# STATISTICAL ANALYSIS PLAN

Final Version 2.0, dated 07 March 2024

## A Phase 1/2, Multicenter, Open-Label, Single Arm, Dose Escalation and Expansion Study of Gilteritinib (ASP2215) Combined with Chemotherapy in Children, Adolescents and Young Adults with FMS-like Tyrosine Kinase 3 (FLT3)/Internal Tandem Duplication (ITD) Positive Relapsed or Refractory Acute Myeloid Leukemia (AML)

ISN/Protocol: 2215-CL-0603
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Sponsor:

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# I. LIST OF ABBREVIATIONS AND KEY TERMS

## List of Abbreviations

| Abbreviations | Description of abbreviations |
|---|---|
| AE | adverse event |
| ALK | anaplastic lymphoma kinase |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase (SGPT) |
| AML | Acute myeloid leukemia |
| ANC | absolute neutrophil count |
| ASCM | Analysis Set Classification Meeting |
| AST | aspartate aminotransferase (SGOT) |
| AUC | area under the concentration-time curve |
| AXL | AXL tyrosine kinase |
| $C_{max}$ | maximum concentration |
| CA | Competent Authorities |
| cEC | concerned Ethics Committee |
| CL/F | oral clearance |
| COA | clinical outcome assessment |
| CR | complete remission |
| CRc | composite complete remission |
| CRF | case report form |
| CRh | complete remission with partial hematologic recovery |
| CRi | complete remission with incomplete hematologic recovery |
| CRO | contract research organization |
| CRp | complete remission with incomplete platelet recovery |
| CT | computed tomography |
| CYP | cytochrome P450 |
| DCR | duration of complete remission |
| DCR/CRh | duration of complete remission/complete remission with partial hematologic recovery |
| DCRc | duration of composite complete remission |
| DCRh | duration of complete remission with partial hematologic recovery |
| DCRi | duration of complete remission with incomplete hematologic recovery |
| DCRp | duration of complete remission with incomplete platelet recovery |
| DEC | Dose Escalation Committee |
| DILI | drug-induced liver injury |
| DLT | dose-limiting toxicity |
| DR | duration of response |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| EFS | event-free survival |
| EOT | end of treatment |
| FAS | full analysis set |
| FLAG | fludarabine, cytarabine and granulocyte colony-stimulating factor |
| FLT3 | FMS-like tyrosine kinase 3 |
| FSH | Follicle stimulating hormone |

| Abbreviations | Description of abbreviations |
|---|---|
| GCP | Good Clinical Practice |
| G-CSF | granulocyte colony-stimulating factor |
| GGT | gamma-glutamyl transferase |
| HSCT | haematopoietic stem cell transplant |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IND | investigational new drug |
| INR | international normalized ratio |
| ISN | international study number |
| ITD | internal tandem duplication |
| LTT | long term treatment |
| MDRD | modification of diet in renal disease |
| MedDRA | medical dictionary for regulatory activities |
| MUGA | multigated acquisition scan |
| MRD | minimal residual disease |
| MTD | maximum tolerated dose |
| NCI-CTCAE | National Cancer Institute's Common Terminology Criteria for Adverse Events |
| NE | not evaluable |
| NR | no response |
| OS | overall survival |
| PGx | pharmacogenomics |
| PIA | plasma inhibitory activity |
| PK | pharmacokinetic |
| PKAS | pharmacokinetic analysis set |
| PR | partial remission |
| PRES | Posterior reversible encephalopathy syndrome |
| QTcF | Fridericia-corrected QT interval |
| RBC | red blood cell |
| RP2D | recommended phase 2 dose |
| R/R | relapsed/refractory |
| RTK | receptor tyrosine kinase |
| SAE | serious adverse event |
| SAF | safety analysis set |
| SOP | standard operating Procedure |
| $t_{1/2}$ | terminal elimination half-life |
| TBL | total bilirubin |
| TEAE | treatment-emergent adverse event |
| $t_{max}$ | time of maximum concentration |
| ULN | upper limit of normal |
| USM | Urgent Safety Measure |
| $V_d/F$ | apparent volume of distribution |
| WBC | white blood cell |

## List of Key Terms

| Terms | Definition of terms |
|---|---|
| Baseline | Assessments of subjects as they enter a study before they receive any treatment. |
| Endpoint | Variable that pertains to the efficacy or safety evaluations of a study. |
| Enroll | To register or enter a subject into a clinical study. NOTE: Once a subject has received the study drug or placebo, the clinical study protocol applies to the subject. |
| Intervention | The drug, device, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics). |
| Investigational period | Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug. |
| Post investigational period | Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period. |
| Randomization | The process of assigning study subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias. |
| Screening | A process of active consideration of potential subjects for enrollment in a study. |
| Screen failure | Potential subject who did not meet 1 or more criteria required for participation in a study. |
| Screening period | Period of time before entering the investigational period, usually from the time when a subject signs the consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject. |
| Study period | Period of time from the first site initiation date to the last site completing the study. |
| Subject/ Participant | An individual who participates in a clinical trial either as a recipient of the investigational product(s) or as a control. The term “subject” is part of the federal regulation and may be used interchangeably with participant. |
| Variable | Any entity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values. |

# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary, secondary, and exploratory endpoints and other data.

This SAP is to be read in conjunction with the study protocol, Data Handling and Reporting Conventions and the Tables, Listings and Figures (TLFs) Specifications. The SAP is finalized and signed prior to database hard lock. The SAP should be developed and approved before First Subject In (FSI). If the expected interval between FSI and soft-lock is less than 12 weeks, then the SAP should be approved by 12 weeks prior to the planned date of soft-lock. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled. The SAP will be finalized before the database soft lock at the latest.

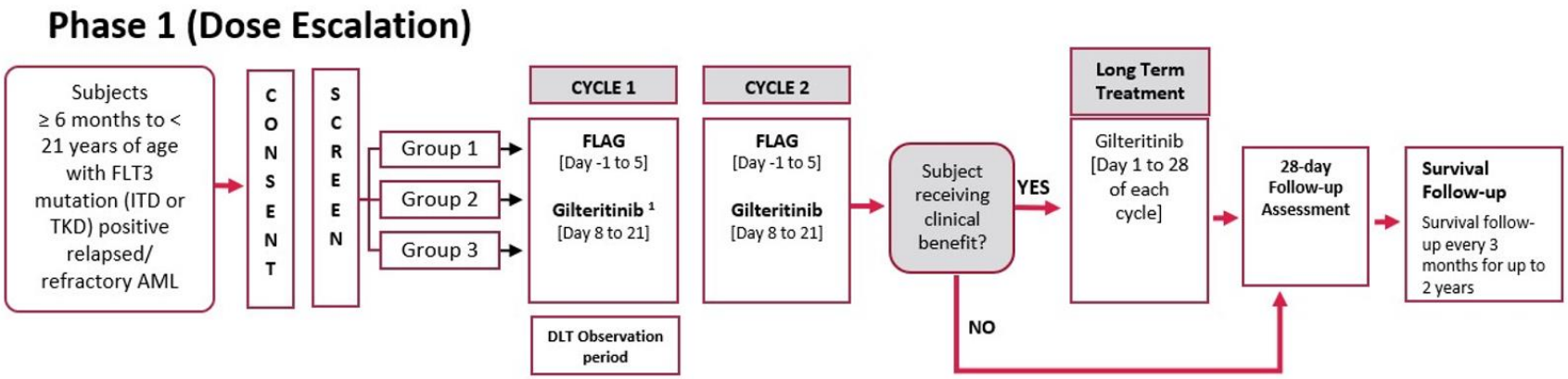
This statistical analysis is coordinated by the responsible biostatistician of GD-US. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a meeting for final review of data and TLFs will be held to allow for a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented.

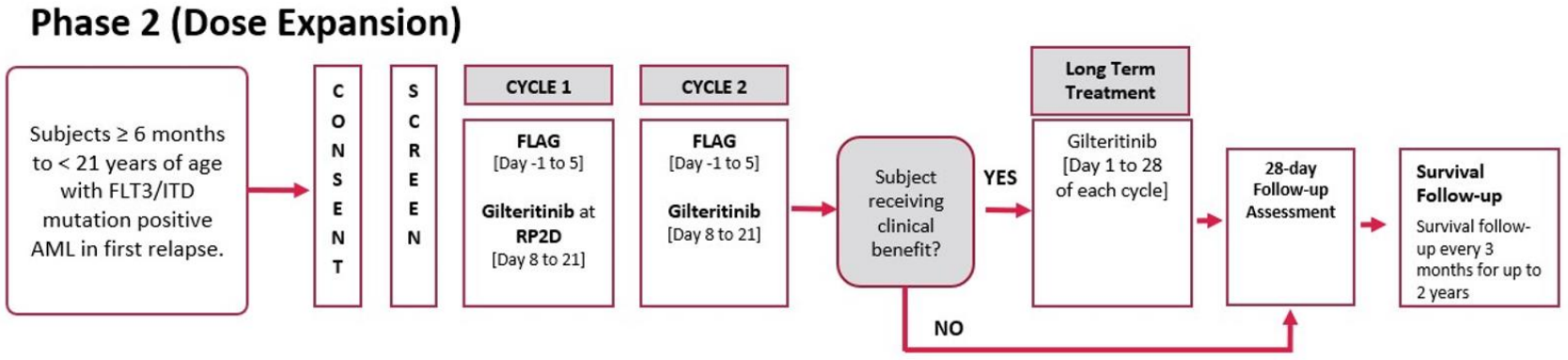
# 2 STUDY OBJECTIVES AND DESIGN

## 2.1 Flow Chart and Visit Schedule

**Figure 1 Flow Chart**




**Group 1:** subjects from 2 years to less than 21 years; **Group 2:** subjects from 1 year to less than 2 years of age; **Group 3:** subjects from 6 months to less than 1 year of age
[1] Starting Dose for Group 1 is 2 mg/kg/day and starting dose for Group 2 and 3 is 1 mg/kg/day.




FLAG: fludarabine, cytarabine and granulocyte colony-stimulating factor; RP2D : Recommended Phase 2 Dose

**Table 1 Schedule of Assessments for Phase 1, Phase 2, and Long Term Treatment (LTT)**

| | | PHASE 1/PHASE 2 | | | | | | | | | | | | | LTT | $EOT_2$ / Pre-HSCT | 28-day Follow-up[v] | Remote Follow-up[w] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assessments** | **Screening** | | **Cycle 1[a]** | | | | | | | **Cycle 2[a]** | | | | | | **Cycle 1 and Subsequent Cycles** | **Visit*** | | |
| Cycle Day → | Days -28 to -2 | Day -1 | Day 1 | Day 4 | Day 8 | Day 15 | Day 21 | Day 28 | Day -1 | Day 1 | Day 4 | Day 8 | Day 15 | Day 21 | Day 28 / $EOT_1$[u] | Day 1 | | | |
| Visit Window (days) → | | | | ±1 | ±1 | ±2 | ±2 | ±2 | | | ±1 | ±1 | ±2 | ±2 | ±2 | ±2 | ±2 | +7 | ±7 |
| Informed consent[b] | X | | | | | | | | | | | | | | | | | | |
| Eligibility criteria | X | | | | | | | | | | | | | | | | | | |
| Medical and disease history | X | | | | | | | | | | | | | | | | | | |
| Vital Signs[c] | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | | |
| Karnofsky/Lansky performance status | X | | | | | | | | | | | | | | X | X | X | | |
| Physical examination[d] | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | | |
| Pregnancy test for WOCBP[e] | X | | X | | | | | | | X | | | | | X | X | X | | |
| Chest x-ray (or chest CT) | X | | | | | | | | | | | | | | | | | | |
| 12-lead ECG[f] | X | | X | | X | X | X | | | X | | X | X | X | X | X | X | | |
| Clinical laboratory tests (chemistry, hematology, coagulation, urinalysis) [g] | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | | |
| Thyroid function tests[h] | X | | X | | | | | | | X | | | | | X | X | | | |
| MUGA or ECHO[i] | X | | | | | | | | | | | | | | X | | | | |
| PK sample collection[j] | | | | | X | X | X | | | | | | X | | | | | | |
| PGx[k] | | X | | | | | | | | | | | | | | | | | |
| Plasma Inhibitory Assay (PIA) & FLT3 Ligand [l] | | | | | X | X | X | | | | | X | X | X | | | | | |
| FLT3 mutations status[m] | X | | | | | | | | | | | | | | | | | | |
| Bone marrow aspirate/biopsy and MRD status analysis[n, o] | X | | | | | | | X | | | | | | | X | X | X | | |
| Gilteritinib dispensing[p] | | | | | X | | | | | | | X | | | | X | | | |

| | | PHASE 1/PHASE 2 | | | | | | | | | | | | | LTT Cycle 1 and Subsequent Cycles | $EOT_2$ / Pre-HSCT Visit* | 28-day Follow-up[v] | Remote Follow-up[w] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assessments** | **Screening** | | **Cycle 1[a]** | | | | | | | **Cycle 2[a]** | | | | | | | | |
| Cycle Day → | Days -28 to -2 | Day -1 | Day 1 | Day 4 | Day 8 | Day 15 | Day 21 | Day 28 | Day -1 | Day 1 | Day 4 | Day 8 | Day 15 | Day 21 | Day 28 / $EOT_1$[u] | Day 1 | | | |
| Visit Window (days) → | | | | ±1 | ±1 | ±2 | ±2 | ±2 | | | ±1 | ±1 | ±2 | ±2 | ±2 | ±2 | ±2 | +7 | ±7 |
| FLAG administration[q] | | X | X | X | | | | | X | X | X | | | | | | | | |
| DLT assessment[r] | | | | | X | X | X | X | | | | | | | | | | | |
| Clinical Outcomes assessment[s] | | | | | X | | X | | | | | | | | | X | | | |
| AE/SAE Assessment[t] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[u] | X | X | X | |
| Prior and concomitant medications[u] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Subsequent anti-leukemic treatments/outcomes | | | | | | | | | | | | | | | | | | X | X |
| Survival | | | | | | | | | | | | | | | | | | X | X |

Footnotes

AE: adverse event; C: cycle; COA: clinical outcome assessment; CT: computed tomography; D: day; DLT: dose limiting toxicity; ECG: electrocardiogram;
ECHO: echocardiogram; EOT: end of treatment; FLAG: fludarabine, cytarabine, and granulocyte colony-stimulating factor;
FLT3: FMS-like tyrosine kinase 3; HSCT: hematopoietic stem cell transplant; ICF: informed consent form; LTT: long term treatment; MRD: minimal residual disease;
MUGA: multigated acquisition; PGx: pharmacogenomics; PIA: plasma inhibitory assay; PK: pharmacokinetic; SAE: serious adverse event;
WOCBP: women of childbearing potential

**Note**: The day after day -1 is day 1. There is no day 0.

a) Visits for each cycle should be based upon day 1 of that cycle. Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up AEs or if deemed necessary by the investigator. Unscheduled visits will include assessment of AEs; additional assessments (e.g., laboratory testing) that may be performed as deemed appropriate by the investigator. Cycle 2 can begin once the subject meets the "Criteria to Begin Cycle 2 (Phases 1 and 2)" as outlined in protocol [Section 2.2.1 Study Design].

b) ICF must be obtained prior to performing any study-specific procedures with the exception of procedures that are performed within the protocol specified windows as part of routine patient management.

c) Vital signs (includes blood pressure, respiratory rate, $O_2$ saturation, pulse rate and temperature) should be collected pre-dose as applicable. All vital sign measures will be obtained with the subject in the sitting or supine position.

d) A complete physical exam will be completed at screening and will be directed towards subject-reported symptoms and areas of disease, as per investigator judgment. Brief physical exams can be completed thereafter and must be obtained predose. Physical examination also includes measurements of height and weight. Weight and Height will be collected at screening, day 1 of each cycle and $EOT_1$ (C2D28 for phase 1/phase 2).

e) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of each cycle.

f) ECG assessment is required at screening. During treatment period, pre-dose ECG must also be obtained within 1 hour prior to dosing. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs with 10 minutes resting prior to first ECG and at least 5 minutes apart per time point) and transmitted electronically for central reading. Triplicate ECGs must also be obtained within 1 hour prior to obtaining the time-matched PK samples, for a particular visit.

g) Laboratory tests performed will include Hematology, Serum hematology, serum chemistries, liver function, coagulation, urinalysis and uric acid. Coagulation and Urinalysis: Screening only. Uric acid: C1D1, C1D4, C1D8 and C1D15 only.

h) For phase 1/phase 2: Thyroid function tests will be performed during screening, C1D1, C2D1 and C2D28 visit. For LTT: Thyroid function tests will be performed on C1D1 and repeated after every 2 cycles of therapy (C3D1, C5D1, C7D1, etc.).

i) MUGA scans or ECHO (per local standard of care) are to be performed at screening and C2D28/EOT1 visit. Note: MUGA scans are not applicable to Germany.

j) PK samples will be collected in cycle1 and cycle 2 at the following time points:

- C1D8 - Predose
- C1D15 (± 2 days) – Predose
- C1D21 (± 2 day) – Predose and 4-6 hours
- C2D15 (± 2 days) – Predose

Predose samples should be collected within 1 hour prior to dosing.

k) Whole blood and buccal swab collected at C1D -1 (predose) for optional PGx study. Sample should be collected prior to the administration of induction chemotherapy.

