Baseline in SF-36 quality of life (PCS and MCS domains and 8 sections)	Weeks, 12, 24, and 36	Descriptive Summary
Pharmacogenomic analyses of genes that may affect treatment response (including α-globin, gamma-globin *XmnI* polymorphism, and BLC11A)	NA	• Descriptive Summary • Subgroup analysis
Proportion of subjects who have an Hb increase of ≥1.0 g/dL from Baseline for ≥14 days in the absence of RBC transfusions	Any consecutive 14-day period through Week 36	CMH analysis: Odds ratios (active arm vs. placebo), 95% CI, p-value, difference in proportions (active arm-Placebo) and corresponding 95% CI will be provided

Proportion of subjects who have an increase from Baseline of ≥1.0 g/dL in Hb in the absence of transfusions	Week 24, Week 36	Descriptive Summary
Proportion of subjects who have an increase from Baseline of ≥1.5 g/dL in Hb in the absence of transfusions	Week 24, and Week 36	Descriptive Summary
Duration of the Hb increase from Baseline of ≥1.0 g/dL over 36 weeks	Over 36 weeks from Baseline	Descriptive Summary
Mean change from Baseline in NTDT-PRO total score and domain scores including T/W and SOB domain scores over a continuous 12-week interval	Week 12 to Week 24, and Week 24 to Week 36.	Descriptive Summary
Mean change from Baseline in NTDT-PRO total score and domain scores including T/W and SOB domain scores	Week 24, Week 36	Analysis of Covariance (ANCOVA) analysis with Baseline value as a covariate: LSMean (95% CI), LSMean difference (95% CI) between each active dose and placebo, and p-value.
Rolling 12-week analysis for Proportion of subjects with an increase in Hb	Rolling time periods – Day 2 to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36)	• Cochran-Mantel Haenszel (CMH) analysis: Odds ratios (OR) (active arms vs. placebo), 2-sided 95% CI, p-value • Summary of number and percentage of responders with difference in proportions (active arm-Placebo) and corresponding 2-sided 95% CI • Forest plots of ORs, 2-sided 95% Cis, p-value – Higher dose vs. placebo, Lower dose vs. placebo
Time to first Hb increase (≥1.0 g/dL)	Over 36 weeks from Baseline	• Kaplan-Meier methods - log rank test and hazard ratios (and 95% CIs) will be estimated from a Cox regression model • Kaplan-Meier for the time to first Hb increase with separate curves for each treatment arm

13.6.6.1 TDT Population

PD Effects of Erythropoiesis, Iron Metabolism, and Hemolysis Endpoints

The mean changes from Baseline in serum PD markers of erythropoiesis, iron metabolism, and hemolysis will each be analyzed with an ANCOVA model with the corresponding Baseline value as a covariate. LSMean estimates and 95% CIs will be presented for each active arm and placebo at Week 36. The

LSMean difference estimates and associated 95% CIs and p-values at Week 36 will also be reported for each active arm vs. placebo and the combined active arms vs. Placebo.

Transfusion Burden Endpoints

Summary statistics of transfusion burden during the 12-week period prior to Baseline (Day 1) and the 24-week post-Baseline time period will be provided.

Boxplots illustrating the observed pRBC of transfused RBCs at Baseline, Week 12 to Week 24, Week 24 to Week 36, and Week 12 to Week 36 will be presented by treatment arm. Additionally, separate boxplots showing the change from the 12-week prior to Baseline (Day 1) timeframe to the Week 12 to Week 24 and Week 24 to Week 36 time periods and from the estimated 24-week period prior to Baseline (Day 1) to the Week 12 to Week 36 time period will be presented by treatment group. The estimated 24-week period prior to Baseline (Day 1) is the same estimate as calculated for the hematological improvement secondary endpoint.

Proportion of Subjects who are Transfusion Independent for ≥8 Weeks During Treatment Endpoint

The number and percentage of subjects who remain transfusion independent for at least 8 weeks during treatment will be tabulated, along with summary statistics of the duration of transfusion independence in weeks. The proportion of subjects who are transfusion independent for at least 8 weeks during treatment will also be analyzed using CMH tests. ORs, 95% CIs, and p-values will be reported. The difference in proportions (active arm-Placebo and the combined active arms-Placebo) and corresponding 95% CI will be also provided.

Number of Transfusion Events Endpoint

The mean number of transfusion events in IMR-687 arms from Baseline to Week 36 compared to placebo will be assessed using an ANCOVA model with baseline value as a covariate and treatment as a factor. Summary statistics of the number of cumulative transfusions at every 3 weeks post-Baseline from Week 3 through Week 24 will be presented. All post-baseline assessments of number of transfusions will be cumulative from baseline. For example, the number of transfusions at Week 24 and Week 36 will include all transfusions from baseline through the Week 24 and Week 36 visits, respectively. The least squares mean (LSMean) estimates and 95% CIs will be presented for each active arm and placebo at Week 24. Additionally, the LSMean difference estimates and associated 95% CIs and p-values at Week 36 will also be reported for each active arm vs. placebo and the combined active arms vs. Placebo.

Box whisker plots of the number of units, and pre-transfusion Hb with outliers over time will be provided by treatment arm.

Transfusion events data will be reported in a by-subject listing using the ITT Analysis Set.

Change from Baseline in Mean Pre-transfusion Hb Endpoint

The Baseline value of pre-transfusion Hb will be defined as the mean of the screening and baseline pre-transfusion Hb values from the Historical Transfusion Burden CRF. Post-Baseline pre-transfusion Hb is defined as the mean of all documented pre-transfusion hemoglobin values collected during each 12-week interval on the Transfusion Burden CRF. If there are any missing values at scheduled collected times, the mean will still be calculated from the remaining non-missing values. To estimate the pre-transfusion change of Hb after dosing within each 12-week interval (Week 12-24, week 24-36) and the 24-week interval (Week 12-36), summary statistics for the Baseline, post-Baseline, and change from Baseline pre-transfusion Hb will be provided by treatment arm.

Scatter box-whisker plots for the mean change in pre-transfusion Hb concentrations over continuous 12-week intervals from Week 12 to Week 24, Week 24 to Week 36, and Week 12 to 36 will be provided by treatment arm.

In addition, the change in mean pre-transfusion Hb concentrations over continuous 12-week intervals from Week 12 to Week 24, and Week 24 to Week 36 and 24-week intervals from Week 12 to Week 36 will be assessed using ANCOVA models with Baseline value as a covariate. Summary statistics for observed values at Baseline, Weeks 12-24, Weeks 24-36, and Weeks 12-36, and change from Baseline

to Weeks 12-24, 24-36, and 12-36 will be presented. LSMean estimates and 95% CIs will be presented for each active arm and placebo at Weeks 12-24, Weeks 24-36, and Weeks 12-36. The LSMean difference estimates and associated 95% CIs and p-values at Weeks 12-24, Weeks 24-36, and Weeks 12-36 will also be reported for each active arm compared to placebo and the combined active arms compared to Placebo.

