Janssen Research & Development *

Clinical Protocol

An Open-label, Multicenter, Phase 2 Study Evaluating the Efficacy and Safety of Daratumumab in Pediatric and Young Adult Subjects ≥1 and ≤30 Years of Age With Relapsed/Refractory Precursor B-cell or T-cell Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma

Protocol 54767414ALL2005; Phase 2
AMENDMENT 3

JNJ-54767414 (daratumumab)

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	11 October 2017
Amendment 1	12 January 2018
Amendment 2	04 September 2018
Amendment 3	22 January 2019

Amendment 3 (22 January 2019)

The overall reason for the amendment: the overall reason for the amendment is in response to identification of a new important risk (hepatitis B virus [HBV] reactivation).

Applicable Section(s)	Description of Change(s)
Rationale: The text for identification of HBV reactivation, testing, and management of subjects with the potential for HBV reactivation was added or modified in response to identification of a new important risk (HBV reactivation).	
Table 1 Time and Events Schedule – Overview	Added rows for HBV serology and HBV DNA test, and identified the timepoints at which HBV serology and HBV DNA test would be conducted.
4.2 Exclusion Criteria (#10.1)	Clarified language to exclude subjects who are seropositive for HBV.
8.2.1.6 Management of Hepatitis B Virus Reactivation	Added a new section providing information for the management of HBV reactivation.
9.1.1 Overview; Attachment 7 Estimated Total Blood Volume Collected During the Study	Corrected the maximum blood volume to be collected during the Screening Visit to approximately 17 mL, thus accounting for HBV serology.
9.5 Safety Evaluations	Added information detailing the conduct of HBV serology and DNA tests.
Rationale: Clarified timepoints and procedures.	
Table 1 Time and Events Schedule – Overview	Clarified that disease evaluations have a visit window of +7 days.
Table 2 Time and Events Schedule – Detailed Procedures and Study Drug Administration; 6.1.3 Daratumumab Continuation Phase Prior to Transplant	Clarified timepoints for daratumumab administration and CBC assessment in the optional daratumumab continuation phase prior to transplant.
6.1.1 B-cell ALL/LL Cohort; 6.1.2 T-cell ALL/LL Cohort	Clarified that on daratumumab dosing days, methylprednisolone 2 mg/kg (maximum 100 mg) pre-infusion medication should be substituted for prednisone 40 mg/m^2.
Rationale: Clarified that the primary and secondary endpoints will be analyzed for the pediatric ALL population only. Subjects aged 18 to 30 years of age and subjects with LL will not be included in the analyses of the primary/secondary endpoints for this study; rather, the data gathered will be summarized descriptively.	
Synopsis; 2.1.1 Objectives; 2.1.2 Endpoints	Clarified that the primary and secondary endpoints will be analyzed for the pediatric ALL population only.

Applicable Section(s)	Description of Change(s)
Rationale: Clarified inclusion and exclusion criteria.	
4.1 Inclusion Criteria (#5.2)	Corrected inadvertent omission of greater than or equal to sign (≥) in inclusion criterion regarding renal function.
4.2 Exclusion Criteria (#18.2)	Correction per French country-specific amendment: Subject is **not** affiliated to, or a beneficiary of, a social security category, per local regulatory requirements, if applicable.
4.2 Exclusion Criteria (New #19)	Added text: Subjects with infant leukemia (defined as under 1 year old at the time of initial diagnosis). These subjects will not be eligible for this study, even if they are greater than 1 year old at the time of relapse.
Rationale: Clarified criteria for disease response and progression categories.	
9.2.1.1 Acute Lymphoblastic Leukemia	Revised text: Refractory disease: failure to achieve CR at end of induction therapy **and does not meet criteria for progressive disease**
Rationale: Clarified requirements for local vs. central bone marrow evaluation.	
9.2.2 Bone Marrow Evaluation	Revised text: **Bone marrow aspirate is required for central bone marrow evaluations; bone marrow biopsy is not acceptable for central testing.** If the aspirate procedure is deemed inadequate, biopsy is required **for local testing**.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (04 September 2018)

The overall reason for the amendment: To incorporate changes from country-specific amendments and to provide additional details and clarifications regarding study procedures.

Applicable Section(s)	Description of Change(s)
Rationale: Clarified the population in which objectives and endpoints will be assessed.	
Synopsis; 2.1.1 Objectives; 2.1.2 Endpoints	Clarified that secondary objectives and endpoints regarding efficacy, safety, PK, and immunogenicity will be assessed in subjects with ALL only. Clarified that efficacy and safety of daratumumab in combination with standard chemotherapy will be assessed.
11.3.1 Primary Endpoint	**For subjects 1 to <18 years of age,** the number and percentage of subjects who achieve a CR including 90% exact CI will be calculated for each cohort. The exact p-value to test the hypothesis, H_0: CR rate ≤15% in the B cell ALL cohort and H_0: CR rate ≤30% in the T-cell ALL cohort, will also be calculated.
Rationale: Clarified requirements for screening procedures.	
Table 1 (Time and Events Schedule – Overview); 9.1.2 Screening Period	Clarified that results from standard of care procedures obtained within 21 days before Cycle 1 Day 1 may be used without these tests being repeated.
Rationale: Provided a visit window for the End-of-Treatment Visit.	
Table 1 (Time and Events Schedule – Overview); 9.1.3 Treatment Period	It was clarified that the End-of-Treatment Visit is to occur 30 days (+7 days) after last dose.
Rationale: Revised the timing of follow-up procedures.	
Table 1 (Time and Events Schedule – Overview); 9.1.4 Posttreatment Period (Follow-Up)	It was clarified that for all subjects who discontinue study drug prior to CR or PD, disease evaluations will continue every 8 weeks until CR, PD, subsequent anticancer therapy is initiated, or study completion. After CR or PD, follow up will occur every 12 weeks to record information on subsequent anticancer therapy, second primary malignancies, documentation of progressive disease or relapsed disease, and survival status. For all subjects proceeding to transplant, the following information will be collected and documented in the eCRF: date of transplant, type of transplant, time to engraftment, and any graft failures. In addition, any maintenance chemotherapy given after discontinuation of study treatment and prior to transplant must be documented in the eCRF.
Rationale: Clarified the procedures and timing of disease evaluations and laboratory assessments.	
Table 1 (Time and Events Schedule – Overview); 9.2.1 Response Categories	Added a window of ±7 days for all disease evaluations. Clarified that if disease evaluations are delayed, treatment should also be delayed.
Table 1 (Time and Events Schedule – Overview); 9.2.3 Lumbar Puncture; 9.5 Safety Evaluations	Clarified that cerebrospinal fluid will be used for cytology evaluations for lymphoblasts as well as RBC and WBC counts, and that methods may include cytospin or flow cytometry.

Applicable Section(s)	Description of Change(s)
Table 1 (Time and Events Schedule – Overview); Attachment 7: Estimated Total Blood Volume Collected During the Study	Clarified that for subjects with B-cell ALL/LL who are Ph+, blood will be collected on Day 1 of Cycles 1 and 2, and then on Day 28 of every other cycle from Cycle 4 until complete response or progressive disease. Clarified that this evaluation is not required for subjects with T-cell ALL/LL.
Table 1 (Time and Events Schedule – Overview)	Clarified that bone marrow aspirate/biopsy is to be collected for subjects with B-cell ALL/LL on Day 28 of every other cycle from Cycle 4 until complete response or progressive disease.
Table 1 (Time and Events Schedule – Overview); 9.2 Efficacy Evaluations; 9.2.1.3 Mediastinal Mass	Clarified the following regarding chest and abdomen/pelvis CT or MRI: • Chest scans can include either CT or MRI. • Chest CT or MRI is required for subjects with ALL with mediastinal mass and all subjects with LL during screening. Screening chest CT or MRI may be delayed until the subject is stable. • Abdomen/pelvis CT or MRI is only required for subjects with LL at screening and on treatment if positive at screening and the subject has not yet achieved CR. • The same imaging modality performed at screening should be used during the treatment period as indicated.
Table 1 (Time and Events Schedule – Overview); 9.2 Efficacy Evaluations; 9.2.1.3 Mediastinal Mass; 9.2.1.4 Lymphoblastic Lymphoma	Removed the optional PET or gallium scans from the planned procedures.
Table 1 (Time and Events Schedule – Overview)	Added collection of hematology and chemistry samples at the End-of-Treatment Visit, and hematology samples during follow-up prior to progressive disease. It was also clarified that at screening, serum chemistry should be performed prior to IT methotrexate treatment.
Rationale: Clarified procedures for the evaluation of vital signs.	
Table 2 (Time and Events Schedule – Detailed Procedures and Study Drug Administration); 9.5 Safety Evaluations; 11.7 Safety Analyses	Removed vital signs assessment on Day 28 of Cycles 1 and 2. Added respiration rate to vital signs. Clarified that statistical evaluations of vital signs will include only post baseline changes.

Applicable Section(s)	Description of Change(s)
Rationale: Clarified procedures for administration of study drugs.	
Table 2 (Time and Events Schedule – Detailed Procedures and Study Drug Administration); 6.1.1 B-cell ALL/LL Cohort; 6.1.2 T-cell ALL/LL Cohort; 6.1.2.1 T-cell ALL/LL Cycle 1; 6.1.2.2 T-cell ALL/LL Cycle 2; 6.1.3 Daratumumab Continuation Phase Prior to Transplant	Clarified that the order of administration of study medications may vary and that a window of ±1 day is allowed in order to meet local requirements. However, on daratumumab dosing days, IT therapy should be given first, then daratumumab should be administered prior to any other study drugs. Routine transfusions should be avoided on daratumumab dosing days. Clarified that for both B-cell and T-cell ALL/LL, acceptable substitutes for IT MTX include both IT ARA-C and triple IT therapy. Removed statement regarding skipping the IT MTX dose if IT therapy was given within 7 days of Cycle 1 Day 1 as part of previous therapy. Clarified that Erwinia asparaginase may be substituted for peg-asparaginase. Added allowance for prednisone taper as clinically indicated per local standard practice. Clarified that for subjects with T-cell ALL/LL, Cycle 2 Day 15 therapy should be held until ANC is $>0.75x10^9$/L and platelets are $>75x10^9$/L. Clarified procedures for both cohorts for the optional daratumumab continuation phase prior to transplant. If daratumumab is given post completion of Cycles 2 to 4, administration of drug and CBC should be done on Day 1 and Day 15. If daratumumab is given post completion of Cycle 5+, administration of drug and CBC should be done on Day 1 only. A maximum of 1 cycle of continuation therapy is allowed prior to transplant.
Rationale: Clarified guidelines regarding DLT evaluation.	
3.4 Dose-Limiting Toxicity	During the safety run-in, 3 subjects in each cohort will be evaluated for dose-limiting toxicities (DLTs). A Safety Evaluation Team (SET) (see Section 11.8) will review the DLT data and determine whether a modification to the dose or schedule of study drugs is needed for any of the treatment cohorts. The DLT Evaluation Period is defined as the first 28 days from the start of the first dose of daratumumab. ~~If a subject receives any amount of daratumumab during the DLT evaluation period, they will be considered evaluable for DLT.~~ DLTs will be evaluated in each cohort separately at the end of Cycle 1. Only toxicities that occur during the DLT evaluation period will be used for the purpose of defining DLT and for subsequent dose or dosing schedule modifications or safety-run in expansion. However, toxicities that occur in all cycles will be considered in the overall decisions of the SET. If a subject receives less than 75% of the planned dose of daratumumab for reasons other than toxicity (eg, disease progression, subject withdrawal, etc.), that subject will be considered non-evaluable for DLTs and may be replaced, but the safety profiles of these subjects will be included in the SET review. Additional safety reviews will be conducted by the SET after Stage 1 of the study in each cohort and as deemed necessary during the conduct of the study. ~~If 1 or more subjects in a cohort experience a DLT, then the safety run-in for that cohort will be expanded to 6 subjects. After the additional 3 subjects complete 1 cycle of therapy, safety will be re-evaluated. If 2/6 or more subjects experience a DLT, the dose or schedule of study drugs may be adjusted in the remaining treatment cycles, and an additional 3 subjects may be treated at a lower dose or adjusted schedule for a given combination regimen. A new safety evaluation will begin with 3 new subjects with the adjusted dosing regimen and will follow the guidelines noted below.~~

Applicable Section(s)	Description of Change(s)
	The following DLT guidelines will apply **to each cohort separately**: • If DLT is not observed in the initial 3 subjects treated with 16 mg/kg of daratumumab for a given combination regimen, then that combination regimen will be considered safe and well tolerated **and the cohort may continue to enroll to pre-specified numbers.** • If DLT is observed in ~~≥33%~~ **1** of the initial 3 subjects, then the safety-run in will be expanded to 6 subjects. o If 1/6 subjects treated with 16 mg/kg of daratumumab for a given combination regimen experience a DLT, then that combination regimen will be considered safe and well tolerated **and the cohort may continue to enroll to pre-specified numbers.** o If ≥2/6 subjects experience a DLT, then that combination regimen will be considered not safe unless the events are due to unexpected circumstances clearly not related to a study procedure or treatment (eg, a passenger in an automobile accident). The dose or schedule of study drugs may be adjusted **and a new safety run-in may begin or the cohort may be closed.** ~~in the remaining treatment cycles, and an additional 3~~ **Three new** subjects may be treated at a lower dose or adjusted schedule for a given combination regimen. ~~If no further toxicities are observed, then the study may continue to enroll to pre-specified numbers.~~ **The safety run-in will follow the rules above.** • **If DLT is observed in ≥2 of the initial 3 subjects, then that combination regimen will be considered not safe unless the events are due to unexpected circumstances clearly not related to a study procedure or treatment (eg, a passenger in an automobile accident). The dose or schedule of study drugs may be adjusted and a new safety run-in may begin or the cohort may be closed. Three new subjects may be treated at a lower dose or adjusted schedule for a given combination regimen. The safety run-in will follow the rules above.**
Rationale: Clarified that for Cohort 2 (the T-cell cohort) only, certain non-hematologic Grade 4 toxicities are not considered DLTs.	
3.5 Dose Tolerability Evaluation Guidelines	• Non-hematologic toxicity of Grade 4 that occurs after the first dose of daratumumab and is considered related to daratumumab with the following exceptions **for Cohort 2 only**: o Fever or infection o Gastrointestinal symptoms (anorexia, vomiting, dehydration, mucositis) o Hypofibrinogenemia o Metabolic/laboratory abnormalities that resolve to ≤Grade 2 within 7 days o Tumor lysis syndrome or hyperuricemia
Rationale: Clarified entry criteria regarding renal and liver function.	
4.1 Inclusion Criteria (#5.1 and #6.2)	Clarified that adequate renal and liver function are required prior to enrollment rather than on Cycle 1 Day 1.
4.2 Exclusion Criteria	If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study**, with the exception of subjects who meet screening liver function criteria but have elevation of liver function tests (≤Grade 3) on Cycle 1 Day 1 after IT methotrexate.**

Applicable Section(s)	Description of Change(s)
Rationale: Clarified definition of female subjects of childbearing potential. Clarified requirements for sexual abstinence to be considered an acceptable method of birth control. Extended the posttreatment contraception duration requirements for female subjects, as well as the time period when female subjects must agree not to donate eggs, to 12 months after the last administration of any component of the treatment regimen.	
4.1 Inclusion Criteria (#7.1)	Female subjects of ~~reproductive~~ **childbearing** potential (defined as ~~a~~ post-menarchal **and sexually active** ~~female who is sexually active prior to initiation of the study or during the study should reproductive potential change during the study~~ **until becoming post-menopausal unless permanently sterile**) must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously during the Treatment Period, during any dose interruptions, and for ~~6~~ **12** months after the last dose of any component of the treatment regimen. **Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. T**he reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.** Birth control methods must include one highly effective method of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants], or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.
4.1 Inclusion Criteria (#8.1)	During the study and for ~~6~~ **12** months after receiving the last dose of any component of the treatment regimen, female subjects must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.
4.2 Exclusion Criteria (#14.1)	Pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within ~~6~~ **12** months after the last dose of any component of the treatment regimen.
Rationale: Clarified exclusion criteria regarding prior cancer immunotherapy.	
4.2 Exclusion Criteria (#8.1)	Prior cancer immunotherapy (ie, CAR-T, inotuzumab) within 4 weeks prior to ~~start of daratumumab treatment~~ **enrollment** or blinatumomab within 2 weeks prior to ~~the start of daratumumab treatment~~ **enrollment**.
Rationale: Clarified exclusion criteria regarding prior anthracycline exposure.	
4.2 Exclusion Criteria (#9.1)	For subjects with T-cell ALL/LL only: prior cumulative anthracycline exposure must not exceed 400 mg/m^2 **of doxorubicin or equivalent** (~~each 10 mg/m^2 of idarubicin should be calculated as the equivalent of 30 mg/m^2 of doxorubicin~~ **see Attachment 8 for conversion**).
New Attachment 8: Doxorubicin Equivalent Conversion; References	• Daunorubicin: multiply total dose in m^2 x 1 • Mitoxantrone: multiply total dose in m^2 x 4 • Idarubicin: multiply total dose in m^2 x 5 • Epirubicin: multiply total dose in m^2 x 0.67 For doses in mg/kg, first multiply dose x 30 for mg/m^2 then apply conversion above. Source: Feijen 2015

Applicable Section(s)	Description of Change(s)
Rationale: Clarified that exclusion due to known allergies to certain treatments applies only to subjects with T-cell ALL/LL.	
4.2 Exclusion Criteria (#12.1)	Known allergies, hypersensitivity, or intolerance to mannitol, glucocorticoid, ~~doxorubicin, cytarabine,~~ methotrexate, vincristine~~, cyclophosphamide, 6-mercaptopurine~~, mAb (IRR is not considered hypersensitivity) or human proteins, or their excipients (refer to respective package inserts and Investigator's Brochure), or known sensitivity to mammalian-derived products. **For subjects with T-cell ALL/LL only, known allergies to doxorubicin, cytarabine, cyclophosphamide, or 6-mercaptopurine.**
Rationale: Revised exclusion criteria to include an affiliation to a social security system.	
4.2 Exclusion Criteria (#18.1)	Added the following requirement for exclusion from the study: Subject is affiliated to, or a beneficiary of, a social security category, per local regulatory requirements, if applicable.
Rationale: Clarified options for daratumumab continuation phase.	
6.1.3 Daratumumab Continuation Phase Prior to Transplant	Clarified that other standard maintenance chemotherapy may also be given after the discontinuation of study treatment and prior to transplant, at the discretion of the investigator. All maintenance therapy must be documented in the eCRF.
Rationale: Increased the dose of preinfusion paracetamol in an effort to prevent IRRs.	
6.3.1 Preinfusion Medications	Increased the dose of preinfusion paracetamol from 650 mg to 1000 mg PO.
Rationale: Revised the instructions for the management of IRRs for consistency with other daratumumab study protocols.	
6.3.3 Management of Infusion-related Reactions	Subjects should be observed carefully during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of ~~an infusion reaction~~ any IRRs, and resources necessary for resuscitation **(eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator)** must be available **at the bedside.** Attention to staffing should be considered when multiple subjects will be dosed at the same time. ~~For infusion-related reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab.~~ **If an IRR develops, then daratumumab administration should be temporarily interrupted. Please see the IPPI for further details. Subjects who experience adverse events during daratumumab administration must be treated for their symptoms. Subjects should be treated with acetaminophen, antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject.** • Grade 1-2 (mild to moderate) **IRRs**: ~~Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate as outlined in Table 6.~~ **If the investigator assesses a Grade 1-2 IRR adverse event to be**

Applicable Section(s)	Description of Change(s)
	related to administration of study drug, then the daratumumab administration should be paused. When the subject's condition is stable, daratumumab administration may be restarted at half of the rate at the investigator's discretion. **If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be permanently discontinued from daratumumab treatment.** • Grade 3 ~~(severe)~~ **or higher IRRs**: ~~Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 6. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion-related reaction.~~ **For IRR adverse events (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped and the subject must be observed carefully until resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be restarted at half of the rate at the investigator's discretion. If the intensity of the adverse event returns to Grade 3 after restart of the daratumumab administration, then the subject must be withdrawn from daratumumab treatment. For IRR adverse events that are Grade 4, the daratumumab administration must be stopped and the subject withdrawn from daratumumab treatment.** • ~~Grade 4 (life threatening): Permanently discontinue daratumumab treatment.~~ • **Recurrent IRRs: If a Grade 3 IRR (or ≥Grade 2 event of laryngeal edema or bronchospasm) recurs during or within 24 hours after a subsequent daratumumab administration, the daratumumab treatment must be discontinued.**
Rationale: Clarified procedures for daratumumab dose delays.	
6.4.1 Daratumumab	Only if any of the following criteria are met and the event cannot be ascribed to components of the chemotherapy regimen **or if the causality is unclear, then** the daratumumab infusion must be held to allow for recovery from toxicity. If daratumumab administration does not commence within the prespecified window (~~Table 2~~ **Table 7**) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up. **Table 7: Daratumumab-Related Toxicity Management** **Cycles** | **Frequency** | **Dose Missed** | **Dosing Resumption** **1-2** | **Weekly** | **>3 days** | **next planned weekly dosing date** **3-6** | **Every 2 weeks** | **>7 days** | **next planned every-2-weeks dosing date** **7+** | **Every 4 weeks** | **>14 days** | **next planned every-4-weeks dosing date** If Day 1 of a cycle is delayed, then Day 1 of subsequent cycles should be adjusted accordingly to maintain the cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. **If a dose delay occurs, then PK assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.** ~~A daratumumab dose that is held for more than the permitted~~

Applicable Section(s)	Description of Change(s)
	~~time (Table 2) from the per protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the Sponsor at the earliest possible time.~~ ~~For Cohort 1 (B-cell cohort): any~~ **Any** adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks ~~(Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond)~~ will result in permanent discontinuation of daratumumab, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon. ~~If a dose delay occurs, then PK assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.~~
Rationale: Updated recommendations for prophylaxis of herpes zoster reactivation in accordance with daratumumab prescribing information.	
8.2.1.4 Prophylaxis for Herpes Zoster Reactivation	Prophylaxis for herpes ~~simplex/~~zoster reactivation is recommended during the Treatment Period, ~~in accordance with~~ **as per** institutional guidelines**, and for 3 months following treatment.**
Rationale: Revised the list of permitted concomitant therapies.	
8.2.2 Permitted Concomitant Therapies	• **Antivirals** • Prevention of constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed) • **Prophylactic antiemetics, with the exception of glucocorticoids and aprepitant/fosaprepitant** • **Colony stimulating factors, erythropoietin, and** transfusion of platelets and red blood cells; ~~except~~ **routine transfusions should not be given** on daratumumab dosing days • Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended
Rationale: Expanded the list of prohibited concomitant therapies.	
8.2.3 Prohibited Concomitant Therapies	**Concomitant administration of the following therapies is prohibited during the study:** • ~~Concomitant administration of~~ Any antineoplastic therapy for the intention of treating ALL or LL is prohibited, including conventional chemotherapy agents, investigational agents, and approved or investigational medications that target CD38 • **Aprepitant/fosaprepitant** • **Strong CYP3A4 and P glycoprotein inhibitors, such as ketoconazole or itraconazole, is prohibited. For an ongoing list of CYP3A inhibitors and inducers, see http://medicine iupui.edu/flockhart/** • **Live vaccines during the study and for 3 months after the last dose of vincristine** The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.
8.2.1.3 Prophylaxis for Nausea	Subjects should be given antiemetics during each chemotherapy course individualized to the subject's best response. However, glucocorticoids and aprepitant/**fosaprepitant** should not be used as antiemetics.