l) PIA and FLT3 Ligand samples will be collected on C1D8 (predose), C1D15 (predose) and C1D21 (predose), C1D21 (4-6 hours post dose), C2D8 (predose), C2D15 (predose) and C2D21 (predose). Samples should be collected at or near the same time as PK samples. Predose samples should be collected within 1 hour prior to dosing.

m) Subject is positive for the FLT3/ITD mutation in bone marrow or blood as determined by the local institution. A bone marrow aspirate or blood sample must be sent to the central laboratory for FLT3 mutational analysis during the screening period.

n) If bone marrow aspirate is unobtainable (e.g., dry tap), an additional EDTA tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required.
Bone marrow samples are required during screening and end of each cycle (C1D28 and C2D28) for phase 1/phase 2.
For LTT: Bone marrow assessments will be performed on C1D1 and repeated after every 3 cycles until 1 year of LTT, followed by every 6 cycles until 2 years of LTT (i.e. C1D1, C4D1, C7D1, C10D1, C13D1, C19D1, etc.). Bone marrow samples are also required at the end of treatment visit and as clinically indicated. Bone marrow assessments do not need to be performed on C1D1 of LTT and EOT2, if a bone marrow assessment was performed within 2 weeks during the previous study visit.

o) For subjects whose response assessment is not evaluable due to hypocellularity, a repeat bone marrow analysis should be performed at least every 14 days until response determination is possible.

p) For phase 1/phase 2: Gilteritinib will be dispensed on day 8 of each cycle and will be taken by the subject from day 8 to day 21 of each cycle.
For LTT: Gilteritinib bottles will be dispensed on day 1 of each cycle and will be taken by the subject once daily for the 28-day cycle.

q) FLAG will be administered on days -1 to 5 of cycle 1 and cycle 2. Refer to protocol table 4: Treatment Plan for cycle 1 and cycle 2 of phases 1 and 2 for detailed scheduled of FLAG administration.

r) DLT assessment is performed in cycle 1 of phase 1 only.

s) Clinical outcome assessment (COA) should be collected immediately after the administration of the study drug on that visit day. For LTT: COA will be collected only on C1D1 visit.

t) AE collection begins after the signing of the informed consent and will be collected until the 28-day Follow-up visit of the subject or the subject is determined to be a screen failure. For subjects who plan to proceed to HSCT and resume gilteritinib treatment after HSCT, AE collection will continue until the start of the HSCT conditioning regimen and AE collection will resume upon the resumption of gilteritinib treatment until 30 days after the last dose of study drug. For subjects who do not plan to resume gilteritinib treatment after HSCT, AE collection will continue until the start of the HSCT conditioning regimen or 30 days after the last dose of study drug, whichever comes first.

u) Includes medications taken within 28 days prior Screening.

v) An EOT visit [EOT1 or EOR2] will be performed within 7 days after last dose of gilteritinib, or prior to initiation of another anticancer therapy, whichever occurs earlier. EOT1 visit (C2D28 for phase 1/phase 2) will be performed for any subject participating in phase 1 or 2 and indicates the end of the respective phase. EOT2 visit (28 days following LTT) will be performed for any subject participating in LTT phase and indicates the end of LTT. For subjects who will undergo HSCT and plan to resume gilteritinib treatment after HSCT, a pre-HSCT visit will be performed.

w) A follow-up visit will be performed 28 days following the C2D28/EOT1 visit in the event the subject is not participating in the LTT phase. In the event the subject is participating in LTT, then the follow-up visit will be performed 28 days following the EOT2 visit.

x) Survival follow-up will be performed every 3 months for up to 2 years after the 28-day follow-up visit. In the event that the patient is not available for an clinic visit, telephone or e-mail correspondence is acceptable.

## 2.2 Study Objectives

### 2.2.1 Primary Objectives

- Phase 1 (Dose Escalation Phase):
  To determine the maximum tolerated dose (MTD) and/or optimally safe and biologically active recommended phase 2 dose (RP2D) of gilteritinib given in sequential combination with FLAG in children, adolescents and young adults with FLT3 [ITD and/or tyrosine kinase domain (TKD)] AML.
- Phase 2 (Dose Expansion Phase):
  To determine complete remission (CR) rates and composite complete remission (CRc) rates after 2 cycles of gilteritinib in sequential combination with FLAG in children, adolescents and young adults with FLT3 (ITD) AML who are refractory to or at the first hematologic relapse after first-line remission induction AML therapy (up to 2 induction cycles).

### 2.2.2 Secondary Objectives

- To assess the safety, tolerability and toxicities of gilteritinib when given in sequential combination with FLAG in children, adolescents, and young adults with R/R FLT3/ITD AML.
- To evaluate FLT3 inhibition due to gilteritinib treatment.
- To characterize gilteritinib pharmacokinetics.
- To perform serial measurements of minimal residual disease (MRD) and examine the relationship with study endpoints.
- To obtain preliminary estimates of 1-year event-free survival (EFS) and overall survival (OS) rate.
- To assess the acceptability and palatability of the formulation.

### 2.2.3 Exploratory Objectives

- To relate the clinical responses to gilteritinib therapy with FLT3 plasma inhibitory activity (PIA).
- To evaluate relationship between FLT3 ligand levels and clinical response if sufficient sample for FLT3 ligand will be presented.
- To assess the mechanisms of innate and acquired resistance to gilteritinib.

## 2.3 Study Design

This study is an open-label, single-arm, phase 1/2 study to evaluate the safety, pharmacokinetics, and anti-leukemic activity of gilteritinib in children, adolescents and young adults with AML.

The study will consist of 2 phases: Phase 1 (Dose Escalation) and Phase 2 (Dose Expansion).

One cycle is defined as 28 days of treatment. A subject completing 1 or 2 treatment cycles in phase 1 or 2 will have the option to participate in long term treatment (LTT) with gilteritinib (for up to 2) years (~26 cycles).

The study treatment will continue until 1 of the discontinuation criteria is met.

### 2.3.1 Phase 1 (Dose Escalation Phase):

The primary objective of phase 1 will be to establish an optimally safe and biologically active RP2D and/or to determine MTD for gilteritinib in combination with FLAG.

Dose Escalation will be performed in 3 groups based on the age of the subject:

- Group 1: Dose Escalation in subjects from 2 years to less than 21 years of age
- Group 2: Dose Escalation in subjects from 1 year to less than 2 years of age
- Group 3: Dose Escalation in subjects from 6 months to less than 1 year of age

The RP2D will be a dose, which is safe (i.e., has an acceptable dose limiting toxicity (DLT) profile) and demonstrates CR, a high degree of gilteritinib biologic activity (as measured by PIA), or a combination of both.

Induction therapy in this phase will consist of 2 cycles of gilteritinib plus FLAG. During each cycle, FLAG chemotherapy will be administered on days -1 to 5 and gilteritinib will be administered once per day on days 8 to 21 at one of the assigned dose levels given in table 2.

**Table 2 Dose Levels**

| Level | Dose |
|---|---|
| -1 | 1 mg/kg/day (maximum 60 mg/day) # |
| 1 | 2 mg/kg/day (maximum 120 mg/day) * |
| 2 | 3 mg/kg/day (maximum 180 mg/day)** |

*the starting dose of gilteritinib for Group 1; #the starting dose of gilteritinib for Groups 2 and 3

** To be evaluated only if there is lack of toxicity or acceptable DLT profile combined with the lack of sufficient gilteritinib activity observed at the Dose Level 1 (2 mg/kg/day). Not applicable for sites in USA.

DLT assessment will occur during the first cycle only. Pharmacokinetic parameters, response assessment and biological activity will be evaluated during cycle 1 and/or cycle 2.

**Dose Escalation Rules**

Dose escalation, stay, or de-escalation between the dose levels in Groups 1, 2 and 3 will be guided by the standard 3 + 3 design. Dose escalation rules to be followed during the DLT Observation Period are outlined in Table 3.

**Table 3 Dose Escalation Rules During the DLT Observation Period**

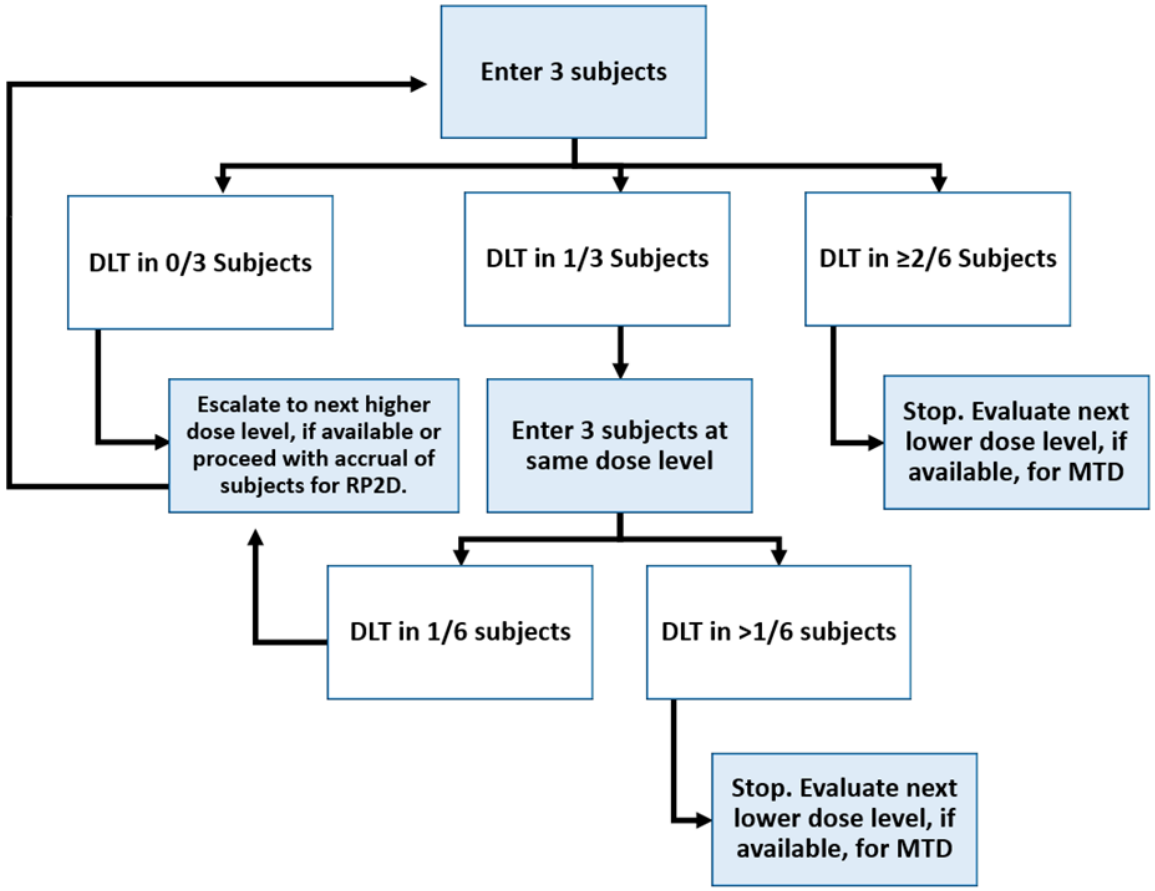
| **Number of Subjects with DLT at the Given Dose** | **Escalation Decision Rules** |
|---|---|
| 0 of 3 or ≤ 1 of 6 subjects | Escalate and enter up to 3 subjects at the next dose level, if the next higher dose level is available. |
| 1 of 3 subjects | Enter up to 3 subjects at the same dose level |
| ≥ 2 subjects | De-escalate, if the next lower dose level is available or stop escalating |

DLT: dose-limiting toxicity

Intra-subject dose escalation is not allowed during the study. Guidance for intra subject dose interruption or reduction for gilteritinib is outlined in the protocol v8.0 [Section 5.1.2 Interruption or Reduction in Dose of the Study Drug].

The Dose Escalation Committee (DEC) will review safety data through the DLT observation period for 3 evaluable subjects at each dose level. In addition to safety data through the DLT observation period, the DEC will review response data and gilteritinib biologic activity (as measured by PIA) through the cycle 1 and/or cycle 2 of the evaluable subjects. The algorithm for differentiation syndrome based on the [Montesinos et al, 2009] criteria, in addition to the preferred term of 'acute promyelocytic leukemia differentiation syndrome', will be used to search for potential cases of differentiation syndrome at every dose level in phase 1. The decision will be made by the DEC to escalate to the next planned dose level, remain at the same dose level, de-escalate to the dose level below or stop escalation. The RP2D and/or MTD will be selected based on the DEC's review of all available data at each dose level, including safety data, pharmacokinetic data (if available), response data and gilteritinib biologic activity data, and the RP2D will become the minimum safe and biologically effective dose level.

**Figure 2 Schematic Representation of Dose Assignments of Each Dose Level in the Standard 3+3 Design**




DLTs: dose-limiting toxicities; MTD: Maximum tolerated dose.

- Group 1: Three subjects will be enrolled in the initial cohort starting at Dose Level 1 (2 mg/kg/day).
- Groups 2 and 3: Three subjects will be enrolled in the initial cohort starting at Dose Level -1 (1 mg/kg/day). Enrollment of subjects in Group 2 will be initiated following the decision by the DEC on the Dose Level 1 (2 mg/kg/day) evaluated in Group 1.

Additional subjects will be accrued as needed at the RP2D of each group (Groups 1, 2 and 3) to ensure that gilteritinib activity is assessable in at least 9 subjects in the respective age group.

For the dose to be considered biologically active, at least 7 of 9 subjects at the RP2D dose in each group must demonstrate CR, a high degree of giltertinib biologic activity (as measured by PIA), or a combination of both with the following conditions for PIA:

- Subjects that complete 2 induction cycles must achieve PIA of > 90% for at least 3 of 4 trough time points; or
- Subjects that complete only 1 induction cycle must achieve PIA of > 90% at 2 of 2 trough time points.

Alternative dose levels can be explored in the following cases:

- A higher Dose Level 2 (3 mg/kg/day) in the event there is lack of toxicity or acceptable DLT profile combined with the lack of sufficient gilteritinib activity at the Dose Level 1 (2 mg/kg/day), after discussion with the DEC. Dose Level 2 (3 mg/kg/day) will not be evaluated in subjects enrolled in USA.
- A lower dose level than Dose Level -1 (1 mg/kg/day) in the event the Dose Level -1 (1 mg/kg/day) demonstrates sufficient gilteritinib activity but DLTs are observed. Exploration of dose level lower that Dose Level -1 will be performed via an amendment to the current study protocol, after discussion with the DEC.

Continued participation in phase 2 portion of the study for each age group will be dependent on the determination of RP2D in Groups 1, 2 and 3, respectively.

**Subject Replacement (Only For Phase 1 – Dose Escalation)**

A subject meeting fulfilling the inclusion/exclusion criteria and receiving 80% of the intended dose of the study treatment regimen (FLAG and gilteritinib) during the DLT observation period will be considered evaluable for DLT.

A subject that receives less than 80% of the intended dose of any of the study regimen (for reasons other than a DLT) during the DLT observation period will not be evaluable for DLT and will be replaced by another subject in the dose level.

In addition, if after enrollment any subject is found not to fulfill any inclusion/exclusion criteria that would adversely affect safety or efficacy evaluation of that subject or are not evaluable for DLT, they may be replaced after discussion with the Dose Escalation Committee.

Subjects without adequate sampling time points to assess biological activity for RP2D determination can be replaced.

### 2.3.2 Phase 2 (Dose Expansion Phase)

The phase 2 part of this study is the dose expansion phase, which will be initiated upon establishment of the optimally safe and biologically effective RP2D and/or MTD dose from phase 1.

Efficacy analysis will be conducted for phase 2 part.

Enrollment of subjects from 6 months to less than 2 years in phase 2 will depend upon the RP2D established in the respective age group (Groups 2 and 3) during the phase 1 portion of the study.

***Applicable only for Germany:*** Enrollment of subjects in phase 2 will be initiated in sites in Germany only after a positive assessment on the phase 1 data of each age group (Group 1, 2 or 3) is received from the competent authority of the country.

This phase will be a single-arm, 2-stage, open-label design with at least 52 response evaluable subjects from 6 months to less than 21 years of age, with:

- at least 2 subjects from 6 months to less than 6 years of age,
- at least 6 subjects from 6 years to less than 12 years of age, and
- at least 10 subjects from 12 years to less than 18 years of age.

Subjects are response evaluable if

1. they are confirmed FLT3/ITD mutation positive,
2. they receive at least 1 dose of gilteritinib, and
3. they are progression/recurrence free during the first 2 cycles of FLAG + gilteritinib and have the required bone marrow evaluations, or have died of disease progression during the first 2 cycles.

Subjects who die during treatment will be counted as nonresponders for purposes of analysis.

Induction therapy in this phase will consist of 2 cycles of gilteritinib plus FLAG. During each cycle, FLAG chemotherapy will be administered on days -1 to 5 and gilteritinib will be administered once per day on days 8 to 21 at the assigned dose (RP2D).

Initially, 22 response evaluable subjects will be needed during the first stage, with 9 CRc responders or 4 CR responders after 1 or 2 cycles of therapy required to continue to a total of 52 response evaluable subjects.

**Applicable only for USA:** If there are less than 4 CR responders in stage 1, the enrollment will be stopped in the USA and the study will not proceed to stage 2 in the USA.