Proportion of Subjects with an Increase from Baseline of ≥1.0 g/dL in Mean Pre-transfusion Hb or a Reduction in RBC Transfusion Burden Endpoint

The number and percentage of subjects meeting the following selected change in pre-transfusion Hb categories will be tabulated by treatment arm:

- Increase ≥1 g/dL
- Increase ≥1 g/dL OR ≥33% reduction in RBC transfusion burden with a reduction of at least 2 units of RBCs (hematological improvement)

The proportion of subjects in meeting each criteria above (at Weeks 12 to 24, Weeks 24 to 36, and Weeks 12 to 36) will be evaluated using a Cochran-Mantel-Haenzel (CMH) test to compare the proportion of subjects who achieved improvement between the placebo group and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose) and the combined active arms. The number and percentage of responders and non-responders at Weeks 12-24, Weeks 24-36, and Weeks 12-36 will be presented for each treatment arm as well as ORs, 95% CIs, and p-values from the CMH tests. The difference in proportions (active arm-Placebo and and the combined active arms-Placebo) and corresponding 95% CI will be also provided. Bar plots will be provided. The proportion of subjects with response in pre-transfusion Hb or hematological improvement at Weeks 12-24, Weeks 24-36, and Weeks 12-36 compared to Baseline, Odds ratios, 95% CI, and p values will be displayed by treatment arm.

Mean Change from Baseline in TranQOL and SF-36 Quality of Life Tools

Subjects in the TDT Population will complete two questionnaires, TranQOL and SF-36, at Baseline and at Weeks 12, 24, and 36.

The TranQOL includes 36 questions spanning five domains. Questions 1 – 10 will be used to calculate Physical Health domain scores, questions 11 – 24 will be used to calculate the Emotional Health domain score, question 25 will be used to calculate the Sexual Activity domain score, questions 26 – 30 will be used to calculate the Family Functioning domain score, and questions 31 – 36 will be used to calculate the School and Career Functioning domain score. Each of the 36 questions has five possible responses which will be coded numerically. For all questions except for items 2, 4, 9, 16, 17, 25, 26, and 27, responses and corresponding numerical values are:

- 5 = Always
- 4 = Often
- 3 = Sometimes
- 2 = Almost Never
- 1 = Never
- -1 = Not Applicable

For the remaining 8 questions, responses and corresponding numerical values are:

- 1 = Always
- 2 = Often
- 3 = Sometimes
- 4 = Almost Never

- 5 = Never
- -1 = Not Applicable

Domain scores are calculated using the equation 100 x (1 – [(Sum of all scores in the domain – number of valid responses in the domain) / (number of valid responses in the domain x 4)]). Scores of -1 are excluded from the calculation. Domain scores can only be calculated if <25% of the total number of questions in that domain are missing. Domain scores range from 0 to 100 where higher scores indicate higher QoL.

Descriptive statistics for the five domain scores will be reported at Baseline and Weeks 12, 24, and 36. Change from Baseline to each post-Baseline assessment will also be presented for each domain score.

The SF-36 includes 36 questions spanning 8 scales which are weighted sums of the questions in their section. Optum Health scoring software will be used to transform individual question responses to the scales which range from 0 to 100 where higher scores indicate less disability. The scales include Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The software will also calculate two overall scores, the Physical Component Score and the Mental Component Score.

Descriptive statistics for the eight scale scores and the two component scores will be tabulated at Baseline and at Weeks 12, 24, and 36. Change from Baseline to each post-Baseline assessment will also be presented for each scale and component score.

By-subject listings of TranQOL data and SF-36 data will be presented on the ITT Analysis Set.

Average Number of Days Between Transfusions Endpoint

Descriptive statistics for the average number of days between transfusions over 36 weeks will be tabulated with the ITT Analysis Set. Tabulations will be repeated on the mITT (if available) and PP Analysis Sets.

13.6.6.2 Imputation Methods for the Hb Endpoints for the NTDT Population

The following imputation rules will be applied for the exploratory efficacy endpoints related to Hb (Proportion of subjects who have an Hb increase of ≥1.0 g/dL from Baseline for ≥14 days in the absence of RBC transfusions, Number of subjects with increase from Baseline of 1.0 g/dL in mean Hb values at Week 24 and Week 36 compared to Baseline in the absence of transfusions, Duration of the mean Hb increase from Baseline of ≥1.0 g/dL over 36 weeks, and Proportion of subjects who have an increase from Baseline of ≥1.5 g/dL in mean of Hb values in the absence of transfusions):

1. For the number of subjects with increase from Baseline of 1.0 g/dL in mean Hb values at Week 24 and Week 36 compared to Baseline in the absence of transfusions endpoint, and the proportion of subjects who have an increase from Baseline of ≥1.5 g/dL in mean of Hb values in the absence of transfusions endpoints, subjects will be treated as non-responders for the Week 24 or Week 36 time point if they received an RBC Transfusion within the prior 8 weeks for that time point (Weeks 16-24 for the Week 24 time point, Weeks 28-36 for the Week 36 time point). For the duration of the mean Hb increase from Baseline of ≥1.0 g/dL over 36 weeks endpoint, an 8 week period following any transfusion will be excluded from the duration total. For the number of subjects and the proportion of subjects with an increase from Baseline endpoints, this means that the subject will not be included in the number or proportion of subjects with an increase.
2. If the subject received an RBC Transfusion during the time periods described above the Hb will be imputed as the last assessment prior to transfusion
3. If some of the Hb values are missing during any of the time periods, the duration of the non-missing values during that time period will be used for the duration of the mean increase from Baseline endpoint and the non-missing values during that time period will be used for the determination of the number or proportion of subjects with an increase from Baseline endpoints.

The number of subjects with imputed values for the exploratory efficacy endpoints and the reason for imputation will also be summarized.

13.6.6.3 NTDT Population

Proportion of Subjects who have an Hb Increase of ≥1.0 g/dL Endpoints

The number and percentage of subjects who have an Hb increase of ≥1.0 g/dL from Baseline for ≥14 days in the absence of RBC transfusions will be calculated at all post-Baseline Hb collection time points. All Hb values, including those collected at unscheduled visits but excluding values collected within 8 weeks after a RBC transfusion, will be sorted by date. For each value and the next subsequent value in time, the values and the time between values will be compared. If both values are increased ≥1.0 g/dL from Baseline and are ≥14 days apart, the subject will be counted as a yes in the proportion. The proportion of subjects who have an Hb increase of ≥1.0 g/dL from Baseline for ≥14 days, in the absence of RBC transfusions, in active arms will be compared to the placebo group using CMH tests. ORs, 95% CIs, and p-values will be reported. The difference in proportions (active arm-Placebo and the combined active arms-Placebo) and corresponding 95% CI will be also provided

The number and percentage of subjects who have an Hb increase of ≥1.0 g/dL from Baseline will be calculated at all post-Baseline Hb collection time points. For Week 24 and Week 36 data, the proportion of subjects with increases from Baseline of ≥1.0 g/dL in active arms will be compared to the placebo group using CMH tests. ORs, 95% CIs, and p-values will be reported. The difference in proportions (active arm-Placebo and the combined active arms-Placebo) and corresponding 95% CI will be also provided.