Applicable Section(s)	Description of Change(s)
Rationale: Clarified the definition of "MRD negative."	
9.2.1.1 Acute Lymphoblastic Leukemia	MRD negative is defined as <0.01% abnormal population counts to ~~total event counts~~ **nucleated mononuclear cells** when measured by flow.
Rationale: Clarified the definition of CNS relapse and added guidelines for discontinuation.	
9.2.1.2 Central Nervous System Disease	Relapse: development of **new** M3 CNS status or development of **new** symptoms of CNS leukemia **Subjects with M2 or M3 CNS status who do not improve to M1 CNS status after 1 cycle of treatment should permanently discontinue all study treatment.**
Rationale: Provided additional details on the procedures for local and central bone marrow evaluations.	
9.2.2 Bone Marrow Evaluation	Fresh bone marrow aspirate will be collected according to the Time and Events Schedule (Table 1 and Table 2). **Local and central bone marrow evaluations will be performed as described in Table 8.** ~~Bone marrow at screening will be evaluated locally for morphology and cytogenetic analysis and centrally for MRD. During treatment, bone marrow aspirate will be collected as per the Time and Events Schedule for both local morphology to evaluate clinical response and central testing for MRD assessment as well as biomarkers predictive of clinical response.~~ If the aspirate procedure is deemed inadequate, biopsy is required. Added the following table:

Table 8: Local and Central Bone Marrow Evaluations

Timepoint	Local Testing	Central Testing
Screening	Disease characterization • Morphology (evaluate percentage of tumorous leukemia/lymphoma cells and cellularity) • Immunohistochemistry, immunofluorescence, or flow cytometry (evaluate presence of tumorous leukemia/lymphoma cells present by immunophenotyping and indicate probes used for immunophenotyping) Cytogenetics • Either by FISH or conventional karyotype	MRD: a portion of fresh bone marrow aspirate collected at Screening will be sent to a central laboratory for assessment of MRD by flow cytometry and PCR Biomarkers: baseline assessment of biomarkers predictive of clinical response or resistance to therapy
Disease evaluations prior to PD or CR, and prior to start of subsequent anticancer therapy[a]	Disease characterization • Morphology (evaluate percentage of tumorous leukemia/lymphoma cells and cellularity)	MRD: a portion of fresh bone marrow aspirate collected at each disease evaluation time point will be sent to a central laboratory Biomarkers: assessment of biomarkers predictive of clinical response or resistance to therapy
End of Treatment (if feasible)	Disease characterization • Morphology (evaluate percentage of tumorous leukemia/lymphoma cells and cellularity)	MRD: a portion of fresh bone marrow aspirate collected will be sent to a central laboratory Biomarkers: assessment of biomarkers predictive of clinical response or resistance to therapy

Abbreviations: CR=complete response; FISH=fluorescence in situ hybridization; LL=lymphoblastic lymphoma; MRD=minimal residual disease; PCR=polymerase chain reaction; PD=progressive disease.

a. For subjects with LL, on-treatment bone marrow evaluations are only required if bone marrow disease is present at Screening.

Applicable Section(s)	Description of Change(s)
Rationale: Revised instructions for hematology and chemistry evaluations.	
9.5 Safety Evaluations	Added instructions that if WBC is too low for automated assessment, a manual differential should be performed to document absolute lymphocyte count, absolute neutrophil count, and peripheral blast count. Clarified that the serum chemistry panel includes amylase or lipase.
Rationale: Added reasons for discontinuation for consistency with other sections of the protocol and for consistency with other daratumumab study protocols.	
10.2 Discontinuation of Study Treatment/ Withdrawal from the Study; 9.1.3 Treatment Period; Synopsis	A subject's study treatment must be discontinued for any of the following reasons: • The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment • The subject becomes pregnant, unless the subject (or the subject's legally acceptable representative), investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study treatment is in the best interest of the subject • Progression of disease or relapse **as defined in Section 9.2.1** • **Subjects with CNS M2 or CNS M3 status at baseline who do not achieve CNS M1 status (ie, 2 successive negative CSF evaluations) after completion of Cycle 1** • Withdrawal of consent • Subject initiates treatment with any prohibited medication • **Subject experiences unacceptable toxicity, including IRRs, as described in Section 6.3.3** • **Subject's daratumumab dose is held for more than 4 weeks due to a daratumumab-related toxicity as described in Section 6.4.1 (unless sponsor approves continuation)** • **Subject experiences a second primary malignancy that cannot be treated by surgery or radiotherapy alone** • Subjects who achieve CR and proceed to allogeneic HSCT If a subject discontinues study treatment for any reason before the end of the treatment period, end-of-treatment and posttreatment assessments should be obtained.
Rationale: Updated the study population definitions for consistency with the Statistical Analysis Plan.	
11.1 Subject Information	The study analysis populations are defined as follows: • ~~All enrolled population~~ **All treated population:** all enrolled subjects who receive **any study treatment. This population will be used for efficacy and safety analyses. All subjects in the all treated analysis population will be analyzed according to the treatment that they actually received.** • Response evaluable population: all ~~enrolled~~ **treated** subjects who ~~receive daratumumab and~~ have at least 1 adequate postbaseline disease assessment. **Sensitivity analyses of CR rate and ORR will be based on the response evaluable population.** • PK evaluable population: all ~~enrolled~~ **treated** subjects who ~~receive daratumumab and~~ provide at least one postinfusion sample. **All PK parameters will be analyzed based on the PK evaluable population.**
Rationale: Clarified that backbone treatment is not to be documented on the drug accountability form as these treatments are commercially available.	
14.5 Drug Accountability	~~The backbone treatment administered to the subject must be documented on the drug accountability form.~~

Applicable Section(s)	Description of Change(s)
Rationale: Added the Cockcroft-Gault formula for eGFR.	
Attachment 3: Serum Creatinine Guidelines	Added the Cockcroft-Gault formula.
Rationale: Updated infusion guidelines for HD MTX to include options to follow local standards.	
Attachment 5: High-Dose Methotrexate (HD MTX) Infusion Guidelines	Clarified that all guidelines for HD MTX are a recommendation and that local standards may be followed as an alternative. Updated infusion guidelines for HD MTX to include options for administration of mannitol if urine output fails to continue at 80% of the fluid intake.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 12 January 2018

The overall reason for the amendment: The overall reason for the amendment is to clarify procedures to be conducted during the follow-up period and to add the collection of relevant information from subjects who proceed to posttreatment, off-study bone marrow transplantation.

Applicable Section(s)	Description of Change(s)
Rationale: Procedures to be conducted during the follow-up period and optional continuation phase were clarified. The collection of data related to posttreatment off-study bone marrow transplantation was added.	
Table 1 (Time and Events Schedule – Overview)	It was clarified that after EoT, subjects without PD will continue to undergo disease evaluations **every 4 weeks until subsequent anticancer therapy is initiated.**
Table 2 (Time and Events Schedule – Detailed Procedures and Study Drug Administration)	For consistency with Section 9.2.2, it was added in the Time and Events Schedule that a bone marrow aspirate/biopsy will be performed at the end of the continuation phase for subjects whose prior assessment was >2 weeks from the start of the conditioning regimen for bone marrow transplantation.
9.1.4 Posttreatment Period (Follow-Up)	For those subjects who discontinue study drug prior to disease progression, disease evaluations will continue to be performed every 4 weeks **until subsequent anticancer therapy is initiated**. **For those subjects proceeding to transplant, the following information will be collected: date of transplant, type of transplant, time to engraftment, and any graft failures. After disease progression is documented or subsequent anticancer therapy is initiated**, follow-up will occur every 8 weeks to record information on subsequent anticancer therapy, second primary malignancies, **documentation of progressive disease or relapsed disease, and survival status.**
Rationale: Requirements for CT scans were clarified.	
Table 1 (Time and Events Schedule – Overview)	For consistency with Section 9.2, it was clarified in the Time and Events Schedule that CT scans of the chest and abdomen/pelvis will be performed for subjects with ALL with mediastinal mass and subjects with LL.
Rationale: It was clarified that PET or gallium scans are optional due to the availability of these procedures in the study site countries.	
Table 1 (Time and Events Schedule – Overview); 9.2.1.3 Mediastinal Mass; 9.2.1.4 Lymphoblastic Lymphoma	The text was updated to clarify that PET or gallium scans are optional.
Rationale: Heart rate and oxygen saturation were added to vital signs measurements to ensure adequate safety monitoring in this first study of daratumumab in pediatric subjects.	
Table 2 (Time and Events Schedule – Detailed Procedures and Study Drug Administration); 9.5 Safety Evaluations; 11.7 Safety Analyses	The text was updated to include heart rate and oxygen saturation.

Applicable Section(s)	Description of Change(s)
Rationale: A typographical error was corrected.	
4.1 Inclusion Criteria (#6)	Adequate liver function at Cycle 1 Day 1 pre-dosing defined as: a. **Alanine** ~~Aspartate~~ aminotransferase level ≤2.5x the upper limit of normal (ULN), b. Aspartate aminotransferase level ≤2.5xULN, and c. Total bilirubin ≤2x ULN or direct bilirubin level ≤2.0xULN
Rationale: Exclusion criterion regarding immunosuppression was clarified.	
4.2 Exclusion Criteria (#3)	Received immunosuppression **post hematopoietic transplant** within 1 month of study entry.
Rationale: Exclusion criteria related to prior treatments was updated to prohibit investigational drugs and medical devices within 4 weeks of first dose of study drug, as well as current treatment in other investigational studies.	
4.2 Exclusion Criteria (#13)	**Received an investigational drug,** ~~Vaccination~~ **was vaccinated** ~~-~~with live attenuated vaccines**, or used an investigational medical device** within 4 weeks ~~of first study agent administration.~~ **before the planned** first **dose of** study **drug, or is currently being treated in an investigational study.**
Rationale: Minor corrections were made to the instructions for daratumumab infusion.	
6.2.2 Daratumumab Administration; Table 6 (Daratumumab Infusion Rates)	Subjects weighing ≥10 to <20 kg will have daratumumab administered in a volume of 250 mL for the first infusion (Cycle 1 Day 1), then in a volume of ~~125~~ **100** mL for all subsequent infusions.
7 Treatment Compliance	The requirement for recording (in the eCRF) the weight of the IV bag before and after infusion was removed.
Rationale: Procedures for substituting Erwinia asparaginase for pegaspargase in the event of anaphylaxis were clarified.	
6.4.6 Asparaginase (Pegaspargase [PEG-Asparaginase] or Erwinia)	Give **6** ~~only 3~~ doses of Erwinia on M/W/F schedule for each dose of pegaspargase except the last dose of pegaspargase~~; give 6 doses of Erwinia over 2 weeks on M/W/F schedule for the last dose of pegaspargase~~
Rationale: Prohibited concomitant therapies were clarified.	
8.2.3 Prohibited Concomitant Therapies	Concomitant administration of **any antineoplastic therapy for the intention of treating ALL or LL is prohibited, including conventional chemotherapy agents,** investigational agents, **and** ~~including~~ approved or investigational medications that target CD38~~, with the intention of treating ALL/LL is prohibited~~. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.
Rationale: Criteria for disease response were clarified.	
9.2.1 Response Categories	**Disease response should reflect response in all areas of disease (ie, bone marrow and mediastinal mass, or bone marrow and extramedullary disease). If a subject does not have a CR in an extramedullary compartment, response will be considered "refractory disease" as per Section 9.2.1.1.**
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

An Open-label, Multicenter, Phase 2 Study Evaluating the Efficacy and Safety of Daratumumab in Pediatric and Young Adult Subjects ≥1 and ≤30 Years of Age With Relapsed/Refractory Precursor B-cell or T-cell Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma

OBJECTIVES

The primary objective is to evaluate the efficacy of daratumumab in addition to standard chemotherapy in pediatric subjects with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) and T-cell ALL as measured by the complete response (CR) rate.

The secondary objectives include the following:

- To assess the efficacy of daratumumab in addition to standard chemotherapy, including overall response rate (ORR), relapse-free survival (RFS), event-free survival (EFS), and overall survival (OS) in pediatric subjects with B-cell and T-cell ALL, and minimal residual disease (MRD) negative rate in subjects with B-cell and T-cell ALL
- To assess the safety and tolerability of daratumumab in addition to standard chemotherapy in pediatric subjects with B-cell and T-cell ALL
- To assess the pharmacokinetics (PK) of daratumumab in pediatric subjects with B-cell and T-cell ALL
- To assess daratumumab immunogenicity in pediatric subjects with B-cell ALL and T-cell ALL
- To assess daratumumab concentration in cerebrospinal fluid (CSF)

The exploratory objectives include the following:

- To explore biomarkers predictive of response or resistance to therapy
- To assess expression of CD38 at study entry and at relapse

OVERVIEW OF STUDY DESIGN

This is a Phase 2, open-label, multicenter study to evaluate the efficacy, safety, and PK of daratumumab in addition to standard chemotherapy in approximately 49 subjects aged ≥1 to <18 with relapsed/refractory ALL and a maximum of 69 total subjects ≥1 and ≤30 years of age with relapsed or refractory ALL/LL. Cohort 1 will evaluate daratumumab in combination with vincristine and prednisone in subjects with B-cell ALL/LL in second relapse or greater. Cohort 2 will evaluate daratumumab in combination with a standard 4-drug re-induction regimen in subjects with T-cell ALL/LL in first relapse. There will be an initial safety run-in period for evaluation of dose-limiting toxicities. A Safety Evaluation Team will be commissioned for this study. The sponsor plans to enroll a minimum of 3 subjects with ALL in each of the following age groups in both cohorts: 1 to 6, 7 to 12, and 13 to <18 years if that cohort proceeds to stage 2 of the study.

DOSAGE AND ADMINISTRATION

Subjects with B-cell ALL/LL will receive treatment continuously in 28-day cycles until disease progression or unacceptable toxicity. Treatment will consist of daratumumab 16 mg/kg IV weekly for 8 doses, then every 2 weeks for 8 doses, then every 28 days thereafter; vincristine 1.5 mg/m^2 (maximum 2 mg) IV weekly for 4 doses, then every 2 weeks for 2 doses, then every 28 days thereafter; and prednisone 40 mg/m^2 orally daily for 28 days, then pulses on the first 5 days of each cycle thereafter.

Subjects with T-cell ALL/LL will receive up to two 28-day cycles of therapy. Subjects who achieve CR should proceed to allogeneic hematopoietic stem cell transplant off study. Cycle 1 treatment consists of daratumumab 16 mg/kg IV weekly for 4 doses, vincristine 1.5 mg/m^2 (maximum 2 mg) IV weekly for 4 doses, prednisone 40 mg/m^2 orally daily for 28 days, doxorubicin 60 mg/m^2 IV once, and peg-asparaginase 2500 U/m^2 IV twice. Cycle 2 treatment consists of daratumumab 16 mg/kg IV weekly for 4 doses, cyclophosphamide IV 1 g/m^2 once, cytarabine 75 mg/m^2 IV/subcutaneous for 8 doses, 6-mercaptopurine 60 mg/m^2 orally daily for 14 doses, and methotrexate 5 g/m^2 IV once.

Subjects in both cohorts will also receive age-adjusted treatment with intrathecal methotrexate (for subjects without central nervous system [CNS] involvement) or intrathecal methotrexate-hydrocortisone-cytarabine (for subjects with CNS involvement).

EFFICACY EVALUATIONS

Disease evaluations will include bone marrow evaluations, CSF evaluations, blood samples to evaluate for BCR-ABL in Philadelphia chromosome positive subjects, and imaging studies.

OTHER EVALUATIONS

Blood samples will be used to characterize the PK of daratumumab and to assess for the generation of anti-daratumumab antibodies. Cerebrospinal fluid samples will also be collected for assessment of daratumumab concentration. Biomarker assessments will focus on 3 main objectives: to evaluate the ability of daratumumab to induce MRD, to confirm pharmacodynamic biomarkers, and to evaluate CD38 expression on blast cells. Safety will be measured by adverse events, laboratory test results (hematology and chemistry), and assessment of Karnofsky or Lansky performance status.

STATISTICAL METHODS

The study utilizes a Simon's 2-stage design for subjects aged less than 18 years. The B-cell ALL cohort will enroll 7 subjects in the first stage. If there is more than 1 responder after these subjects have received 2 cycles of treatment, then an additional 18 subjects will be enrolled in Stage 2. If 25 subjects are enrolled, then there is 80% power to show that the true CR rate is >15% at a one-sided alpha of 5%. The T-cell ALL cohort will enroll 8 subjects in the first stage. If there are more than 3 responders after these subjects have received at least 1 cycle of treatment, then an additional 16 subjects will be enrolled in Stage 2. If 24 pediatric subjects are enrolled, then there is 80% power to show that the true CR rate is >30% at a one-sided alpha of 5%.

A maximum of 10 young adult subjects (aged 18 to 30 years) with ALL and a maximum of 10 subjects with LL (aged 1 to 30 years) will be included in Stage 2 to evaluate the safety and efficacy in this patient population in addition to the 49 pediatric subjects included for the Simon's 2- stage design and the data from these additional young adult subjects with ALL and subjects with LL will be summarized descriptively.

Table 1: Time and Events Schedule – Overview

	Screening Period (Day -21 to Day -1)[a]	Treatment Cycles 1-2	Treatment Cycles 3-4 (B-ALL/LL only)	Treatment Cycles 5+ (B-ALL/LL only)	EoT[b]	Follow-up Q8W pre- CR or PD	Follow-up[c] Q12W	Notes
Cycles are 28 days. To accommodate the schedule of the site or subject, a window of +3 days is allowed for the start of Cycle 2 onward, while a window of ±1 day is allowed for individual doses within a cycle. After EoT, subjects without CR or PD will continue to undergo disease evaluations every 8 weeks until CR or PD is confirmed or until subsequent anticancer therapy is initiated. After CR or PD is confirmed, subjects will be followed for survival, subsequent anticancer therapy, and any new second primary malignancies.								
Procedures								
Informed consent/assent	X							Before first study-related procedure.
Eligibility criteria	X							See Section 17.4.
Demography/medical history	X							
Height	X							
Weight	X	Refer to Table 2						
Karnofsky or Lansky performance status	X	D1 of each cycle	B-ALL/LL: D1 of each cycle T-ALL/LL: not applicable					See Attachment 1.
Physical examination	X	Symptom and disease directed physical examination as clinically indicated						At screening, physical examination includes neurological examination. Any change from baseline must be recorded as an adverse event.
12-lead electrocardiogram	X							See Section 9.5.
Vital signs	X	Refer to Table 2			X			See Section 9.5.
Disease Evaluations (a window of +7 days is allowed for all disease evaluations)								
Cerebrospinal fluid	X	Obtain with each intrathecal therapy						Cytology evaluation for lymphoblasts (ie, cytospin, flow cytometry) and cell counts collected prior to intrathecal therapy delivery.
Blood (Ph+ subjects only)	X	B-ALL/LL: D1 of C1 and C2, then D1 of every other cycle from C4 until CR or PD T-ALL/T-LL: not applicable						Assessment of BCR-ABL (local laboratory).

	Screening Period (Day -21 to Day -1)[a]	Treatment Cycles 1-2	Treatment Cycles 3-4 (B-ALL/LL only)	Treatment Cycles 5+ (B-ALL/LL only)	EoT[b]	Follow-up Q8W pre- CR or PD	Follow-up[c] Q12W	Notes
Bone marrow aspirate/biopsy	X	All subjects*: C1 D28 and C2 D28	B-ALL/LL: D28 of every other cycle from C4 until CR or PD T-ALL/LL: not applicable		B-ALL and T-ALL: if feasible			See Section 9.2.2 for details on local and central evaluations. Fresh aspirate required. Biopsy is only required if the aspirate procedure is deemed inadequate. For subjects with LL, on-study bone marrow evaluation is only required if bone marrow disease is present at study entry. *If there is no hematologic recovery, repeat bone marrow evaluation when count recovery occurs (ANC >1.0x10^9/L platelets >100x10^9/L) unless there is evidence of blasts, then continue to next cycle.
Chest X-ray	X	As clinically indicated						Not required if chest CT obtained.
CT or MRI of chest*, CT or MRI of abdomen/pelvis^	ALL and LL*: X	ALL with mediastinal mass and LL: C1 D28^ and C2 D28^	B-ALL with mediastinal mass and B-LL: D28 of every other cycle from C4 until CR or PD^ T-ALL and T-LL: not applicable					*Chest CT or MRI required for subjects with ALL with mediastinal mass and all subjects with LL during screening. Screening chest CT or MRI may be delayed until subject is stable. ^Abdomen/pelvis CT or MRI only required for subjects with LL at screening and on treatment if positive at screening and subject has not yet achieved CR. The same imaging modality performed at screening should be used during the treatment period as indicated.
Follow-up period: disease evaluations Q8W for subjects who discontinue study drug prior to CR or PD and who have not initiated subsequent therapy						X		

	Screening Period (Day -21 to Day -1)[a]	Treatment Cycles 1-2	Treatment Cycles 3-4 (B-ALL/LL only)	Treatment Cycles 5+ (B-ALL/LL only)	EoT[b]	Follow-up Q8W pre- CR or PD	Follow-up[c] Q12W	Notes
Collection of information related to subsequent anti-ALL/LL therapy, second primary malignancy, documentation of PD or relapsed disease, and survival							X	
Clinical Laboratory Assessments								
Blood group and type assessment and IAT results/wallet card	Within 3 days prior to C1 D1							Includes ABO, Rh, and IAT results.
Pregnancy test	X	Prior to each cycle						Female subjects of reproductive potential only, within 14 days prior to first dose.
Hematology	X	Refer to Table 2			X	X		
Serum chemistry	X*	Refer to Table 2			X			*At screening, serum chemistry should be performed prior to IT methotrexate treatment.
HBV serology	X	Once for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment 3 is implemented						Local testing for HBsAg, Anti-HBs, and Anti-HBc. Refer to Section 9.5.
HBV DNA testing	X	D1 of each cycle			X	Q12W for up to 6 months after the last dose		For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Refer to Section 9.5.
Study Drug Administration								
Refer to Table 2. If disease evaluations are delayed, treatment should also be delayed.								
Pharmacokinetics/Immunogenicity								
Refer to Table 3								
Biomarkers								
Whole blood sample		C1D1, C2D1			X			See Section 9.4.

	Screening Period (Day -21 to Day -1)[a]	Treatment Cycles 1-2	Treatment Cycles 3-4 (B-ALL/LL only)	Treatment Cycles 5+ (B-ALL/LL only)	EoT[b]	Follow-up Q8W pre- CR or PD	Follow-up[c] Q12W	Notes
Ongoing Subject Review								
Concomitant medications	Continuous from the time of signing of ICF until 30 days after last dose of last study drug							See Section 8 for detailed instructions.
Adverse events	Continuous from the time of signing of ICF until 30 days after last dose of last study drug							See Section 12 for detailed instructions.

Abbreviations: ALL=acute lymphoblastic leukemia; Anti-HBc=hepatitis B core antibody; Anti-HBs=hepatitis B surface antibody; C=cycle; CR=complete response; CT=computed tomography; D=day; EoT=End of Treatment; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; IAT=indirect antiglobulin test; ICF=informed consent form; LL=lymphoblastic lymphoma; MRD=minimal residual disease; PCR=polymerase chain reaction; PD=progressive disease; Ph+=Philadelphia chromosome positive; Q12W=every 12 weeks.

a. Results from standard of care procedures obtained within 21 days before Cycle 1 Day 1 may be used without these tests being repeated.
b. The EoT Visit should occur 30 days (+7 days) after last dose.
c. Q12W follow-up beginning after confirmation of CR or PD. In subjects for whom CR or PD cannot be confirmed, Q12W after the EoT Visit.