**A Bayesian posterior probability for safety monitoring will be used for phase 2**. Subjects in phase 2 will be continued to be monitored for ≥ grade 3 non-hematologic AEs considered at least possibly related to protocol therapy, and AEs of any grade leading to treatment discontinuation or death considered at least possibly related to protocol therapy. The event rate will be reviewed for the first 6 evaluable subjects at the end of cycle 1. After that, the event rate will be reviewed continuously. The estimated event rate based on the Bayesian beta-binomial model will be provided for safety monitoring. If the event rate is ≥ 20% with a posterior probability of at least 80%, then the enrollment to phase 2 will be paused and safety will be reassessed by the DEC. With a non-informative prior Beta(1,1) distribution, the numbers of subjects with event for certain evaluable subjects, which trigger the enrolment pause for safety review, are listed in [Table 4 of the protocol]. The algorithm for differentiation syndrome based on the [Montesinos et al, 2009] criteria, in addition to the preferred term of 'acute promyelocytic leukemia differentiation syndrome', will be used to search for potential cases of differentiation syndrome in every 6 subjects in phase 2.

# 3 SAMPLE SIZE

## 3.1 Phase 1

*Group 1:*

Three subjects will be enrolled in a cohort at one of a series of doses of gilteritinib with a starting dose of 2 mg/kg per day according to the standard 3 +3 design. Additional subjects will be accrued as needed at the determined RP2D of group 1 to ensure that gilteritinib activity is assessable in at least 9 subjects.

The RP2D will be a safe dose of gilteritinib that demonstrates sufficient activity.

The number of subjects enrolled will depend on the dose levels evaluated, evaluation of biological activity, and the availability of time points for PIA assessments.

*Groups 2 and 3:*

Three subjects will be enrolled in a cohort at one of a series of doses of gilteritinib with a starting dose of 1 mg/kg per day according to the standard 3 + 3 design.

Additional subjects will be accrued as needed to ensure that gilteritinib activity is assessable in at least 9 subjects.

The RP2D will be a safe dose of gilteritinib that demonstrates sufficient activity.

The number of subjects enrolled will depend on the dose levels evaluated, evaluation of biological activity, and the availability of time points for PIA assessments.

## 3.2 Phase 2

The phase 2 portion of this study will be a single-arm, 2-stage, open-label design with a total of 52 response evaluable subjects. In the available dataset (COG AAML 06P1, 1-BFM AML 2001-01, Costa dataset), there are 26 CRc responders out of 73 subjects (a CRc rate of about 35%). With a 1-sided Type 1 error rate of 2.5%, there will be about 80% power to detect a 30% CR rate (i.e., a 16% increase in CR rate from the null hypothesis value of 14%). The 52 response evaluable subjects will provide about 90% power to detect a 56% CRc rate (i.e., a 21% increase in CRc rate from the null hypothesis value of 35%), with 1-sided Type error rate of 5%. Operationally, 22 response evaluable subjects will be needed during the first stage, with 4 CR responders or 9 CRc responders after 1 or 2 cycles of therapy required to continue to a total of 52 response evaluable subjects. If there are less than 4 CR responders in stage 1, the enrollment will be stopped in the USA and the study will not proceed to stage 2 in the USA. Ultimately, 13 or more CR responders or 24 CRc responders will be required to meet the efficacy threshold of FLAG + gilteritinib. The sample size was calculated in East Version 6.4 for CR.

# 4 ANALYSIS SETS

In accordance with International Council for Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard lock.

Safety Analysis Set (SAF) will be used for the analyses of safety and biomarker variables. Full Analysis Set (FAS) will be used for efficacy analysis. Pharmacokinetic Analysis Set (PKAS) will be used for pharmacokinetic analyses. Pharmacodynamic Analysis Set (PDAS) will be used for the analyses of pharmacodynamic data. The Minimal Residual Disease (MRD) Analysis Set (MAS) will be used for the analysis of available MRD data.

The data from all patients who were enrolled or allocated to treatment will be included in the data listings. All allocated/enrolled subjects are those who signed the informed consent form, had an enrollment/registration date and received drug assignment through either the Astellas clinical study manager or the IRT system.

## 4.1 Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all subjects who are enrolled and receive at least 1 dose of the treatment regimen. This will be the primary analysis set for efficacy analyses.

The selection of subjects for the FAS will be confirmed in the Analysis Set Classification Meeting (ASCM).

## 4.2 Safety Analysis Set (SAF)

The safety analysis set (SAF) consists of all subjects who took at least 1 dose of the treatment regimen, and will be used for safety analyses.

For the statistical summary of the safety data, the SAF will be used. Note that the SAF and FAS are the same in this study.

## 4.3 Pharmacokinetics Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) consists of the administered population for which sufficient plasma concentration data is available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling is known. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time-points from the PKAS will be documented in the in the Classification Specifications and determined at the Classification Meeting.

## 4.4 Pharmacodynamic Analysis Set (PDAS)

The PDAS consists of a subset of the SAF for which sufficient pharmacodynamic measurements were collected. Inclusion of subjects in the PDAS with missing data or major protocol deviations will be considered on a case-by-case basis.

The PDAS will be used for all summaries and analyses of pharmacodynamic data.

## 4.5 Minimal Residual Disease Analysis Set (MAS)

The MRD Analysis Set (MAS) will consist of a subset of the FAS for which subjects were enrolled, received at least 1 dose of the treatment regimen, and had at least 1 post-baseline sample with MRD data.

# 5 ANALYSIS VARIABLES

## 5.1 Efficacy Endpoints

Efficacy analysis will be conducted for both phase 1 and phase 2.

### 5.1.1 Response Definitions

Response to treatment will be defined per modified Cheson criteria [2003] as outlined below.

Derived and investigator-assessed responses will be performed.

**Complete Remission (CR)**

For subjects to be classified as being in complete remission (CR) at a post-baseline visit, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state and must have an ANC $\geq 1 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L and normal marrow differential with < 5% blasts, and they will be red blood cell (RBC) and platelet transfusion independent (defined as 1 week without RBC transfusion and 1 week without platelet transfusion). There should be no evidence of extramedullary leukemia and no evidence of Auer rods. The blast counts in peripheral blood must be ≤ 2%.

**Complete Remission with Incomplete Platelet Recovery (CRp)**

For subjects to be classified as being in complete remission with incomplete platelet recovery (CRp) at a post-baseline visit, they must achieve CR except for incomplete platelet recovery ($< 100 \times 10^9$/L).

**Complete Remission with Incomplete Hematologic Recovery (CRi)**

For subjects to be classified as being in complete remission with incomplete hematologic recovery (CRi) at a post-baseline visit, they must fulfill all the criteria for CR except for incomplete hematological recovery with residual neutropenia $< 1 \times 10^9$/L with or without complete platelet recovery. RBC and platelet transfusion independence is not required.

**Composite Complete Remission (CRc)**

For subjects to be classified as being in composite complete remission (CRc) at a post-baseline visit, they must either achieve CR, CRp or CRi at the visit.

**Complete Remission with Partial Hematologic Recovery (CRh)**

At a post-baseline visit, subjects will be classified as being in complete remission with partial hematologic recovery (CRh) if they have marrow blasts < 5%, partial hematologic recovery ANC ≥ 0.5 x $10^9$/L and platelets ≥ 50 x $10^9$/L, blasts in peripheral blood must be ≤ 2%, no evidence of extramedullary leukemia and cannot be classified as CR.

**Partial Remission (PR)**

For subjects to be classified as being in partial remission (PR) at a post-baseline visit, they must have bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or only a few regenerating) circulating blasts and with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate with the total marrow blasts between 5% and 25%. A value of less or equal than 5% blasts is also considered a PR if Auer rods are present.

**Not Evaluable (NE) /No Response (NR)**

In the situation where no bone marrow assessments are performed or myeloblast value is missing, blast value from peripheral blood is missing or ≤ 2%, and extramedullary leukemia is missing or not done, the response will be classified as not evaluable (NE). In any case response cannot be categorized as CR, CRp, CRi, CRh, PR or NE, it will be categorized as no response (NR).

**Relapse**

Relapse after CR, CRh, CRp or CRi is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow aspirate not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to > 25% not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

Last Relapse-free Disease Assessment Date

Last relapse-free disease assessment refers to the date of the subject's last disease assessment upon which subject was classified as either CR, CRi, CRp, PR or NR using bone marrow aspiration or biopsy assessment. In the event that central bone marrow assessment is not performed or bone marrow is not adequate, local bone marrow assessment date will be used. If no aspirate or biopsy is available and subject is evaluated based on blast count from peripheral blood at a visit that bone marrow is expected to be collected, the date when the peripheral blood sample is drawn will be used.

**Best Response**

Best response is defined as the best measured response to treatment for all visits (in the order of CR, CRp, CRi, PR, NR and NE). Subjects with best responses of CR, CRp, CRi or PR

will be considered responders. Subjects who do not achieve at least a best response of PR will be considered nonresponders.

### 5.1.2 Response Rates

Subjects with unknown or missing response, or who provide no information on response at the end of study will be treated as non-responders and will be included in the denominator when calculating rates.

**Complete Remission Rate**

Defined as the number of subjects with best response of CR divided by the number of subjects in the analysis population.

**Composite Complete Remission Rate**

CRc rate is the confirmed remission rate of all complete and incomplete CRs (CR, CRp or CRi). The CRc rate is defined as the number of subjects who achieve the best response of CRc (i.e., CR + CRp + CRi) divided by the number of subjects in the analysis population.

**Complete Remission with Partial Hematologic Recovery Rate**

CRh rate is defined as the number of subjects who achieve CRh at any of the post-baseline visits and do not have best response of CR, divided by the number of subjects in the analysis population.

**Complete Remission and Complete Remission with Partial Hematologic Recovery Rate**

CR/CRh rate is defined as the number of subjects who achieve either CR or CRh at any of the post-baseline visits, divided by the number of subjects in the analysis population.

**Best Response Rate**

Defined as the number of responders (i.e. subjects with best response of CR, CRp, CRi, or PR) divided by the number of subjects in the analysis population.

### 5.1.3 Survival Time

**Overall Survival (OS)**

Overall survival (OS) is defined as the time from the date of enrollment until the date of death from any cause (death date –enrollment date + 1). For a subject who is not known to have died by the end of study follow-up, OS is censored at the date of last contact (date of last contact – enrollment date + 1).

Date of last contact is the latest date the subject is known to be alive. Date of last contact is defined as the latest of the following dates: treatment discontinuation date, 28-day follow-up date, last dosing administration date (starting/stopping dose dates), last disease assessment date (including bone marrow, lab, ECG, ECOG, vital signs, ophthalmology, PRO, resource

utilization assessment dates), AE (starting/stopping dates), last known alive date from long term follow-up, and enrollment date, data cutoff date (if applicable).

**Event-free Survival (EFS)**

Event-free survival (EFS) is defined as the time from the date of enrollment until the date of documented relapse (excluding relapse after PR), treatment failure, or death from any cause, whichever occurs first [earliest of (relapse date, treatment failure date, death date) – enrollment date + 1]. For a subject who is not known to have had a relapse or treatment failure or death event, EFS is censored, and the event date is the date of last relapse-free disease assessment (last relapse-free disease assessment date – enrollment date +1). Subject is not censored at HSCT.

If a subject experiences relapse or death, the subject is defined as having EFS event related to either "relapse" or "death", and the event date is the date of relapse or death.

A subject can be classified as having an EFS event related to "treatment failure" if one of the following occurs:

- If a subject fails to achieve any of the response of CR, CRp, CRi, CRh or PR during the treatment period. In this case, the event date is the enrollment date.
- If a subject discontinues the treatment due to "progressive disease" or "lack of efficacy" during the treatment period, without a previous response of CR, CRp, CRi, CRh or PR. In this case, the event date is the enrollment date.
- If a subject discontinues the treatment due to "progressive disease" or "lack of efficacy" during the treatment period and seeks alternative anti-leukemia therapy. In this case, the event date is the start date of new anti-leukemia therapy. If the new anti-leukemia therapy date is not available, the event date is the last treatment evaluation date.

If a subject experiences any of the above, the subject is defined as having EFS event related to "treatment failure," and the event date is the earliest date of treatment failure.

**Leukemia-free Survival (LFS)**

Leukemia-free survival (LFS) is defined as the time from the date of first CRc until the date of documented relapse or death for subjects who achieve CRc (relapse date or death date – first CRc disease assessment date + 1). For a subject who is not known to have relapsed or died, LFS is censored on the date of last relapse-free disease assessment date (last relapse-free disease assessment date – first CRc disease assessment date + 1).

### 5.1.4 Duration

**Duration of CRc (DCRc)**

Duration of CRc is defined as the time from the date of first CRc until the date of documented relapse for subjects who achieve CRc (relapse date – first CRc disease

assessment date + 1). Subjects who die without report of relapse are considered nonevents and censored at their last relapse-free disease assessment date (last relapse-free disease assessment date – first CRc disease assessment date + 1). Other subjects who do not relapse on study are considered nonevents and censored at the last relapse-free disease assessment date.

**Duration of CR/CRh, CRh, CR, CRp, CRi**

Duration of CR/CRh, CRh, CR, CRp, CRi is defined similarly as duration of CRc.

**Duration of Response (DR)**

Duration of response is defined as the time from the date of either first CRc or PR until the date of documented relapse of any type for subjects who achieve CRc or PR [relapse date – (first CRc or PR disease assessment date )+ 1]. Subjects who die without report of relapse are considered nonevents and censored at their last relapse-free disease assessment date [last relapse-free disease assessment date – (first CRc or PR disease assessment date) + 1]. Other subjects who do not relapse on study are considered nonevents and censored at the last relapse-free assessment date.

**Duration of Remission**

Duration of remission includes duration of CRc (DCRc), duration of CR/CRh (DCR/CRh), duration of CRh (DCRh), duration of CR (DCR), duration of CRi (DCRi), duration of CRp (DCRp), and duration of response (DR) (i.e. CRc + PR).

### 5.1.5 Transplantation Rate

Transplantation rate is defined as the percentage of subjects undergoing HSCT during the study period i.e. the number of subjects undergoing HSCT during the study period divided by the number of subjects in the analysis population.

### 5.1.6 Survival Status and Subsequent Antileukemic Treatments and Their Outcomes

Information on survival status, subsequent antileukemic treatments and outcomes will be collected for all subjects.

The first survival status will occur at the 28 day follow-up visit where telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related adverse events (AEs).

After the 28 day follow-up visit, the subject or caregiver will continue to be contacted via telephone by site personnel for follow-up every 3 months for up to 2 years. Data may be supplemented by site records when available at the time of the contact (e.g., treatment records, outcomes). Follow-up will continue until the final database lock, which is estimated to be up to 2 years of follow-up post completion of treatment.

If a subject death occurs during the serious adverse event (SAE) reporting period or if the death occurs after the SAE reporting period, but is determined by the investigator to be possibly related to study drug, then the associated AE with outcome of death will also be reported on the case report form (CRF) and SAE form. If a subject death does not meet the criteria of an SAE, then death and antileukemic treatment and outcome up through the date of death should be collected and entered in CRF.

## 5.2 Safety Endpoints

Safety will be assessed by evaluation of the following variables listed in this section; for a detailed explanation of how these variables will be collected and analyzed, see section 6.5 Analysis of Safety.

### 5.2.1 Adverse Events (AEs)

An adverse event (AE) is any untoward medical occurrence in a subject administered a study drug, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

AE collection begins after the signing of the informed consent and will be continued until 28 days after the last dose of study drug (or until the 28-day follow-up visit of the subject, whichever is later) or the subject is determined to be a screen failure.

The coding dictionary for this study will be the Medical Dictionary for Regulatory Activities (MedDRA). It will be used to summarize AEs by system organ class (SOC) and preferred term (PT).

#### Treatment-Emergent Adverse Events (TEAEs)

A treatment-emergent adverse event (TEAE) is defined as an adverse event observed after starting administration of the study treatment (gilteritinib and/or FLAG) until 30 days after the last dose of study treatment. All TEAEs will be collected and analyzed based on: frequency, CTCAE grade, seriousness, and relationship to study drug.

If an adverse event occurs on Day -1 (dose escalation phase) or Cycle 1 Day 1 (dose expansion phase) and the onset check box is marked “Onset after first dose of study drug” or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day -1(dose escalation phase) or Cycle 1 Day 1 (dose expansion phase) and the onset check box is marked “Onset before first dose of study drug”, then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the pre-investigational period and during the investigational

period, the event will be considered as TEAE only if it has worsened in severity (i.e. it is reported with a new start date).

All adverse events collected that begin within 30 days after taking the last dose of study drug will also be counted as TEAE, except for subjects that undergo HSCT without leaving the study and plan to resume study treatment after HSCT. For these subjects, TEAE is defined as:

- adverse events observed after starting administration of the study treatment until the last dose before on study HSCT plus 30 days whichever comes first, or
- adverse events that begin after resumption of study treatment and within 30 days after the last dose of study drug

Any AEs with onset dates completely missing will be considered TEAEs in summaries. AEs with partially missing onset dates will be assumed TEAEs unless the available portion of the date indicates that the onset was strictly before start of study medication.

A drug-related TEAE is defined as any TEAE with at least possible relationship (possibly or probably related) to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

**Serious Adverse Events (SAEs)**

An AE is considered "serious" if include adverse events that are flagged as serious by the investigator on eCRF, or upgraded according to the Important Medical Event process.