Proportion of Subjects who are RBC Transfusion-Free Over 36 Weeks Endpoint

The number and percentage of subjects who remain RBC transfusion free throughout the 36-week treatment period will be reported. Additionally, the number and percentage of subjects who have remained transfusion free since Baseline at each post-Baseline timepoint prior to Week 36 will be reported. Transfusion burden data will also be listed on the ITT Analysis Set.

Duration of the Mean Hb Increase from Baseline of ≥1.0 g/dL Over 36 Weeks

Duration of Hb increase from Baseline of ≥1.0 g/dL over 36 weeks will be summarized descriptively by treatment arm. The duration will be calculated according to the following:

1. Sort all post-baseline non-missing laboratory Hb values for a subject, including unscheduled, chronologically.
2. For any Hb change from baseline values that are ≥1.0 g/dL, compute the following:
    a. Date of Hb change from baseline value ≥1.0 g/dL – (Date of previous non-missing laboratory Hb value)
    b. Note: The date of the previous non-missing laboratory Hb value may include baseline values.
3. For each subject, sum up all values from #2 above.

Mean Change from Baseline in NTDT-PRO and SF-36 Quality of Life Tools

Subjects in the NTDT Population will complete two questionnaires, SF-36 and NTDT-PRO, at Baseline and Weeks 12, 24, and 36.

Similar to the TDT Population, descriptive statistics for the eight scale scores and the two component scores of the SF-36 will be tabulated at Baseline and at Weeks 12, 24, and 36. Change from Baseline to each post-Baseline assessment will also be presented for each scale and component score.

The NTDT-PRO consists of eight items. Questions 1 and 2 assess tiredness with and without physical activity. Questions 3 and 4 assess weakness with and without physical activity. Questions 5 and 6 assess shortness of breath with and without physical activity. The final two items assess the overall severity and progression of thalassemia symptoms. Items 1 – 4 are grouped into the Tiredness/Weakness Domain and Items 5 – 6 are grouped into the Shortness of Breath Domain.

Scores for the 6 domain related questions range from 0 (no tiredness/weakness/shortness of breath) to 10 (extreme tiredness/weakness/shortness of breath).

The Tiredness/Weakness domain score will be calculated by averaging the responses to questions 1-4. The Shortness of Breath domain score will be calculated by averaging the responses to questions 5-6. If any responses are missing in questions 1-4 or 5-6 for the timepoint of evaluation, then the Tiredness/Weakness and Shortness of Breath domain scores cannot be calculated, respectively.

The total score will be calculated by averaging the responses to questions 1-6. If any responses are missing at the time point in question, then the total score cannot be calculated.

Descriptive statistics of the Tiredness/Weakness and Shortness of Breath domain scores and total score, and changes from Baseline, will be reported at Baseline and at Weeks 12, 24, and 36 by treatment group, as well as changes from the last assessment, i.e., from Week 12 to Week 24 and Week 24 to Week 36.

The mean change from Baseline in the NTDT-PRO total score will be assessed using an ANCOVA model with Baseline value as a covariate. Summary statistics for observed values at Baseline and Week 24 and change from Baseline to Week 24 will be presented. LSMean estimates and 95% CIs will be presented for each active arm and placebo at Week 24. The LSMean difference estimates and associated 95% CIs and p-values at Week 24 will also be reported for each active arm compared to placebo and the combined active arms-Placebo. The Week 36 NTDT-PRO total score will be analyzed with a similar model, as will the NTDT-PRO T/W and SOB domain scores at Weeks 24 and 36.

By-subject listings of SF-36 data and NTDT-PRO data will be presented on the ITT Analysis Set.

Proportion of Subjects with an Increase from Baseline of ≥3% in Mean HbF Over 12 Week Rolling Time Periods Endpoint

The proportion of subjects with increase from Baseline of ≥3% in mean HbF values measured over 12-week intervals (from Day 2 to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36)) will be assessed using a CMH test. The number and percentage of responders and non-responders at each of the rolling time periods will be presented for each treatment group as well as ORs, 95% CIs, and p-values from the CMH tests. The difference in proportions (active arm-Placebo and the combined active arms-Placebo) and corresponding 95% CI will be also provided. Bar plots will be provided. The proportion of subjects with response in HbF, where a responder has an increase of ≥3% at each of the rolling time periods compared to Baseline, Odds ratios, 95% CI, and p values will be displayed by treatment arm.

Proportion of Subjects with an Increase from Baseline of ≥1.0 g/dL in Mean Hb Over 12 Week Rolling Time Periods Endpoint

The proportion of subjects with increase from Baseline of ≥1.0 g/dL in mean Hb values measured over 12 week intervals (from Day 2 to 85, Day 3 to 86, etc. through Day 170 to Day 253 (Week 36)) will be evaluated using a Cochran-Mantel-Haenzel (CMH) test to compare the proportion of subjects who achieved improvement between the placebo group and each of the 2 active treatment arms (IMR-687 lower dose and IMR-687 higher dose) and the combined active arms. The number and percentage of responders and non-responders, ORs, 95% CIs, p-values from the CMH tests and the difference in proportions and corresponding 95% CI will be provided similarly to the HbF above.

Time to First Hb Increase (≥1.0 g/dL)

The time to first Hb increase will be analyzed using Kaplan-Meier methods. Time in months to the first Hb increase can be calculated as ([date of first Hb increase – date of first dose + 1] / 30.4375).

Subjects who experience no Hb increase during the study will be censored at their study end date (or data cut-off date if the study end date is not available). The number and percentage of subjects with events (subjects who experienced at least 1 Hb increase on-study) and censored (subjects who did not experience any Hb increase on-study) will be presented. The 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% CIs based on the Brookmeyer and Crowley method will be presented. The p-values from a log rank test and hazard ratios (and 95% CIs) estimated from a Cox regression

model will be presented for comparison of each treatment arm to placebo. Kaplan-Meier figures will be produced for the time to first Hb increase with separate curves for each treatment arm.

13.6.6.4 Sensitivity Analyses

All sensitivity analyses will be performed on the PP Analysis Set unless otherwise specified.