Table 2: Time and Events Schedule – Detailed Procedures and Study Drug Administration

	Cycles 1-2					Cycles 3-6 (B-ALL/LL only)		Cycles 7+ (B-ALL /LL only)	EoT	Notes
	D1	D8	D15	D22	D28	D1	D15	D1		
Procedures										
Hematology	X	X	X	X	X*	X	X	X	X	To be performed by local laboratory. Results of hematology tests must be evaluated before each study drug administration. Testing may be performed up to 2 days before infusions. Perform at additional timepoints as clinically indicated. * If bone marrow sample for disease evaluation is delayed, repeat hematology evaluations on the day of bone marrow assessment.
Serum chemistry	X	X	X	X		X	X	X	X	
Weight	X					X		X		
Vital signs	X	X	X	X		X	X	X		Vital signs (heart rate, blood pressure, oxygen saturation, temperature, and respiration rate) measured in sitting position. For C1D1, vital signs will be measured immediately before the start of daratumumab infusion; at 0.5, 1, 1.5, 2, 3.5 hrs after the start of the infusion; at end of infusion; and 0.5 and 1 hr after end of infusion. For all other infusions, vital signs will be measured immediately before infusion start and at end of infusion.
Diary review	X	X	X	X	X	X	X	X	X	Accountability/exposure check.

Preinfusion and Postinfusion Medications, see Section 6.3					
B-cell ALL/LL Cohort Study Drug Administration (28-day cycles), refer to Section 6.1.1 for additional details					
Study Drugs	**Cycle 1**	**Cycle 2**	**Cycle 3-6**	**Cycles 7+**	**Notes**
Intrathecal MTX (all subjects)	D1				Give up to 72 h prior to C1D1 as part of diagnostic LP (IT ARA-C or triple IT therapy are acceptable substitutes). Give prior to daratumumab infusion if given on C1D1.
Vincristine	D1, 8, 15, and 22	D1, 15	D1 of each cycle	D1 of each cycle	Minimum 6 days apart.
Prednisone	D1-28	D1-5	D1-5 of each cycle	D1-5 of each cycle	Dispense on D1 for self-administration. Prednisone should be held on daratumumab infusion days as the pre-infusion steroids substitute for the daily steroid on these days. Taper as clinically indicated per local standard practice.
Daratumumab	D1, 8, 15, 22	D1, 8, 15, 22	D1, D15 of each cycle	D1 of each cycle	Daratumumab should be given after intrathecal therapy but prior to any other scheduled chemotherapy agents.
Intrathecal MTX (CNS negative subjects [CNS 1 or 2])		D1	D1 of each cycle	D1 of each cycle	Give prior to daratumumab infusion.
Intrathecal MTX/HC/ARA-C (CNS positive subjects [CNS 3])	D8, 15, 22, (28)*	D1	D1 of each cycle	D1 of each cycle	Give prior to daratumumab infusion. For CNS positive subjects, triple intrathecal therapy is required on D8, D15, and D22. For subjects who achieve a negative CSF after the first dose of intrathecal therapy, the subject can continue the same schedule but with IT MTX alone. * For subjects who do not have 2 successive negative CSF evaluations, they will receive additional triple intrathecal therapy on D28. If CNS status is not cleared by Day 35, then the subject will be discontinued from study therapy. If a subject requires 4 triple intrathecal treatments, then the start of Cycle 2 must be delayed by 1 week.

T-cell ALL/LL Cohort Study Drug Administration (28-day cycles), refer to Section 6.1.2 for additional details			
Study Drugs	**Cycle 1**	**Cycle 2**	**Notes**
Intrathecal MTX (all subjects)	D1		Give up to 72 h prior to C1D1 as part of diagnostic LP (IT ARA-C or triple IT therapy are acceptable substitutes). Give prior to daratumumab infusion if given on C1D1.
Daratumumab	D1, 8, 15, 22	D1, 8, 15*, 22	Daratumumab should be given after intrathecal therapy but prior to any other scheduled chemotherapy agents. *Hold C2D15 therapy until ANC >0.75x10^9/L and platelets >75x10^9/L.
Vincristine	D1, 8, 15, and 22		Minimum 6 days apart.
Prednisone	D1-28		Dispense on D1 for self-administration. Prednisone should be held on daratumumab infusion days as the pre-infusion steroids substitute for the daily steroid on these days. Taper as clinically indicated per local standard practice.
Doxorubicin	D1		
Peg-asparaginase	D2, D16		Erwinia asparaginase may be substituted; see Section 6.4.6.
Intrathecal MTX (CNS negative subjects [CNS 1 or 2])	D15, D22	D2, D15*	Give prior to daratumumab infusion. *Hold C2D15 therapy until ANC >0.75x10^9/L and platelets >75x10^9/L.
Intrathecal MTX/HC/ARA-C (CNS positive subjects [CNS 3])	D8, D15, D22, D28*	D2, D15^	Give prior to daratumumab infusion. For CNS positive subjects, triple intrathecal therapy is required on D8, D15, and D22. For subjects who achieve a negative CSF after the first dose of intrathecal therapy, the subject can continue the same schedule but with IT MTX alone. * For subjects who do not have 2 successive LPs free of lymphoblasts, they will receive additional triple intrathecal therapy on D28. If CNS status is not cleared, then the subject will be discontinued from study therapy. If a subject requires 4 triple intrathecal treatments, then the start of Cycle 2 must be delayed by 1 week. ^ Hold C2D15 therapy until ANC >0.75x10^9/L and platelets >75x10^9/L.

T-cell ALL/LL Cohort Study Drug Administration (28-day cycles), refer to Section 6.1.2 for additional details (continued)			
Methotrexate		D2	Infusion should begin within 6 hours of IT therapy.
Cyclophosphamide		D15*	*Hold C2D15 therapy until ANC >0.75x10^9/L and platelets >75x10^9/L.
Cytarabine		D16-19; D23-26	
6-mercaptopurine		D15*-28	Dispense on D15 for self-administration. *Hold C2D15 therapy until ANC >0.75x10^9/L and platelets >75x10^9/L.
Both Cohorts: Optional Daratumumab Continuation Phase Prior to Transplant			
Study drug: daratumumab	If given post completion of Cycle 1, administer on D1, D8, D15, D22. If given post completion of Cycles 2 to 6, administer on D1, D15. If given post completion of Cycle 7+, administer once on D1 only.		Continuation phase for subjects who have achieved CR and require a short continuation phase prior to transplant. Allow for a 2-week interval between last dose of daratumumab and start of transplant conditioning regimen. Maximum of 1 cycle of continuation therapy prior to transplant.
Assessment: CBC	Continuation post completion of Cycle 1: D1, D8, D15, D22. Continuation post completion of Cycles 2 to 6: D1, D15. Continuation post completion of Cycle 7+: D1 only.		To be done by local laboratory. Testing may be performed up to 2 days before infusions. Results of hematology tests must be evaluated before each study drug administration.
Assessment: bone marrow aspirate/biopsy	At end of continuation phase if prior assessment was >2 weeks from start of conditioning regimen for bone marrow transplantation		See Section 9.2.2 for details on local and central evaluations. Fresh aspirate required. Biopsy is only required if the aspirate procedure is deemed inadequate. For subjects with LL, on-study bone marrow evaluation is only required if bone marrow disease is present at study entry.

Abbreviations: ALL=acute lymphoblastic leukemia; ARA-C=cytarabine; ANC=absolute neutrophil count; C=cycle; CBC=complete blood cell count; CNS=central nervous system; D=day; EoT=End-of-Treatment; HC=hydrocortisone; IM=intramuscular; IT=intrathecal: IV=intravenous; LL=lymphoblastic lymphoma; LP=lumbar puncture; MTX=methotrexate.

Table 3: Time and Events Schedule –Pharmacokinetics and Immunogenicity

Visit/Timepoint		B-cell ALL/LL Cohort			T-cell ALL/LL Cohort		
		PK Blood Sample[a]	Immunogenicity (taken from PK blood sample)[b]	PK CSF Sample[c]	PK Blood Sample[a]	Immunogenicity (taken from PK blood sample)[b]	PK CSF Sample[c]
Cycle 1 Day 1	predose	X	X	X	X	X	X
	end of infusion	X			X		
Cycle 1 Day 15	predose						X
	end of infusion						
Cycle 2 Day 1	predose	X	X	X	X	X	
	end of infusion	X			X		
Cycle 2 Day 2	predose						X
	end of infusion						
Cycle 2 Day 15	predose						X
	end of infusion						
Cycle 2 Day 22	predose				X		
	end of infusion				X		
Cycle 3 Day 1	predose	X		X			
	end of infusion	X					
Cycle 4 Day 1	predose			X			
	end of infusion						
Cycle 6 Day 1	predose	X	X	X			
	end of infusion	X					
Cycle 9 Day 1	predose	X	X	X			
	end of infusion	X					
EoT		X	X		X	X	
Follow-up		X – 8 weeks (±1 week) after last dose of daratumumab			X – 8 weeks (±1 week) after last dose of daratumumab		

Abbreviations: ALL=acute lymphoblastic leukemia; EoT=end of treatment; IT=intrathecal; LL=lymphoblastic lymphoma; PK=pharmacokinetics.

a. Predose samples may be taken up to 4 hours before the start of the infusion. Postdose samples may be taken immediately after the end of the infusion or up to 2 hours after the end of the infusion.

b. For planned timepoints, no additional sample is required; assessment will be performed on aliquot of PK sample (see Section 9.3.4). If an infusion reaction occurs at the second dose of daratumumab or later, obtain an unscheduled blood sample as soon as possible.

c. PK CSF sample to be collected prior to injection of IT therapy.

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
ALL	acute lymphoblastic leukemia
ANC	absolute neutrophil count
Anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
ARA-C	cytarabine
CAR-T	chimeric antigen receptor T-cell
CDC	complement-dependent cytotoxicity
CI	confidence interval
CNS	central nervous system
COG	Children's Oncology Group
CR	complete response
CRi	complete response with only partial hematological recovery
CRu	complete response unconfirmed
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DRd	daratumumab in combination with lenalidomide and dexamethasone
DVd	daratumumab in combination with bortezomib and dexamethasone
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EFS	event-free survival
EU	European Union
FEV1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	hydrocortisone
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
IAT	indirect antiglobulin test
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
IMiD	immunomodulatory drug
IRB	Institutional Review Board
IRR	infusion-related reaction
IT	intrathecal
LL	lymphoblastic lymphoma
LP	lumbar puncture
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities

MRD	minimal residual disease
MRI	magnetic resonance imaging
MTX	methotrexate
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer (cell)
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PDX	patient-derived xenograft
PFS	progression-free survival
Ph	Philadelphia chromosome
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PQC	product quality complaint
PR	partial response
RBC	red blood cell
Rd	lenalidomide and dexamethasone
RFS	relapse-free survival
SAE	serious adverse event
sCR	stringent complete response
SD	standard deviation
SET	Safety Evaluation Team
SPD	sum of the products of the diameter
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
Vd	bortezomib and dexamethasone
WBC	white blood cell

DEFINITIONS OF TERMS

AUC	area under the concentration-time curve
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration

1. INTRODUCTION

1.1. Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma

Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL) comprise a heterogeneous group of lymphoid disorders that result from a monoclonal proliferation and expansion of immature lymphoid cells in the bone marrow, blood, and other organs.[17] Immunophenotypic analysis permits sub-classification into B-cell and T-cell lineage types. As a result of leukemic blast infiltration of the bone marrow, patients present with signs of bone marrow failure, including anemia, thrombocytopenia, and neutropenia. Clinical manifestations include fatigue, bleeding, and fever. Clinical signs include pallor, petechiae, weight loss, lymphadenopathy, and hepatosplenomegaly. Other symptoms of ALL and LL include bone pain and dyspnea.[25] Central nervous system (CNS) involvement may include leptomeningeal disease or an intracranial or spinal mass.[25] Testicular involvement occurs in less than 3% of boys, who may present with painless testicular enlargement, which is most often unilateral on initial presentation.[25] Patients with mediastinal masses, which commonly occur in T-cell ALL and LL, may present with dyspnea, wheezing, or shortness of breath and possibly with superior vena cava syndrome.

ALL is the most common pediatric malignancy, accounting for up to 30% of newly diagnosed cases of cancer in children.[18] The estimated annual incidence of ALL is 6,500 in the United States (US) and 5,000 in the European Union (EU).[32,42] B-cell ALL accounts for 80 to 85% of cases of ALL and T-cell ALL accounts for approximately 10 to 15% cases of ALL.[35,39] LL is considered a form of non-Hodgkin lymphoma (NHL). It accounts for 20% of NHL in children.[4,34,40] T-cell LL accounts for 75% of the cases of LL and B-cell LL accounts for 25% of cases.[30,40] The World Health Organization classifies LL as the same disease as ALL.[43] As such, both diseases commonly are studied in the same treatment protocols.

1.1.1. Treatment of Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma

While pediatric ALL and LL remain highly curable, 20 to 25% of patients will be refractory to or relapse after frontline treatment.[9,15,31] In B-cell ALL, relapse is risk-stratified and treatment is assigned accordingly based on timing of relapse from initial diagnosis and the site of relapse (extramedullary vs. medullary or combined).[2] For B-cell ALL, depending on the site of relapse and the timing of relapse, 5-year overall survival (OS) ranges from 25% for the very early medullary/combined relapsed patients to 60%-70% for patients with isolated extramedullary relapse.[2] Relapsed T-cell ALL is associated with an even worse prognosis with only 7 to 23% of patients surviving for 3 to 5 years.[16,30] Patients with B-cell LL and T-cell LL have particularly dismal long-term outcomes due to difficulty of achieving second remission, with reported 5-year OS 14% and 8-year OS of 9%.[5,28] The best chance for achieving long-term survival for T-cell ALL and LL is to induce a second complete remission followed by hematopoietic stem cell transplant (HSCT).[2,5]

First re-induction consists of multi-drug chemotherapy with the goal to achieve CR. Additionally, CNS-directed therapy is provided via intrathecal chemotherapy with methotrexate alone or methotrexate with cytarabine and hydrocortisone (triple intrathecal chemotherapy) to clear CNS leukemia or to prophylax against spread of disease to the CNS.[37] For many patients who achieve CR, this is followed by an allogeneic HSCT.

One re-induction regimen (prednisone, vincristine, doxorubicin, and PEG-asparaginase) was evaluated in a single-arm Phase 2 study of patients with relapsed B-cell and T-cell ALL in first relapse. The rate of CR was 68% for patients with B-cell ALL with early relapse (n=63) and 17% for patients with T-cell ALL with early relapse (n=6).[38] The 4-month event-free survival (EFS) was 62% and the 12-month EFS was only 35% for all early relapses (<36 months); no subjects with relapsed T-cell ALL survived longer than 10 months. The most common Grade 3 or higher adverse events in 124 subjects overall other than hematologic toxicity (neutropenia 97.6%, thrombocytopenia 79.8%, and anemia 62.9%) were febrile neutropenia (40.3%), hypofibrinogenemia (32.3%), and infection with Grade 3/4 neutropenia (19.4%). Given the high CR rate and tolerable safety profile of this regimen, this has become the standard backbone for the Children's Oncology Group (COG) with which to evaluate the addition of novel therapies. As such, bortezomib was combined with this standard backbone of prednisone, vincristine, doxorubicin, and PEG-asparaginase, in the Phase 2 COG study AALL07P1 for patients with B-cell ALL in early relapse or T-cell ALL/LL in first relapse.

Several new approaches to treating patients with relapsed B-cell ALL/LL have been developed in the last 5 years, including agents that target CD19, such as the bispecific antibody blinatumomab. The CR rate after single-agent blinatumomab treatment for relapsed/refractory B-ALL was 39%.[47] This agent is now being evaluated in combination with chemotherapy for the treatment of patients with relapsed B-cell ALL. However, neurological toxicity is a concern with this agent and can lead to treatment interruptions or discontinuations.

Another strategy being actively investigated in ALL is chimeric antigen receptor (CAR) T-cell immunotherapy. Among 30 subjects (25 pediatric, 5 adult) with relapsed or refractory ALL treated with CTL019, there was a CR rate of 90% at 1 month post-infusion.[27] At 6 months, the EFS rate was 67% and the OS rate was 78%. Cytokine-release syndrome was seen in all subjects (mild to moderate in 22 subjects and severe [requiring intensive care with respiratory support] in 8 subjects), while neurologic toxic effects were seen in 13 subjects. Long-term outcomes remain unclear with this novel therapy.

Inotuzumab ozogamicin, an antibody-drug conjugate targeting CD22, has been evaluated in adults; however, while initial response rates are high (CR of 80.7%) in the Phase 3 pivotal trial, the duration remains short with a median OS of only 5 months.[20] Liver-related toxicity is common with 11% of subjects experiencing veno-occlusive disease. This agent is now being evaluated in children.

The most recent drug approved for T-cell ALL/LL is nelarabine, which was approved in 2005.[23] In a phase 2 study, nelarabine treatment resulted in an overall response rate (ORR) of 55% (n=34) and CR rate of 47% for patients with T-cell ALL in first relapse/refractory disease and an ORR of 43% with a CR rate of 14% in patients with relapsed T-cell LL (n=7).[1] Nelarabine has significant neurologic toxicity that can be irreversible. Combining nelarabine with cyclophosphamide and etoposide as a re-induction regimen for relapsed T-cell ALL/LL resulted in a 44% CR rate in subjects with T-cell ALL/LL in first relapse.[48]

While novel treatment modalities including BiTEs (blinatumomab), monoclonal antibodies (mAbs) (inotuzumab), CAR T-cell immunotherapy, and the deoxyguanosine analogue nelarabine have shown improved rates of complete remission in relapsed/refractory ALL/LL, these gains have not translated to improvements in median OS and duration of response remains limited. Additionally, these novel agents have significant side effects that influence their tolerability. New agents are needed with improved safety profiles and the ability to improve duration of response and long-term survival in relapsed/refractory B-cell and T-cell ALL/LL.

1.2. Daratumumab for Intravenous Infusion

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including multiple myeloma. Daratumumab induces lysis of CD38-expressing tumor cells, including multiple myeloma tumor cells that were freshly isolated from patients, by a wide spectrum of mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis, through activation of complement proteins, natural killer (NK) cells, and macrophages, respectively.[10,33]

In the US, intravenously administered daratumumab is indicated for use as follows: (1) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy; (2) in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor; (3) as monotherapy, for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) or who are double refractory to a PI and an IMiD.

In the EU, daratumumab IV is indicated for use as follows: (1) as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy; (2) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the Investigator's Brochure. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.2.1. Nonclinical Studies

CD38 is expressed in many hematologic malignancies including multiple myeloma, chronic lymphocytic leukemia, ALL, acute myeloid leukemia, NK cell leukemia, and NK/T-cell lymphoma.[45] For daratumumab to be an effective agent for pediatric leukemias, the CD38 target must be present on pediatric ALL cells. Therefore, several studies were conducted to evaluate CD38 expression and daratumumab efficacy in leukemia cell lines, patients' samples, and xenograft mouse models.

Quantitative flow cytometry analysis of 9 ALL cell lines showed that CD38 expression levels varied among cell lines, but the majority (n=8/9) had >3000 CD38 receptors per cell.[11] CD38 was also expressed on a large proportion of tumor cells from patients with pediatric and adult B-cell and T-cell ALL (Table 4).[3] CD38 expression level was comparable in pediatric and adult B-cell ALL.[3] CD38 expression levels were also comparable in pediatric T-cell ALL and T-cell LL.[46] Furthermore, average CD38 receptor density in B-cell (91,000 receptors/cell[b]) or T-cell (118,000 receptors/cell[b]) ALL blasts from adult patient samples was comparable to that observed in multiple myeloma[34] (125,000 receptors/cell, n=10).

Table 4: Percent of CD38+ Tumors in Pediatric and Adult Patient ALL Samples

Condition	Assay	Pediatric Samples[a]	Adult Samples[b]
T-cell ALL	Flow	100% (n=15)	91% (n=20)
B-cell ALL	Flow	85% (n=115)	78% (n=59)
MM[a]	Flow	Not applicable	100% (n=49)

Abbreviation: ALL=acute lymphoblastic leukemia; MM=multiple myeloma.
a. Samples with greater than 70% of the tumor expressing CD38. Positive expression was based on a threshold greater than 10^3 mean fluorescence intensity (a receptor density surrogate) established from a CD38 negative tumor.
b. Percent of CD38+ ALL tumors was derived based on conversion of receptors/cell to percent CD38 positive tumors. Positive expression was based on a threshold greater than 30,000 CD19 receptors/cell.
Source: Bras 2016[3]; Data on file.

In vitro studies were conducted to evaluate several of daratumumab's mechanisms of action. CD38 expression was sufficient to induce daratumumab-mediated CDC, ADCC, and apoptosis in ALL cell lines (Table 5).[11] Daratumumab induced ≥20% apoptosis in 6 of 9 cell lines in the presence of a cross-linking agent. Evaluation of effector cell and complement-mediated tumor cell-killing assays revealed limited killing by CDC (max 5%); however, >10% ADCC occurred in 6 of 9 cell lines. These observations support previously reported studies showing that CD38 antibody-drug conjugates were sufficient to induce in vitro killing of ALL cell lines.[13] While no clear threshold/correlation was observed between CD38 expression and daratumumab-induced killing, other factors, possibly disease related, may also influence daratumumab activity.

Table 5: Efficacy of Daratumumab in ALL Cell Lines

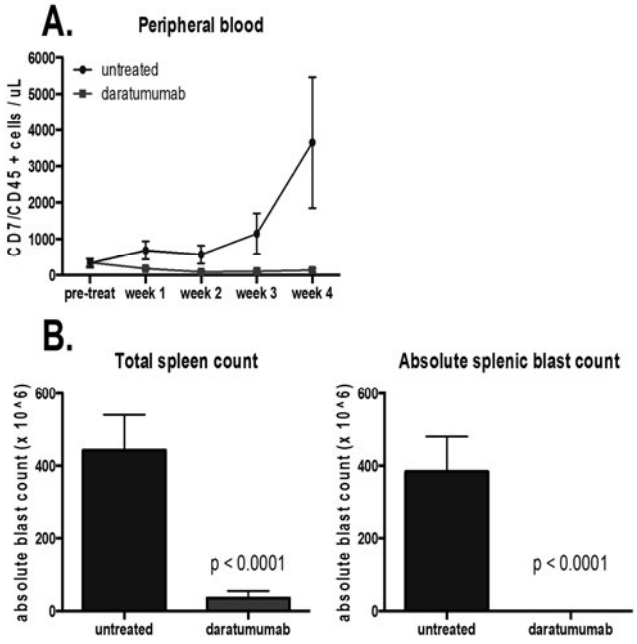
Mechanisms of Daratumumab-induced Cell Death in ALL Cell Lines			
	Mechanism of cell death		
Cell lines	Apoptosis with crosslinker (%)	CDC (%)	ADCC (%)
NALM-6	22	5	9.9
Molt-4	45	4	17.7
PEER IE6	20	3	5.0
RS4;11	40-50	3	15.8
MHH-CALL-2	40-50	0	14.7
Jurkat	24	0	18.9
CCRF-SB	9	5	13.0
MUTZ-5	14	2	11.0
SUP-B15	8	5	8.5

ALL, acute lymphoblastic leukemia; CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity.