**Adverse Events of Special Safety Interest (AESI)**

Adverse events of special safety interest (AESI) are defined in the Safety Review Plan for gilteritinib. Targeted medical events are identified using MedDRA preferred terms, MedDRA Queries (SMQs), and laboratory filters. Details are provided in table 4 below.

**Table 4 Special Safety Interest AEs for Gilteritinib**

| **Targeted Medical Event** | **Search Strategy (MedDRA Preferred Terms, MedDRA SMQ, and/or Lab Filter)** |
|---|---|
| Acute Renal Failure | Acute Renal Failure (SMQ) |
| Anaphylactic reaction | Anaphylactic reaction (SMQ) |
| Cardiac Failure | Cardiac failure (SMQ) |
| Creatine Phosphokinase Increased | Rhabdomyolysis/myopathy (SMQ) |
| Diarrhea | Noninfectious diarrhoea (SMQ) |
| Differentiation syndrome[1] | Differentiation syndrome |

| | |
|---|---|
| Gastrointestinal obstruction | Gastrointestinal obstruction (SMQ) |
| Gastrointestinal perforation | Gastrointestinal perforation (SMQ) |
| Liver Transaminase Increased | Liver related investigations, signs and symptoms (SMQ) |
| Myalgia, Myositis, and Muscular weakness | Rhabdomyolysis/myopathy (SMQ) |
| Pancreatitis | Acute pancreatitis (SMQ),<br>Acute and chronic pancreatitis |
| Pericarditis/Pericardial Effusion | Noninfectious pericarditis (HLT),<br>Pericardial effusion (PT) |
| Posterior Reversible Encephalopathy Syndrome (PRES) | Noninfectious encephalopathy/delirium (SMQ) |
| QT Prolongation | Torsade de pointes/QT prolongation (SMQ) |
| Teratogenicity and Embryo-Fetal Deaths | Teratogenicity and Embryo-Fetal Deaths [Pregnancy and neonatal topics (SMQ) (Broad) (but without Normal pregnancy conditions and outcomes (SMQ))] |

1.Only AEs that occur within the first 90 days.

### 5.2.2 Dose-limiting Toxicity (DLT)

A dose-limiting toxicity (DLT) event is defined as any event meeting the DLT criteria (outlined in section 5.2.2.2) that occurs during the observation period and that is considered to be possibly or probably related to gilteritinib.

**DLT Observation Period**

The DLT observation period will be 28 days from the start of cycle 1 day 1; for the first cycle only.

**DLT Criteria**

Nonhematologic Dose-limiting Toxicity

Nonhematologic Dose-limiting Toxicity will be defined as grade 3 nonhematologic toxicity at least possibly related to protocol therapy that persists for > 48 hours without resolution to grade ≤ 2 or grade 4 nonhematologic toxicity, regardless of duration, at least possibly related to protocol therapy. Hy's law (as defined in [Section 12.5 of the protocol]) or treatment-related deaths will be considered as a DLT. Gilteritinib dosing will be interrupted if nonhematologic

DLT occurs. Exceptions include the following toxicities commonly seen with intensive AML reinduction regimens:

- Alopecia, anorexia, or fatigue.
- Grade 3 vomiting or diarrhea that resolves (with or without supportive care) to ≤ grade 2 within 48 hours
- Grade 3 nausea that resolves (with or without supportive care) to ≤ grade 2 within 7 days
- Grade 3 elevation in total bilirubin (TBL) that is asymptomatic and that returns to ≤ grade 2 elevation within 7 days
- Grade 3 elevation in hepatic transaminases (ALT/SGPT, AST/SGOT and gamma-glutamyl transferase [GGT]) or Alkaline Phosphatase (ALP) level that returns to ≤ grade 2 elevation within 14 days
- Grade 3 fever with neutropenia, with or without infection
- Grade 3 infection or grade 4 infections expected as direct complication of cytopenia due to active underlying leukemia
- Grade 3 mucositis

Hematologic Dose-limiting Toxicity

Hematologic Dose-limiting Toxicity will be defined as failure to recover a peripheral absolute neutrophil count (ANC) > 500/µL and non-transfusion dependent platelet count > 20000/µL due to documented bone marrow aplasia/hypoplasia at day 42 from the start of cycle 1 day 1.

Failure to recover peripheral counts due to disease involvement of the bone marrow will not be considered as a DLT.

### 5.2.3 Vital signs

Vital signs, including systolic and diastolic blood pressures (mmHg), radial pulse rate (beats per minute), respiratory rate, $O_2$ saturation and temperature will be obtained and recorded at the times specified in the Schedule of Assessments [Table 1]. All vital sign measurements will be obtained with the subject in the sitting or supine position.

### 5.2.4 Laboratory Assessments

The laboratory tests that will be performed during the conduct of the study are described below [Table ]. Safety assessments will be obtained using local laboratories. See Schedule of Assessments [Table 1] for study visit involving sample collection. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician.

**Table 5 Laboratory Tests Performed During the Conduct of the Study**

| Panel/Assessment | Parameters to be Analyzed | Estimated sample volume |
|---|---|---|
| Hematology | White Blood Cell Count (WBC)<br>WBC Differential<br>Red Blood Cell Count (RBC)<br>Hemoglobin (Hgb)<br>Hematocrit (Hct)<br>Mean Corpuscular Volume<br>Platelet Count<br>MCHC<br>MCH | 1.0 mL of whole blood |
| Biochemistry | Sodium<br>Potassium<br>Chloride<br>Bicarbonate<br>Blood Urea Nitrogen<br>Creatinine<br>Glomerular filtration rate<br>Uric acid†<br>Glucose<br>Calcium<br>Phosphate<br>Magnesium<br>Albumin<br>Total Protein<br>Alkaline Phosphatase<br>Lactate Dehydrogenase<br>Creatine Phosphokinase<br>Triglycerides<br>Total Cholesterol<br>Liver Function Tests including:<br>Total Bilirubin<br>Alanine Aminotransferase<br>Aspartate Aminotransferase | 1.1 mL of whole blood |
| Thyroid Function Tests | TSH<br>Free T4 | 2.5 of whole blood |
| Serum Pregnancy Test | Human Chorionic Gonadotropin or alternatively pregnancy dipstick can be used | 1.4 ml of whole blood |
| Coagulation Profile | INR (with PT if reported)<br>aPTT<br>Fibrinogen (Screening Only)<br>D-dimer (Screening Only) | 2.0 mL of whole blood |

*Table continued on next page*

| Panel/Assessment | Parameters to be Analyzed | Estimated sample volume |
|---|---|---|
| Urinalysis | Color<br>Appearance<br>Specific Gravity<br>pH<br>Bilirubin<br>Blood<br>Glucose<br>Ketones<br>Leukocyte Esterase<br>Nitrite<br>Protein<br>Urobilinogen | Dipstick |
| Bone Marrow | Blast Count and Cell Counts^^<br>Flow Cytometry for Blasts<br>MRD<br>FLT3 Mutation Status | Bone marrow aspirate 1 to mL in EDTA tube. If aspirate is unavailable, then biopsy and whole blood is required.<br>2 to 3 bedside bone marrow aspirate smear slides in addition to the sample (aspirate/biopsy and whole blood) |
| Bone Marrow Aspirate and/or Blood** | FLT3 Mutation Analysis | Bone marrow aspirate 0.25 mL to 0.75 mL or in the event of dry tap 1 to 3 mL of peripheral blood |
| PIA & FLT3 Ligand | FLT3 inhibition (PIA)<br>FLT3 Ligand | 2 mL of whole blood |
| PK | Gilteritinib | 1.0 mL of whole blood |
| PGx | Pharmacogenomics Analysis | 3 mL of whole blood and a buccal swab sample |
| aPTT: activated partial thromboplastin time; eCRF: Electronic Case Report Form; FLT3: FMS-like tyrosine kinase; INR: international normalization ratio; MRD: minimal residual disease; PK: pharmacokinetics; PGx: Pharmacogenomics; PIA: plasma inhibitory assay; PT: prothrombin time; T4: thyroxin; TSH: thyroid stimulating hormone.<br>† On days 1, 4, 8 and 15 in cycle 1 of phase 1 or phase 2.<br>** Screening only<br>^^ In addition to the central read of these values, available local results will also be entered into the electronic case report form. | | |

### 5.2.5 Physical Examination

Standard, full physical examinations will be performed to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status, and lymphatic systems. Genitourinary and rectal system exam are to be performed only if clinically indicated. Height and weight will be measured at Screening and on Day 1 of each cycle.

### 5.2.6 Electrocardiogram

A 12-lead ECG will be performed as outlined in the Schedule of Assessment [Table 1] using a central ECG reading laboratory. Predose assessments should be taken within 1 hour prior to study drug administration.

### 5.2.7 Imaging

#### Chest X-ray or Computed Tomography Scan

Local chest X-ray or computed tomography (CT) scan is to be performed at screening. A chest X- ray (or CT of chest) performed as part of routine patient management within 2 weeks prior to start of screening can be used if available.

#### Multigated Acquisition Scan (MUGA) or Echocardiogram (ECHO)

A local MUGA scan or ECHO is to be performed as outlined in the Schedule of Assessment [Table 1], i.e., at screening and $EOT_1$ for each subject. Additional MUGA scans or ECHO will be performed while on study treatment when clinically indicated.

### 5.2.8 Order of Assessments

#### Predose Assessments

Predose indicates dosing prior to gilteritinib or chemotherapy. The following sequence order for study activities is recommended during cycle 1 and 2 of phase 1 or 2:

- Vitals signs
- Triplicate ECGs (within 1 hour prior to dosing)
- Any type of blood draw (includes clinical laboratory tests, thyroid function test, pharmacokinetic sample, PIA/FLT3 Ligand sample, Pregnancy test)

#### Postdose Assessments

The postdose assessments includes pharmacokinetic samples and ECG. Triplicate ECGs are to be obtained within 1 hour prior to the time-matched pharmacokinetic sample during cycle 1 and 2 of phase 1 or 2.

## 5.3 Pharmacokinetic Endpoints/Variables

Plasma concentrations of gilteritinib will be evaluated for the escalation (phase 1) and expansion (phase 2) phases as outlined in Schedule of Assessments [Table 1].

For phase 1 and phase 2, pharmacokinetic samples will be collected in cycle 1 and cycle 2 at the following time points:

- Cycle 1 day 8 – Predose
- Cycle 1 day 15 (±2 days) – Predose
- Cycle 1 day 21 (±2 day) – Predose and 4 to 6 hours

- Cycle 2 day 15 (±2 days) – Predose

Predose samples should be collected within 1 hour prior to dosing. For each sample, 1.0 mL of blood will be collected and processed.

Plasma samples may also be used for metabolite profiling of gilteritinib. The reports for the metabolite profiling and identification will not be incorporated to the clinical study report.

The following PK parameters will be determined:

Dose Escalation Phase

- Cycle 1 day 21(±2 days):
    - steady state $C_{max}$ and $C_{trough}$

## 5.4 Pharmacodynamic Endpoints/Variables

Pharmacodynamic variables are exploratory endpoints of the study. Blood samples will be analyzed for PIA and FLT3 ligand assay in relation to dose and clinical response if sufficient sample for FLT3 ligand will be presented.

## 5.5 Additional Endpoints/Variables

### 5.5.1 Bone Marrow Aspiration and/or Biopsy Assessments

Bone marrow samples are required during screening and end of each cycle (C1D28 and C2D28) for phase 1 and phase 2.

For subjects whose response assessment is not evaluable due to hypocellularity, a repeat bone marrow analysis should be performed at least every 14 days until response determination is possible.

For LTT, bone marrow assessments will be performed on C1D1 and repeated after every 3 cycles until 1 year of LTT, followed by after every 6 cycles until 2 years of LTT (i.e., C1D1, C4D1, C7D1, C10D1, C13D1, C19D1 etc.). Bone marrow samples are also required at the pre-HSCT /end of treatment visit and as clinically indicated. Bone marrow assessments does not need to be repeated if collected within 2 weeks of the $EOT_2$ Visit. If bone marrow aspirate is unobtainable (e.g., dry tap), an additional EDTA tube of whole blood should be collected instead. Bone marrow aspirate is required, and bone marrow biopsy is preferred. In case of inadequate aspirate, bone marrow biopsy is required.

### 5.5.2 Exploratory Biomarker Analysis

Any exploratory biomarker analysis performed for this study may be further described in a separate biomarker SAP.

#### FMS-like Tyrosine Kinase (FLT3) Gene Mutation Status

Mutation types (internal tandem duplication [ITD] alone or ITD with concurrent TKD [D835/I836]) and frequency, along with mechanisms of acquired resistance, will be measured in both bone marrow and blood samples at screening/baseline and $EOT_1$ for phase 1 and phase 2 (at a minimum – see the Schedule of Assessments [Table 1] for details). Subgroup analysis for both efficacy and safety will be performed based on baseline status.

#### Minimal Residual Disease (MRD)

FLT3 mutation allelic frequencies will be measured in relation to total FLT3 in both bone marrow and blood samples. MRD analysis will be carried out at the time points defined in the Schedule of Assessments [Table 1]. It is possible that bone marrow samples will be analyzed for MRD at other timepoints. Blood samples may be analyzed for MRD at any time point. Changes in FLT3 mutation allelic frequencies from baseline will be compared.

FLT3-ITD signal ratio is defined as the ratio of FLT3-ITD sequence reads divided by the total number of FLT3 sequence reads. This is being calculated by central laboratory. For subjects with more than one FLT3-ITD variant, the FLT3-ITD signal ratio will be summed at each timepoint.

MRD negative is defined as summed FLT3-ITD signal ratio of any post-baseline sample ≤10^(-4). MRD positive is defined as summed FLT3-ITD signal ratio of any post-baseline sample>10^(-4).

#### Other Possibly Predictive Biomarkers

Blood and bone marrow samples may be analyzed for mutations in AML-related genes and changes in proteins in relation to treatment effects at screening/baseline and $EOT_1$ for phase 1 and phase 2, and may be analyzed for mutations in AML related genes and changes in proteins in relation to treatment effects at other time points.

### 5.5.3 Dose Exposure

Dose exposure variables will be collected and considered for gilteritinib and FLAG. The following variables will be calculated based on the dose exposure:

#### Duration of Exposure

Duration of exposure to each treatment will be calculated in days, using the following formula:

- Duration of exposure for each treatment cycle is defined as Last dose date - First dose date + 1 - (on-study HSCT period for subjects undergo on-study HSCT) for each

cycle. For Phase1 part, last dose date of study drug exposure = (initial dose date of the cycle + 14 – 1) if last dose date of the cycle is not captured on dosing CRF.

- Duration of exposure for each treatment period is calculated as sum of the duration of exposure for each treatment cycle.

When the last date of exposure is beyond cutoff date, the cutoff date will be used as the last date of exposure. When the start or stop date is missing, then the exposure will be treated as missing.

**Number of dosing days (days)**

Number of dosing days is defined as number of days with non-zero dosing.

Number of dosing days is calculated for each treatment period.

**Cumulative Dose**

Cumulative dose (mg) = sum of all doses of study drug taken during the study.

- ASP2215: Sum of (actual dose level * number of dosing days within each dose level)
- Chemotherapy: Sum of actual dose across the days when administered.

Actual dose is calculated as:

(Actual volume administered / Total volume prepared)* Intended dose * Body surface area.

If number of doses taken is unknown, it will be treated as missing.

Cumulative dose is calculated for each treatment period.

**Average of daily dose (mg/day or g/day)**

Defined as cumulative dose divided by number of dosing days.

Average of daily dose is calculated for each treatment period.

**Dose intensity (mg/day or g/day)**

Represents unit of dose given to a patient per unit of time, calculated as cumulative dose divided by duration of exposure.

Dose intensity is calculated for each treatment period.

**Relative dose intensity (%)**

Defined as dose intensity divided by planned dose intensity * 100%.

Relative dose intensity is calculated for each treatment period.

Where planned dose intensity (mg/day or µg /day) will be calculated as follows:

- ASP2215: 1 / 2 / 3 mg/kg * Weight depends on Group
- Fludarabine for Phase 1 and 2: 30 mg/m^2 * BSA
- Cytarabine for Phase 1 and 2: 2000 mg/m^2 * BSA

- G-CSF for Phase 1 and 2: 5 µg/kg * Weight

Average of BSA or Weight and Calculated Dose across the days when administered will be used in the calculation of planned dose intensity.

### 5.5.4 Other Variables

**Body Mass Index (BMI)**

Body mass index will be calculated based on a subject's height and weight using the formula BMI = weight (kg) / [height (m)]$^2$.

**Duration of AML**

Duration of AML will be calculated in days using the following formula:

(Enrollment date – date of initial diagnosis of AML) + 1.

**Previous and Concomitant Medication/Transfusion**

Previous medication is defined as medication with at least one dose taken before the date of the first dose of study drug.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug.

Previous transfusion is defined as transfusion received before the date of first dose of study drug, i.e. transfusion completed before the date of first dose.

Concomitant transfusion is defined as transfusion received between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug.