13.6.6.4.1 TDT Population

Proportion of subjects who are transfusion-free (independent) for ≥12 weeks during treatment

The number and percentage of subjects who remain transfusion independent for at least 12 weeks during treatment will be tabulated, along with summary statistics of the duration of transfusion independence in weeks. The proportion of subjects who are transfusion independent for at least 12 weeks during treatment will also be analyzed using CMH tests. ORs, 95% CIs, and p-values will be reported. The difference in proportions (active arm-Placebo and the combined active arms-Placebo) and corresponding 95% CI will be also provided. A bar plot will be provided, including both the proportions of subjects who are transfusion-free for ≥ 8 weeks and ≥12 weeks.

13.6.6.4.2 NTDT Population

Proportion of subjects who are transfusion-free (independent) for ≥12 weeks during treatment

The number and percentage of subjects who remain transfusion independent for at least 12 weeks during treatment will be tabulated, along with summary statistics of the duration of transfusion independence in weeks. The proportion of subjects who are transfusion independent for at least 12 weeks during treatment will also be analyzed using CMH tests. ORs, 95% CIs, and p-values will be reported. The difference in proportions (active arm-Placebo and the combined active arms-Placebo) and corresponding 95% CI will be also provided. A bar plot will be provided, including both the proportions of subjects who are transfusion-free for ≥ 8 weeks and ≥12 weeks.

13.6.7 Specialty Hematology Endpoints

Specialty hematology laboratory assessments will be summarized and listed using the ITT and Per-Protocol Analysis sets similarly but separately for each population. Assessments will include:

- HbF
- F-cells (%)

Descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, and maximum) for the observed and change from Baseline values will be presented at Baseline and each post-Baseline collection.

Specialty hematology tabulations will be repeated stratified by genotype (concomitant alpha gene deletion vs. concomitant alpha gene duplication vs. concomitant alpha gene triplication).

The following figures will be provided for all specialty hematology parameters:

- Shift plot from Baseline to post-Baseline maximum for each specialty hematology parameter by treatment arm and for the combined IMR-687 treatment arms;
- Box and whisker plot for each specialty hematology parameter by visit for each treatment arm and the combined IMR-687 treatment arms

13.6.8 Pharmacodynamic Endpoints

Pharmacodynamic laboratory assessments will be summarized and listed using the Per Protocol, ITT, and mITT Analysis sets, for the TDT population. Assessments will include:

- Iron Metabolism

  - Serum ferritin
  - Hepcidin-25
  - Serum iron and total iron binding capacity (TIBC) for calculated transferrin saturation
- Erythropoiesis
  - Erythropoietin
  - Soluble transferrin receptor (STFR)
- Hemolysis
  - Haptoglobin
  - LDH
  - Indirect Bilirubin
  - Reticulocytes (absolute and %)
- Cardiac/inflammation
  - Serum N-terminal pro-B-type natriuretic peptide (serum NT-proBNP)
  - High-sensitivity C-reactive protein (hsCRP)
- Adhesion
  - Soluble E-selectin
  - Soluble P-selectin
  - Soluble intercellular adhesion molecule 1 (ICAM-1)
  - Vascular cell adhesion molecule 1 (VCAM-1)
- Hematology
  - RDW
  - MCV
  - Hb

Descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, and maximum) for the observed and change from Baseline values will be presented at Baseline and each post-Baseline collection.

PD tabulations will be repeated stratified by genotype (concomitant alpha gene deletion vs. concomitant alpha gene duplication vs. concomitant alpha gene triplication) and Beta-Thalassemia Major (B0 / B0, B0 / B+), Beta-Thalassemia Intermedia (B+ / B+, B0 / B+, B+ / B, B0 / B, B0 / B0), and HbE/Beta-Thalassemia (BE / B+, BE / B0).

The following figures will be provided for all PD parameters:

- Shift plot from Baseline to post-Baseline maximum for each PD parameter and treatment arm and for the combined IMR-687 treatment arms;
- Box and whisker plot of PD parameters by visit and treatment arm and the combined IMR-687 treatment arms.

13.7 Other Data

Pregnancy test results will be listed on the Safety Analysis Set.

Virology available data will be summarized and listed by treatment group on the Safety Analysis Set. Blood samples will be collected for serum virology (screening assessment) only if clinically indicated. Testing will be performed through a central laboratory and may include hepatitis B surface antigen (HBsAg), hepatitis A immunoglobulin M (IgM), and hepatitis C virus (HCV) antibody, as well as HIV testing.

14.0 References

FDA, ICH. (2013, January) Guidance for Industry E3 Structure and Content of Clinical Study Reports Questions and Answers (R1). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e3-structure-and-content-clinical-study-reports-questions-and-answers-r1.

ICH. (2005, May 12) The Clinical Evaluation of QT/QTC Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs E14. https://database.ich.org/sites/default/files/E14_Guideline.pdf.

Klaassen RJ, Barrowman N, Merelles-Pulcini M, Vichinsky EP, Sweeters N, et al. Validation and reliability of a disease-specific quality of life measure (the TranQol) in adults and children with thalassaemia major. Br J Haematol. 2014 Feb;164(3):431-7 (PubMed Abstract)

Taher A, Viprakasit V, Cappellini MD, Sutcharitchan P, Ward R, Mahmoud D, et al. Development of a patient-reported outcomes symptom measure for patients with nontransfusion-dependent thalassemia (NTDT-PRO©). Am J Hematol. 2019 Feb;94(2):171-6.

Cappellini et al., Health-related quality of life outcomes for patients with transfusion-dependent beta-thalassemia treated with luspatercept in the BELIEVE trial. American Society of Hematology. 2020 Nov 12. https://acceleronpharma.com/wp-content/uploads/2020/12/Cappellini-ASH-2020-BELIEVE-HRQoL-Oral_Nov-12-1.pdf

15.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Classification
AUC_{0-24}	Area Under the Concentration-Time Curve from Time 0 to 24 Hours Postdose
AUC_{inf}	Area Under the Concentration-Time Curve from Time 0 to Infinity
AUC_{last}	Area Under the Concentration-Time curve from Time 0 to the Last Measurable Concentration Postdose
BLQ	Below the Limit of Quantification
CI	Confidence Interval
C_{last}	Last Observed Measurable Plasma Concentration
CL/F	Apparent Total Body Clearance from Oral Administration after Single Dose
CL_{ss}/F	Apparent Total Body Clearance from Oral Administration at Steady State
C_{max}	Maximum Plasma Concentration Postdose after Single Dose
$C_{max,ss}$	Maximum Plasma Concentration Postdose at Steady State
C_{min}	Minimum Plasma Concentration over the Dosing Interval
C_{trough}	Concentration at the End of the Dosing Interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
Hb	Hemoglobin
HbF	Fetal Hemoglobin
IXRS/IVRS	Interactive Voice Response System
$Lambda_z$	Apparent Terminal Elimination Phase Rate Constant
LLOQ	Lower Limit of Quantification
LSMean	Least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
NTDT	Non-transfusion dependent
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol

pRBC	Packed red blood cells
PT	Preferred Term
QD	Once daily
QoL	Quality of Life
R_{AUC}	Accumulation Ratio
RBC	Red blood cells
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
$T_{1/2}$	Apparent Terminal Elimination Half-life
T_{last}	Time of Last Measurable Plasma Concentration
T_{max}	Time to Maximum Plasma Concentration Postdose after Single Dose
$T_{max,ss}$	Time to Maximum Plasma Concentration Postdose at Steady State
TDT	Transfusion dependent
TEAE	Treatment-Emergent Adverse Event
V_z/F	Apparent Total Body Clearance from Oral Administration after Single Dose or Steady State