Abbreviations: ADCC=antibody-dependent cell-mediated cytotoxicity; ALL=acute lymphoblastic leukemia; CDC=complement-dependent cytotoxicity.
Source: Data on file

In vivo cell line xenograft and patient-derived xenograft (PDX) models were investigated to further qualify daratumumab efficacy. A xenograft NALM-6 cell line model treated with daratumumab alone or combined with vincristine exhibited prolonged survival compared with vehicle or vincristine alone ($p<0.001$).[11] In adult PDX mouse models, single-agent daratumumab showed strong anti-tumor effects compared with control-treated animals in both B-cell ALL ($p<0.001$) and T-cell ALL ($p<0.05$). This therapeutic benefit was corroborated in 23 ALL pediatric PDX mouse models, in which strong anti-tumor effects were observed when daratumumab monotherapy was administered compared with control-treated animals (B-cell ALL, n=2/5; T-cell ALL n=10/18). Of note, daratumumab monotherapy was highly efficacious in aggressive subsets of early T-cell precursor ALL pediatric PDX models (n=8/9) (data on file; Figure 1).

Figure 1: Efficacy of Daratumumab in ALL PDX models



Abbreviations: ALL=acute lymphoblastic leukemia; ETP=early T-cell precursor; PDX= patient-derived xenograft.
Single-agent daratumumab efficacy was observed in both pediatric B-cell and T-cell ALL (ETP [above] and non-ETP) PDX models by reduction in blast counts from peripheral blood (A) and spleen (B).
Source: Data on file.

These data suggest that daratumumab significantly inhibits tumor growth and induces long-term tumor regression in CD38-expressing adult and pediatric ALL xenograft models.

Expression of CD38 on ALL cell lines and primary adult and pediatric patient samples coupled with multiple daratumumab mechanisms of action in vitro and in vivo suggest that CD38 may be targeted with daratumumab for the treatment of pediatric ALL/LL. CD38 is a distinct target from those of other approved agents for ALL/LL therapy. Therefore, treatment with daratumumab offers a promising new approach to treating ALL/LL.

1.2.2. Clinical Studies

Daratumumab was initially developed as a treatment for multiple myeloma. There is a comprehensive development plan across various hematologic malignancies. As of 30 June 2017, approximately 2700 subjects have been treated with daratumumab monotherapy or combination therapy in 21 clinical studies.

1.2.2.1. Monotherapy Studies

Daratumumab as monotherapy induces deep and durable responses in subjects with heavily pretreated multiple myeloma. Phase 2 Study MMY2002 and Phase 1/2 Study GEN501 Part 2 (Part 1 was the dose-escalation phase of this first-in-human study) were both single-arm, open-label studies in which subjects with relapsed and refractory multiple myeloma were administered IV daratumumab as monotherapy weekly for 8 weeks, every 2 weeks for an

additional 16 weeks, and every 4 weeks thereafter until disease progression or unacceptable toxicity. One hundred forty-eight (148) subjects treated with IV daratumumab 16 mg/kg monotherapy were included in a combined analysis of efficacy in Study GEN501 and Study MMY2002. The ORR for the combined data set was 31% (95% confidence interval [CI], 23.7%-39.2%). Responses included 3 subjects with stringent complete response (sCR; 2.0%), 4 subjects with CR (2.7%), 13 subjects with very good partial response (8.8%) and 26 subjects with partial response (PR; 17.6%). Within the individual studies, the ORR was 35.7% (95% CI, 21.6%-52.0%) in Study GEN501 and 29.2% (95% CI, 20.8%-38.9%) in Study MMY2002. After a median duration of follow-up of 20.7 months, the Kaplan-Meier based median OS was 20.1 months.

Among 156 subjects treated with IV daratumumab 16 mg/kg as monotherapy in Studies GEN501, MMY2002, and MMY1002 (a single-arm, open-label Phase 1 study of PK and safety conducted in Japanese subjects), 6 subjects (4%) discontinued treatment due to a treatment-emergent adverse event (TEAE). Three subjects (2%) died due to TEAEs. The most frequently reported TEAEs were fatigue (40%), nausea (28%), anemia (28%), back pain (26%), cough (24%), neutropenia (23%), pyrexia (22%), upper respiratory tract infection (22%), and thrombocytopenia (21%). Serious adverse events (SAEs) were reported in 34% of subjects; the most frequently reported SAEs were pneumonia (6%), pyrexia (3%), hypercalcemia (3%), and general physical health deterioration (3%).

1.2.2.2. Combination Therapy Studies

Two Phase 3 studies examined the safety and efficacy of IV daratumumab in combination with other therapies in the treatment of relapsed multiple myeloma:

- In Study MMY3003, subjects with multiple myeloma received IV daratumumab in combination with lenalidomide and dexamethasone (DRd). At the time of the first interim analysis, treatment with DRd resulted in a 63% reduction in the risk of disease progression or death compared with Rd alone. The median progression-free survival (PFS) was not reached in the daratumumab group; median PFS was 18.4 months in the Rd group. The ORRs were 91% for the DRd group and 75% for Rd group.
- In Study MMY3004, subjects with multiple myeloma received IV daratumumab in combination with bortezomib and dexamethasone (DVd). At the time of the first interim analysis, treatment with DVd showed a 61% reduction in the risk for disease progression or death compared with Vd alone. The median PFS was not estimable in the DVd group; median PFS was 7.2 months, in the Vd group. The ORRs were 79% for the DVd group and 60% for the Vd group.

1.2.2.3. Pharmacokinetics

Pharmacokinetic data are not available in pediatric subjects. In adult subjects with multiple myeloma, over the dose range of 1 to 24 mg/kg as monotherapy or 1 to 16 mg/kg of daratumumab in combination with other treatments, increases in area under the concentration-time curve (AUC) were more than dose-proportional. Following the recommended dose of 16 mg/kg when daratumumab was administered as monotherapy or in combination therapy, the mean serum maximal concentration (C_{max}) value at the end of weekly dosing was

approximately 2.7- to 3-fold higher compared with the mean serum C_{max} following the first dose. The mean ± standard deviation (SD) trough serum concentration (C_{min}) at the end of weekly dosing was 573 ± 332 µg/mL when daratumumab was administered as monotherapy and 502 ± 196 to 607 ± 231 µg/mL when administered as combination therapy. Daratumumab steady-state was achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion). The mean ± SD ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6 ± 0.5. In the current study, subjects with B-cell ALL would expect to reach steady-state in this same timeframe (approximately the twenty-first daratumumab infusion) while subjects with T-cell ALL would stop therapy after 8 weekly doses of daratumumab and therefore not reach a steady-state concentration. At the recommended dose of 16 mg/kg, the mean ± SD central volume of distribution was 4.7 ± 1.3 L when administered as monotherapy and 4.4 ± 1.5 L when administered as combination therapy. Daratumumab clearance decreased with increasing dose and with multiple dosing. At the recommended dose of 16 mg/kg of daratumumab as monotherapy, the mean ± SD linear clearance was estimated to be 171.4 ± 95.3 mL/day. The mean ± SD estimated terminal half-life associated with linear clearance was 18 ± 9 days when daratumumab was administered as monotherapy and 23 ± 12 days when daratumumab was administered as combination therapy.

1.3. Overall Rationale for the Study

Patients with relapsed B-cell ALL/LL or patients with refractory disease have dismal prognoses. While several active agents exist for B-cell ALL/LL in first relapse, there is a subset of patients whose disease relapses a second time or remains resistant to these therapies. For these patients, with each subsequent relapse, the leukemia becomes more resistant to chemotherapy due to loss of antigens and other resistance mechanisms. These patients are also accumulating organ toxicity with exposure to each subsequent salvage therapy.[22] Thus, novel agents with novel targets and limited toxicity are needed for patients with relapsed or refractory B-cell ALL/LL. Hence, daratumumab, which targets a novel antigen for B-cell ALL/LL, will be combined with the less intensive regimen of vincristine and prednisone for the heavily pretreated group of patients who are now experiencing a second or greater relapse of disease.

Treating relapsed T-cell ALL/LL in pediatric patients is challenging as responses to standard agents remain poor and no efficacious novel agents are available. Thus, daratumumab, which targets a novel antigen for T-cell ALL/LL, will be added to a standard intensive induction and consolidation regimen in this study for patients in first relapse or with refractory disease.

CD38 provides a novel treatment approach for both B-cell and T-cell ALL/LL in settings in which treatment resistance to the standard chemotherapies is seen. Daratumumab may be used in combination with other targeted agents or standard chemotherapy with minimal additional toxicity, which has been done successfully in multiple myeloma studies. Thus, daratumumab has the potential to provide therapeutic benefit for patients with relapsed/refractory B-cell or T-cell ALL/LL.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective is to evaluate the efficacy of daratumumab in addition to standard chemotherapy in pediatric subjects with relapsed/refractory B-cell ALL and T-cell ALL as measured by the CR rate.

Secondary Objectives

The secondary objectives include the following:

- To assess the efficacy of daratumumab in addition to standard chemotherapy, including ORR, relapse-free survival (RFS), EFS, and OS in pediatric subjects with B-cell and T-cell ALL, and minimal residual disease (MRD) negative rate in subjects with B-cell and T-cell ALL
- To assess the safety and tolerability of daratumumab in addition to standard chemotherapy in pediatric subjects with B-cell and T-cell ALL
- To assess the PK of daratumumab in pediatric subjects with B-cell and T-cell ALL
- To assess daratumumab immunogenicity in pediatric subjects with B-cell ALL and T-cell ALL
- To assess daratumumab concentration in cerebrospinal fluid (CSF)

Exploratory Objectives

The exploratory objectives include the following:

- To explore biomarkers predictive of response or resistance to therapy
- To assess expression of CD38 at study entry and at relapse

2.1.2. Endpoints

Primary Endpoint

The primary endpoint is CR rate within 2 cycles of therapy for B-cell ALL and at the end of Cycle 1 for T-cell ALL. CR is defined as:

- Less than 5% blasts in the bone marrow
- No evidence of circulating blasts or extramedullary disease
- Full recovery of peripheral blood counts:
  - Platelets >$100x10^9$/L
  - Absolute neutrophil count (ANC) >$1.0x10^9$/L

Secondary Endpoints

The secondary endpoints include:

- ORR, defined as CR or CRi for ALL
  - CR is defined as above
  - CRi is defined as:
    - Less than 5% blasts in the bone marrow
    - No evidence of circulating blasts or extramedullary disease
    - Partial recovery of peripheral blood counts not meeting criteria for CR noted above
- EFS, defined as the time from the date of first treatment to the first documented treatment failure (ie, disease progression) or date of relapse from CR or death due to any cause, whichever occurs first
- RFS, defined as the time from CR to relapse from CR or death due to any cause, whichever occurs first
- OS, defined as the time from the date of first treatment to the date of death due to any cause
- MRD negative rate, defined as the proportion of subjects who are MRD negative
- Proportion of subjects who receive an allogeneic HSCT after treatment with daratumumab
- PK of daratumumab (C_{max} and C_{min})
- Daratumumab immunogenicity incidence
- Concentration of daratumumab in CSF

Exploratory Endpoints

The exploratory endpoints include:

- Biomarkers predictive of response or resistance to therapy
- Expression of CD38 at study entry and at relapse

Refer to Section 9, Study Evaluations, for evaluations related to endpoints.

2.2. Hypothesis

The primary hypothesis for each ALL subtype is as follows:

- For relapsed/refractory precursor B-cell ALL, treatment with daratumumab in combination with vincristine and prednisone will result in a CR rate of 40% or higher.

- For relapsed/refractor T-cell ALL, treatment with daratumumab in combination with doxorubicin, prednisone, vincristine, and asparaginase will result in a CR rate of 60% or higher.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This open-label, multicenter, Phase 2 study will enroll approximately 49 subjects aged ≥1 to <18 years with relapsed/refractory ALL and a maximum of 69 total subjects ≥1 and ≤30 years of age with relapsed/refractory ALL/LL. Cohort 1 will evaluate the safety and efficacy of daratumumab in combination with vincristine and prednisone in subjects with B-cell ALL/LL in second relapse or greater. Cohort 2 will evaluate the safety and efficacy of daratumumab in combination with a standard 4-drug re-induction regimen (prednisone, vincristine, doxorubicin, and PEG-asparaginase) in subjects with T-cell ALL/LL in first relapse.

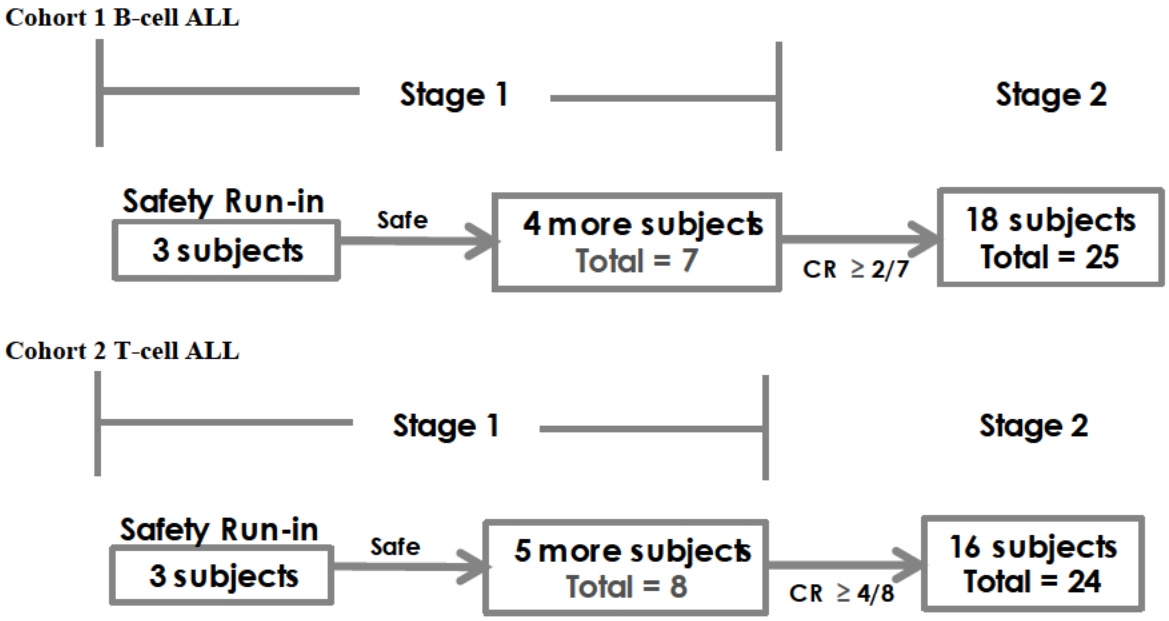
Subject participation will include a Screening Period, a Treatment Period, and a Posttreatment Period. The Screening Period will be up to 21 days before first dose. During the Treatment Period, cycles are 28 days. Subjects with B-cell ALL/LL will receive treatment until disease progression, unacceptable toxicity, or achievement of CR followed by HSCT. Subjects with T-cell ALL/LL will receive treatment for up to 2 cycles (induction and consolidation). There is an optional maintenance phase for all subjects who achieve CR and need to bridge therapy until an allogeneic HSCT. The Posttreatment Period begins immediately following the End-of-Treatment Visit, and will continue until death, loss to follow-up, or consent withdrawal for study participation, whichever occurs first.

A diagram of the study design is provided below in Figure 2. The study has 2 stages. Stage 1 will evaluate the initial safety and efficacy in each cohort. Only B-cell or T-cell ALL subjects aged 1 to <18 years will be enrolled in their respective cohorts in Stage 1. Stage 1 will include a safety run-in which will evaluate the initial 3 subjects with B-cell ALL and initial 3 subjects with T-cell ALL. Enrollment will continue after safety is confirmed in each cohort separately. After confirming safety (see Section 3.4), Cohort 1 (B-cell ALL) will enroll an additional 4 subjects aged 1 to <18 years in Stage 1 and Cohort 2 (T-cell ALL) will enroll an additional 5 subjects aged 1 to <18 years in Stage 1. During Stage 1, the dose of daratumumab will be evaluated with ongoing PK analysis to confirm the therapeutic dose of daratumumab to be used in Stage 2 of the study. The study will have a futility analysis for each cohort after Stage 1 is completed before enrolling subjects to Stage 2 (see Section 11.2). All subjects enrolled into Stage 1, including subjects in the safety run-in at the confirmed safe dosing regimen will be included in the futility analysis.

In Stage 2, an additional 18 subjects with B-cell ALL and 16 subjects with T-cell ALL aged 1 to <18 years will be enrolled for a total of 25 subjects with B-cell ALL and 24 subjects with T-cell ALL aged 1 to <18 years. The sponsor plans to enroll a minimum of 3 subjects with ALL in each of the following age groups in both cohorts if an individual cohort proceeds to Stage 2: 1 to 6, 7 to 12, and 13 to <18 years. In Stage 2 subjects with LL and young adults with ALL will also be enrolled. A maximum of 10 subjects aged 1 to 30 years with LL and a maximum of 10 subjects aged 18 to 30 years with ALL will be enrolled to the respective B-cell and T-cell cohorts. The data from these subjects with LL (pediatric and young adult) and young adult subjects aged 18 to 30 years with ALL will be descriptively summarized.

The primary endpoint of the study is CR rate in subjects with ALL aged 1 to <18 years. For B-cell ALL, the timepoint for evaluation of CR was chosen as within 2 cycles to allow time for optimal response with a 3-drug regimen which may take longer than a traditional 4-drug induction. For T-cell ALL, the timepoint for evaluation of CR is at the end of Cycle 1, as most subjects are expected to achieve CR with the 4-drug combination with daratumumab and then proceed quickly to allogeneic HSCT off study.

Figure 2: Schematic Overview of the Study



Abbreviations: ALL=acute lymphoblastic leukemia; CR=complete response; LL=lymphoblastic lymphoma.
Note: In addition to the pediatric subjects with ALL included in this study, young adult subjects with ALL, aged 18 to 30 years, and subjects with LL, aged 1 to 30 years, will be enrolled in Stage 2.

3.2. Study Design Rationale

Given the differences in the response to relapse therapy and in the relapse regimens currently available, B-cell ALL/LL and T-cell ALL/LL will be studied in separate cohorts.

Several active agents and regimens exist for B-cell ALL/LL in first relapse, which have high response rates, however the duration of response remains short. Thus, there is a subset of patients whose disease will relapse a second time or may remain resistant to these therapies. These therapies have many associated toxicities, thus patients in second relapse or greater have difficulty tolerating intensive regimens due to accumulated organ damage and as a result response rates are lower, and outcomes are extremely poor. As such, this is the appropriate patient population to explore novel agents. Thus, Cohort 1 will include subjects with B-cell ALL/LL in second or greater relapse or refractory to at least 2 prior induction regimens.

In Cohort 1, subjects with B-cell ALL/LL will be treated with daratumumab in combination with vincristine and prednisone with the intent to achieve CR. There are no standard therapies for B-cell ALL in second relapse or greater. Treatment is generally tailored to individual patients based on prior therapies and residual toxicities. Vincristine and prednisone are active agents that are commonly used in this setting and the toxicity profile is amenable to the addition of daratumumab. Additionally, preclinical data with daratumumab combined with vincristine showed promising results in a xenograft model (see Section 1.2). CNS-directed therapy will be provided according to standard of care according to CNS status (CNS 1, 2, or 3). Treatment of testicular disease, if present, will proceed according to institutional standards.

In contrast, there are very few active agents or regimens for T-cell ALL/LL in first relapse. Response rates and long-term outcomes are dismal for any patients with T-cell ALL/LL who relapse or are resistant to initial therapy. Further intensification of re-induction is required to improve outcomes by adding novel agents to standard re-induction therapy for T-cell ALL/LL patients in first relapse. Thus, Cohort 2 will include subjects with T-cell ALL/LL in first relapse or refractory to at least 1 prior induction/consolidation regimen.

In Cohort 2, subjects with T-cell ALL/LL will be treated with daratumumab in combination with a standard 4-drug re-induction regimen. Several re-induction regimens have been utilized by various cooperative groups. However, based on the toxicity profile of these induction regimens, the 4-drug combination of doxorubicin, prednisone, vincristine, and PEG-asparaginase appears to be most amenable to the addition of a novel agent as toxic deaths and severe infections were lower with this regimen than other standard re-induction regimens such as the R3 regimen. The second cycle of therapy is optional to allow further treatment for those subjects who do not achieve CR after the first cycle of therapy or to consolidate the response prior to HSCT. The second cycle of therapy is a combination of therapy commonly utilized in the relapsed setting for T-cell ALL/LL. Subjects who achieve CR after Cycle 1 or 2 are expected to proceed to allogeneic HSCT off study. For those subjects who do not achieve CR after 2 cycles of therapy, treatment will be continued off study at the investigator's discretion. CNS treatment will follow the standard of care for relapsed T-cell ALL/LL according to CNS status (CNS 1, 2, or 3). Treatment of testicular disease, if present, will proceed according to institutional standards.

There is growing evidence that EFS and OS are better when pediatric protocols are utilized in treating young adults.[19] Therefore, a maximum of 10 young adult subjects (aged 18 to 30 years) will be included in Stage 2 to evaluate the safety and efficacy in this patient population to inform future studies and the data will be summarized descriptively by cohort as B-cell or T-cell lineage. Additionally, a maximum of 10 subjects with LL aged 1 to 30 years will be included in Stage 2 of the study to establish safety in efficacy in this patient population to inform future studies. Patients with LL historically have a worse prognosis and different methodology for response assessment compared to ALL, therefore subjects with LL will be summarized descriptively by cohort as B-cell or T-cell lineage.

3.3. Dose Rationale

There are no PK data for daratumumab in pediatric subjects. The sponsor plans to analyze the PK of daratumumab during this Phase 2 study to confirm the pediatric dose.

As an IgG1κ mAb, daratumumab is presumably biotransformed by degradation into small peptides and amino acids by catabolic pathways.[26,44] These biotransformation pathways are expected to be similar in adults and children. A comparison of PK parameters for most mAbs shows comparable PK for adults and the pediatric population, especially for patients older than 12 years after adjusting for body size.[49] Some differences in clearance and volume can be observed in children under 12 years of age, which may require a dose adjustment (typically a higher dose) to achieve similar concentrations as older subjects; assessment of PK exposure and response, as is planned in this study, is warranted to confirm the dose in these subjects.

Daratumumab exhibits target-mediated drug disposition, and therefore a complex nonlinear, non-stationary PK. Daratumumab binds to CD38 receptors in the body. The complex with daratumumab is rapidly cleared. As the dose is increased, and after repeated administration, CD38 becomes saturated, and the effect of target binding clearance is minimized. The PK of daratumumab may be similar in adult multiple myeloma and pediatric subjects, because the target (receptor) density is similar in adult multiple myeloma and pediatric ALL cell lines. A population PK model was developed for daratumumab for adult patients with multiple myeloma. Model-based population PK simulations have been conducted for subjects aged 1 to 18 years, demonstrating that based on PK considerations, the 16 mg/kg IV dose may be a feasible starting dose to be evaluated in this Phase 2 pediatric study. As expected, younger patients with lower body weight tend to have slightly lower concentrations when adult standard mg/kg dose is given. This is consistent with the allometric theory which suggests that CL cannot be adjusted proportionally with weight.[49] Nonetheless, the standard 16 mg/kg dose and schedule for daratumumab could produce >99% and >90% target saturation after weekly dosing and every 4 week dosing, respectively, in all age groups based on the primary simulation scenario.[49]

The PK samples collected during the first 2 cycles from the first 10 subjects will be evaluated to confirm that the exposure is within the range of the adult multiple myeloma data. Further evaluations of the PK, efficacy, and safety data from Stage 1 may be performed to confirm the dose for Stage 2 of the study.