**Baseline Hepatic Function Group**

Baseline hepatic function group is defined per the NCI-ODWG criteria based on total bilirubin and aspartate aminotransferase (AST) at the baseline from central lab as follows:

Normal: total bilirubin <= ULN and AST <= ULN

Mild HD: ULN < total bilirubin < = 1.5 x ULN or AST > ULN

Moderate HD: 1.5 x ULN < total bilirubin <= 3 x ULN, any AST

Severe HD: 3 x ULN < total bilirubin <= 10 x ULN, any AST

**Baseline Renal Function Group**

Baseline rental function group is defined using baseline estimated glomerular filtration rate eGFR as follows:

Normal: eGFR >= 90

Mild: 60 <= eGFR < 90

Moderate: 30 <= eGFR < 60

Severe: eGFR < 30

eGFR is estimated by modification of diet in renal disease (MDRD) formula as follows:

eGFR (mL/min/1.73 $m^2$) = 175 x (serum creatinine in mg/dL)$^{-1.154}$ x (age in years)$^{-0.203}$ x 0.742(if female) x 1.212(if African American)

Serum creatinine values from central lab will need to be converted from micro moL/L to mg/dL (1 mg/dL = 88.4 micro mol/L).

# 6 STATISTICAL METHODOLOGY

## 6.1 General Considerations

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g.10%, 25%, 75% and 90%) will be mentioned in the relevant section. In addition, for plasma concentrations and continuous PK parameters, the coefficient of variation and the geometric mean will also be calculated. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%. Kaplan-Meier survival curves will be displayed for time-to-event variables and median survival time will be estimated with 2-sided 95% confidence interval (CI).

Summaries based on FAS (e.g. disposition, baseline and efficacy data) will be presented by planned dose level, unless specifically stated otherwise. Safety analysis, exposure information, and other summaries based on SAF will be presented by actual dose level received. Pharmacokinetic summaries based on PKAS and pharmacodynamic summaries based on PDAS will be presented by actual dose level received. For subjects with dose increase/decrease, actual dose level refers to the initial dose level received before dose change.

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 or higher on Unix. Specifications for table, figure, and data listing formats can be found in the TLF specifications for this study.

Baseline is defined as the last available measurement prior to the first dose of study drug. Unless otherwise specified, all summaries and analysis will be presented by phase and dose level.

For the definition of subgroups of interest please refer to section 6.9 Subgroups of Interest.

## 6.2 Study Population

### 6.2.1 Disposition of Subjects

The following subject data will be presented for all enrolled subjects:

- Number and percentage of subjects with informed consent, discontinued before allocation to treatment, allocated to treatment (overall only);
- Number and percentage of subjects allocated to treatment in each analysis set, by phase, dose level and overall;
- Number and percentage of subjects completed and discontinued treatment, by primary reason for treatment discontinuation for FAS, by phase and dose level;
- Number and percentage of subjects completed and discontinued the study, by primary reason for study discontinuation for FAS, by phase and dose level;
- Number and percentage of subjects completed and discontinued the post-study period, by primary reason for post-study period discontinuation for FAS, by phase and dose level.

### 6.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.3 Major Protocol Deviations) will be assessed for all subjects allocated to treatment. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by phase, dose level, and total as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

### 6.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by dose level for the SAF using descriptive statistics.

Number and percentage of subjects allocated to treatment in each country and site will be presented by phase and dose level for the SAF.

Descriptive statistics for age, weight, BMI and height at study entry will be presented. Frequency tabulations for sex, ethnicity, age group (defined in section 6.9) and race will be

presented. This will be done for the subjects not allocated to treatment (screen failures), as well as for the SAF, FAS by phase and dose level.

Baseline hepatic function and renal function will be summarized using frequency tables by phase and dose level for SAF.

Frequency tabulations for AML disease history including AML subtype as classified by World Health Organization (WHO) classification and French-American-British (FAB) classification, risk status, antecedent hematological disorder, central nervous system leukemia, local FLT3-ITD mutation status, local FLT3 point mutation status will be presented by phase and dose level for the SAF.

Medical history other than AML and conditions existing at baseline will be coded in MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by phase and dose level for the SAF. Baseline conditions are defined as those ongoing at the time of informed consent or arise following the time of informed consent and before the first dose of study drug. For ongoing medical conditions, Common Terminology Criteria for Adverse Events (CTCAE) grade will be provided in listing.

### 6.2.4 Previous and Concomitant Medications

Previous medications are coded with WHO-DD, and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by phase and dose level for the SAF.

As with previous medication, concomitant medication will be summarized for each phase and dose level by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

### 6.2.5 Previous and Concomitant Treatment (Medication and Non-Medication)

Frequency tabulations of subjects received transfusions and blood product will be presented for previous transfusion and concomitant transfusion by phase and dose level for SAF. Descriptive statistics will be presented for number of transfusion unit received per subject.

Previous and concomitant treatment (medication and non-medication) for SAF will be provided in listing.

For subjects who undergo on-study HSCT, HSCT conditioning regimen and post-HSCT re-eligibility assessment for resuming study drug will be provided in listings.

## 6.3 Study Drugs

### 6.3.1 Exposure

The following information on FLAG and gilteritinib drug exposure will be presented by phase and dose level for the SAF:

- Descriptive statistics for cumulative amount of the drug subject was exposed to, number of dosing days (for gilteritinib only), average of daily dose (for gilteritinib only), dose intensity, and relative dose intensity; and
- Number and percent of subjects with dose increases, decreases or interruptions, including the number of intra-subject dose reductions.

Duration of exposure will be summarized in two ways.

- Descriptive statistics will be presented by phase and dose level.
- Exposure time will be categorized according to the following categories by phase and dose level (for giltertinib only):
  - less than or equal to 5 days
  - at least 6 days, less than 28 days
  - at least 28 days, less than 84 days
  - at least 84 days, less than 168 days
  - 168 days or more
  - Unknown.

Counts and percentages of subjects in each of these categories will be summarized by phase and dose level for the SAF.

Listing of subjects with dose interruption and dose reduction will also be provided.

Descriptive statistics for duration of exposure, cumulative amount of the drug subject was exposed to and average daily dose will be presented for FLAG by cycle, phase and dose level for the SAF.

## 6.4 Analysis of Efficacy

The efficacy analysis will be conducted on the FAS unless specified otherwise. The interpretation of results from statistical tests will be based on the FAS.

### 6.4.1 Analysis of Primary Efficacy Endpoint

#### Best Overall Response

Best response will be summarized by phase and dose level for the FAS. The number and percentage of subjects in each category will be presented along with 2-sided exact 95% confidence interval.

Derived and investigator-assessed responses will be performed.

**Complete Remission Rate**

The CR rate will be evaluated according to Simon's minimax two-stage design (Simon, 1989). The null hypothesis H0 for CR is that the true CR rate is $p0 \leq 0.14$, and the alternative hypothesis H1 is that the true CR rate is $p1 \geq 0.30$.

H0: $p0 \leq 0.14$

H1: $p1 \geq 0.30$

In stage I, a total number of 22 patients is accrued. If there are 3 or fewer CR responses among these 22 patients, the study will be early stopped. Otherwise, an additional 30 patients will be accrued in stage II, resulting in a total number sample size of 52. If there are 13 or more CR or 24 CRc responses among these 52 patients, we reject the null hypothesis. The design controls the type I error rate at 0.025 and yields the power of 0.8.

The CR rate and the CRc rate will be summarized and its 95% confidence interval will be constructed by Clopper-Pearson method.

Derived and investigator-assessed responses will be performed.

### 6.4.2 Analysis of Secondary Efficacy Endpoints

**Minimal Residual Disease (MRD)**

MRD analysis will be conducted on the MAS. MRD will be assessed in relation to the following efficacy variables:

- CR rate
- CRc rate
- Overall survival (OS)

MRD negative status will be defined as FLT3-ITD signal ratio $\leq 10^{-4}$. Other FLT3-ITD signal ratio cut points may be assessed.

**Overall Survival**

The time of OS will be summarized using descriptive statistics. The survival curve and median for time-to-event variables and OS rates at 6 months/1 year/2 years will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval.

**Event-free Survival**

The time of EFS will be summarized using descriptive statistics. The survival curve and median for time-to-event variables and EFS rates at 6 months/1 year/2 years will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval.

**FLT3 Mutation Status and PIA**

FLT3 mutation status and the mutational status of other AML-related genes will be classified as either 'positive' or 'negative' by the local institution at screening/baseline and EOT (for patients who relapse), and will be assessed in relation to the following efficacy variables:

- CR rate
- CRc rate
- Overall survival (OS)

Plasma inhibitory activity assay as compared to baseline sampling will be summarized at each time point by phase and dose levels.

Further analyses may be performed to explore relationships between mutational status and changes in proteins in relation to pharmacodynamic parameters and clinical response.

### 6.4.3 Analysis of Exploratory Efficacy Endpoints

#### Leukemia-Free Survival

The time of LFS will be summarized using descriptive statistics. The survival curve and median for time-to-event variables and 1 year LFS rate will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval.

#### Duration of Remission

The duration of remission will be summarized for each remission category on the FAS. The number and percentage of subjects in each category will be presented along with 2-sided exact 95% confidence interval.

#### Time to Remission

The time to remission will be summarized for each remission category on the FAS. The number and percentage of subjects in each category will be presented along with 2-sided exact 95% confidence interval.

#### Best Overall Response

Best response will be summarized by phase and dose level for the FAS. The number and percentage of subjects in each category will be presented along with 2-sided exact 95% confidence interval.

Derived and investigator-assessed responses will be performed.

#### Transplantation Rate

Transplantation rate will be summarized by phase and dose level for the FAS. The number and percentage of subjects in each category will be presented along with 2-sided exact 95% confidence interval.

#### FLT3 Ligand

If sufficient sample will be available increase in FLT3 ligand as compared to baseline sampling will be summarized at each time point by phase and dose levels.

## 6.5 Analysis of Safety

All analysis of safety will be presented by phase and dose level for SAF, unless specified otherwise. Safety endpoints are considered the primary endpoints for this study.

### 6.5.1 Adverse Events

For the purpose of safety assessments in this study, events recorded during the pre-investigational period will be classified as Baseline Signs and Symptoms. All adverse event (AE) recorded on treatment (gilteritinib and/or FLAG) including within 30 days from the last study treatment (i.e. all TEAEs) will be summarized.

Summaries and listings of SAEs and Serious TEAEs include SAEs upgraded by the sponsor according to the Important Medical Event process if any upgrade was done.

The coding dictionary for this study will be MedDRA 27.0. It will be used to summarize TEAEs by SOC and PT. TEAEs will be graded using National Cancer Institute's Common Terminology Criteria for AEs (NCI-CTCAE) version 5.0.

An overview table will include the following details by phase and dose level:

- Number and percentage of subjects with TEAEs,
- Number and percentage of subjects with causally drug related TEAEs,
- Number and percentage of subjects with serious TEAEs and Astellas upgraded serious TEAE,
- Number and percentage of subjects with serious drug related TEAEs and Astellas upgraded serious drug related TEAE,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with drug related TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with grade 3 or higher TEAE,
- Number and percentage of deaths.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by phase and dose level. Summaries will be provided for:

- TEAEs
- drug related TEAEs,
- serious TEAEs and Astellas upgraded serious TEAE,
- drug related serious TEAEs and drug related Astellas upgraded serious TEAE,
- TEAEs leading to permanent discontinuation of study drug,
- drug related TEAEs leading to permanent discontinuation of study drug,
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5% in any dose level,
- common TEAEs that equal to or exceed a threshold of 5% in any dose level,
- Grade 3 or higher TEAEs.

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized by phase and dose level.

AE summary tables will include subject counts as opposed to AE counts. If a subject experiences more than one episode of a particular AE, that subject will be counted only once for that event. If a subject has more than one AE that code to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a body system, the subject will be counted only once in that body system.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by NCI-CTCAE severity grade and by relationship to study drug. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity grade or relationship, then the subject will be counted only once with the worst severity grade and highest degree of relationship. However, if any of the severity grade or relationship values are missing then the subject will be counted only once with missing severity grade or relationship. Drug related TEAEs will be presented in a similar way byseverity grade only.

The number and percentage of subjects with AESIs, as classified by PT, will be summarized by phase and dose level.

All AEs, deaths, SAEs, withdrawals due to adverse events, AEs during on-study HSCT period will be displayed in listings.

### 6.5.2 Dose-limiting Toxicity (DLT)

A DLT event, as defined in protocol Section 2.3.2 Dose Limiting Toxicity Criteria and outlined in section 5.2.2 of this SAP, will be summarized by dose level. Details of DLTs will be presented in listings and subject narratives.

### 6.5.3 Clinical Laboratory Evaluation

The baseline visit is the last measurement taken prior to initial study drug administration.

Quantitative clinical laboratory variables, i.e. hematology, biochemistry, coagulation and urinalysis will be summarized using mean, standard deviation, minimum, maximum and median by phase and dose level at each visit. Additionally, a within-subject change in baseline will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

The number and percentage of subjects below and above reference range will be summarized for each phase and dose level at each visit.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented by phase and dose level at each visit.

For hematology and biochemistry two types of shift tables will be presented:

- Shift tables of reference range changes from baseline to each treatment visit (low, normal, high) as well as worst finding during the treatment period, and
- Summary shifts of reference range changes from baseline to each treatment visit (shift from normal or high to low, shift from normal or low to high, categorized increase [shift from low to normal or from normal to high], categorized no change [value stays in the same reference range], categorized decrease [shift from high to normal or from normal to low]).

Laboratory results will also be graded using NCI-CTCAE version 5.0, where possible. Parameters that have criteria available for both low and high values, i.e., hypo- and hyper-, will be summarized for both criteria. The same subject can be counted for both values if the subject has different laboratory values meeting each criterion. NCI-CTCAE grade of laboratory evaluations will be summarized by number and percentage of subjects for each visit. Shift tables of NCI-CTCAE grade change from baseline to worst post-baseline grade will also be presented.

Laboratory results based on central assessment will be used for summaries as described above. Laboratory results based on local assessment and bone marrow results will be listed only. The laboratory results may be displayed in figures.

**Liver Enzymes and Total Bilirubin**

The following potentially clinically significant criteria in liver function tests for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are given in , below. The subject's highest value during the investigational period will be used.

**Table 6 Liver Function Test Criteria**

| Parameter | Criteria |
|---|---|
| ALT | > 3xULN<br>> 5xULN<br>> 10xULN<br>> 20xULN |
| AST | > 3xULN<br>> 5xULN<br>> 10xULN<br>> 20xULN |
| ALT or AST | > 3xULN |
| Total Bilirubin | > 2xULN |
| ALP | > 1.5xULN |
| ALT and/or AST AND Total Bilirubin(*) | (ALT and/or AST > 3xULN) and (Total bilirubin > 2xULN) |

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver enzymes and total bilirubin during the investigational period will be presented by phase and dose level.

### 6.5.4 Vital Signs

The baseline visit is the last measurement taken prior to initial study drug administration.

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and body temperature) will be summarized using mean, standard deviation, minimum, maximum and median by phase, dose level and visit. Additionally, a within-subject change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by phase, dose level and visit.

Tables for potentially clinically significant vital signs will be generated using the highest value obtained during treatment for each subject for each phase and dose level. Note that for pediatric studies, potentially clinically significant vitals are dependent on the age, sex, and height (or height percentile) of each subject. Including subjects with overweight and obesity will create potential bias.

The following potentially clinically significant blood pressure (SBP/DBP) criteria are defined based on 90th blood pressure percentiles with 50th height percentile in normal-weight children. Formal categorization of subjects will be done by comparing subject vital sign measurements to the cutoff values provided in complete pediatric blood pressure tables, which consider the age, sex, and height of each subject (see BP Level for Boys/Girls by Age and Height Percentile tables [Flynn, Joseph et. al., 2017] Appendix 9.1). :

**Table 7 Potentially Significant Vital Sign Criteria**

| Age category | Age Subcategory | Criteria |
|---|---|---|
| 6mo - <1 year | >0.5- <1* | Boys: SBP ≥ 100 mmHg and/or DBP ≥ 53 mmHg<br>Girls: SBP ≥ 100 mmHg and/or DBP ≥ 56 mmHg |
| 1 - 2 years | ≥1 - <2* | Boys: SBP ≥ 100 mmHg and/or DBP ≥ 53 mmHg<br>Girls: SBP ≥ 100 mmHg and/or DBP ≥ 56 mmHg |
| | 2 | Boys: SBP ≥ 102 mmHg and/or DBP ≥ 56 mmHg<br>Girls: SBP ≥ 103 mmHg and/or DBP ≥ 60 mmHg |
| >2 years | >2 - <13 | SBP, DBP, or both ≥90th percentile |
| | ≥13 | SBP ≥ 120 mmHG and/or DBP ≥ 80 mmHg |

*90th percentile at 1 year will be used for all subjects from ages ≥6 months to <2 years.

### 6.5.5 Electrocardiograms (ECGs)

12-lead ECGs will be recorded in triplicate at the scheduled time points in the Schedule of Assessments (Table 1). Each ECG tracing will be taken 5 minutes apart. ECGs will be read at the site for clinical decision making and transmitted to a central reviewer. Data from the

central reviewer will be used in summary presentations. The three values of each ECG parameter within a time point from the central reviewer will be averaged to determine time-specific parameter for a subject, and used in summaries.

ECG variables will be summarized using mean, standard deviation, minimum, maximum and median for each phase and dose level at each treatment visit and time point, including changes from baseline.

Number and percentage of subjects with normal and abnormal results as assessed by central review for the overall interpretation will be tabulated by phase and dose level at each treatment visit and time point. A shift analysis table showing shift in overall ECG interpretation from baseline to each time point will be provided. The worst of the three overall ECG interpretations will be used as the time-specific overall ECG interpretation for a subject.

The QT interval corrected for heart rate by Fridericia's formula, QTcF, is defined as: $QTc\ (F) = QT/(RR)^{0.33}$, where RR interval is inversely proportional to heart rate (approximately RR = 60/heart rate).