16.0 Appendices

Appendix 1 Schedule of Assessments – TDT Population

	Screening	Baseline	Double-blind, Placebo-controlled Treatment													EOT[a] / ET	End of Study (Safety FU)
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Study Week(s)	-4 to 0	NA	1	2	3	6	9	12	15	18	21	24	27	30	33	36	40
Study Day(s)	-28 to -1	1[b]	7 ±2	14 ±2	21 ±7	42 ±7	63 ±7	84 ±7	105 ±7	126 ±7	147 ±7	168 ±7	189 ±7	210 ±7	231±7	252±7	280±7
On-site visits	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone visits[c]				X													
Informed consent	X																
PGx ICF and blood draw (optional)[d]	X																
Demographic information	X																
Medical/disease history[e]	X																
Inclusion/exclusion criteria	X	X															
ECOG score	X																
Clinically indicated virology (Hep A, B, and C and HIV)	X																
Historical transfusion burden[f]	X	X															
Randomization		X															
Vital signs[g]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Baseline	Double-blind, Placebo-controlled Treatment													EOT[a] / ET	End of Study (Safety FU)
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Week(s)	**-4 to 0**	**NA**	**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**40**
Study Day(s)	**-28 to -1**	**1[b]**	**7 ±2**	**14 ±2**	**21 ±7**	**42 ±7**	**63 ±7**	**84 ±7**	**105 ±7**	**126 ±7**	**147 ±7**	**168 ±7**	**189 ±7**	**210 ±7**	**231±7**	**252±7**	**280±7**
Height	X																
Transfusion burden[h]					X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[j]	X	X	X		X	X		X		X		X		X		X	X
Hematology and Chemistry	X	X	X		X	X		X		X		X		X		X	X
Coagulation studies	X							X				X				X	
Urinalysis	X	X			X			X				X				X	
Pregnancy testing[k]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Specialty hematology[l]	X	X			X			X		X		X		X		X	
PD markers[m]	X	X			X			X		X		X				X	
IMR-687 plasma PK[n]		X	X		X							X				X	
QOL assessments[o]		X						X				X				X	
Study drug dispensing		X			X	X	X	X	X	X	X	X	X	X	X		
Study drug admin at site[p]		X	X		X	X		X		X		X		X		X	
Study drug admin		Oral administration of IMR-687 or placebo qd															
AEs and concomitant medications	Continuous[q]																

AE = adverse event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ET= early termination; EOT = end of treatment; FU = follow-up;

Hb = hemoglobin; HbF = fetal hemoglobin; HIV = human immunodeficiency virus; hsCRP = highly sensitive C-reactive protein; ICAM-1 = intercellular adhesion molecule 1; ICF = informed consent form; NT-proBNP = N-terminal pro B-type natriuretic peptide; PD = pharmacodynamics; PE = physical examination; PGx = pharmacogenomics;
PK = pharmacokinetic; pRBC = packed red blood cells; QOL = quality of life; SD = standard deviation; SF-36 = Short Form (36) Health Survey; TEAE = treatment-emergent adverse event, TIBC = total iron binding capacity; TranQOL = Transfusion-dependent QoL Questionnaire; VCAM-1 = vascular cell adhesion molecule 1.
Note: Unless otherwise specified, all assessments should be completed prior to dosing at any given timepoint.
Note: Unscheduled visits may occur, limited to visits resulting from potential TEAEs, drug dispensation, or other urgent study-related procedures
a The last day of dosing will be at Week 36 visit; subject should consume their last dose of study drug on site, after pre-dose assessments have been completed. The Week 36 visit will also be the ET visit. During the study visit, assessments should be collected from any subject who discontinues study drug or study prematurely. Early termination visits will have the same procedures as the Week 36 visit, except that study drug will not be administered and trough PK will not be collected.
b The first day study drug is taken is considered Baseline (Day 1). Day 1 assessments should be performed prior to study drug administration. If a subject requires a transfusion on this day, the transfusion may occur only after all study assessments are completed.
c Qualified site personnel will contact the subject by telephone at Week 2 to capture potential TEAEs and concomitant medications. Subjects will also be reminded of compliance with drug and the next visit schedule. If any AEs of significant clinical concern are identified during the telephonic visit, the subject will be requested to come into the site to be assessed.
d Pharmacogenomic evaluation is optional and may be performed at screening if subject provides informed consent.
e Disease history should contain a confirmed diagnosis of β-thalassemia or hemoglobin E/β-thalassemia. Concomitant alpha gene deletion, duplication, or triplication is allowed. f After obtaining signed informed consent, the subject's transfusion history for the 12 weeks prior to Baseline (Day 1) visit date should be recorded. In order to be eligible for the
study, the dates of transfusion events and the number of pRBC units per event within the 12 weeks prior to the Baseline (Day 1) visit must be available. If available, the following data should also be collected for each transfusion event: volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.
g Vital signs include heart rate, respiratory rate, blood pressure, and body temperature. At Day 1 and Week 3, vital signs will be taken pre-dose and 2 hours (± 20 minutes)
post-dose, during the PK assessments. At all other timepoints, vital signs can be taken irrespective of taking study drug. Vital signs should be consistently measured in either the sitting or semi-supine position.
h Transfusion burden will be assessed using the following variables: dates of transfusion events, number of pRBC units per event, volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.
i Complete PEs will be performed at Screening, Week 24, and Week 36 and will include a general examination of the body including the abdomen, heart, lungs, lymph nodes, back/neck, neurological system, skin, extremities, head, eyes, nose, and throat. At all other visits, symptom-directed PEs will be obtained after identification of AEs deemed by the investigator to be of significant clinical concern.
j All ECGs to be performed in triplicate. At Baseline and Week 3, ECGs will be obtained at pre-dose and 2 hours (±30 minutes) post-dose. At all other timepoints, ECGs will be taken pre-dose.
k Females of childbearing potential only. A serum pregnancy test will be performed at screening via a central laboratory; all subsequent tests will be urine performed locally (with test kits provided by the central laboratory).
l Includes HbF and percent F cells. Blood samples should be obtained prior to administration of study drug.
m Includes serum ferritin, soluble transferrin receptor, hepcidin-25, haptoglobin, E-selectin, P-selectin, ICAM-1, VCAM-1, hsCRP, serum NT-proBNP, serum iron and TIBC for calculated transferrin saturation, and erythropoietin. Blood samples should be obtained prior to administration of study drug. PD markers will need to be collected prior to RBC transfusion (if applicable).
n At Baseline and Week 3, serial blood samples for IMR-687 and concentrations of metabolite(s) will be drawn pre-dose (within 30 minutes) and at 15 minutes (±5 minutes), 30 minutes (±5 minutes), and 3 hours (±20 minutes) after administration of study drug. A trough blood sample will be drawn pre-dose at Week 1, Week 24, and Week 36. The date/time of the previous dose will be recorded. If a subject requires a transfusion on the day of a PK draw, the transfusion can only be performed after the final PK sampling. For ET visits, a trough blood sample will not be collected. Patients dosed prior to protocol version 5.0 (15 Mar 2021) used