3.4. Dose-Limiting Toxicity

During the safety run-in, 3 subjects in each cohort will be evaluated for dose-limiting toxicities (DLTs). A Safety Evaluation Team (SET) (see Section 11.8) will review the DLT data and determine whether a modification to the dose or schedule of study drugs is needed for any of the treatment cohorts. The DLT Evaluation Period is defined as the first 28 days from the start of the first dose of daratumumab. DLTs will be evaluated in each cohort separately at the end of Cycle 1. Only toxicities that occur during the DLT evaluation period will be used for the purpose of defining DLT and for subsequent dose or dosing schedule modifications or safety-run in expansion. However, toxicities that occur in all cycles will be considered in the overall decisions of the SET. If a subject receives less than 75% of the planned dose of daratumumab for reasons

other than toxicity (eg, disease progression, subject withdrawal, etc.), that subject will be considered non-evaluable for DLTs and may be replaced, but the safety profiles of these subjects will be included in the SET review. Additional safety reviews will be conducted by the SET after Stage 1 of the study in each cohort and as deemed necessary during the conduct of the study.

The following DLT guidelines will apply to each cohort separately:

- If DLT is not observed in the initial 3 subjects treated with 16 mg/kg of daratumumab for a given combination regimen, then that combination regimen will be considered safe and well-tolerated and the cohort may continue to enroll to pre-specified numbers.
- If DLT is observed in 1 of the initial 3 subjects, then the safety-run in will be expanded to 6 subjects.
    - If 1/6 subjects treated with 16 mg/kg of daratumumab for a given combination regimen experience a DLT, then that combination regimen will be considered safe and well-tolerated and the cohort may continue to enroll to pre-specified numbers.
    - If ≥2/6 subjects experience a DLT, then that combination regimen will be considered not safe unless the events are due to unexpected circumstances clearly not related to a study procedure or treatment (eg, a passenger in an automobile accident). The dose or schedule of study drugs may be adjusted and a new safety run-in may begin or the cohort may be closed. Three new subjects may be treated at a lower dose or adjusted schedule for a given combination regimen. The safety run-in will follow the rules above.
- If DLT is observed in ≥2 of the initial 3 subjects, then that combination regimen will be considered not safe unless the events are due to unexpected circumstances clearly not related to a study procedure or treatment (eg, a passenger in an automobile accident). The dose or schedule of study drugs may be adjusted and a new safety run-in may begin or the cohort may be closed. Three new subjects may be treated at a lower dose or adjusted schedule for a given combination regimen. The safety run-in will follow the rules above.

3.5. Dose Tolerability Evaluation Guidelines

DLTs will be evaluated at the end of Cycle 1. Only toxicities that occur during the DLT evaluation period will be used for the purposes of defining DLT and for subsequent dose modifications or cohort expansion. However, toxicities that occur in all cycles will be considered in the overall decisions of the SET. Subjects considered non-evaluable for DLTs (ie, a subject who receives less than 75% of the planned dose of daratumumab for reasons other than toxicity) may be replaced, but the safety profiles of these subjects will be included in the SET review.

DLTs are based on daratumumab-related toxicities and defined as any of the following events in the DLT evaluation period. However, infusion-related reactions (IRRs) may result from either the first infusion or subsequent infusions. Noncompliance with the protocol-defined requirements for infusion of the study drug may influence the evaluation of DLTs. If noncompliance with the protocol-defined requirements (eg, antiviral prophylaxis) results in toxicities of ≥Grade 3, then these toxicities will not qualify as DLTs.

The following are considered to be DLTs:

- Grade 4 IRR occurring within 48 hours of the infusion of daratumumab
- Grade 3 IRR occurring within 48 hours of the infusion of daratumumab that does not resolve after the initiation of supportive care and symptomatic therapy such as administration of glucocorticoid and antihistamine
- Non-hematologic toxicity of Grade 4 that occurs after the first dose of daratumumab and is considered related to daratumumab with the following exceptions **for Cohort 2 only**:
  - Fever or infection
  - Gastrointestinal symptoms (anorexia, vomiting, dehydration, mucositis)
  - Hypofibrinogenemia
  - Metabolic/laboratory abnormalities that resolve to ≤Grade 2 within 7 days
  - Tumor lysis syndrome or hyperuricemia
- Non-hematologic toxicity Grade 3 or higher that is considered related to daratumumab and results in delay of the subsequent course of chemotherapy for >7 days, with the exception of fever or infection
- Persistent neutropenia (ANC $<0.5x10^9$/L) or thrombocytopenia ($<50x10^9$/L) without transfusion) lasting longer than 45 days from Cycle 1 Day 1 that is not clearly due to another identifiable factor such as persistent disease, leukemia progression/relapse, or infection

The rate and severity of infections will be evaluated at the end of Stage 1 to confirm safety of the regimens before proceeding to Stage 2.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 21 days before administration of the study drug. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, then the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

Each potential subject must satisfy all the following criteria to be enrolled in the study:

1. ≥1 and ≤30 years of age.

2. Documented ALL or LL as defined by the criteria below:
   - B-cell cohort:
     - Stage 1:
       - ALL in second or greater relapse or refractory to 2 prior induction regimens with ≥5% blasts in the bone marrow and aged 1 to <18 years
     - Stage 2:
       - ALL in second or greater relapse or refractory to 2 prior induction regimens with ≥5% blasts in the bone marrow and aged 1 to 30 years
       - LL in second or greater relapse or refractory to 2 prior induction regimens and biopsy proven and with evidence of measurable disease by radiologic criteria and aged 1 to 30 years (see Section 9.2.1.4)
   - T-cell cohort:
     - Stage 1:
       - ALL in first relapse or refractory to 1 prior induction/consolidation regimen with ≥5% blasts in the bone marrow and aged 1 to <18 years
     - Stage 2:
       - ALL in first relapse or refractory to 1 prior induction/consolidation regimen with ≥5% blasts in the bone marrow and aged 1 to 30 years
       - LL in first relapse or refractory to 1 prior induction/consolidation regimen biopsy proven and with evidence of measurable disease by radiologic criteria and aged 1 to 30 years (see Section 9.2.1.4)
3. Performance status ≥70 by Lansky scale (for subjects <16 years of age) or Karnofsky scale (for subjects ≥16 years of age) (Attachment 1).

4. Adequate hematology laboratory values at Cycle 1 Day 1 pre-dosing defined as follows:

   a. Hemoglobin ≥7.5 g/dL (≥5 mmol/L; prior red blood cell [RBC] transfusion is permitted)

   b. Platelet count ≥10×10^9/L (prior platelet transfusion is permitted)

5. Criterion modified per Amendment 2

Criterion modified per Amendment 3

5.2 Adequate renal function defined as normal serum creatinine for the subject's age or creatinine clearance or radioisotope glomerular filtration rate (GFR) ≥70 mL/min/1.73 m^2 prior to enrollment (see Attachment 3).

6. Criterion modified per Amendment 1

Criterion modified per Amendment 2

6.2 Adequate liver function prior to enrollment defined as:

a. Alanine aminotransferase level ≤2.5x the upper limit of normal (ULN),

b. Aspartate aminotransferase level ≤2.5xULN, and

c. Total bilirubin ≤2x ULN or direct bilirubin level ≤2.0xULN

7. Criterion modified per Amendment 2

7.1 Female subjects of childbearing potential (defined as post-menarchal and sexually active until becoming post-menopausal unless permanently sterile) must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously during the Treatment Period, during any dose interruptions, and for 12 months after the last dose of any component of the treatment regimen. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. Birth control methods must include one highly effective method of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants], or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.

8. Criterion modified per Amendment 2

8.1 During the study and for 12 months after receiving the last dose of any component of the treatment regimen, female subjects must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

9. Male subjects of reproductive potential who are sexually active with females of reproductive potential must always use a latex or synthetic condom during the study and for 6 months after discontinuing study treatment (even after a successful vasectomy).

10. Male subjects of reproductive potential must not donate sperm during the study or for 6 months after the last dose of study treatment.

11. The informed consent form (ICF) must be signed by a legally authorized representative or by the subject if at legal age of consent indicating understanding of the purpose of, and procedures required for, the study and willingness to participate in the study. Assent is also required of children capable of understanding the nature of the study according to country-specific or site-specific standards as described in Section 16.2.3, Informed Consent and Assent Form.

12. Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Received an allogeneic hematopoietic transplant within 3 months of screening.

2 Active acute graft-versus-host disease of any grade or chronic graft-versus-host disease of Grade 2 or higher.

3. Criterion modified per Amendment 1

   3.1 Received immunosuppression post hematopoietic transplant within 1 month of study entry.

4. Philadelphia chromosome positive (Ph+) B-cell ALL eligible for tyrosine kinase inhibitor therapy.

5. Has either of the following:

   a. Evidence of dyspnea at rest or oxygen saturation ≤94%.

   b. Known moderate or severe persistent asthma within the past 2 years (see Attachment 4), or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma may participate in the study.

6. Down syndrome, juvenile myelomonocytic leukemia, Fanconi anemia, Kostmann syndrome, Shwachman syndrome, or any other known bone marrow failure syndrome.

7. Prior exposure to daratumumab or other anti-CD38 therapies.

8. Criterion modified per Amendment 2

   8.1 Prior cancer immunotherapy (ie, CAR-T, inotuzumab) within 4 weeks prior to enrollment or blinatumomab within 2 weeks prior to enrollment.

9. Criterion modified per Amendment 2

   9.1 For subjects with T-cell ALL/LL only: prior cumulative anthracycline exposure must not exceed 400 mg/m^2 of doxorubicin or equivalent (see Attachment 8 for conversion).

10. Criterion modified per Amendment 3

    10.1 Subject is:

    - known to be seropositive for human immunodeficiency virus (HIV).
    - seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [Anti-HBc] and/or antibodies to hepatitis B surface antigen [Anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
    - known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

11. Screening 12-lead electrocardiogram (ECG) showing a baseline QT interval >470 msec or Grade 3 or higher cardiac disorders (according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 4.03).

12. Criterion modified per Amendment 2

    12.1 Known allergies, hypersensitivity, or intolerance to mannitol, glucocorticoid, methotrexate, vincristine, mAb (IRR is not considered hypersensitivity) or human proteins, or their excipients (refer to respective package inserts and Investigator's Brochure), or known sensitivity to mammalian-derived products. For subjects with T-cell ALL/LL only, known allergies to doxorubicin, cytarabine, cyclophosphamide, or 6-mercaptopurine.

13. Criterion modified per Amendment 1

    13.1 Received an investigational drug, was vaccinated with live attenuated vaccines, or

used an invasive investigational medical device within 4 weeks before the planned first dose of study drug, or is currently being treated in an investigational study.

14. Criterion modified per Amendment 2

    14.1 Pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 12 months after the last dose of any component of the treatment regimen.

15. Plans to father a child while enrolled in this study or within 6 months after the last dose of any component of the treatment regimen.

16. Subject has any concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.

17. Major surgery within 2 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration.

    Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

18. Criterion modified per Amendment 2

    Criterion modified per Amendment 3

    18.2 Subject is known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Subject is taking any prohibited medications listed in Section 8. Subject is not affiliated to, or a beneficiary of, a social security category, per local regulatory requirements, if applicable.

19. Criterion added per Amendment 3

    Subjects with infant leukemia (defined as under 1 year old at the time of initial diagnosis). These subjects will not be eligible for this study, even if they are greater than 1 year old at the time of relapse.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from

participation in the study, with the exception of subjects who meet screening liver function criteria but have elevation of liver function tests (≤Grade 3) on Cycle 1 Day 1 after IT methotrexate. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the study to be eligible for participation.

1. Refer to Section 8 Prestudy and Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5. TREATMENT ALLOCATION AND BLINDING

As this is an open-label study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

6.1. Study Drug Administration for Each Cohort

6.1.1. B-cell ALL/LL Cohort

Subjects with B-cell ALL/LL will receive daratumumab in combination with vincristine and prednisone continuously in 28-day cycles as specified in the Time and Events Schedule (Table 2) until disease progression, unacceptable toxicity, or proceeding to HSCT after achievement of CR. Subjects proceeding to HSCT may receive bridging daratumumab prior to transplant as described in Section 6.1.3.

The treatment schedule for subjects with B-cell ALL/LL is as follows. Disease status definitions for CNS leukemia are provided in Section 9.2.3. The order of administration for study medications may vary and a window of ±1 day is allowed in order to meet local requirements. However, on daratumumab dosing days, intrathecal therapy should be given first, then daratumumab should be administered prior to any other study drugs. Routine transfusions should be avoided on daratumumab dosing days. A steroid taper may be used as clinically indicated as per local standard practice.

- Intrathecal methotrexate (MTX) on Cycle 1 Day 1 (all subjects) and Cycles 2 and later Day 1 of each cycle for CNS negative subjects (CNS 1 or 2 at study entry). Cycle 1 Day 1 IT therapy may be given up to 72 hours prior as part of diagnostic lumbar puncture (LP) during screening. IT cytarabine (ARA-C) is an acceptable substitute for Cycle 1 Day 1 only.
    - Age 1 to <2 years=8 mg
    - Age 2 to <3 years=10 mg
    - Age 3 to <9 years=12 mg
    - Age ≥9 years=15 mg
- Intrathecal MTX/hydrocortisone (HC)/ARA-C (CNS positive subjects; CNS 3 only at study entry) on Cycle 1 Days 8, 15, 22, 28 (if indicated; refer to Table 2) and Cycles 2 and later Day 1 of each cycle
    - Age 1 to <2 years=MTX 8 mg, HC 8 mg, ARA-C 16 mg
    - Age 2 to <3 years=MTX 10 mg, HC 10 mg, ARA-C 20 mg
    - Age 3 to <9 years=MTX 12 mg, HC 12 mg, ARA-C 24 mg
    - Age ≥9 years=MTX 15 mg, HC 15 mg, ARA-C 30 mg
- Daratumumab 16 mg/kg IV weekly for 8 doses, then every 2 weeks for 8 doses, then every 28 days thereafter
    - Cycles 1 and 2: Days 1, 8, 15, and 22 of each cycle
    - Cycles 3 to 6: Days 1 and 15 of each cycle
    - Cycle 7 and later: Day 1 of each cycle
- Vincristine 1.5 mg/m^2 (maximum dose 2 mg) IV push or mini bag (according to institutional standards) weekly for 4 doses, then every 2 weeks for 2 doses, then every 28 days thereafter
    - Cycle 1: Days 1, 8, 15, and 22
    - Cycle 2: Days 1 and 15
    - Cycle 3 and later: Day 1 of each cycle

- Prednisone 40 mg/m^2 given as 2 doses (20 mg/m^2 per dose) orally for 28 days, then pulses of 5 days per month thereafter,
    - Cycle 1: Days 1 to 28
    - Cycles 2 and later: Days 1 to 5 of each cycle

    NOTE: On daratumumab dosing days, substitute methylprednisolone 2 mg/kg (maximum 100 mg) pre-infusion medication for prednisone 40 mg/m^2.

6.1.2. T-cell ALL/LL Cohort

Subjects with T-cell ALL/LL will receive up to 2 cycles (28-day cycles) of therapy as specified in Table 2 with subjects achieving CR proceeding to allogeneic HSCT off study if available. Subjects who do not achieve a CR or do not proceed to transplant at the end of Cycle 2 will discontinue study treatment and enter the Posttreatment Period. Subjects proceeding to HSCT may receive bridging daratumumab prior to transplant as described in Section 6.1.3.

6.1.2.1. T-cell ALL/LL Cycle 1

Subjects will receive the following treatment during Cycle 1. Disease status definitions for CNS leukemia are provided in Section 9.2.3. The order of administration for study medications may vary and a window of ±1 day is allowed in order to meet local requirements. However, on daratumumab dosing days, intrathecal therapy should be given first, then daratumumab should be administered prior to any other study drugs. Routine transfusions should be avoided on daratumumab dosing days. A steroid taper after Cycle 1 may be used as clinically indicated as per local standard practice. For subjects in the T-cell ALL/LL cohort who achieve a CR after Cycle 1, subjects may proceed directly to allogeneic HSCT, or receive bridging therapy to transplant as per Section 6.1.3 or proceed to Cycle 2 therapy prior to HSCT as clinically indicated.

- Intrathecal methotrexate (MTX) on Cycle 1 Day 1 (all subjects) and for CNS negative subjects (CNS 1 or 2 at study entry) on Cycle 1 Days 15 and 22. Cycle 1 Day 1 IT therapy can be given up to 72 hours prior as part of diagnostic LP during screening. IT cytarabine (ARA-C) is an acceptable substitute for Cycle 1 Day 1 only.
    - Age 1 to <2 years=8 mg
    - Age 2 to <3 years=10 mg
    - Age 3 to <9 years=12 mg
    - Age ≥9 years=15 mg

- Intrathecal MTX/HC/ARA-C (CNS positive subjects; CNS 3 only at study entry) on Days 8, 15, 22, and 28 (if indicated; refer to Table 2)
    - Age 1 to <2 years=MTX 8 mg, HC 8 mg, ARA-C 16 mg
    - Age 2 to <3 years=MTX 10 mg, HC 10 mg, ARA-C 20 mg
    - Age 3 to <9 years=MTX 12 mg, HC 12 mg, ARA-C 24 mg
    - Age ≥9 years=MTX 15 mg, HC 15 mg, ARA-C 30 mg
- Daratumumab 16 mg/kg IV weekly for 4 doses on Days 1, 8, 15, and 22
- Doxorubicin 60 mg/m^2 IV once on Day 1
- Vincristine 1.5 mg/m^2 (maximum dose 2 mg) IV push or mini bag (according to institutional standards) once weekly for 4 doses on Days 1, 8, 15, and 22
- Prednisone 40 mg/m^2 given as 2 doses (20 mg/m^2 per dose) orally daily on Days 1 to 28

NOTE: On daratumumab dosing days, substitute methylprednisolone 2 mg/kg (maximum 100 mg) pre-infusion medication for prednisone 40 mg/m^2.

- Peg-asparaginase 2500 U/m^2 IM or IV (IV given over 1 to 2 hours is preferred) on Days 2 and 16 (Erwinia asparaginase may be substituted; see Section 6.4.6)

6.1.2.2. T-cell ALL/LL Cycle 2

Subjects with M2 or M3 bone marrow status will start Cycle 2 therapy immediately following completion of Cycle 1. If intrathecal therapy was given less than 1 week prior to start of Cycle 2, then the start of Cycle 2 should be delayed for one week. For subjects with M1 bone marrow status at the end of Cycle 1, subjects must have peripheral count recovery with ANC >0.75x10^9/L and platelets >75x10^9/L and at least 1 week since last intrathecal therapy was given prior to initiation of Cycle 2. Disease status definitions for bone marrow status are provided in Section 9.2.2.

Subjects will receive the following treatment during Cycle 2. Disease status definitions for central nervous system (CNS) leukemia are provided in Section 9.2.3. The order of administration for study medications may vary and a window of ±1 day is allowed in order to meet local requirements. However, on daratumumab dosing days, intrathecal therapy should be given first, then daratumumab should be administered prior to any other study drugs. Routine transfusions should be avoided on daratumumab dosing days.

- Intrathecal methotrexate (CNS negative subjects; CNS 1 or 2 at study entry) on Days 2 and 15
    - Age 1 to <2 years=8 mg
    - Age 2 to <3 years=10 mg
    - Age 3 to <9 years=12 mg
    - Age ≥9 years=15 mg
- Intrathecal MTX/HC/ARA-C (CNS positive subjects; CNS 3 only at study entry) on Days 2 and 15
    - Age 1 to <2 years=MTX 8 mg, HC 8 mg, ARA-C 16 mg
    - Age 2 to <3 years=MTX 10 mg, HC 10 mg, ARA-C 20 mg
    - Age 3 to <9 years=MTX 12 mg, HC 12 mg, ARA-C 24mg
    - Age ≥9 years=MTX 15 mg, HC 15 mg, ARA-C 30 mg
- Daratumumab 16 mg/kg IV weekly for 4 doses on Days 1, 8, 15, and 22
- Methotrexate 5 g/m^2 IV once on Day 2 (see Attachment 5 for infusion guidelines)
- Cyclophosphamide IV 1 g/m^2 once on Day 15
- Cytarabine 75 mg/m^2 IV/subcutaneous for 8 doses on Days 16 to 19 and 23 to 26
- 6-mercaptopurine 60 mg/m^2 orally daily for 14 doses on Days 15 to 28

For subjects in the T-cell ALL/LL arm who achieve a CR after Cycle 1, the second cycle of therapy will be optional as a bridge to allogeneic HSCT.

6.1.3. Daratumumab Continuation Phase Prior to Transplant

For those subjects in either cohort who achieve a CR and require a short interval of treatment prior to transplant, daratumumab may be given at a dose of 16 mg/kg IV in weekly doses for a total of 4 doses after completion of Cycle 1 or every 2 weeks for a total of 2 doses after completion of Cycles 2 to 6, or once after completion of Cycles 7+. There should be a 2-week interval from the last dose of daratumumab and the start of conditioning therapy for the transplant.

Other standard maintenance chemotherapy may also be given after the discontinuation of study treatment and prior to transplant, at the discretion of the investigator. All maintenance therapy must be documented in the eCRF.

6.2. Daratumumab Preparation and Administration

6.2.1. Daratumumab Preparation

Infusion solution will be prepared as a dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 µM) during the infusion. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

6.2.2. Daratumumab Administration

Daratumumab will be administered as an IV infusion. Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose of daratumumab will remain constant throughout the study, unless the subject's weight changes more than 10% from Cycle 1 Day 1. Daratumumab infusion on Cycle 1 Day 1 will be given in the hospital; subsequent doses may be given in an outpatient clinic. Subjects will receive preinfusion medications and postinfusion medications (if indicated) as detailed in the protocol (Sections 6.3.1 and 6.3.2, respectively).

The dilution volumes, initial infusion rates, and increments for the first, second, and subsequent doses are provided in Table 6. For volume requirements, please see below:

- Subjects weighing <10 kg: please consult the medical monitor.
- Subjects weighing ≥10 to <20 kg will have daratumumab administered in a volume of 250 mL for the first infusion (Cycle 1 Day 1), then in a volume of 100 mL for all subsequent infusions.
- Subjects weighing ≥20 to ≤40 kg will have daratumumab administered in a volume of 500 mL for the first infusion (Cycle 1 Day 1), then in a volume of 250 mL for all subsequent infusions.
- Subjects weighing >40 kg will have daratumumab administered in a volume of 1000 mL for the first infusion (Cycle 1 Day 1), then in a volume of 500 mL for all subsequent infusions.

Table 6: Daratumumab Infusion Rates

	Subject Weight	Dilution Volume	Initial Infusion Rate (first hour)	Increments of Increase of Infusion Rate[a]	Maximum Infusion Rate
First infusion	≥10 to <20 kg	250 mL	10 mL/hr	10 mL every hr until maximum rate	40 mL/hr
	≥20-≤40 kg	500 mL	20 mL/hr	20 mL every hr until maximum rate	80 mL/hr
	>40 kg	1000 mL	50 mL/hr	50 mL every hr until maximum rate	200 mL/hour
Second infusion[b]	≥10 to <20 kg	100 mL	10 mL/hr	10 mL every hr until maximum rate	40 mL/hr
	≥20-≤40 kg	250 mL	20 mL/hr	20 mL/hr every hr until maximum rate	80 mL/hr
	>40 kg	500 mL	50 mL/hr	50 mL every hr until maximum rate	200 mL/hour
Subsequent infusions[c]	≥10 to <20 kg	100 mL	20 mL/hr	10 mL every hr until maximum rate	40 mL/hr
	≥20-≤40 kg	250 mL	40 mL/hr	20 mL every hr until maximum rate	80 mL/hr
	>40kg	500 mL	100 mL/hr	50 mL every hour until maximum rate	200 mL/hour

[a] Consider titration of the infusion rate only in the absence of infusion reactions.
[b] A decreased dilution volume should be used only if there were no Grade 1 (mild) or greater IRRs during the first 3 hours of the first infusion. Otherwise, continue to use the first infusion dilution volume and follow instructions for the first infusion.
[c] Use a modified initial rate for subsequent infusions (ie, third infusion onwards) only if there were no Grade 1 (mild) or greater IRRs during the first 3 hours of the prior infusion. Otherwise, continue to use instructions for the second infusion.