The QTcF interval will be summarized using frequency tables for each treatment visit and time point for values of clinical importance using the range criteria below.

**Table 8 QTc Interval Criteria**

| | QTc Interval Criteria Value (msec) | |
|---|---|---|
| | **Cumulative Category** | **Interval Category** |
| Normal | ≤ 450 | ≤ 450 |
| Borderline | > 450 | > 450 to ≤ 480 |
| Prolonged | > 480 | > 480 to ≤ 500 |
| Clinically significant | > 500 | > 500 |

The QTcF interval will also be summarized by the frequencies of subjects with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each treatment visit and time point.

**Table 9 QTc Interval Change from Baseline**

| | Change from Baseline | |
|---|---|---|
| **Variable** | **Cumulative Category** | **Interval Category** |
| QTc Interval (msec) | <0 | <0 |
| | ≥ 0 | ≥ 0 to ≤ 30 |
| | > 30 | > 30 to ≤ 60 |
| | > 60 | > 60 |

Number and percent of subjects with 12 lead ECG abnormalities as well as number and percent of subjects whose 12 lead ECG reading changed from normal at baseline to abnormal will be tabulated by phase and dose level at each treatment visit and time point.

### 6.5.6 Pregnancies

A detailed listing of all pregnancies will be provided.

## 6.6 Analysis of Pharmacokinetics (PK)

All pharmacokinetic analysis will be conducted on the PKAS.

### 6.6.1 Estimation of PK Parameters

Pediatic pharmacokinetic data from studies 2215-CL-0603 and 2215-CL-0604 will be used to establish a gilteritinib population pharmacokinetic model. The population pharmacokinetic plan and analysis of pharmacokinetic parameters will be provided in a separate document.

Subjects with sufficient PK samples will have PK parameter estimates for gilteritinib to include steady state $C_{max}$ and $C_{trough}$.

### 6.6.2 Statistical Analysis

#### Plasma Concentrations and Pharmacokinetics Parameters

Plasma concentrations and PK parameters will be summarized by age group (2-<6, 6-<12, 12-<18, 18-<22) and where appropriate by nominal time points (including visit and sample collection window) using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV). Time-course of drug concentrations obtained from serial PK sampling will be plotted by age group (spaghetti and mean plots).

Additional exploratory analyses may be performed after examination of the data.

## 6.7 Analysis of Pharmacodynamics

Pharmacodynamic (PD) analysis will be conducted on the PDAS.

PIA will be summarized descriptively using mean, standard deviation, minimum, median, maximum, geometric mean, and CV of the mean and geometric mean by phase and dose level at each visit.

Graphical assessment of percent inhibition vs. time will be evaluated on dose level.

Where time matched plasma concentration data are available, graphical assessment of percent inhibition vs. gilteritinib will be evaluated. If adequate data are available, mathematical models will be explored, e.g., logistic or Imax model, with an appropriate model selected based on overall goodness of fit, residual analysis, and precision of the parameter estimates.

Plasma inhibitory activity (PIA) will be explored in relation to clinical responses to gilteritinib therapy.

## 6.8 Analysis of Biomarkers

Analyses of associations between biomarkers listed in SAP section 5.5.2 and clinical results may be performed on subjects in the SAF who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest. Biomarkers may be summarized graphically or descriptively as they relate to clinical measures, as applicable. Summary statistics may be tabulated. Additional post-hoc analyses not specified in the protocol, such as alternative modeling approaches, may be conducted. All analyses described in this section are based on availability of the data. Additional details regarding exploratory biomarker analysis performed for this study may be provided in a separate biomarker SAP.

## 6.9 Subgroups of Interest

Descriptive analysis of subgroups will be presented. The subgroup variable for age is defined by three categories

- 6 months to less than 6 years of age,
- 6 years to less than 12 years of age, and
- 12 years to less than 18 years of age.

## 6.10 Other Analyses

### 6.10.1 Exploratory Biomarker Analyses

Exploratory biomarker variables is FLT3 mutation status.

FLT3 mutation status will be summarized by the number and percentage of subjects in each category by phase and dose level for each visit. FLT3 signal ratio based on central assessment, if available, will be summarized by phase and dose level.

Additional details regarding exploratory biomarker analysis performed for this study may be provided in a separate biomarker SAP.

### 6.10.2 PK-PD Analysis

#### Other Exposure–Pharmacodynamic Relationships

Additional exploratory analysis of PK-PD relationships may be conducted based on initial data assessment.

## 6.11 Interim Analysis (and Early Discontinuation of the Clinical Study)

The phase 2 portion of this study will be a 2-stage design [see Section 2.3.2). No other interim analysis is planned.

# 6.12 Handling of Missing Data, Outliers, Visit Windows, and Other Information

## 6.12.1 Missing Data

### Missing Dates

Every effort will be made to resolve incomplete dates for death and disease relapse. If a partial date cannot be resolved, the most conservative imputation methods will be used to complete the missing information.

For OS and EFS results, missing or incomplete death date will be imputed as the earliest feasible date on or after the date of last contact. The date of last contact will be obtained as described in Section 0.

Missing or partial start and stop dates of adverse events and concomitant medication will be imputed using the following algorithm:

- Imputation rules for partial or missing stop dates:
  - If the month and year are present, then impute as the last day of that month.
  - If only the year is present, impute as December 31 of that year.
  - If the stop date is entirely missing, assume the event or medication is ongoing.
- Imputation rules for partial or missing start dates:

| Start Date | | Stop Date: Complete: *yyyymmdd* | | Stop Date: Partial: *yyyymm* | | Stop Date: Partial: *yyyy* | | Stop Date: missing |
|---|---|---|---|---|---|---|---|---|
| | | < 1st dose | ≥ 1st dose | < 1st dose *yyyymm* | ≥ 1st dose *yyyymm* | < 1st dose *yyyy* | ≥ 1st dose *yyyy* | |
| Partial: *yyyymm* | = 1st dose *yyyymm* | 2 | 1 | 2 | 1 | n/a | 1 | 1 |
| | ≠ 1st dose *yyyymm* | | 2 | | 2 | 2 | 2 | 2 |
| Partial: *yyyy* | = 1st dose *yyyy* | 3 | 1 | 3 | 1 | n/a | 1 | 1 |
| | ≠ 1st dose *yyyy* | | 3 | | 3 | 3 | 3 | 3 |
| Missing | | 4 | 1 | 4 | 1 | 4 | 1 | 1 |

1 = Impute as the date of first dose; 2 = Impute as the first of the month; 3 = Impute as January 1 of the year; 4 = Impute as January 1 of the stop year

The imputed dates will be used to determine whether an AE is/is not treatment emergent.

Listings of AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

Concentrations below the lower limit of quantification (LLOQ) in PK should be assigned to be zero in the estimation of individual pharmacokinetic parameters.

#### Missing PK Data

In general, missing PK data should not be imputed if an appropriate method for imputation is not provided prospectively. Missing samples should not be assigned concentration values and consequently should not be included in the pharmacokinetic analysis.

#### Other Missing Data

Imputation methods for other missing data, if applicable, are described in individual sections.

### 6.12.2 Outliers

Outliers of individual plasma concentrations can be identified by pharmacokinetic plausibility (e.g. concentration at pre-dose) or by appropriate statistical methods, and the dataset which excludes outliers can be used to calculate pharmacokinetic parameters for primary analysis. An additional analysis may be conducted as exploratory analysis using the original dataset before excluding the outliers may be performed and the differences between their results may be discussed if primary analysis is performed without outliers. A listing of outliers must be described in the pharmacokinetic analysis report along with the reasons for exclusion.

All values will be included in the non-PK analyses.

### 6.12.3 Visit Windows

Visit windows are allowed for certain visits per the schedule of assessments. Subject data will not be excluded from analyses due to the subject's failure to comply with the visit schedule. The visit windows for assessments are described in the following table.

**Table 10 Visit Windows**

| CRF visit | Visit Window |
|---|---|
| Cycle 1 Day 4 | C1D4 ± 1 |
| Cycle 1 Day 8 | C1D8 ± 1 |
| Cycle 1 Day 15 | C1D15 ± 2 |
| Cycle 1 Day 21 | C1D21 ± 2 |
| Cycle 1 Day 28 | C1D28 ± 2 |
| Cycle 2 Day 4 | C2D1 ± 1 |
| Cycle 2 Day 8 | C2D8 ± 1 |
| Cycle 2 Day 15 | C2D15 ± 2 |
| Cycle 2 Day 21 | C2D21 ± 2 |
| Cycle 2 Day 28 | C2D28 ± 2 |
| LTT: Cycle X Day 1 | CXD1 ± 2 |
| End of Treatment Visit | Last dose date + 7 |
| Follow Up Visit | EOT + 28 (± 7) |
| Remote Follow Up Visit | Follow-up visit date + 3 months (± 7) |

Scheduled visit will be calculated using number of days relative to the first dose date based on the fact that gilteritinib will be administered over continuous 28-day cycles. In the case of multiple observations at a specific visit, the observation which is closest to the target date will be used. If the observations have the same distance to the target visit, the latest one will be used.

In PK analysis, actual sampling times should be used in all calculations for individual pharmacokinetic parameters if an appropriate allowance of the deviation between actual and scheduled sampling times cannot be defined prospectively.

For ease of summarization, scheduled sampling times can be used to present results in tables, listings, and figures. Allowance of plasma concentrations for calculation of summary parameters will be based on sample time point:

- Pre-dose – Within 30 minutes before drug administration
- Post dose 0.5, 1, 1.5, 2 and 3 hours – Within ± 10 minutes of nominal time
- Post dose 4 and 6 hours – Within ±20 minutes of nominal time
- Post dose 24 hours – Within ±90 minutes of nominal time

### 6.12.4 COVID-19 Impact Assessment

Assessments affected by the COVID-19 pandemic will be listed for visit-based assessments and for non-visit-based assessments.

For visit-based assessments affected by COVID-19, the listing shows if an assessment was not performed due to COVID-19, if it was out of window, if the assessment was performed at an alternative location or if it was a virtual assessment. Other information and comments reported on assessments affected by COVID-19 are also included.

For non-visit-based assessments affected by COVID-19, subjects who experience any of the following items: treatment discontinuation due to COVID-19, COVID-19 medical history,

COVID-19 adverse event, hospitalization due to COVID-19, dose changing due to COVID-19, or COVID-19 death, will be flagged in a listing.

Any events like discontinuation of treatment, medical history, adverse events, hospitalization, dose changing, or death, which are related to COVID-19, will be flagged in the corresponding listing.

# 7 DOCUMENT REVISION HISTORY

| Version | Date | Changes | Comment/rationale for change |
|---|---|---|---|
| 0.1 | 10-SEP-2018 | NA | Initial SAP draft |
| 0.2 | 28-SEP-2018 | multiple updates in all sections, including but not limited to: removing comments regarding re-enrollment (not allowed in this study), changing duration variables to be calculated from first dose date vs. enrollment date, multiple updates to maintain consistency between SAP and protocol | based on comments/review from Astellas lead study statistician |
| 0.3 | 08JUL2019 | significant updates made in multiple sections based on approved substantial protocol amendment (SAM1 24MAY2019) | changes made to maintain consistency between study SAP and study protocol |
| 0.4 | 29JUL2019 | updated to reference separate biomarker SAP | based on comments/review from Astellas lead study statistician |
| 0.5 | 30AUG2019 | updates made to DLT criteria (section 5.2.2) based on updates from protocol version 3 – UK [02AUG2019] and version 4 CA [15AUG2019] | changes made to maintain consistency between study SAP and most recent versions of study protocol |
| 0.6 | 05FEB2020 | updates made to sample size calculations, study objectives and efficacy endpoints, dose levels, lab tests (table 5), references and interim analysis due to updates from protocol v6 (draft for FDA) based on country-specific substantial amendment 5. | changes made to maintain consistency between study SAP and most recent version of study protocol |
| 0.7 | 06APR2020 | update to clinically significant vitals, including associated reference | based on recommended BP levels for pediatric patients vs standard adult metrics |
| 0.8 | 21MAY2020 | update to clinically significant vitals | based on pediatric research materials, expertise from medical, and decisions from previous studies |
| 0.9 | 24NOV2020 | update to include information about COVID-19 affected assessments | based on updates to the eCRF to collect information related to COVID-19 |
| 1.0 | 18FEB2021 | finalize all comments | Stable SAP V1.0 |
| 1.1 | 17FEB2022 | update to include changes in Protocol V6.0 | Stable SAP V1.1 |

| | | | |
|---|---|---|---|
| 1.2 | 27OCT2022 | update made to exposure section, update to include changes in Protocol V7.0 and V8.0 | based on comments/review from Astellas lead study statistician, changes made to maintain consistency between study SAP and most recent version of study protocol |
| 1.3 | 01JUN2023 | update made to exploratory biomarker analysis section, update to duration of exposure definition | changes made to specify definitions |
| 1.4 | 20AUG2024 | update made to PK analysis | based on comments/review from Astellas PK team |
| 2.0 | 22AUG2024 | finalize all comments | Stable SAP V2.0 |

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# 9 APPENDICES

## 9.1 Appendix 1: Blood Pressure Levels by Age, Gender, and Height Percentile [Flynn, Joseph et. al., 2017]

TABLE 4 BP Levels for Boys by Age and Height Percentile

| Age (y) | BP Percentile | SBP (mm Hg) | | | | | | | DBP (mm Hg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Height Percentile or Measured Height | | | | | | | Height Percentile or Measured Height | | | | | | |
| | | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 1 | Height (in) | 30.4 | 30.8 | 31.6 | 32.4 | 33.3 | 34.1 | 34.6 | 30.4 | 30.8 | 31.6 | 32.4 | 33.3 | 34.1 | 34.6 |
| | Height (cm) | 77.2 | 78.3 | 80.2 | 82.4 | 84.6 | 86.7 | 87.9 | 77.2 | 78.3 | 80.2 | 82.4 | 84.6 | 86.7 | 87.9 |
| | 50th | 85 | 85 | 86 | 86 | 87 | 88 | 88 | 40 | 40 | 40 | 41 | 41 | 42 | 42 |
| | 90th | 98 | 99 | 99 | 100 | 100 | 101 | 101 | 52 | 52 | 53 | 53 | 54 | 54 | 54 |
| | 95th | 102 | 102 | 103 | 103 | 104 | 105 | 105 | 54 | 54 | 55 | 55 | 56 | 57 | 57 |
| | 95th + 12 mm Hg | 114 | 114 | 115 | 115 | 116 | 117 | 117 | 66 | 66 | 67 | 67 | 68 | 69 | 69 |
| 2 | Height (in) | 33.9 | 34.4 | 35.3 | 36.3 | 37.3 | 38.2 | 38.8 | 33.9 | 34.4 | 35.3 | 36.3 | 37.3 | 38.2 | 38.8 |
| | Height (cm) | 86.1 | 87.4 | 89.6 | 92.1 | 94.7 | 97.1 | 98.5 | 86.1 | 87.4 | 89.6 | 92.1 | 94.7 | 97.1 | 98.5 |
| | 50th | 87 | 87 | 88 | 89 | 89 | 90 | 91 | 43 | 43 | 44 | 44 | 45 | 46 | 46 |
| | 90th | 100 | 100 | 101 | 102 | 103 | 103 | 104 | 55 | 55 | 56 | 56 | 57 | 58 | 58 |
| | 95th | 104 | 105 | 105 | 106 | 107 | 107 | 108 | 57 | 58 | 58 | 59 | 60 | 61 | 61 |
| | 95th + 12 mm Hg | 116 | 117 | 117 | 118 | 119 | 119 | 120 | 69 | 70 | 70 | 71 | 72 | 73 | 73 |
| 3 | Height (in) | 36.4 | 37 | 37.9 | 39 | 40.1 | 41.1 | 41.7 | 36.4 | 37 | 37.9 | 39 | 40.1 | 41.1 | 41.7 |
| | Height (cm) | 92.5 | 93.9 | 96.3 | 99 | 101.8 | 104.3 | 105.8 | 92.5 | 93.9 | 96.3 | 99 | 101.8 | 104.3 | 105.8 |
| | 50th | 88 | 89 | 89 | 90 | 91 | 92 | 92 | 45 | 46 | 46 | 47 | 48 | 49 | 49 |
| | 90th | 101 | 102 | 102 | 103 | 104 | 105 | 105 | 58 | 58 | 59 | 59 | 60 | 61 | 61 |
| | 95th | 106 | 106 | 107 | 107 | 108 | 109 | 109 | 60 | 61 | 61 | 62 | 63 | 64 | 64 |
| | 95th + 12 mm Hg | 118 | 118 | 119 | 119 | 120 | 121 | 121 | 72 | 73 | 73 | 74 | 75 | 76 | 76 |
| 4 | Height (in) | 38.8 | 39.4 | 40.5 | 41.7 | 42.9 | 43.9 | 44.5 | 38.8 | 39.4 | 40.5 | 41.7 | 42.9 | 43.9 | 44.5 |
| | Height (cm) | 98.5 | 100.2 | 102.9 | 105.9 | 108.9 | 111.5 | 113.2 | 98.5 | 100.2 | 102.9 | 105.9 | 108.9 | 111.5 | 113.2 |
| | 50th | 90 | 90 | 91 | 92 | 93 | 94 | 94 | 48 | 49 | 49 | 50 | 51 | 52 | 52 |
| | 90th | 102 | 103 | 104 | 105 | 105 | 106 | 107 | 60 | 61 | 62 | 62 | 63 | 64 | 64 |
| | 95th | 107 | 107 | 108 | 108 | 109 | 110 | 110 | 63 | 64 | 65 | 66 | 67 | 67 | 68 |
| | 95th + 12 mm Hg | 119 | 119 | 120 | 120 | 121 | 122 | 122 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| 5 | Height (in) | 41.1 | 41.8 | 43.0 | 44.3 | 45.5 | 46.7 | 47.4 | 41.1 | 41.8 | 43.0 | 44.3 | 45.5 | 46.7 | 47.4 |
| | Height (cm) | 104.4 | 106.2 | 109.1 | 112.4 | 115.7 | 118.6 | 120.3 | 104.4 | 106.2 | 109.1 | 112.4 | 115.7 | 118.6 | 120.3 |
| | 50th | 91 | 92 | 93 | 94 | 95 | 96 | 96 | 51 | 51 | 52 | 53 | 54 | 55 | 55 |
| | 90th | 103 | 104 | 105 | 106 | 107 | 108 | 108 | 63 | 64 | 65 | 65 | 66 | 67 | 67 |
| | 95th | 107 | 108 | 109 | 110 | 111 | 112 | 112 | 66 | 67 | 68 | 69 | 70 | 70 | 71 |
| | 95th + 12 mm Hg | 119 | 120 | 121 | 122 | 123 | 124 | 124 | 78 | 79 | 80 | 81 | 82 | 82 | 83 |
| 6 | Height (in) | 43.4 | 44.2 | 45.4 | 46.8 | 48.2 | 49.4 | 50.2 | 43.4 | 44.2 | 45.4 | 46.8 | 48.2 | 49.4 | 50.2 |
| | Height (cm) | 110.3 | 112.2 | 115.3 | 118.9 | 122.4 | 125.6 | 127.5 | 110.3 | 112.2 | 115.3 | 118.9 | 122.4 | 125.6 | 127.5 |
| | 50th | 93 | 93 | 94 | 95 | 96 | 97 | 98 | 54 | 54 | 55 | 56 | 57 | 57 | 58 |
| | 90th | 105 | 105 | 106 | 107 | 109 | 110 | 110 | 66 | 66 | 67 | 68 | 68 | 69 | 69 |
| | 95th | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| | 95th + 12 mm Hg | 120 | 121 | 122 | 123 | 124 | 125 | 126 | 81 | 82 | 82 | 83 | 84 | 84 | 85 |
| 7 | Height (in) | 45.7 | 46.5 | 47.8 | 49.3 | 50.8 | 52.1 | 52.9 | 45.7 | 46.5 | 47.8 | 49.3 | 50.8 | 52.1 | 52.9 |
| | Height (cm) | 116.1 | 118 | 121.4 | 125.1 | 128.9 | 132.4 | 134.5 | 116.1 | 118 | 121.4 | 125.1 | 128.9 | 132.4 | 134.5 |
| | 50th | 94 | 94 | 95 | 97 | 98 | 98 | 99 | 56 | 56 | 57 | 58 | 58 | 59 | 59 |
| | 90th | 106 | 107 | 108 | 109 | 110 | 111 | 111 | 68 | 68 | 69 | 70 | 70 | 71 | 71 |
| | 95th | 110 | 110 | 111 | 112 | 114 | 115 | 116 | 71 | 71 | 72 | 73 | 73 | 74 | 74 |
| | 95th + 12 mm Hg | 122 | 122 | 123 | 124 | 126 | 127 | 128 | 83 | 83 | 84 | 85 | 85 | 86 | 86 |