the following PK sampling schedule: At Baseline and Week 3, serial blood samples for IMR-687 and concentrations of metabolite(s) were drawn pre-dose (within 30 minutes) and at 30 minutes (± 5 minutes), 1.5 hours (±15 minutes), 4 hours (±15 minutes), 6 hours (±1 hour) and 24 hours (± 2 hours) after administration of study drug. On these full profile PK days, food details were also recorded at the clinical sites. A trough blood sample was drawn pre-dose at Week 1, Week 24, and Week 36. Transfusion should not have coincided with Baseline (Day 1) or the Week 3 visit, due to the PK assessment that day. For ET visits, a trough blood sample was not collected.

o Quality of life assessments will be assessed by the TranQOL and SF-36 QoL tools. The QoL assessments will be administered at Baseline and at Weeks 12, 24, and 36. Baseline QoL assessments should be completed before administration of study drug.

p On days when study drug is taken in the clinic, food details will also be recorded.

q Adverse events and concomitant medications, including iron chelation therapy and hydroxyurea use, will be recorded at each visit throughout the study from Screening (after signing the ICF) through the end of study visit (Week 40).

Appendix 2 Schedule of Assessments – NTDT Population

	Screening	Baseline	Double-blind, Placebo-controlled Treatment										EOT[a] / ET	End of Study (Safety FU)
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Week(s)	**-4 to 0**	**NA**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Study Day(s)	**-28 to -1**	**1[b]**	**7±2**	**14±2**	**28±5**	**56±7**	**84±7**	**112±7**	**140±7**	**168±7**	**196±7**	**224±7**	**252±7**	**280±7**
On-site visits	X	X	X		X	X	X	X	X	X	X	X	X	X
Telephone visits[c]				X										
Informed consent	X													
PGx ICF and blood draw (optional)[d]	X													
Demographic information	X													
Medical/disease history[e]	X													
Inclusion/exclusion criteria	X	X												
ECOG score	X													
Clinically indicated virology (Hep A, B, and C and HIV)	X													
Historical transfusion burden[f]	X	X												
Randomization		X												
Vital signs[g]	X	X	X		X	X	X	X	X	X	X	X	X	X
Weight	X	X	X		X	X	X	X	X	X	X	X	X	X
Height	X													
Transfusion burden[h]					X	X	X	X	X	X	X	X	X	X

	Screening	Baseline	Double-blind, Placebo-controlled Treatment										EOT[a] / ET	End of Study (Safety FU)
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Week(s)	**-4 to 0**	**NA**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Study Day(s)	**-28 to -1**	**1[b]**	**7±2**	**14±2**	**28±5**	**56±7**	**84±7**	**112±7**	**140±7**	**168±7**	**196±7**	**224±7**	**252±7**	**280±7**
Physical examination[i]	X	X	X		X	X	X	X	X	X	X	X	X	X
12-Lead ECG[j]	X	X	X		X	X	X	X	X	X	X	X	X	X
Hematology and chemistry	X	X	X		X	X	X	X	X	X	X	X	X	X
Coagulation studies	X						X			X			X	
Urinalysis	X	X			X		X			X			X	
Pregnancy testing[k]	X	X	X		X	X	X	X	X	X	X	X	X	X
Specialty hematology[l]	X	X			X		X			X			X	
PD markers[m]	X	X			X		X			X			X	
IMR-687 plasma PK[n]		X	X		X					X			X	
QOL assessments[o]		X					X			X			X	
Study drug admin at site[p]		X	X		X	X	X	X	X	X	X	X	X	
Study drug dispensing		X			X	X	X	X	X	X	X	X		
Study drug admin		Oral administration of IMR-687 or placebo qd												
AEs and concomitant medications	Continuous[q]													

AEs = adverse events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ET= early termination; EOT = end of treatment; FU = follow-up; Hb = hemoglobin; HIV = human immunodeficiency virus; hsCRP = highly sensitive C-reactive protein; ICAM-1 = intercellular adhesion molecule 1; ICF = informed consent form; NTDT-PRO = non- -thalassemia patient reported outcome; NT-proBNP = N-terminal pro B-type natriuretic peptide; PD = pharmacodynamics; PE = physical