As noted in the Time and Events Schedule (Table 2), vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab and subjects will be hospitalized overnight due to the long duration of the first infusion. For all other infusions, vital signs should be measured before the start of the infusion and at the end of the infusion. If a subject experiences a significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE.

6.3. Guidelines for Prevention and Management of Infusion-related Reactions

6.3.1. Preinfusion Medications

In an effort to prevent IRRs, all subjects will receive the following medications 1 to 3 hours prior to each study drug administration (1 hour prior to study drug administration is preferred):

- An antipyretic: paracetamol (acetaminophen) 15 mg/kg (maximum 1000 mg) PO
- An antihistamine: diphenhydramine or equivalent, 0.5 to 1 mg/kg (maximum 50 mg) IV or PO (see Attachment 6 for list of antihistamines that may be used)
- A glucocorticoid: methylprednisolone 2 mg/kg (maximum 100 mg) IV or PO (IV preferred). Substitutions for methylprednisolone are allowed (refer to Attachment 2).

Predose administration of a leukotriene inhibitor (montelukast 5 to 10 mg PO [age appropriate dosing]) is optional on Cycle 1 Day 1 and can be administered up to 24 hours before infusion as per investigator discretion.

If necessary, all PO preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.

6.3.2. Postinfusion Medications

For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with underlying pulmonary conditions, the following postinfusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled; use nebulizer, if necessary) glucocorticoid ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled glucocorticoid for subjects with pulmonary conditions)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after daratumumab administration. If subjects are hospitalized, then an improvement in either oxygen saturation as measured by pulse oximetry or forced expiratory volume in 1 second (FEV1), if the test is feasible, should be documented prior to discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE. Investigators may prescribe bronchodilators, H1-antihistamines, and glucocorticoid that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major IRRs, then these postinfusion medications may be waived after 4 doses at the investigator's discretion.

6.3.3. Management of Infusion-related Reactions

Subjects should be observed carefully during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an IRR develops, then daratumumab administration should be temporarily interrupted. Please see the IPPI for further details. Subjects who experience adverse events during daratumumab administration must be treated for their symptoms. Subjects should be treated with acetaminophen, antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated.

For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject.

- **Grade 1-2 (mild to moderate) IRRs**: If the investigator assesses a Grade 1-2 IRR adverse event to be related to administration of study drug, then the daratumumab administration should be paused. When the subject's condition is stable, daratumumab administration may be restarted at half of the rate at the investigator's discretion.

  If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be permanently discontinued from daratumumab treatment.
- **Grade 3 or higher IRRs:** For IRR adverse events (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped and the subject must be observed carefully until resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be restarted at half of the rate at the investigator's discretion. If the intensity of the adverse event returns to Grade 3 after restart of the daratumumab administration, then the subject must be withdrawn from daratumumab treatment. For IRR adverse events that are Grade 4, the daratumumab administration must be stopped and the subject withdrawn from daratumumab treatment.
- **Recurrent IRRs:** If a Grade 3 IRR (or ≥Grade 2 event of laryngeal edema or bronchospasm) recurs during or within 24 hours after a subsequent daratumumab administration, the daratumumab treatment must be discontinued.

6.4. Delay and Modifications

Subjects who need to discontinue treatment with any one component of study treatment may continue to receive treatment with the other components of study treatment.

6.4.1. Daratumumab

Dose modification of daratumumab is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities.

On the first day of each new treatment cycle and before each daratumumab dose, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to NCI-CTCAE, Version 4.03. Dose modifications or delays will be made based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle.

Only if any of the following criteria are met and the event cannot be ascribed to components of the chemotherapy regimen or if the causality is unclear, then the daratumumab infusion must be held to allow for recovery from toxicity. If there are any questions regarding dose delay, contact the medical monitor.

The criteria for dose delay are:

- Grade 4 thrombocytopenia with bleeding
- Grade 4 febrile neutropenia
- Grade 4 infection
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

If daratumumab administration does not commence within the prespecified window (Table 7) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 7: Daratumumab-Related Toxicity Management

Cycles	Frequency	Dose Missed	Dosing Resumption
1-2	Weekly	>3 days	next planned weekly dosing date
3-6	Every 2 weeks	>7 days	next planned every-2-weeks dosing date
7+	Every 4 weeks	>14 days	next planned every-4-weeks dosing date

If Day 1 of a cycle is delayed, then Day 1 of subsequent cycles should be adjusted accordingly to maintain the cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. If a dose delay occurs, then PK assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks will result in permanent discontinuation of daratumumab, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.4.2. Intrathecal Methotrexate/Triple Intrathecal Therapy

The criteria for dose delay or modifications are as follows:

- Systemic toxicity: the dosage for intrathecal methotrexate will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.). Leucovorin may be used if a subject experiences myelosuppression with ANC $<0.5x10^9$/L or mucositis. Start leucovorin at a dose of 5 mg/m^2/dose every 12 hours x 2 doses, beginning 48 hours after the intrathecal therapy.

- Acute neurotoxicity: discuss with medical monitor before administration of intrathecal therapy.

- Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy through LP: intraventricular chemotherapy through Ommaya catheter may be used in place of intrathecal therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, but at 50% of the corresponding age-based doses that would be given by LP. NOTE: Obstruction to CSF flow may be a contraindication to intrathecal or intraventricular therapy.

- Viral, bacterial, or fungal meningitis: hold intrathecal therapy until infection is resolved.

6.4.3. Vincristine

The criteria for dose delay or modifications are as follows:

- Severe neuropathic pain (Grade 3 or greater): hold dose. When symptoms resolve to Grade 1 or baseline, resume at 50% dose reduction (maximum dose: 1 mg), then escalate to full dose as tolerated.

- Vocal cord paralysis: hold dose. When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated.

- Foot drop, paresis (Grade 3 or higher): consider holding or decreasing dose.

- Jaw pain: treat with analgesics; do not modify vincristine dose.

- Hyperbilirubinemia.

Direct Bilirubin %	**Dose Reduction**
<3.1 mg/dL	Full dose (maximum dose: 2 mg)
3.1 – 5.0 mg/dL	50% of calculated dose (maximum dose: 1 mg)
5.1 – 6.0 mg/dL	75% of calculated dose (maximum dose: 0.5 mg)
>6.0 mg/dL	Hold dose and administer next scheduled dose if toxicity has resolved. *

*Do not make up missed doses.

- Constipation or ileus (≥Grade 3) or typhlitis: hold dose; initiate treatment. When symptoms resolve, resume at 50% of dose (maximum dose: 1 mg) and escalate to full dose as tolerated.

- Extravasation: in the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines.

6.4.4. Glucocorticoid (Prednisone)

Toxicities related to glucocorticoids should be managed clinically without dose modifications. If there is any consideration of discontinuation, then the investigator must consult with the medical monitor.

If there is an inability to use oral doses, substitute IV methylprednisolone at 80% of the oral prednisone dose. Note that if substituting oral prednisolone for prednisone, the doses are the same.

6.4.5. Doxorubicin (Anthracycline)

The criteria for dose delay or modifications are as follows:

- Hyperbilirubinemia:

Direct Bilirubin %	Dose Reduction
<1.2 mg/dL	Full dose
1.2 – 3.0 mg/dL	50%

- Extravasation: in the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines.

6.4.6. Asparaginase (Pegaspargase [PEG-Asparaginase] or Erwinia)

The criteria for dose delay or modifications are as follows:

- Allergy

    - Local allergic reactions (inflammation at injection site, swelling): continue pegaspargase administration in the presence of Grade 1 allergy as defined by CTCAE Version 4.03 (transient flushing or rash; drug fever <38ºC).

    - Systemic allergic reactions: discontinuation may be considered for severe Grade 2 or higher allergic reactions as defined by CTCAE Version 4.03.

      Note: Premedication with antihistamines to decrease the risk of overt allergy symptoms is strongly discouraged because antihistamine use may mask the appearance of systemic allergy. In the event of severe systemic or recurrent local allergic reaction, Erwinia asparaginase should be substituted as noted in the table below.

- Anaphylaxis: discontinue pegaspargase if the subject develops Grade 3 anaphylaxis as defined by CTCAE Version 4.03 (symptomatic bronchospasm, with or without urticaria, parenteral intervention indicated; allergy-related edema/angioedema; hypotension). If this occurs, then Erwinia asparaginase should be substituted as noted in the table below.

  Substitute Erwinia asparaginase for pegaspargase utilizing the following schedule.

Phase(s) of Treatment	**Drug(s)**	**Replacement Schedule for Erwinia asparaginase***
Cycle 1 T-cell ALL cohort	Pegaspargase (2,500 IU/m^2)	25,000 IU/m^2/dose IM Give 6 doses of Erwinia on M/W/F schedule for each dose of pegaspargase except the last dose of pegaspargase

*If a subject develops a Grade 3 or higher anaphylaxis to Erwinia, discontinue future asparaginase therapy. Consider discontinuation for severe Grade 2 or higher allergic reactions.

- Coagulopathy: if symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider prophylaxis for coagulopathy. No dose modification for abnormal laboratory findings without clinical symptoms.

- Hyperglycemia:

  - Grade 1 or 2: no dose modification required. Treat hyperglycemia as medically indicated.

  - Grade 3 or 4 including ketoacidosis: hold asparaginase until blood glucose can be regulated with insulin, then asparaginase can be resumed.

- Pancreatitis (Grade 3 or 4): permanently discontinue asparaginase in the presence of hemorrhagic pancreatitis or severe pancreatitis. In the case of mild pancreatitis, asparaginase should be held until symptoms and signs subside, and amylase levels return to normal and then resumed.

- Thrombosis: withhold asparaginase until resolved, and treat with appropriate antithrombotic therapy, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing low molecular weight heparin or antithrombotic therapy. Do not withhold dose for abnormal laboratory findings without clinical correlate.

6.4.7. Cyclophosphamide

The criteria for dose delay or modifications are as follows:

- Hematuria: hold dose if there is macroscopic hematuria. If there is a history of previous significant hematuria, hydrate before cyclophosphamide until specific gravity is < 1.010 and hydrate at 125 mL/m^2/hr for 24 hours after dose. Monitor for adequate urine output according to institution guidelines. Give IV mesna at a total dose that is 60% of the cyclophosphamide dose divided into 3 doses (eg, if the cyclophosphamide dose is 1000 mg/m^2, the total mesna dose is 600 mg/m^2 or 200 mg/m^2/dose x 3). Give the first mesna dose 15 minutes before or at the same time as the cyclophosphamide dose and repeat 4 and 8 hours after the start of cyclophosphamide. This total daily dose of mesna may also be administered as an IV continuous infusion. The continuous infusion should be started 15 to 30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of cyclophosphamide infusion.

- Renal dysfunction: if creatinine clearance or radioisotope GFR is < 10 mL/min/1.73 m^2, reduce dose of cyclophosphamide by 50%. Prior to dose adjustment of cyclophosphamide, the creatinine clearance should be repeated with good hydration.

6.4.8. Cytarabine (ARA-C)

Withhold ARA-C for Grade 3 or 4 rash until resolved. Do not withhold ARA-C for fever if it is likely to have been caused by the ARA-C. Obtain blood cultures if a central line is present.

6.4.9. Mercaptopurine

No dose adjustments should be made to mercaptopurine dosing.

6.4.10. High-dose Methotrexate (HD MTX)

The criteria for dose delay or modifications are as follows:

- Nephrotoxicity: hold MTX if serum creatinine is >1.5 x baseline or GFR creatinine clearance <65 mL/min/1.73 m^2. For subjects who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G_2)

- Liver toxicity: ALT >20 x ULN or hyperbilirubinemia (direct bilirubin >2.0 mg/dL.): delay IV MTX until resolved.

- Mucositis: for Grade 3 or 4 mucositis from a previous course of chemotherapy, delay IV MTX until resolved.

- Myelosuppression: hold IV methotrexate until ANC >0.75x10^9/L and platelets >75x10^9/L.

7. TREATMENT COMPLIANCE

Study drug (daratumumab) and all backbone therapies except for prednisone and 6-mercaptopurine, will be administered by qualified study-site personnel as specified in Table 2. The details of each administration will be recorded in the electronic case report form (eCRF), including date, start and stop times of infusions, and the volume infused. Prednisone and 6-mercaptopurine will be dispensed for self-administration. Subjects/caregivers will be provided with a diary card to record intake at home. Site personnel are to instruct the subject/caregiver to bring the diary card and any unused prednisone to the site at the beginning of each treatment cycle to check dosing compliance.

The Interactive Web Response System will be used to assign centrally open-label supplied study treatment (daratumumab) kits for each subject. The investigator or the site pharmacist will maintain a log of all daratumumab dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

8. PRESTUDY AND CONCOMITANT THERAPY

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the eCRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication.

8.1. Prestudy Therapy

All prior oncologic therapies, including those administered since diagnosis of ALL or LL, must be recorded at screening. Transfusions administered up to 2 weeks prior to screening must also be recorded at screening. All other prestudy therapies administered up to 30 days before first dose of study drug must be recorded at screening.

8.2. Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.2.3. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Routine systemic use of concomitant medications will be collected in the eCRF and recorded in the source documents beginning with signing of the ICF/assent form until 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier.

8.2.1. Recommended Concomitant Therapies

8.2.1.1. Prophylaxis for Tumor Lysis Syndrome

Subjects should be monitored for symptoms of tumor lysis syndrome. Subjects should be treated prophylactically in accordance with local standards (including vigorous hydration, alkalinization, diuretics, and allopurinol or rasburicase prior to initiation of therapy).

8.2.1.2. Prophylaxis for Infection

Prophylaxis for infection (including bacterial, fungal, and Pneumocystis pneumonia/Pneumocystis carinii/ jirovecii pneumonia) should be performed according to local institutional practice.

8.2.1.3. Prophylaxis for Nausea

Subjects should be given antiemetics during each chemotherapy course individualized to the subject's best response. However, glucocorticoids and aprepitant/fosaprepitant should not be used as antiemetics.

8.2.1.4. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation is recommended during the Treatment Period, as per institutional guidelines, and for 3 months following treatment.

8.2.1.5. Prophylaxis for Glucocorticoid-Induced Gastritis

Glucocorticoids may induce gastritis. Medications to prevent gastritis may be given according to institutional guidelines (eg, proton pump inhibitors [omeprazole or equivalent], sucralfate, or H2 blockers [ranitidine or equivalent]).

8.2.1.6. Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation; see Section 9.5.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

8.2.2. Permitted Concomitant Therapies

Subjects are to receive full supportive care during the study. The following medications and supportive therapies are examples of support therapies that may be used during the study:

- Antivirals
- Prevention of constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed)
- Prophylactic antiemetics, with the exception of glucocorticoids and aprepitant/fosaprepitant
- Colony stimulating factors, erythropoietin, and transfusion of platelets and red blood cells; routine transfusions should not be given on daratumumab dosing days
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended

Other symptoms may be managed according to institutional guidelines provided prohibited therapies are not administered (see Section 8.2.3).

8.2.3. Prohibited Concomitant Therapies

Concomitant administration of the following therapies is prohibited during the study:

- Any antineoplastic therapy for the intention of treating ALL or LL is prohibited, including conventional chemotherapy agents, investigational agents, and approved or investigational medications that target CD38
- Aprepitant/fosaprepitant
- Strong CYP3A4 and P glycoprotein inhibitors, such as ketoconazole or itraconazole, is prohibited. For an ongoing list of CYP3A inhibitors and inducers, see http://medicine.iupui.edu/flockhart/
- Live vaccines during the study and for 3 months after the last dose of vincristine

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The study is divided into 3 periods: a Screening Period, a Treatment Period, and a Posttreatment Period. The Time and Events Schedule summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, and safety measurements applicable to this study. Study assessments will be performed only after written informed consent is obtained.

The total blood volume to be withdrawn during the study will vary depending on the number of cycles of treatment that each subject receives. It is not expected to exceed approximately 17 mL during screening, 38 mL per cycle, and 18 mL for End of Treatment and follow-up assessments (Attachment 7). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples but should not exceed allowable daily blood volume limits according to local standards.

9.1.2. Screening Period

All subjects, or their legally acceptable representatives, must sign an ICF prior to the conduct of any study-related procedures. Where applicable, subjects below the age of legal consent should sign an assent form prior to the conduct of any study-related procedures.

The Screening Period begins when the first screening procedure is conducted. During the Screening Period, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Events Schedule (Table 1). Screening procedures will be performed within 21 days before first dose, except for pregnancy tests, which are to be performed within 14 days before Cycle 1 Day 1 for female subjects of childbearing potential

only. Results from standard of care procedures obtained within 21 days before Cycle 1 Day 1 may be used without these tests being repeated.

9.1.3. Treatment Period

Details of the procedures performed during the Treatment Period are outlined in the Time and Events Schedule (Table 1). Subjects will be closely monitored for adverse events (AEs), laboratory abnormalities, and clinical response. Subjects with B-cell ALL/LL will receive treatment until disease progression, unacceptable toxicity, or achievement of CR followed by HSCT. Subjects with T-cell ALL/LL will receive treatment for up to 2 cycles. There is an optional maintenance phase in all subjects who achieve CR to bridge therapy to allogeneic HSCT. If disease progression is confirmed, then the subject will discontinue study treatment, complete the End-of-Treatment Visit, and enter the Posttreatment Period.

End-of-Treatment Visit

Unless a subject/caregiver withdraws consent for study participation or the subject is lost to follow-up, an End-of-Treatment Visit is to occur 30 days (+7 days) after the last dose of study treatment. If a subject is unable to return to the site for the End-of-Treatment Visit, then the subject should be contacted to collect information on AEs that occur up to 30 days after the last dose of study treatment. Additional information on reporting of AEs is presented in Section 12.

9.1.4. Posttreatment Period (Follow-Up)

For all subjects who discontinue study drug prior to CR or PD, disease evaluations will continue every 8 weeks until CR, PD, subsequent anticancer therapy is initiated, or study completion (see Section 17.9.1). After CR or PD, follow-up will occur every 12 weeks to record information on subsequent anticancer therapy, second primary malignancies, documentation of progressive disease or relapsed disease, and survival status.

For all subjects proceeding to transplant, the following information will be collected and documented in the eCRF: date of transplant, type of transplant, time to engraftment, and any graft failures. In addition, any maintenance chemotherapy given after discontinuation of study treatment and prior to transplant must be documented in the eCRF. If the information is obtained by telephone contact, then written documentation of the communication must be available for review in the source documents. If the subject has died, then the date and cause of death will be collected and documented on the eCRF. Serious adverse events that are considered related to daratumumab within the Follow-up Period must be reported using the Serious Adverse Event Form (see Section 12.3.1).

The study will end 1 year after the last subject has initiated treatment or when the Sponsor decides to stop the study.

9.2. Efficacy Evaluations

Bone marrow evaluations will be performed as specified in the Time and Events Schedule (Table 1). CSF will be evaluated at the time of each IT therapy per the Time and Events Schedule (Table 1); status at the closest evaluation to Day 28 of a cycle will define response of CNS. Blood samples will be collected for Ph+ subjects only for assessment of BCR-ABL locally.

A chest X-ray will be performed at screening and as clinically indicated thereafter to evaluate for mediastinal masses. Computed tomography (CT) or MRI scans of the chest will be performed for subjects with ALL and mediastinal mass at screening and on treatment until resolution of the mass. CT or MRI scan of the chest and abdomen/pelvis with contrast is required for all subjects with LL at screening and during treatment if positive at screening as specified in the Time and Events Schedule (Table 1) for subjects with ALL with mediastinal mass and subjects with LL. IV contrast is required for chest CT scan; IV and oral contrast is required for abdomen/pelvis CT scan, and IV contrast is required for the MRI. CT or MRI scans can be deferred until the subject is medically stable if unable to perform due to subject's medical condition (ie, large mediastinal mass with cardiorespiratory compromise).

9.2.1. Response Categories

Disease evaluations will be performed as specified in Table 1 on the scheduled assessment day (window of +7 days). If treatment has been delayed for any reason, then the disease evaluations must continue to be performed as scheduled, regardless of any changes to the dosing regimen schedule. Disease evaluations scheduled for treatment days should be collected before study drug is administered. Disease response should reflect response in all areas of disease (ie, bone marrow and mediastinal mass, or bone marrow and extramedullary disease). If a subject does not have a CR in an extramedullary compartment, response will be considered "refractory disease" as per Section 9.2.1.1.

9.2.1.1. Acute Lymphoblastic Leukemia

Assessments of disease response and progression for subjects with ALL will be based on the modified National Comprehensive Cancer Network (NCCN) criteria[29]:

- CR:
  - Less than 5% blasts in the bone marrow
  - No evidence of circulating blasts or extramedullary disease
  - Full recovery of peripheral blood counts:
    - Platelets >100x10^9/L
    - ANC >1.0x10^9/L
- CRi:
  - Less than 5% blasts in the bone marrow
  - No evidence of circulating blasts or extramedullary disease

  - Partial recovery of peripheral blood counts not meeting criteria for CR noted above
- ORR=CR+CRi
- Relapse from CR
  - Reappearance of leukemia blasts in the peripheral blood or >5% blasts in the bone marrow
  - Reappearance of extramedullary disease or new extramedullary disease
- Refractory disease: failure to achieve CR at end of induction therapy and does not meet criteria for progressive disease
- Progressive disease: increase of at least 25% in the absolute number of circulating peripheral or bone marrow blasts, or development of new extramedullary disease

MRD negative is defined as <0.01% abnormal population counts to nucleated mononuclear cells when measured by flow.

9.2.1.2. Central Nervous System Disease

Response criteria for CNS disease (M2 or M3 subjects only) are as follows:

- Remission: achievement of M1 CNS status
- Relapse: development of new M3 CNS status or development of new symptoms of CNS leukemia

Subjects with M2 or M3 CNS status who do not improve to M1 CNS status after 1 cycle of treatment should permanently discontinue all study treatment.

9.2.1.3. Mediastinal Mass

Response criteria for mediastinal mass (subjects with ALL only) are as follows:

- CR: complete resolution of the mediastinal mass by CT or MRI
- PR: a decrease of ≥50% in the sum of the products of the diameter (SPD) of the lesions with no new lesions
- Progressive disease: an increase of ≥25% in the size of any lesions or appearance of new lesions
- Stable disease: not meeting criteria for CR or PR noted above
- Relapse: recurrence of mass or new lesions

9.2.1.4. Lymphoblastic Lymphoma

Measurable disease is defined as any nodal mass with longest transverse diameter > 2 cm, or any measurable, focal mass lesion of a visceral organ (such as liver, spleen, kidney). Measurable lesions in a visceral organ are lesions that can be accurately measured in 2 axial dimensions by CT.