TABLE 4 Continued

| Age (y) | BP Percentile | SBP (mm Hg) | | | | | | | DBP (mm Hg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Height Percentile or Measured Height | | | | | | | Height Percentile or Measured Height | | | | | | |
| | | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 8 | Height (in) | 47.8 | 48.6 | 50 | 51.8 | 53.2 | 54.6 | 55.5 | 47.8 | 48.6 | 50 | 51.8 | 53.2 | 54.6 | 55.5 |
| | Height (cm) | 121.4 | 123.5 | 127 | 131 | 135.1 | 138.8 | 141 | 121.4 | 123.5 | 127 | 131 | 135.1 | 138.8 | 141 |
| | 50th | 95 | 96 | 97 | 98 | 99 | 99 | 100 | 57 | 57 | 58 | 59 | 59 | 60 | 60 |
| | 90th | 107 | 108 | 109 | 110 | 111 | 112 | 112 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| | 95th | 111 | 112 | 112 | 114 | 115 | 116 | 117 | 72 | 73 | 73 | 74 | 75 | 75 | 75 |
| | 95th + 12 mm Hg | 123 | 124 | 124 | 126 | 127 | 128 | 129 | 84 | 85 | 85 | 86 | 87 | 87 | 87 |
| 9 | Height (in) | 49.6 | 50.5 | 52 | 53.7 | 55.4 | 56.9 | 57.9 | 49.6 | 50.5 | 52 | 53.7 | 55.4 | 56.9 | 57.9 |
| | Height (cm) | 126 | 128.3 | 132.1 | 136.3 | 140.7 | 144.7 | 147.1 | 126 | 128.3 | 132.1 | 136.3 | 140.7 | 144.7 | 147.1 |
| | 50th | 96 | 97 | 98 | 99 | 100 | 101 | 101 | 57 | 58 | 59 | 60 | 61 | 62 | 62 |
| | 90th | 107 | 108 | 109 | 110 | 112 | 113 | 114 | 70 | 71 | 72 | 73 | 74 | 74 | 74 |
| | 95th | 112 | 112 | 113 | 115 | 116 | 118 | 119 | 74 | 74 | 75 | 76 | 76 | 77 | 77 |
| | 95th + 12 mm Hg | 124 | 124 | 125 | 127 | 128 | 130 | 131 | 86 | 86 | 87 | 88 | 88 | 89 | 89 |
| 10 | Height (in) | 51.3 | 52.2 | 53.8 | 55.6 | 57.4 | 59.1 | 60.1 | 51.3 | 52.2 | 53.8 | 55.6 | 57.4 | 59.1 | 60.1 |
| | Height (cm) | 130.2 | 132.7 | 136.7 | 141.3 | 145.9 | 150.1 | 152.7 | 130.2 | 132.7 | 136.7 | 141.3 | 145.9 | 150.1 | 152.7 |
| | 50th | 97 | 98 | 99 | 100 | 101 | 102 | 103 | 59 | 60 | 61 | 62 | 63 | 63 | 64 |
| | 90th | 108 | 109 | 111 | 112 | 113 | 115 | 116 | 72 | 73 | 74 | 74 | 75 | 75 | 76 |
| | 95th | 112 | 113 | 114 | 116 | 118 | 120 | 121 | 76 | 76 | 77 | 77 | 78 | 78 | 78 |
| | 95th + 12 mm Hg | 124 | 125 | 126 | 128 | 130 | 132 | 133 | 88 | 88 | 89 | 89 | 90 | 90 | 90 |
| 11 | Height (in) | 53 | 54 | 55.7 | 57.6 | 59.6 | 61.3 | 62.4 | 53 | 54 | 55.7 | 57.6 | 59.6 | 61.3 | 62.4 |
| | Height (cm) | 134.7 | 137.3 | 141.5 | 146.4 | 151.3 | 155.8 | 158.6 | 134.7 | 137.3 | 141.5 | 146.4 | 151.3 | 155.8 | 158.6 |
| | 50th | 99 | 99 | 101 | 102 | 103 | 104 | 106 | 61 | 61 | 62 | 63 | 63 | 63 | 63 |
| | 90th | 110 | 111 | 112 | 114 | 116 | 117 | 118 | 74 | 74 | 75 | 75 | 75 | 76 | 76 |
| | 95th | 114 | 114 | 116 | 118 | 120 | 123 | 124 | 77 | 78 | 78 | 78 | 78 | 78 | 78 |
| | 95th + 12 mm Hg | 126 | 126 | 128 | 130 | 132 | 135 | 136 | 89 | 90 | 90 | 90 | 90 | 90 | 90 |
| 12 | Height (in) | 55.2 | 56.3 | 58.1 | 60.1 | 62.2 | 64 | 65.2 | 55.2 | 56.3 | 58.1 | 60.1 | 62.2 | 64 | 65.2 |
| | Height (cm) | 140.3 | 143 | 147.5 | 152.7 | 157.9 | 162.6 | 165.5 | 140.3 | 143 | 147.5 | 152.7 | 157.9 | 162.6 | 165.5 |
| | 50th | 101 | 101 | 102 | 104 | 106 | 108 | 109 | 61 | 62 | 62 | 62 | 62 | 63 | 63 |
| | 90th | 113 | 114 | 115 | 117 | 119 | 121 | 122 | 75 | 75 | 75 | 75 | 75 | 76 | 76 |
| | 95th | 116 | 117 | 118 | 121 | 124 | 126 | 128 | 78 | 78 | 78 | 78 | 78 | 79 | 79 |
| | 95th + 12 mm Hg | 128 | 129 | 130 | 133 | 138 | 138 | 140 | 90 | 90 | 90 | 90 | 90 | 91 | 91 |
| 13 | Height (in) | 57.9 | 59.1 | 61 | 63.1 | 65.2 | 67.1 | 68.3 | 57.9 | 59.1 | 61 | 63.1 | 65.2 | 67.1 | 68.3 |
| | Height (cm) | 147 | 150 | 154.9 | 160.3 | 165.7 | 170.5 | 173.4 | 147 | 150 | 154.9 | 160.3 | 165.7 | 170.5 | 173.4 |
| | 50th | 103 | 104 | 105 | 108 | 110 | 111 | 112 | 61 | 60 | 61 | 62 | 63 | 64 | 65 |
| | 90th | 115 | 116 | 118 | 121 | 124 | 126 | 126 | 74 | 74 | 74 | 75 | 76 | 77 | 77 |
| | 95th | 119 | 120 | 122 | 125 | 128 | 130 | 131 | 78 | 78 | 78 | 78 | 80 | 81 | 81 |
| | 95th + 12 mm Hg | 131 | 132 | 134 | 137 | 140 | 142 | 143 | 90 | 90 | 90 | 90 | 92 | 93 | 93 |
| 14 | Height (in) | 60.8 | 61.8 | 63.8 | 65.9 | 68.0 | 69.8 | 70.9 | 60.6 | 61.8 | 63.8 | 65.9 | 68.0 | 69.8 | 70.9 |
| | Height (cm) | 153.8 | 156.9 | 162 | 167.5 | 172.7 | 177.4 | 180.1 | 153.8 | 156.9 | 162 | 167.5 | 172.7 | 177.4 | 180.1 |
| | 50th | 105 | 106 | 109 | 111 | 112 | 113 | 113 | 60 | 60 | 62 | 64 | 65 | 66 | 67 |
| | 90th | 119 | 120 | 123 | 126 | 127 | 128 | 129 | 74 | 74 | 75 | 77 | 78 | 79 | 80 |
| | 95th | 123 | 125 | 127 | 130 | 132 | 133 | 134 | 77 | 78 | 79 | 81 | 82 | 83 | 84 |
| | 95th + 12 mm Hg | 135 | 137 | 139 | 142 | 144 | 145 | 146 | 89 | 90 | 91 | 93 | 94 | 95 | 96 |

TABLE 4 Continued

| Age (y) | BP Percentile | SBP (mm Hg) | | | | | | | DBP (mm Hg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Height Percentile or Measured Height | | | | | | | Height Percentile or Measured Height | | | | | | |
| | | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 15 | Height (in) | 62.6 | 63.8 | 65.7 | 67.8 | 69.8 | 71.5 | 72.5 | 62.6 | 63.8 | 65.7 | 67.8 | 69.8 | 71.5 | 72.5 |
| | Height (cm) | 159 | 162 | 166.9 | 172.2 | 177.2 | 181.6 | 184.2 | 159 | 162 | 166.9 | 172.2 | 177.2 | 181.6 | 184.2 |
| | 50th | 108 | 110 | 112 | 113 | 114 | 114 | 114 | 61 | 62 | 64 | 65 | 66 | 67 | 68 |
| | 90th | 123 | 124 | 126 | 128 | 129 | 130 | 130 | 75 | 76 | 78 | 79 | 80 | 81 | 81 |
| | 95th | 127 | 129 | 131 | 132 | 134 | 135 | 135 | 78 | 79 | 81 | 83 | 84 | 85 | 85 |
| | 95th + 12 mm Hg | 139 | 141 | 143 | 144 | 146 | 147 | 147 | 90 | 91 | 93 | 95 | 96 | 97 | 97 |
| 16 | Height (in) | 63.8 | 64.9 | 66.8 | 68.8 | 70.7 | 72.4 | 73.4 | 63.8 | 64.9 | 66.8 | 68.8 | 70.7 | 72.4 | 73.4 |
| | Height (cm) | 162.1 | 165 | 169.6 | 174.6 | 179.5 | 183.8 | 186.4 | 162.1 | 165 | 169.6 | 174.6 | 179.5 | 183.8 | 186.4 |
| | 50th | 111 | 112 | 114 | 115 | 115 | 116 | 116 | 63 | 64 | 66 | 67 | 68 | 69 | 69 |
| | 90th | 126 | 127 | 128 | 129 | 131 | 131 | 132 | 77 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 95th | 130 | 131 | 133 | 134 | 135 | 136 | 137 | 80 | 81 | 83 | 84 | 85 | 86 | 86 |
| | 95th + 12 mm Hg | 142 | 143 | 145 | 146 | 147 | 148 | 149 | 92 | 93 | 95 | 96 | 97 | 98 | 98 |
| 17 | Height (in) | 64.5 | 65.5 | 67.3 | 69.2 | 71.1 | 72.8 | 73.8 | 64.5 | 65.5 | 67.3 | 69.2 | 71.1 | 72.8 | 73.8 |
| | Height (cm) | 163.8 | 166.5 | 170.9 | 175.8 | 180.7 | 184.9 | 187.5 | 163.8 | 166.5 | 170.9 | 175.8 | 180.7 | 184.9 | 187.5 |
| | 50th | 114 | 115 | 116 | 117 | 117 | 118 | 118 | 65 | 66 | 67 | 68 | 69 | 70 | 70 |
| | 90th | 128 | 129 | 130 | 131 | 132 | 133 | 134 | 78 | 79 | 80 | 81 | 82 | 82 | 83 |
| | 95th | 132 | 133 | 134 | 135 | 137 | 138 | 138 | 81 | 82 | 84 | 85 | 86 | 86 | 87 |
| | 95th + 12 mm Hg | 144 | 145 | 146 | 147 | 149 | 150 | 150 | 93 | 94 | 96 | 97 | 98 | 98 | 99 |

Use percentile values to stage BP readings according to the scheme in Table 3 (elevated BP: ≥90th percentile; stage 1 HTN: ≥95th percentile; and stage 2 HTN: ≥95th percentile + 12 mm Hg). The 90th, 95th, and 99th percentiles were derived by using quantile regression on the basis of normal-weight children (BMI <85th percentile).[27]