examination; PGx = pharmacogenomics; PK = pharmacokinetic; pRBC = packed red blood cells; QOL = quality of life; RBC = red blood cell; SD = standard deviation; SF-36 = Short Form (36) Health Survey; TEAE = treatment-emergent adverse event; TIBC = total iron binding capacity; VCAM-1 = vascular cell adhesion molecule
1.
Note: Unless otherwise specified, all assessments should be completed prior to dosing at any given timepoint.
Note: In the case of a subject receiving a transfusion after signing the ICF, but prior to randomization, the investigator would inform the medical monitor. The intent is to avoid transfusions within the 2-week period leading to randomization. Approval could be obtained for the screening period to be extended by a maximum of 14 days.
Note: Unscheduled visits may occur, limited to visits resulting from potential TEAEs, drug dispensation, or other urgent study-related procedures.
a The last day of dosing will be at Week 36 visit; subject should consume their last dose of study drug on site, after pre-dose assessments have been completed. The Week 36 visit will also be the ET visit. During the study visit, assessments should be collected from any subject who discontinues study drug or study prematurely. Early termination visits will have the same procedures as the Week 36 visit, except that study drug will not be administered and trough PK will not be collected.
b The first day study drug is taken is considered Baseline (Day 1). Day 1 assessments should be performed prior to study drug administration. If a subject requires a transfusion on this day, the transfusion may occur only after all study assessments are completed.
c Qualified site personnel will contact the subject by telephone at Week 2 to capture potential TEAEs and concomitant medications. Subjects will also be reminded of compliance with drug and the next visit schedule. If any AEs of significant clinical concern are identified during the telephonic visit, the subject will be requested to come into the site to be assessed.
d Pharmacogenomic evaluation is optional and may be performed at screening if subject provides informed consent.
e Disease history should contain a confirmed diagnosis of β-thalassemia or hemoglobin E/β-thalassemia. Concomitant alpha gene deletion, duplication, or triplication is allowed.
f After obtaining signed informed consent, the subject's transfusion history for the 12 weeks prior to Baseline (Day 1) visit date should be recorded. In order to be eligible for the study, the dates of transfusion events and the number of pRBC units per event within the 12 weeks prior to the Baseline (Day 1) visit must be available. If available, the following data should also be collected for each transfusion event: volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.
g Vital signs include heart rate, respiratory rate, blood pressure, and body temperature. At Day 1 and Week 4, vital signs will be taken pre-dose and 2 hours (± 20 minutes) post-dose, during the PK assessments. At all other timepoints, vital signs can be taken irrespective of taking study drug. Vital signs should be consistently measured in either the sitting or semi-supine position.
h Transfusion burden will be assessed using the following variables: dates of transfusion events, number of pRBC units per event, volume and hematocrit of each pRBC unit, pre-transfusion Hb, and pre-transfusion weight.
i Complete PEs will be performed at Screening, Week 24, and Week 36 and will include a general examination including the abdomen, hear
neurological system, skin, extremities, head, eyes, nose, and throat. At all other visits, symptom-directed PEs will be obtained after identification of AEs deemed by the investigator to be of significant clinical concern.
j All ECGs to be performed in triplicate. At Baseline and Week 4, ECGs will be obtained at pre-dose and 2 hours (±30 minutes) post-dose. At all other timepoints, ECGs will be taken pre-dose.
k Females of childbearing potential only. A serum pregnancy test will be performed at screening via central laboratory; all subsequent tests will be urine performed locally (with test kits provided by the central laboratory).
l Includes HbF and percent F cells. Blood samples should be obtained prior to administration of study drug.
m Includes serum ferritin, soluble transferrin receptor, hepcidin-25, haptoglobin, E-selectin, P-selectin, ICAM-1, VCAM-1, hsCRP, serum NT-proBNP, serum iron and TIBC for calculated transferrin saturation, and erythropoietin. Blood samples should be obtained prior to administration of study drug. PD markers will need to be collected prior to RBC transfusion (if applicable).
n At Baseline and Week 4, serial blood samples for IMR-687 and concentrations of metabolite(s) will be drawn pre-dose (within 30 minutes) and at 15 minutes (±5 minutes), 30 minutes (±5 minutes), and 3 hours (±20 minutes) after administration of study drug. A trough blood sample will be drawn pre-dose at Week 1, Week 24, and Week 36. The date/time of the previous dose will be recorded. If a subject requires a transfusion on the day of a PK draw, the transfusion can only be performed after the final PK sampling. For ET visits, a trough blood sample will not be collected. Patients dosed prior to protocol version 5.0 (15 Mar 2021) used the following PK

sampling schedule: At Baseline and Week 4, serial blood samples for IMR-687 and concentrations of metabolite(s) were drawn predose (within 30 minutes) and at 30 minutes (± 5 minutes), 1.5 hours (± 15 minutes), 4 hours (±15 minutes), 6 hours (±1 hour), and 24 hours (±2 hours) after administration of study drug. On these full profile PK days, food details was also recorded at the clinical sites. A trough blood sample was drawn predose at Week 1, Week 24, and Week 36. Transfusion should not have coincided with Baseline (Day 1) or the Week 4 visit, due to the PK assessment that day. For ET visits, a trough blood sample was not collected.
o Quality of life assessments will be performed by the NTDT-PRO and SF-36 QoL tools. The QoL assessments will be administered at Baseline and at Weeks 12, 24, and 36. Baseline QoL assessments should be completed before administration of study drug.
p On days when study drug is taken in the clinic, food details will also be recorded.
q Adverse events and concomitant medications, including iron chelation therapy and hydroxyurea use, will be recorded at each visit throughout the study from Screening (after signing the ICF) through the end of study visit (Week 40).

Appendix 3 Data Handling Rules

Category	Description	Data Handling Rule
1. Age (years)	Age (years)	Age is collected from Demographics CRF page.
2. First Dose Date/Time of Study Drug	date/time of first dose of study drug	The date and time (24 hr. clock) of the first dose of study drug will be taken from the Study Drug Administration CRF.
3. Last Dose Date of Study Drug	date of last dose of study drug	The date of the last dose of study drug will be the Date of last dose from the End of Treatment CRF. If it is missing for the IA, DMC, and final analyses use the data cutoff date. If it is missing at the database lock, the date of the last dose of study drug will be imputed as the later of last visit date, last dispensing date (from Drug Accountability CRF), date of Completion/Discontinuation, and death date.
4. Last Visit Date	Date of Last Visit	Date of last visit according to the Clinic Visit CRF.
5. Last Study Participation Date (STDM variable, typically named RFPENDTC)	Last Study Participation Date (STDM variable, RFPENDTC), where SDTM denotes Study Data Tabulation Model	Last study participation date is defined as last known date of contact which would be the later of the following dates: last visit date, date of the last dose, date of Completion/Discontinuation, date of clinical study follow-up, or death date.
6. Study Day Definitions	**Study Day** for an assessment/event which occurred on or after the start of study drug	Study Day = Date of assessment/event – date of the first dose of study drug + 1.
	Study Day for an assessment/event which occurred on a day prior to the first dose of study drug in the study	Study Day = date of assessment/event – first dose date of study drug in the study.
	Study Day of Randomization	Study Day of Randomization = date of randomization – date of the first dose of study drug in the study + 1. Study Day is 1 if Baseline is on the day of randomization.
	First Dose Day	**First Dose Day** in the study is defined as the study day of the first dose of study drug in the study (Study Day 1).
	Last Dose Day	**Last Dose Day** in the study is defined as the study day of the last dose of study drug in the study.
7. Duration of an event	The duration of an event	The duration of an event is defined as (stop date – start date + 1).
8. Multiple assessments for the same visit	Vital Sign, ECG and Laboratory assessments	• All ECG assessments are to be performed in triplicate. Valid assessments will be averaged to get the analysis value for that visit. • Other than for ECG assessments, the last non-missing measurement taken prior to the date/time of first study drug (including unscheduled assessments) will be the analysis Baseline. • Windowing will be applied for by-visit analyses. Unscheduled or Screening visits that occurred before the Baseline visit will not be assigned an analysis visit. The early discontinuation visit will be eligible for allocation to an analysis visit.