Response criteria for subjects with LL are as follows (based on response criteria in adult NHL[8]):

- CR: disappearance of all evidence of disease from all sites. This will be determined by physical examination and appropriate imaging studies. Bone marrow aspirate/biopsy must be normal and any macroscopic nodules in any organs detectable on imaging techniques should no longer be present.
- CR unconfirmed (CRu): a residual lymph node mass >1.5 cm in greatest transverse diameter that has regressed by >75% in sum of the products of the greatest perpendicular diameters.
- PR: a decrease of ≥50% in the SPD of the lesions of up to 6 of the largest dominant nodes or nodal masses with no new lesions.
- Stable disease: failure to qualify for a CR, CRu, PR, or progressive disease. No new lesions.
- Progressive disease: an increase of ≥25% in the size of any lesions or appearance of new lesions.

9.2.2. Bone Marrow Evaluation

Fresh bone marrow aspirate will be collected according to the Time and Events Schedule (Table 1 and Table 2). Local and central bone marrow evaluations will be performed as described in Table 8. Bone marrow aspirate is required for central bone marrow evaluations; bone marrow biopsy is not acceptable for central testing. If the aspirate procedure is deemed inadequate, biopsy is required for local testing.

Table 8: Local and Central Bone Marrow Evaluations

Timepoint	Local Testing	Central Testing
Screening	Disease characterization • Morphology (evaluate percentage of tumorous leukemia/lymphoma cells and cellularity) • Immunohistochemistry, immunofluorescence, or flow cytometry (evaluate presence of tumorous leukemia/lymphoma cells present by immunophenotyping and indicate probes used for immunophenotyping) Cytogenetics • Either by FISH or conventional karyotype	MRD: a portion of fresh bone marrow aspirate collected at screening will be sent to a central laboratory for assessment of MRD by flow cytometry and PCR Biomarkers: baseline assessment of biomarkers predictive of clinical response or resistance to therapy
Disease evaluations prior to PD or CR, and prior to start of subsequent anticancer therapy[a]	Disease characterization • Morphology (evaluate percentage of tumorous leukemia/lymphoma cells and cellularity)	MRD: a portion of fresh bone marrow aspirate collected at each disease evaluation time point will be sent to a central laboratory Biomarkers: assessment of biomarkers predictive of clinical response or resistance to therapy
End of Treatment (if feasible)	Disease characterization • Morphology (evaluate percentage of tumorous leukemia/lymphoma cells and cellularity)	MRD: a portion of fresh bone marrow aspirate collected will be sent to a central laboratory Biomarkers: assessment of biomarkers predictive of clinical response or resistance to therapy

Abbreviations: CR=complete response; FISH=fluorescence in situ hybridization; LL=lymphoblastic lymphoma; MRD=minimal residual disease; PCR=polymerase chain reaction; PD=progressive disease.

a. For subjects with LL, on-treatment bone marrow evaluations are only required if bone marrow disease is present at Screening.

If there is no hematologic recovery at the end of Cycle 1, bone marrow evaluations will be repeated when count recovery occurs (ANC >1.0x109/L, platelets >100x109/L) within 7 days of Cycle 1 Day 28 unless there is evidence of blasts, then continue to Cycle 2.

For subjects with LL, on-study bone marrow evaluation is only required if bone marrow disease is present at study entry.

If subject receives continuation therapy with daratumumab prior to transplant, a repeat bone marrow evaluation must be performed within 2 weeks of transplant.

The definitions for bone marrow status are as follows:

- M1 <5% lymphoblasts
- M2 5 to 25% lymphoblasts
- M3 >25% lymphoblasts

9.2.3. Lumbar Puncture

Cerebrospinal fluid will be collected to evaluate for CNS leukemia as described in the Time and Events Schedule (Table 1) for assessment of disease status. The definitions for CNS leukemia are as follows:

- CNS 1: in CSF, absence of blasts in pathology evaluation (ie, cytospin or flow cytometry) regardless of the number of white blood cells (WBCs).
- CNS 2: in CSF, presence <5/µL WBCs and pathology evaluation (ie, cytospin or flow cytometry) positive for blasts, or ≥5/µL WBCs but negative by Steinherz/Bleyer algorithm (see below):
    - CNS 2a: <10/µL RBCs; <5/µL WBCs and pathology evaluation (ie, cytospin or flow cytometry) positive for blasts;
    - CNS 2b: ≥10/µL RBCs; <5/µL WBCs and pathology evaluation (ie, cytospin or flow cytometry) positive for blasts; and
    - CNS 2c: ≥10/µL RBCs; ≥5/µL WBCs and pathology evaluation (ie, cytospin or flow cytometry) positive for blasts but negative by Steinherz/Bleyer algorithm (see below);
- CNS 3: in CSF, presence of ≥5/µL WBCs and pathology evaluation (ie, cytospin or flow cytometry) positive for blasts or clinical signs of CNS leukemia:
    - CNS 3a: <10/µL RBCs; ≥5/µL WBCs and pathology evaluation (ie, cytospin or flow cytometry) positive for blasts;
    - CNS 3b: ≥10/µL RBCs, ≥5/µL WBCs and positive by Steinherz/Bleyer algorithm (see below);
    - CNS 3c: clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

Method of Evaluating Initial Traumatic Lumbar Punctures

If the subject has leukemic cells in the peripheral blood and the LP is traumatic and contains ≥5 WBC/µL and blasts, then the following Steinherz/Bleyer algorithm should be used to distinguish between CNS2 and CNS3 disease:

(CSF WBC/CSF RBC) >2X (Blood WBC/Blood RBC)

A subject with CSF WBC ≥5/µL blasts, whose CSF WBC/RBC ratio is 2x greater than the blood WBC/RBC ratio, has CNS disease at diagnosis. Example: CSF WBC=60/µL; CSF RBC=1,500/µL; blood WBC=46,000/µL; blood RBC=3.0X10^6/µL: (60/1500)=0.04 >2X (46,000/3.0X10^6) = 0.015

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

Serum samples to assess both the serum concentration (PK) of daratumumab and the generation of anti-daratumumab antibodies (immunogenicity) will be obtained from all subjects according to the Time and Events Schedule (Table 3). At specified time points, venous blood samples (1.1 to 5 mL per sample according to the Laboratory Manual) will be collected and the serum will be divided into 2 or 3 aliquots according to the Laboratory Manual (PK analysis, immunogenicity assessment [when appropriate], and back-up). Up to 1 mL of CSF will also be collected for assessment of daratumumab concentrations as specified in the Time and Events Schedule
(Table 2).

The exact dates and times of blood and CSF sampling must be recorded. Refer to the Laboratory Manual or equivalent document for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the Laboratory Manual.

Samples collected for determining serum concentrations of daratumumab in this study may be retained to address questions about drug characteristics that may arise at a later time point. Genetic analyses will not be performed on these samples, and subject confidentiality will be maintained.

9.3.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of daratumumab or generation of anti-daratumumab antibodies using validated immunoassay methods by or under the supervision of the sponsor's bioanalytical facility. Cerebrospinal fluid samples will be analyzed to determine concentrations of daratumumab using a validated assay method by or under the supervision of the sponsor's bioanalytical facility. For the immunogenicity assessments, serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined from confirmed positive samples. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

9.3.3. Pharmacokinetic Assessments

The PK parameters are defined as:

C_{max}: Maximum observed concentration

C_{min}: Minimum observed concentration

For daratumumab, the PK evaluations include C_{min} and C_{max}. If sufficient data are available, then other PK parameters may be calculated. The C_{min} and C_{max} will be determined based on the assigned collection timepoints. Population PK analysis of serum concentration-time data of daratumumab will be performed and include data from other clinical studies; details will be provided in a population PK analysis plan and results would be presented in a separate report.

9.3.4. Immunogenicity Assessments

Serum from venous blood samples will be assessed for the generation of anti-daratumumab antibodies (immunogenicity) according to the Time and Events Schedule (Table 3). Daratumumab concentration is also evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data. When both serum concentration and immunogenicity analyses are specified, they are performed on aliquots from the same blood draw and no additional sampling is required. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document.

A blood sample should be drawn, if possible, for determination of anti-daratumumab antibodies any time an infusion reaction is observed or reported for the second or later infusion. Daratumumab serum concentration will also be determined from the same infusion reaction sample for the purpose of interpreting immunogenicity data. These samples will be stored and evaluated if deemed necessary. If the infusion reaction results in treatment discontinuation, then subjects should undergo all scheduled safety and efficacy evaluations. Samples collected for the analysis of daratumumab immunogenicity/serum concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers by the sponsor or sponsor's designee.

9.3.5. Pharmacokinetic/Pharmacodynamic Evaluations

If sufficient data are available, then other PK/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy and safety. If these analyses are performed, then the details and results will be presented in a separate report.

9.4. Biomarkers

Biomarker assessments will focus on 3 main objectives: to evaluate the ability of daratumumab to induce MRD, to confirm pharmacodynamic biomarkers, and to evaluate CD38 expression on blast cells. All biomarker assessments will be performed centrally.

Bone marrow aspirate will be collected as specified in the Time and Events Schedule (Table 1). MRD assessments will be done by flow cytometry with baseline bone marrow aspirate to define tumor burden, posttreatment samples to determine MRD negativity (end of both Cycle 1 and Cycle 2 for T-cell cohort), and End of Treatment, if feasible, to monitor CD38 expression kinetics and depth of response. Residual bone marrow aspirate cells collected for MRD flow analysis will be stored as frozen pellets. Exploratory MRD analysis may be performed using PCR on DNA isolated from these pellets. Any genomic research on samples will only include specific changes related to the disease (somatic). Comparison of MRD assessment by flow and PCR could inform future trial designs as PCR is a preferred method for MRD assessment in the EU. If these methodologies are unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be utilized. A portion of aspirate may be evaluated by flow cytometry to determine CD38 expression in both B-cell and T-cell ALL/LL subtypes

and will be sent to the central laboratory. Characterization of CD38 levels could clarify the in vivo pharmacology and identify potential response trends.

Previous observations from daratumumab monotherapy studies in multiple myeloma have included immune changes (ie, reduction of NK cells and CD38 positive regulatory T cells) post drug administration. This reduction did not lead to any decrease in response or emergence of AEs. However, due to this observation, immune cell pharmacodynamics may be evaluated in whole blood samples by flow cytometry collected at times as indicated in the Time and Events Schedule (Table 1).

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed, if during or at the end of the study it becomes clear that the analysis will have no scientific value, or if there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

9.5. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the adverse event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. The study will include the following evaluations of safety and tolerability per the time points provided in the Time and Events Schedule (Table 1).

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

The following tests will be performed by the local laboratory:

- Hematology panel

-hemoglobin
-white blood cell count, absolute lymphocyte count, ANC, and peripheral blast count (if WBC is too low for automated assessment, a manual differential should be performed to document absolute lymphocyte count, ANC, and peripheral blast count)
-platelet count

- Serum chemistry panel

-sodium
-potassium
-creatinine
-aspartate aminotransferase
-alanine aminotransferase
-total bilirubin (direct bilirubin if total bilirubin is abnormal)
-amylase or lipase
-alkaline phosphatase
-lactic acid dehydrogenase
-uric acid
-calcium
-phosphate
-albumin
-total protein

- Cerebrospinal fluid
  - RBC count
  - WBC count
  - Pathologic evaluation for lymphoblast count (ie, cytospin or flow cytometry)
- Serum or urine pregnancy testing for female subjects of childbearing potential only

HBV Serology

All subjects will be tested locally for HBsAg, Anti-HBs, and Anti-HBc at Screening. Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment 3 is implemented will be required to have HBV serology performed locally once upon signing the updated ICF.

HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose.

HBV DNA Tests

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for HBV DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule (Table 1). Where required by local law, the results of HBV testing may be reported to the local health authorities.

Indirect Antiglobulin Test

Blood type, Rh, and indirect antiglobulin test (IAT) should be done locally within 3 days prior to Cycle 1 Day 1. Subject RBC phenotyping or genotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a subject's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very

low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a subject identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT).[6,7]

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

a. Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units

b. Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently in accordance with local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the daratumumab Investigator's Brochure.

Electrocardiogram

Electrocardiograms will be performed locally at screening. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Vital Signs

Vital signs will include heart rate, blood pressure, oxygen saturation, temperature, and respiration rate. Blood pressure should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Physical Examination

Physical examinations will be performed as specified in the Time and Events Schedule (Table 1). At screening, the physical examination includes neurological examination. Any change from baseline must be recorded as an adverse event.

Karnofsky and Lansky Performance Status

The Karnofsky and Lansky performance status scales provided in Attachment 1 will be used to determine the functional status of each subject. The frequency of performance status assessment is provided in the Time and Events Schedule (Table 1).

9.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Time and Events Schedule (Table 1) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has finished all protocol-specified procedures before the end of the study, has died before the end of the study, has not been lost to follow-up, or has not withdrawn consent for study participation before the end of the study.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject's study treatment must be discontinued for any of the following reasons:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant, unless the subject (or the subject's legally acceptable representative), investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study treatment is in the best interest of the subject
- Progression of disease or relapse as defined in Section 9.2.1
- Subjects with CNS M2 or CNS M3 status at baseline who do not achieve CNS M1 status (ie, 2 successive negative CSF evaluations) after completion of Cycle 1
- Withdrawal of consent
- Subject initiates treatment with any prohibited medication
- Subject experiences unacceptable toxicity, including IRRs, as described in Section 6.3.3
- Subject’s daratumumab dose is held for more than 4 weeks due to a daratumumab-related toxicity as described in Section 6.4.1 (unless sponsor approves continuation)

- Subject experiences a second primary malignancy that cannot be treated by surgery or radiotherapy alone
- Subjects who achieve CR and proceed to allogeneic HSCT

If a subject discontinues study treatment for any reason before the end of the treatment period, end-of-treatment and posttreatment assessments should be obtained.

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Sponsor discontinues the study

If a subject discontinues study drug and withdraws from the study before the end of the treatment period, end-of-treatment and posttreatment assessments should be obtained. If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of the treatment phase, then end-of-treatment and posttreatment assessments should be obtained.

10.3. Withdrawal From the Use of Research Samples

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan. All statistical testing will be performed using a 1-sided test at the 5% level of significance, unless otherwise noted. Confidence intervals will be presented as two-sided 90% CIs. Summary statistics for continuous variables include mean, SD, median, minimum, and maximum unless otherwise specified. Categorical data will be presented as frequencies and percentages.

11.1. Subject Information

The study analysis populations are defined as follows:

- All treated population: all enrolled subjects who receive any study treatment. This population will be used for efficacy and safety analyses. All subjects in the all treated analysis population will be analyzed according to the treatment that they actually received.
- Response evaluable population: all treated subjects who have at least 1 adequate postbaseline disease assessment. Sensitivity analyses of CR rate and ORR will be based on the response evaluable population.
- PK evaluable population: all treated subjects who provide at least one postinfusion sample. All PK parameters will be analyzed based on the PK evaluable population.

11.2. Sample Size Determination

The study utilizes a Simon's 2-stage design and will require 49 subjects age 1 year up to 18 years.

For the B-cell ALL cohort, the following hypotheses will be tested:

- H_0: CR rate ≤15% vs.
- H_a: CR rate ≥40%

These hypotheses are based on recent response rates with novel therapies indicating that a CR rate of 15% or less is considered of no clinical interest, while a CR of 40% is deemed clinically meaningful for this population of subjects with pediatric B-cell ALL, consistent with the recent results from a Phase 1/2 single-agent study of blinatumomab.[47]

The B-cell ALL cohort will enroll 25 subjects age 1 year to <18 years, which provides 80% power to show that the true CR rate is >15% at a one-sided alpha of 5%. Stage 1 of the cohort will accrue 7 subjects (including the first 3 subjects in a safety run-in). After the seventh subject has received 2 cycles of treatment at the dose and regimen determined to be safe in the safety run-in, a futility analysis will be conducted. If the futility criterion is met (1 or 0 responders), no expansion will be planned. Otherwise, an additional 18 subjects will be enrolled into Stage 2. If 6 or fewer subjects in the B-cell ALL arm respond, then the drug will be considered ineffective and further development in this disease will be stopped.

A similar design applies to the T-cell ALL cohort, which tests the following hypotheses:

- H_0: CR rate ≤30% vs.
- H_a: CR rate ≥60%

These hypotheses are based on response rates observed in recent studies indicating that a CR rate of 30% is considered of no clinical interest, while a CR of 60% is deemed clinically meaningful for this population of pediatric subjects with T-cell ALL. This is consistent with study COGALL07P1 utilizing this backbone in combination with bortezomib which achieved a CR of about 68% (COG data on file). The T-cell ALL cohort will enroll 24 subjects aged 1 to <18

years, 8 in Stage 1 (including 3 subjects in a safety run-in) and 16 in Stage 2, which provides 80% power to show that the true CR rate is >30% at a one-sided alpha of 5%. After the eighth subject has received 1 cycles of treatment at the dose and regimen determined to be safe in the safety run-in, a futility analysis will be conducted. This cohort will be terminated for futility if 3 or fewer responders are observed in Stage 1, and for ineffectiveness if 10 or fewer subjects respond at the end of Stage 2.

A maximum of 10 young adult subjects (aged 18 to 30 years) and a maximum of 10 subjects with LL (aged 1 to 30 years) will be included in addition to the pediatric subjects included for the Simon's 2-stage study design to evaluate the safety and efficacy in this patient population and the data will be summarized descriptively.

11.3. Efficacy Analyses

11.3.1. Primary Endpoint

For subjects 1 to <18 years of age, the number and percentage of subjects who achieve a CR including 90% exact CI will be calculated for each cohort. The exact p-value to test the hypothesis, H_0: CR rate ≤15% in the B-cell ALL cohort and H_0: CR rate ≤30% in the T-cell ALL cohort, will also be calculated.

11.3.2. Secondary Endpoints

- ORR: The proportion of ALL subjects who have an OR (CR + CRi) and the 90% exact CI will be calculated for each cohort.
- EFS: The median EFS and 90% CI will be estimated using the Kaplan-Meier method for each cohort.
- RFS: The median RFS and 90% CI will be estimated using the Kaplan-Meier method for each cohort.
- OS: The median OS and 90% CI will be estimated using the Kaplan-Meier method for each cohort.
- MRD negative rate: The proportion of subjects who are MRD negative and the exact 90% CI will be calculated for each cohort.
- Allogeneic HSCT rate: The proportion of subjects who received an allogeneic HSCT after treatment with daratumumab will be calculated. An exact 90% CI will also be calculated.

11.4. Pharmacokinetic Analyses

The PK evaluable population includes all enrolled subjects who receive daratumumab and provide at least one postinfusion sample. All serum concentrations below the lowest quantifiable concentration in a sample or missing data will be labeled as such in the concentration data listings. Concentrations below the lowest quantifiable concentration in a sample will be treated as zero in the summary statistics.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling timepoint and PK parameters of daratumumab: C_{min} and C_{max}. Other PK parameters, if

available, will also be summarized. Descriptive statistics will be used to summarize daratumumab CSF concentrations at each sampling timepoint.

Population PK analysis of serum concentration-time data of daratumumab will be performed and the analysis may include data from other studies. The population PK details will be specified in an analysis plan and the results will be presented in a separate report. If an exposure-response analysis is performed, it will also be detailed in a separate analysis plan and report.

11.5. Immunogenicity Analyses

The incidence of anti-daratumumab antibodies will be summarized for all subjects who receive at least 1 dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab. A listing of subjects who are positive for anti-daratumumab antibodies will be provided.

11.6. Biomarker Analyses

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Analyses will be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance, or survival analysis, depending on the endpoint). Correlation of baseline expression levels or changes in expression levels with response to time-to-event endpoints will identify responsive (or resistant) subgroups in addition to genes and pathways attenuated following treatment with daratumumab.

Any pharmacodynamic measures will be listed, tabulated, and where appropriate, plotted. Subjects may be grouped by dose schedule or clinical response. As this is an open-label study without a control treatment, statistical analyses will be done to aid in the understanding of the results.

Results of biomarker and pharmacodynamic analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

11.7. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be included in the analysis.

Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline, and occur during treatment or within 30 days following the last dose of study treatment, or any adverse event that is considered study treatment-related regardless of the start date of the event. The number and percent of subjects with TEAEs will be summarized according to intensity using the NCI-CTCAE (Version 4.03), drug relationship, and outcome. For each adverse event, the percentage

of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point.

Parameters with predefined National Cancer Institute CTCAE toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Vital Signs

Descriptive statistics of post baseline changes in temperature, heart rate, oxygen saturation, blood pressure (systolic and diastolic), and respiration rate will be summarized.

Karnofsky and Lansky Performance Status

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

11.8. Safety Evaluation Team

Subject safety will be monitored in each cohort separately during the safety run-in of the first 3 subjects in each cohort by the SET established by the sponsor. This committee will monitor all available treatment-emergent data on an ongoing basis during the safety run-in and as needed during the conduct of the study for the purpose of ensuring the continued safety of subjects enrolled in this study.

The SET will consist of the participating principal investigators, the sponsor's responsible medical officer, sponsor's statistician, sponsor's clinical pharmacologist and sponsor's safety management team chair. Other sponsor's medical representatives may participate in the SET, if deemed necessary. The team will meet after the first 3 subjects have completed 1 cycle of daratumumab therapy during the safety run-in and throughout the study conduct as deemed necessary; documentation of meeting outcomes will be maintained by the sponsor. Decisions with the potential to effect subject safety (eg, unfavorable change in risk/benefit assessment) will be documented and promptly communicated to investigators and regulatory authorities as appropriate.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality), other than progressive disease of ALL/LL. Progressive disease of ALL/LL should not be reported as a serious and unexpected adverse event.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Reference Safety Information of the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the NCI-CTCAE, Version 4.03. The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study drug, unless the subject withdraws consent for study participation, or starts subsequent anticancer therapy. For subjects who have received additional treatment with therapeutic intent for ALL/LL during the adverse event reporting period, only AEs that are considered to be possibly, probably, or definitely related to study drug must be reported (unless the subject has been withdrawn from the study). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, and those that are considered related to daratumumab within the follow-up phase, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Progressive disease should not be reported as an adverse event, but instead symptoms/clinical signs of disease progression may be reported, which then should be attributed to progressive disease.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). No anticipated events are required to be monitored as all the anticipated events identified in the study population, such as anemia, neutropenia, thrombocytopenia, infection, and fatigue, are known adverse drug reactions for daratumumab. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Blood profile (ABO, Rh, and IAT results; see Section 9.5)

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event. Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- If the subject is hospitalized overnight due to slow daratumumab infusion or for observation after daratumumab infusion and in the absence of a significant medical event.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event. If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

For the purposes of this study, “study drug” refers to daratumumab and daratumumab will be provided by the sponsor. The backbone treatment will be purchased from commercial sources by each study site, unless local legal requirements state differently. For backbone therapies, refer to local prescribing information for instructions on preparation, handling, and storage.

14.1. Physical Description of Study Drugs

The daratumumab supplied for IV infusion is a colorless to yellow liquid and sterile concentrate of 20 mg/mL as a liquid vial. The study agent should be essentially free of visible particulate matter at the time of dosage preparation and drug product administration. It will be manufactured and provided under the responsibility of the sponsor.

14.2. Packaging

Daratumumab for IV infusion is supplied in glass vials containing daratumumab at a concentration of 20 mg/mL. It will be supplied to the site/pharmacy as open-label supply.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number.