TABLE 5 BP Levels for Girls by Age and Height Percentile

| Age (y) | BP Percentile | SBP (mm Hg) | | | | | | | DBP (mm Hg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Height Percentile or Measured Height | | | | | | | Height Percentile or Measured Height | | | | | | |
| | | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 1 | Height (in) | 29.7 | 30.2 | 30.9 | 31.8 | 32.7 | 33.4 | 33.9 | 29.7 | 30.2 | 30.9 | 31.8 | 32.7 | 33.4 | 33.9 |
| | Height (cm) | 75.4 | 76.6 | 78.6 | 80.8 | 83 | 84.9 | 86.1 | 75.4 | 76.6 | 78.6 | 80.8 | 83 | 84.9 | 86.1 |
| | 50th | 84 | 85 | 86 | 86 | 87 | 88 | 88 | 41 | 42 | 42 | 43 | 44 | 45 | 46 |
| | 90th | 98 | 99 | 99 | 100 | 101 | 102 | 102 | 54 | 55 | 56 | 56 | 57 | 58 | 58 |
| | 95th | 101 | 102 | 102 | 103 | 104 | 105 | 105 | 59 | 59 | 60 | 60 | 61 | 62 | 62 |
| | 95th + 12 mm Hg | 113 | 114 | 114 | 115 | 116 | 117 | 117 | 71 | 71 | 72 | 72 | 73 | 74 | 74 |
| 2 | Height (in) | 33.4 | 34 | 34.9 | 35.9 | 36.9 | 37.8 | 38.4 | 33.4 | 34 | 34.9 | 35.9 | 36.9 | 37.8 | 38.4 |
| | Height (cm) | 84.9 | 86.3 | 88.6 | 91.1 | 93.7 | 96 | 97.4 | 84.9 | 86.3 | 88.6 | 91.1 | 93.7 | 96 | 97.4 |
| | 50th | 87 | 87 | 88 | 89 | 90 | 91 | 91 | 45 | 46 | 47 | 48 | 49 | 50 | 51 |
| | 90th | 101 | 101 | 102 | 103 | 104 | 105 | 106 | 58 | 58 | 59 | 60 | 61 | 62 | 62 |
| | 95th | 104 | 105 | 106 | 106 | 107 | 108 | 109 | 62 | 63 | 63 | 64 | 65 | 66 | 66 |
| | 95th + 12 mm Hg | 116 | 117 | 118 | 118 | 119 | 120 | 121 | 74 | 75 | 75 | 76 | 77 | 78 | 78 |
| 3 | Height (in) | 35.8 | 36.4 | 37.3 | 38.4 | 39.6 | 40.6 | 41.2 | 35.8 | 36.4 | 37.3 | 38.4 | 39.6 | 40.6 | 41.2 |
| | Height (cm) | 91 | 92.4 | 94.9 | 97.6 | 100.5 | 103.1 | 104.6 | 91 | 92.4 | 94.9 | 97.6 | 100.5 | 103.1 | 104.6 |
| | 50th | 88 | 89 | 89 | 90 | 91 | 92 | 93 | 48 | 48 | 49 | 50 | 51 | 53 | 53 |
| | 90th | 102 | 103 | 104 | 104 | 105 | 106 | 107 | 60 | 61 | 61 | 62 | 63 | 64 | 65 |
| | 95th | 106 | 106 | 107 | 108 | 109 | 110 | 110 | 64 | 65 | 65 | 66 | 67 | 68 | 69 |
| | 95th + 12 mm Hg | 118 | 118 | 119 | 120 | 121 | 122 | 122 | 76 | 77 | 77 | 78 | 79 | 80 | 81 |
| 4 | Height (in) | 38.3 | 38.9 | 39.9 | 41.1 | 42.4 | 43.5 | 44.2 | 38.3 | 38.9 | 39.9 | 41.1 | 42.4 | 43.5 | 44.2 |
| | Height (cm) | 97.2 | 98.8 | 101.4 | 104.5 | 107.6 | 110.5 | 112.2 | 97.2 | 98.8 | 101.4 | 104.5 | 107.6 | 110.5 | 112.2 |
| | 50th | 89 | 90 | 91 | 92 | 93 | 94 | 94 | 50 | 51 | 51 | 53 | 54 | 55 | 55 |
| | 90th | 103 | 104 | 105 | 106 | 107 | 108 | 108 | 62 | 63 | 64 | 65 | 66 | 67 | 67 |
| | 95th | 107 | 108 | 109 | 109 | 110 | 111 | 112 | 66 | 67 | 68 | 69 | 70 | 70 | 71 |
| | 95th + 12 mm Hg | 119 | 120 | 121 | 121 | 122 | 123 | 124 | 78 | 79 | 80 | 81 | 82 | 82 | 83 |
| 5 | Height (in) | 40.8 | 41.5 | 42.6 | 43.9 | 45.2 | 46.5 | 47.3 | 40.8 | 41.5 | 42.6 | 43.9 | 45.2 | 46.5 | 47.3 |
| | Height (cm) | 103.6 | 105.3 | 108.2 | 111.5 | 114.9 | 118.1 | 120 | 103.6 | 105.3 | 108.2 | 111.5 | 114.9 | 118.1 | 120 |
| | 50th | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 52 | 52 | 53 | 55 | 56 | 57 | 57 |
| | 90th | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 64 | 65 | 66 | 67 | 68 | 69 | 70 |
| | 95th | 108 | 109 | 109 | 110 | 111 | 112 | 113 | 68 | 69 | 70 | 71 | 72 | 73 | 73 |
| | 95th + 12 mm Hg | 120 | 121 | 121 | 122 | 123 | 124 | 125 | 80 | 81 | 82 | 83 | 84 | 85 | 85 |
| 6 | Height (in) | 43.3 | 44 | 45.2 | 46.6 | 48.1 | 49.4 | 50.3 | 43.3 | 44 | 45.2 | 46.6 | 48.1 | 49.4 | 50.3 |
| | Height (cm) | 110 | 111.8 | 114.9 | 118.4 | 122.1 | 125.6 | 127.7 | 110 | 111.8 | 114.9 | 118.4 | 122.1 | 125.6 | 127.7 |
| | 50th | 92 | 92 | 93 | 94 | 96 | 97 | 97 | 54 | 54 | 55 | 56 | 57 | 58 | 59 |
| | 90th | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 67 | 67 | 68 | 69 | 70 | 71 | 71 |
| | 95th | 109 | 109 | 110 | 111 | 112 | 113 | 114 | 70 | 71 | 72 | 72 | 73 | 74 | 74 |
| | 95th + 12 mm Hg | 121 | 121 | 122 | 123 | 124 | 125 | 126 | 82 | 83 | 84 | 84 | 85 | 86 | 86 |
| 7 | Height (in) | 45.6 | 46.4 | 47.7 | 49.2 | 50.7 | 52.1 | 53 | 45.6 | 46.4 | 47.7 | 49.2 | 50.7 | 52.1 | 53 |
| | Height (cm) | 115.9 | 117.8 | 121.1 | 124.9 | 128.8 | 132.5 | 134.7 | 115.9 | 117.8 | 121.1 | 124.9 | 128.8 | 132.5 | 134.7 |
| | 50th | 92 | 93 | 94 | 95 | 97 | 98 | 99 | 55 | 55 | 56 | 57 | 58 | 59 | 60 |
| | 90th | 106 | 106 | 107 | 109 | 110 | 111 | 112 | 68 | 68 | 69 | 70 | 71 | 72 | 72 |
| | 95th | 109 | 110 | 111 | 112 | 113 | 114 | 115 | 72 | 72 | 73 | 73 | 74 | 74 | 75 |
| | 95th + 12 mm Hg | 121 | 122 | 123 | 124 | 125 | 126 | 127 | 84 | 84 | 85 | 85 | 86 | 86 | 87 |

TABLE 6 Continued

| Age (y) | BP Percentile | SBP (mm Hg) | | | | | | | DBP (mm Hg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Height Percentile or Measured Height | | | | | | | Height Percentile or Measured Height | | | | | | |
| | | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 8 | Height (in) | 47.6 | 48.4 | 49.8 | 51.4 | 53 | 54.5 | 55.5 | 47.6 | 48.4 | 49.8 | 51.4 | 53 | 54.5 | 55.5 |
| | Height (cm) | 121 | 123 | 126.5 | 130.6 | 134.7 | 138.5 | 140.9 | 121 | 123 | 126.5 | 130.6 | 134.7 | 138.5 | 140.9 |
| | 50th | 93 | 94 | 95 | 97 | 98 | 99 | 100 | 58 | 58 | 57 | 59 | 60 | 61 | 61 |
| | 90th | 107 | 107 | 108 | 110 | 111 | 112 | 113 | 69 | 70 | 71 | 72 | 72 | 73 | 73 |
| | 95th | 110 | 111 | 112 | 113 | 115 | 116 | 117 | 72 | 73 | 74 | 74 | 75 | 75 | 75 |
| | 95th + 12 mm Hg | 122 | 123 | 124 | 125 | 127 | 128 | 129 | 84 | 85 | 86 | 86 | 87 | 87 | 87 |
| 9 | Height (in) | 49.3 | 50.2 | 51.7 | 53.4 | 55.1 | 56.7 | 57.7 | 49.3 | 50.2 | 51.7 | 53.4 | 55.1 | 56.7 | 57.7 |
| | Height (cm) | 125.3 | 127.6 | 131.3 | 135.6 | 140.1 | 144.1 | 146.6 | 125.3 | 127.6 | 131.3 | 135.6 | 140.1 | 144.1 | 146.6 |
| | 50th | 95 | 95 | 97 | 98 | 99 | 100 | 101 | 57 | 58 | 59 | 60 | 60 | 61 | 61 |
| | 90th | 108 | 108 | 109 | 111 | 112 | 113 | 114 | 71 | 71 | 72 | 73 | 73 | 73 | 73 |
| | 95th | 112 | 112 | 113 | 114 | 116 | 117 | 118 | 74 | 74 | 75 | 75 | 75 | 75 | 75 |
| | 95th + 12 mm Hg | 124 | 124 | 125 | 126 | 128 | 129 | 130 | 86 | 86 | 87 | 87 | 87 | 87 | 87 |
| 10 | Height (in) | 51.1 | 52 | 53.7 | 55.5 | 57.4 | 59.1 | 60.2 | 51.1 | 52 | 53.7 | 55.5 | 57.4 | 59.1 | 60.2 |
| | Height (cm) | 129.7 | 132.2 | 136.3 | 141 | 145.8 | 150.2 | 152.8 | 129.7 | 132.2 | 136.3 | 141 | 145.8 | 150.2 | 152.8 |
| | 50th | 98 | 97 | 98 | 99 | 101 | 102 | 103 | 58 | 59 | 59 | 60 | 61 | 61 | 62 |
| | 90th | 109 | 110 | 111 | 112 | 113 | 115 | 116 | 72 | 73 | 73 | 73 | 73 | 73 | 73 |
| | 95th | 113 | 114 | 114 | 116 | 117 | 119 | 120 | 75 | 75 | 76 | 76 | 76 | 76 | 76 |
| | 95th + 12 mm Hg | 125 | 126 | 126 | 128 | 129 | 131 | 132 | 87 | 87 | 88 | 88 | 88 | 88 | 88 |
| 11 | Height (in) | 53.4 | 54.5 | 56.2 | 58.2 | 60.2 | 61.9 | 63 | 53.4 | 54.5 | 56.2 | 58.2 | 60.2 | 61.9 | 63 |
| | Height (cm) | 135.6 | 138.3 | 142.8 | 147.8 | 152.8 | 157.3 | 160 | 135.6 | 138.3 | 142.8 | 147.8 | 152.8 | 157.3 | 160 |
| | 50th | 98 | 99 | 101 | 102 | 104 | 105 | 106 | 60 | 60 | 60 | 61 | 62 | 63 | 64 |
| | 90th | 111 | 112 | 113 | 114 | 116 | 118 | 120 | 74 | 74 | 74 | 74 | 74 | 75 | 75 |
| | 95th | 115 | 116 | 117 | 118 | 120 | 123 | 124 | 76 | 77 | 77 | 77 | 77 | 77 | 77 |
| | 95th + 12 mm Hg | 127 | 128 | 129 | 130 | 132 | 135 | 136 | 88 | 89 | 89 | 89 | 89 | 89 | 89 |
| 12 | Height (in) | 58.2 | 57.3 | 59 | 60.9 | 62.8 | 64.5 | 65.5 | 58.2 | 57.3 | 59 | 60.9 | 62.8 | 64.5 | 65.5 |
| | Height (cm) | 142.8 | 145.5 | 149.9 | 154.8 | 159.6 | 163.8 | 166.4 | 142.8 | 145.5 | 149.9 | 154.8 | 159.6 | 163.8 | 166.4 |
| | 50th | 102 | 102 | 104 | 105 | 107 | 108 | 108 | 61 | 61 | 61 | 62 | 64 | 65 | 65 |
| | 90th | 114 | 115 | 116 | 118 | 120 | 122 | 122 | 75 | 75 | 75 | 75 | 76 | 76 | 76 |
| | 95th | 118 | 119 | 120 | 122 | 124 | 125 | 126 | 78 | 78 | 78 | 78 | 79 | 79 | 79 |
| | 95th + 12 mm Hg | 130 | 131 | 132 | 134 | 136 | 137 | 138 | 90 | 90 | 90 | 90 | 91 | 91 | 91 |
| 13 | Height (in) | 58.3 | 59.3 | 60.9 | 62.7 | 64.5 | 66.1 | 67 | 58.3 | 59.3 | 60.9 | 62.7 | 64.5 | 66.1 | 67 |
| | Height (cm) | 148.1 | 150.6 | 154.7 | 159.2 | 163.7 | 167.8 | 170.2 | 148.1 | 150.6 | 154.7 | 159.2 | 163.7 | 167.8 | 170.2 |
| | 50th | 104 | 105 | 106 | 107 | 108 | 108 | 109 | 62 | 62 | 63 | 64 | 65 | 65 | 66 |
| | 90th | 116 | 117 | 119 | 121 | 122 | 123 | 123 | 75 | 75 | 75 | 76 | 76 | 76 | 76 |
| | 95th | 121 | 122 | 123 | 124 | 126 | 126 | 127 | 79 | 79 | 79 | 79 | 80 | 80 | 81 |
| | 95th + 12 mm Hg | 133 | 134 | 135 | 136 | 138 | 138 | 139 | 91 | 91 | 91 | 91 | 92 | 92 | 93 |
| 14 | Height (in) | 59.3 | 60.2 | 61.8 | 63.5 | 65.2 | 66.8 | 67.7 | 59.3 | 60.2 | 61.8 | 63.5 | 65.2 | 66.8 | 67.7 |
| | Height (cm) | 150.6 | 153 | 156.9 | 161.3 | 165.7 | 169.7 | 172.1 | 150.6 | 153 | 156.9 | 161.3 | 165.7 | 169.7 | 172.1 |
| | 50th | 105 | 106 | 107 | 108 | 109 | 109 | 109 | 63 | 63 | 64 | 65 | 66 | 66 | 66 |
| | 90th | 118 | 118 | 120 | 122 | 123 | 123 | 123 | 76 | 76 | 76 | 76 | 77 | 77 | 77 |
| | 95th | 123 | 123 | 124 | 125 | 126 | 127 | 127 | 80 | 80 | 80 | 80 | 81 | 81 | 82 |
| | 95th + 12 mm Hg | 135 | 135 | 136 | 137 | 138 | 139 | 139 | 92 | 92 | 92 | 92 | 93 | 93 | 94 |

TABLE 5 Continued

| Age (y) | BP Percentile | SBP (mmHg) | | | | | | | DBP (mmHg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Height Percentile or Measured Height | | | | | | | Height Percentile or Measured Height | | | | | | |
| | | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 15 | Height (in) | 59.7 | 60.6 | 62.2 | 63.9 | 65.6 | 67.2 | 68.1 | 59.7 | 60.6 | 62.2 | 63.9 | 65.6 | 67.2 | 68.1 |
| | Height (cm) | 151.7 | 154 | 157.9 | 162.3 | 166.7 | 170.6 | 173 | 151.7 | 154 | 157.9 | 162.3 | 166.7 | 170.6 | 173 |
| | 50th | 105 | 106 | 107 | 108 | 109 | 109 | 109 | 64 | 64 | 64 | 65 | 66 | 67 | 67 |
| | 90th | 118 | 119 | 121 | 122 | 123 | 123 | 124 | 78 | 78 | 76 | 77 | 77 | 78 | 78 |
| | 95th | 124 | 124 | 125 | 126 | 127 | 127 | 128 | 80 | 80 | 80 | 81 | 82 | 82 | 82 |
| | 95th + 12 mm Hg | 136 | 136 | 137 | 138 | 139 | 139 | 140 | 92 | 92 | 92 | 93 | 94 | 94 | 94 |
| 16 | Height (in) | 59.9 | 60.8 | 62.4 | 64.1 | 65.8 | 67.3 | 68.3 | 59.9 | 60.8 | 62.4 | 64.1 | 65.8 | 67.3 | 68.3 |
| | Height (cm) | 152.1 | 154.5 | 158.4 | 162.8 | 167.1 | 171.1 | 173.4 | 152.1 | 154.5 | 158.4 | 162.8 | 167.1 | 171.1 | 173.4 |
| | 50th | 106 | 107 | 108 | 109 | 109 | 110 | 110 | 64 | 64 | 65 | 66 | 66 | 67 | 67 |
| | 90th | 119 | 120 | 122 | 123 | 124 | 124 | 124 | 78 | 76 | 76 | 77 | 78 | 78 | 78 |
| | 95th | 124 | 125 | 125 | 127 | 127 | 128 | 128 | 80 | 80 | 80 | 81 | 82 | 82 | 82 |
| | 95th + 12 mm Hg | 136 | 137 | 137 | 139 | 139 | 140 | 140 | 92 | 92 | 92 | 93 | 94 | 94 | 94 |
| 17 | Height (in) | 60.0 | 60.9 | 62.5 | 64.2 | 65.9 | 67.4 | 68.4 | 60.0 | 60.9 | 62.5 | 64.2 | 65.9 | 67.4 | 68.4 |
| | Height (cm) | 152.4 | 154.7 | 158.7 | 163.0 | 167.4 | 171.3 | 173.7 | 152.4 | 154.7 | 158.7 | 163.0 | 167.4 | 171.3 | 173.7 |
| | 50th | 107 | 108 | 109 | 110 | 110 | 110 | 111 | 64 | 64 | 65 | 66 | 66 | 66 | 67 |
| | 90th | 120 | 121 | 123 | 124 | 124 | 125 | 125 | 76 | 76 | 77 | 77 | 78 | 78 | 78 |
| | 95th | 125 | 125 | 126 | 127 | 128 | 128 | 128 | 80 | 80 | 80 | 81 | 82 | 82 | 82 |
| | 95th + 12 mm Hg | 137 | 137 | 138 | 139 | 140 | 140 | 140 | 92 | 92 | 92 | 93 | 94 | 94 | 94 |

Use percentile values to stage BP readings according to the scheme in Table 3 (elevated BP, ≥90th percentile; stage 1 HTN, ≥95th percentile; and stage 2 HTN, ≥95th percentile + 12 mm Hg). The 50th, 90th, and 95th percentiles were derived by using quantile regression on the basis of normal-weight children (BMI <85th percentile).[22]

## 9.2 Appendix 2: Signatures

Primary author(s):

PPD

Date: _____
Date (DD Mmm YYYY)

Contributors and Reviewers:

PPD

Date: _____
Date (DD Mmm YYYY)

PPD

Date: _____
Date (DD Mmm YYYY)

PPD

Date: _____
Date (DD Mmm YYYY)