Category	Description	Data Handling Rule
		• If one or more results for a variable are assigned to the same analysis visit, the result with the date closest to the protocol scheduled day will be used in the analysis. If 2 measurements in the same analysis visit window are equidistant from the protocol scheduled study day, the earliest measurement will be used in the analysis. • If multiple assessments are available on the same day (or for the same time point for ECG assessments), then the average of the assessments will be used in the analysis. • If both central and local assessments of the same lab test are available on the same day, the central result will take precedence over the local result. • All data will be listed in data listings.
9. Special Lab Value Handling	Lab values with a prefix such as: '>', '<', '+' and 'Less than' Etc.	• '>': use the available original value +0.001 in the analyses. • '<': use the available original value –0.001 in the analyses. • '+': use the available original value without the prefix in the analyses. • '≥': use the available original value in the analyses. • '≤': use the available original value in the analyses.
10. Prior and concomitant, medication / treatment	Prior, concomitant, and post-treatment medication/treatment	• Any medication that was used at any time prior to the date of first study drug is a Prior Medication. • Any medication that was used at any time on or after the date of first study drug and within 30 days of the last dose of study drug is a Concomitant Medication. • If the date of first study medication is missing, then the date of randomization is used (as long as the subject is known to have received study drug on at least one day during the study). Otherwise, in the case of missing dates, any period (Prior and Concomitant) that is possible based on the available information should be applied.
11. Adverse event	Missing CTCAE severity (toxicity grade)	For the AE summary by CTCAE severity grade, an AE with missing CTCAE severity grade will not be imputed. Imputed values will not be listed in data listings.
	Missing relationship to study drug	For the AE summary by relationship, an AE with a missing relationship to study drug will not be imputed. Imputed values will not be listed in data listings.
	Treatment-emergent adverse event	An adverse event is considered treatment-emergent if emerges on or after initiation of study drug, or an AE that existed pre-treatment and worsened in severity on or after initiation of study drug, through 30 days after the last dose of study drug. An adverse event that begins on the same date as the first dose of study drug is treatment-emergent if the AE begins after the time of first dose or if the time of AE onset is unknown.

Category	Description	Data Handling Rule
		If the AE start date is partial/missing, then • If AE start date is completely missing, then the AE is considered as treatment-emergent. • If both AE start month and day are missing and AE start year is the same or after the first dose year, then the AE is considered as treatment-emergent. • If AE start day is missing and AE start year and month are the same or after the first dose year and month, then the AE is considered as treatment-emergent. Missing/incomplete (partial) AE start and end dates will not be imputed for data listings.
12. Treatment Duration (days)	Treatment Duration (days)	Treatment duration is defined as Date of last dose of a study drug - Date of first dose of a study drug +1.
13. Duration of Exposure (days)	Duration of Exposure (days)	Exposure is defined as (Date of the last dose of the study drug – Date of first dose of the study drug + 1).
14. General	Conversion of Duration in Days to Duration in Years/Months/Days	Duration in Years = Duration in Days/365.25 Duration in Months = Duration in Days/30.4375 Duration in Weeks = Duration in Days/7
15. Hard coding	Hard coding for data analysis	Hard Coding is not allowed during data analysis unless if agreed in writing by Imara.

Appendix 4 Clinical Laboratory CTCAE Grading

Investigations				
	Grade			
Laboratory Analyte	1	2	3	4
aPTT (activated partial thromboplastin time) prolonged	>ULN - 1.5 x ULN	>1.5 – 2.5 x ULN	>2.5 x ULN	-
Alanine aminotransferase increased	>ULN – 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 – 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	>ULN – 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase increased	>ULN – 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 – 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Blood bilirubin increased	>ULN – 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 – 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 – 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Creatinine increased	>ULN -1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 -3.0 x ULN	>3.0 baseline; >3.0 – 6.0 xULN	>6.0 x ULN
GGT (gamma-glutamyl transferase) increased	>ULN – 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Hemoglobin increased (a)	Increase in >0 – 2 gm/dL above ULN (a)	Increase in >2 – 4 gm/dL above ULN (a)	Increase in >4 gm/dL above ULN (a)	n/a

Investigations				
	Grade			
Laboratory Analyte	1	2	3	4
Anemia (hemoglobin decreased)	LLN- 10g/dL; <LLN – 6.2 mmol/L; <LLN – 100 g/L	<10.0 – 8.0 g/dL; <6.2 – 4.9 mmol/L; <100 – 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
INR increased	>1.2 – 1.5; >1 -1.5 x baseline if on anticoagulation (use of anticoagulation identified using the B01A ATC code)	>1.5 – 2.5; >1.5 – 2.5 x baseline if on anticoagulation (use of anticoagulation identified using the B01A ATC code)	>2.5; >2.5 x baseline if on anticoagulation (use of anticoagulation identified using the B01A ATC code)	-
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10^9/L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10^9/L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10^9/L	<25,000/mm3; <25.0 x 10^9/L
White blood cell decreased	<LLN – 3000/mm^3; <LLN – 3.0 x 10^9/L	<3000 – 2000/mm^3; <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3; <2.0 – 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
(a) Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal – i.e. above ULN.				

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Hypercalcemia (Calcium Increased)	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
Hyperkalemia (Potassium Increased)	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Hypermagnesemia (Magnesium Increased)	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	n/a	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
Hypernatremia (Sodium Increased)	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
Hypoalbuminemia (Albumin Decreased)	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
Hypocalcemia (Calcium Decreased)	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium<LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0- 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9- 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L;Ionized calcium <0.8 mmol/L;life-threatening consequences
Hypoglycemia (Glucose Decreased)	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Hypokalemia (Potassium Decreased)	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Hypomagnesemia (Magnesium Decreased)	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences
Hyponatremia (Sodium Decreased)	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences

Renal and Urinary Disorders				
	Grade			
Adverse Event	1	2	3	4
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m^2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m^2	eGFR or CrCl 29 - 15 ml/min/1.73 m^2	eGFR or CrCl <15 ml/min/1.73 m^2; dialysis or renal transplant indicated

Appendix 5 Regions

The following geographic regions include the countries listed below:

Europe/North America:
Denmark
France
Italy
Greece
Netherlands
Georgia
Turkey
UK
US

Asia/Africa:
Israel
Lebanon
Malaysia
Tunisia
Morocco

Appendix 6 Shell Column Headers

For shells with all treatment arms and a total column, the column headers will be displayed as:

Placebo (N=XX)	IMR-687 200/300 mg (N=XX)	IMR-687 300/400 mg (N=XX)	IMR-687 Pooled Dose (N=XX)	Total (N=XX)

For shells with all treatment arms and a pooled active arms column, the column headers will be displayed as:

Placebo (N=XX)	IMR-687 200/300 mg (N=XX)	IMR-687 300/400 mg (N=XX)	IMR-687 Pooled Dose (N=XX)