14.4. Preparation, Handling, and Storage

Daratumumab for IV infusion must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C until it is removed for dose preparation. Study drug must not be utilized after the expiry date printed on the label. The daratumumab product must be protected from light and must not be frozen. Daratumumab does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded. Refer to the investigational product and procedures instruction manual and study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers. All study treatment will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for daratumumab
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory Manual
- NCI-CTCAE Version 4.03
- Study drug diary
- Electronic data capture (eDC) Manual
- Sample ICF and assent form
- Subject wallet card indicating blood type

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This study has been designed to evaluate daratumumab in subjects with relapsed or refractory ALL or LL. B-cell ALL/LL is being studied in second or greater relapse or subjects with refractory disease. It is expected that subjects will have exhausted available standard therapeutic options prior to enrolling in this study. Due to the accumulation of toxicity with each subsequent therapy after multiple relapses, it is anticipated that the combination of daratumumab with vincristine and prednisone will provide disease control with minimal added toxicity. T-cell ALL/LL is being studied in first relapse or subjects with refractory disease as there are fewer therapeutic options for this disease, and outcomes are dismal, even in first relapse. Thus, subjects will receive daratumumab in combination with a 4-drug re-induction therapy followed by further intensive therapy for those subjects who achieve a response to this therapy.

The primary safety profile of daratumumab is predominantly characterized by IRRs; see Section 6.3 for guidelines for prevention and management of IRRs. Based on the mechanism of action of daratumumab, a potential risk could be infection; therefore, the protocol requires the review of hematological laboratory results prior to daratumumab administration. CD38 is distributed in erythrocytes and platelets. A significant reduction of platelets was reported in an animal study. In a human clinical study of subjects with relapsed or refractory multiple myeloma (Study GEN501), thrombocytopenia was also reported. However, safety laboratory monitoring did not show a clinically meaningful reduction of platelets, and no bleeding events were observed. Safety data from a Phase 3 clinical study (MMY3004) in subjects with relapsed or refractory multiple myeloma comparing daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd), showed daratumumab may increase thrombocytopenia associated with bortezomib-based regimens. However, the incidence of bleeding events was low and the majority of events were mild (less than 1% of subjects experienced Grade 3 or 4 bleeding events). Anemia was also reported in Study GEN501. Free hemoglobin was mildly elevated, but other parameters did not support hemolysis. Anemia, all grades and Grade 3 or 4 in the

MMY3004 study, were similar among the 2 treatment groups. Routine safety laboratory measurement of hemoglobin and platelets will be closely monitored in this study.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study; refer to local regulations. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The volume of blood collected will be consistent with the recommendations of the EMA for study-related blood loss (see Attachment 7).[12] Sample volumes will be adjusted according to standards for pediatric subjects.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF and assent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF/assent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care

- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF/assent revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s). At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent and Assent Form

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining

all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study; please refer to local regulations. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent or if applicable legally acceptable representative.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand daratumumab, to understand ALL/LL, to understand differential drug responders, and to develop tests/assays related to daratumumab and ALL/LL. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research.

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF/assent, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific

protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.

- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness. The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not enrolled into the study, the date seen and date of birth (as allowed by local regulations) will be used. The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document). The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. Electronic data capture (eDC) will be used for this study. Study site personnel must log into eDC in a secure manner (ie, using a personal password). The individual password must be kept confidential for personal use). The investigator must verify that all data entries in the eCRF are accurate and correct. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

The study data will be transcribed by study-site personnel from the source documents onto an electronic eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

If necessary, queries will be generated in the eDC tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study

documents before having obtained written approval from the sponsor. If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study. The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study will end 1 year after the last subject has initiated treatment or when the Sponsor decides to stop the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

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

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding daratumumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of daratumumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic exploratory biomarker analyses performed after the Clinical Study Report has

been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

REFERENCES

1. Berg SL, Blaney SM, Devidas M, et al. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. J Clin Oncol. 2005;23(15):3376-3382.
2. Bhojwani D, Pui C-H. Relapsed childhood acute lymphoblastic leukemia. Lancet Oncol. 2013;14:e205-e217.
3. Bras AE, Beishuizen A, Langerak AW, et al. CD38 expression in paediatric leukaemia and lymphoma: implications for antibody targeted therapy. Br J Haematol. 2016 Sep 8. doi: 10.1111/bjh.14310. [Epub ahead of print]
4. Burkhardt B, Zimmermann M, Oschlies I, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol. 2005;131(1):39-49.
5. Burkhardt B, Reiter A, Landmann E, et al. Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: a report from the Berlin-Frankfurt-Muenster group. J Clin Oncol. 2009;27(20):3363-3369.
6. Chapuy CI, Nicholson R, Aguad MD, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015;55:1545-1554.
7. Chapuy CI, Aguad MD, Nicholson RT, et al. International validation of a dithiothreitol (DTT)-based method to resolve the daratumumab interference with blood compatibility testing. Transfusion. 2016;56(12):2964-2972.
8. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999;17:1244-1253.
9. Chessells JM, Veys P, Kempski H, et al. Long-term follow-up of relapsed childhood acute lymphoblastic leukemia. Br J Haematol. 2003;123(3):396-405.
10. de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186(3):1840-1848.
11. Doshi P, Sasser AK, Axel A, van Bueren JL. Daratumumab Treatment Alone or in Combination with Vincristine Results in the Inhibition of Tumor Growth and Long-term Survival in Preclinical Models of Acute Lymphoblastic Leukemia. European Hematology Association (EHA) 19th Congress. Haematologica 2014;99(s1):4, abstract P109.
12. European Medicines Agency. Ethical considerations for clinical trials on medicinal products with the paediatric population. 2008. Available at: http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf. Accessed 13 July 2017.
13. Feijen EAM, Leisenring WM, Stratton KL, et al. Equivalence ratio for daunorubicin to doxorubicin in relation to late heart failure in survivors of childhood cancer. J Clin Oncol. 2015;33(32):3774-3780.
14. Flavell DJ, Cooper S, Okayama K, et al. Comparison of the performance of anti CD7 and anti-CD38 bispecific antibodies and immunotoxins for the delivery of saporin to a human T-cell acute lymphoblastic leukemia cell line. Hematol Oncol. 1995;13(4):185-200.
15. Gaynon PS, Qu RP, Chappell RJ, et al. Survival after relapsed in childhood acute lymphoblastic leukemia: impact of site and time to first relapse – the Children's Cancer Group Experience. Cancer. 1998;82(7):1387-1395.
16. Gaynon PS, Harris RE, Altman AJ, et al. Bone marrow transplantation versus prolonged intensive chemotherapy for children with acute lymphoblastic leukemia and an initial bone marrow relapse within 12 months of the completion of primary therapy: Children's Oncology Group study CCG-1941. J Clin Oncol. 2006;24:3150-3156.
17. Jabbour E, O'Brien S, Konopleva M, Kantarjian H. New insights into the pathophysiology and therapy of acute lymphoblastic leukemia. Cancer. 2015;121(15):2517-2528.
18. Kaatsch P. Epidemiology of childhood cancer. Cancer Treatment Reviews 2010;36:277-285.

19. Kansagra A., Litzow M. Treatment of young adults with acute lymphoblastic leukemia. Curr Hematol Malig Rep. epub March 28, 2017.

20. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoid leukemia. N Eng J Med. 2016;375:470-753.

21. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In Evaluation of chemotherapeutic agents. Edited by MacLeod CM. New York: Columbia University Press; 1949:191

22. Ko RH, Ji L, Barnette P, et al. Outcomes of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol. 2010;28(4):648-654.

23. Kurtzberg J, Ernst TJ, Keating MJ, et al. Phase I study of 506U78 administered on a consecutive 5-day schedule in children and adults with refractory hematologic malignancies. J Clin Oncol. 2005;23(15):3396-3403.

24. Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. Cancer. 1987;60(7):1651-1656.

25. Madhusoodhan PP, Carroll WL, Bhatla T. Progress and prospects in pediatric leukemia. Curr Probl Pediatr Adolesc Health Care. 2016;46(7):229-241.

26. Mascelli MA, Zhou H, Sweet R, et al. Molecular, biologic, and pharmacokinetic properties of monoclonal antibodies: impact of these parameters on early clinical development. J Clin Pharmacol. 2007;47:553-565.

27. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Eng J Med. 2014;371:1507-1517.

28. Michaux K, Bergeron C, Gandemer V, et al. Relapsed or refractory lymphoblastic lymphoma in children: results and analysis of 23 patients in the EORTC 58951 and the LMT96 protocols. Pediatr Blood Cancer. 2016;63(7):1214-1221.

29. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia. Version 2.2016.

30. Neth O, Seidemann K, Jansen P, et al. Precursor B-cell lymphoblastic lymphoma in childhood and adolescence: clinical features, treatment, and results in trials NHL-BFM 86 and 90. Med Pediatr Oncol. 2000;35(1):20-27.

31. Nguyen K, Devidas M, Cheng SC, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia. 2008;22(12):2142-2150.

32. Orphanet. Acute lymphoblastic leukemia. Accessed 13 January 2017.

33. Overdijk MB, Verploegen S, Bogels M, et al. Phagocytosis is a Mechanism of Action for Daratumumab. American Society of Hematology (ASH) 2012. Abstract 51257.

34. Overdijk MB, Verploegen S, Bogels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. MAbs. 2015;7(2):311-321.

35. Percy CL, Smith MA, Linet M, et al. Lymphomas and reticuloendothelial neoplasms. In: Ries LA, Smith MA, Gurney JG, et al., eds. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda, Md: National Cancer Institute, SEER Program, 1999. NIH Pub.No. 99-4649, pp 35-50. Available at: https://seer.cancer.gov/archive/publications/childhood/childhood-monograph.pdf. Accessed 27 July 2017.

36. Pui CH, Sandlund JT, Pei D, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. Blood. 2004;104(9):2690-2696.

37. Pullen J, Boyett J, Shuster J, et al. Extended triple intrathecal chemotherapy trial for prevention of CNS relapse in good-risk and poor-risk patients with B-progenitor acute lymphoblastic leukemia: a Pediatric Oncology Group study. J Clin Oncol. 1993:11(5):839-849.

38. Raetz EA, Borowitz MJ, Devidas M, et al. Reinduction platform for children with first marrow relapse in acute lymphoblastic lymphoma. J Clin Oncol. 2008;26(24):3971-3978.

39. Sallan SE. Myths and lessons from the adult/pediatric interface in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2006;128-132.

40. Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. N Engl J Med. 1996;334(19):1238-1248.

41. Schwartz GJ, Gauthier B. A simple estimate of glomerular filtration rate in adolescent boys. J Pediatr. 1985;106(3):522-526.

42. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.

43. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-2390.

44. Tabrizi MA, Tseng CM, Roskos LK. Elimination mechanisms of therapeutic monoclonal antibodies. Drug Discov Today. 2006;11(1-2):81-88.

45. van de Donk NW, Janmaat ML, Mutis T, et al. Monoclonal antibodies targeting CD38 in hematologocial malignancies and beyond. Immunolog Reviews. 2016;270:95-112.

46. van der Velden VH, de Launaij D, de Vries JF, et al. New cellular markers at diagnosis are associated with isolated central nervous system relapse in paediatric B-cell precursor acute lymphoblastic leukemia. Br J Haematol. 2016;172(5):769-781.

47. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/Phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016;34(36):4381-4389.

48. Whitlock JA, dalla Pozza K, Goldberg JM, et al. Nelarabine in combination with etoposide and cyclophosphamide is active in first relapse of childhood T-acute lymphocytic leukemia (T-ALL) and T-lymphoblastic lymphoma (T-LL). Blood ASH Abstracts 2014;124:Abstract 795.

49. Zhang Y, Wei X, Bajaj G, Barrett JS, Meibohm B, Joshi A, Gupta M. Challenges and considerations for development of therapeutic proteins in pediatric patients. J Clin Pharmacol. 2015;55(s3): S103-S115.

Attachment 1: Karnofsky and Lansky Performance Status Scales

Karnofsky Scale[a] (recipient age ≥16 years)	Lansky Scale[b] (recipient age <16 years)
100: Normal, no complaints, no evidence of disease	100: Fully active, normal
90: Able to carry on normal activity. Minor signs or symptoms of disease.	90: Minor restriction with strenuous physical activity
80: Normal activity with effort. Some signs or symptoms of disease.	80: Active, but gets tired more quickly
70: Cares for self, unable to carry on normal activity or to do active work	70: Both greater restrictions of, and less time spent in, active play
60: Requires occasional assistance but is able to care for most of personal needs	60: Up and around, but minimal active play; keeps busy with quieter activities
50: Requires considerable assistance and frequent medical care	50: Lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40: Disabled, requires special care and assistance	40: Mostly in bed; participates in quiet activities
30: Severely disabled, hospitalization indicated, although death not imminent	30: Stuck in bed; needs help even for quiet play
20: Hospitalization necessary. Very sick, active supportive treatment necessary.	20: Often sleeping; play is entirely limited to very passive activities
10: Moribund, fatal process progressing rapidly	10: Does not play or get out of bed to play
0: Dead	0: Unresponsive

a Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In Evaluation of chemotherapeutic agents. Edited by MacLeod CM. New York: Columbia University Press; 1949:191-205.[21]

b Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. Cancer. 1987;60(7):1651-1656.[24]

Attachment 2: Conversion Table for Glucocorticoid Dose

Glucocorticoid	Approximate Equivalent Dose (mg)	Half-life (Biologic) hours
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 – 0.75	36-54
Dexamethasone	0.75	36-54

Attachment 3: Serum Creatinine Guidelines

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

Note: The threshold creatinine values in this table were derived from the Schwartz formula for estimating glomerular filtration rate[41] utilizing child length and stature data published by the CDC.

Cockcroft-Gault formula:

To calculate the subject's creatinine clearance (CrCl), use the following Cockcroft-Gault formula:

$$\text{CrCl} = \frac{(140 - \text{age [in years]}) \times \text{weight (kg)}}{(72 \times \text{serum creatinine [mg/dL]})} \quad (\times 0.85 \text{ for females})$$

If the serum creatinine is obtained using the International System of Units (SI) (ie, micromol/L), use the following formula to convert SI units to conventional (mg/dL) units (Manual of Laboratory & Diagnostic Tests, 2004):

serum creatinine (micromol/L) divided by 88.4 = serum creatinine (mg/dL).

Attachment 4: Asthma Guidelines

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment	Symptoms	≤ 2 days/week			≥ 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x	Daily			Several times per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Normal FEV_1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function FEV1 FEV1/FVC	N/A	Normal FEV1 between exacerbations > 80% > 85%	Normal FEV1 between exacerbations > 80% Normal	N/A	> 80% > 80%	> 80% Normal	N/A	60-80% 75-80%	60-80% Reduced 5%	N/A	< 60% < 75%	< 60% Reduced
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.											
Recommended Step for Initiating Treatment		Step 1			Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust herapy accordingly.											

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Components of Control		Classification of Asthma Control								
		Well Controlled			Not Well Controlled			Very Poorly Controlled		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
	Symptoms	≤ 2 days/week but not more than once on each day		≤ 2 days/ week	> 2 days/week or multiple times on ≤2 days/week		> 2 days/ week	Throughout the day		
Impairment	Nighttime awakenings	≤ 1x/month		≤ 2x/month	> 1x/month	≥ 2x/month	1-3x/week	> 1x/week	≥ 2x/week	≥ 4x/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			> 2 days/week			Several times per day		
	Lung function FEV_1 or peak flow FEV_1/FVC	N/A	> 80% > 80%	> 80%	N/A	60-80% 75-80%	60-80%	N/A	< 60% < 75%	< 60%
	Validated questionnaires ATAQ ACQ ACT			0 ≤ 0.75 ≥ 20			1-2 ≥ 1.5 16-19			3-4 N/A ≤ 15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2/year					
		Consider severity and interval since last exacerbation								
	Reduction in lung growth/ Progressive loss of lung function	Evaluation requires long-term follow-up								
Recommended Action for Treatment		• Maintain current step • Regular follow-up every 1-6 months • Consider step down if well controlled for at least 3 months			Step up 1 step	Step up at least 1 step	• Step up 1 step • Reevaluate in 2-6 weeks • For side effects, consider alternative treatment options	• Consider short course of oral steroids • Step up 1-2 steps		• Consider short course of oral steroids • Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

Before step up:
Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step.
- **Reevaluate the level of asthma control in 2-6 weeks to achieve control**.

0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy.
5-11 years: Adjust therapy accordingly.
- **For side effects**, consider alternative treatment options.

Attachment 5: High-Dose Methotrexate (HD MTX) Infusion Guidelines

When intrathecal therapy and HD MTX are scheduled for the same day, deliver the intrathecal therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus) or as per local standards.

Hold TMP-SMX on the days of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 μM. *In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 μM or as per local standards.*

Hold any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 μM. *In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 μM or as per local standards.*

Prehydrate with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 min) may be given to raise the urine pH relatively quickly, a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout HD MTX infusion, and for a minimum of 48 hours after its completion. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below 0.1 μM or as per local standards.

Hour 0: MTX 500 mg/m_2 IV mixed in a final volume of 65 mL/m_2 D5 ¼ NS with 30 mEq $NaHCO_3$/L and infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m_2 mixed in a final volume of 2935 mL/m^2 D5 ¼ NS with 30 mEq $NaHCO_3$/L given by continuous IV infusion over 23.5 hours at 125 mL/m^2/hr. Be certain that the HD MTX infusion is completed in the 24-hour period. Unintentional prolongation to as long as 26 hours though not encouraged is acceptable. Alternatively, follow local standards.

Hours 24, (36), 42 and 48: Draw MTX level and serum creatinine; NOTE: 36-hour level is only drawn if needed (see below) or as per local standards.

For MTX levels that exceed these expected values, follow local standard of care guidelines or follow the rescue regimen as noted below and increase hydration to 200 mL/m_2/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If serum creatinine rises significantly, at any time point, assure appropriate urine pH and urine volume as above and draw a 42-hour level. If urine output fails to continue at 80% of the fluid intake, consider furosemide or mannitol. Regardless of urine output, also consider glucarpidase (carboxypeptidase G_2) (see below). For

patients with delayed clearance during a previous course, begin the following course with the increased hydration (200 mL/m^2/hr) or as per local standards.

If the 24-hour level is < 150 μM draw the next level at hour 42 and refer to table below or as per local standards.

If the 24-hour level is ≥ 150 μM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. If the value is "real" refer to the changes in hydration, etc. described above and repeat the level with a serum Cr at hour 36. Then refer to the table below or as per local standards.

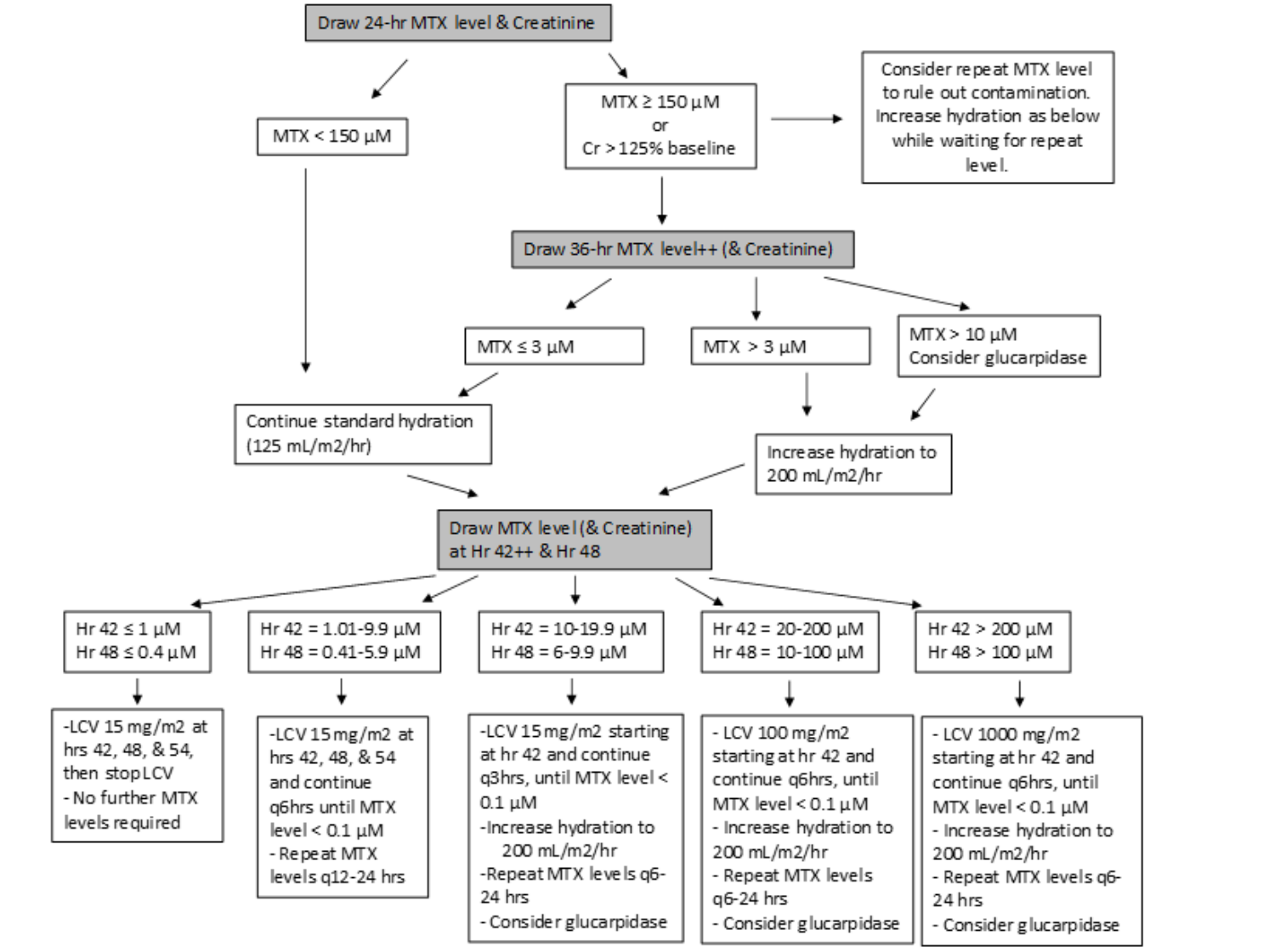
Start Leucovorin rescue for all subjects at 42 hr post start of methotrexate infusion. For dose and timing of dosing follow table below based on subject's methotrexate level at specific time points or as per local standards.

If the 42 and 48-hour levels are ≤ 1 and 0.4 μM, respectively, give leucovorin at 15 mg/m^2 IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose. No additional levels are needed, nor is additional leucovorin. Alternatively, follow local standards.

(36 hr MTX level)	42 hr MTX level	48 hr MTX level	Leucovorin Rescue++
Only required if 24 hr level is ≥ 150 μM. See below for guidelines**.	1.01 to 9.9 μM	0.41 to 5.9 μM	Continue 15 mg/m^2 q 6h until MTX level < 0.1 μM (draw q12-24 h).
	10 to 19.9 μM	6 to 9.9 μM	Increase to 15 mg/m^2 q 3h until MTX level < 0.1 μM (draw q 6-24 h). Consider glucarpidase.
	20 to 200 μM	10 to 100 μM	Increase to 100 mg/m^2 q 6h until MTX level < 0.1 μM (draw q 6-24 h). Consider glucarpidase.
	> 200 μM	> 100 μM	Increase to 1000 mg/m^2 q 6h until MTX level < 0.1 μM (draw q 6-24 h). Consider glucarpidase.

**** If the 36-hour level exceeds 3** μM, increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If urine output fails to continue at 80% of the fluid intake, consider furosemide or mannitol. Regardless of urine output, also **consider glucarpidase if 36-hour MTX level exceeds 10** μM (see below).
++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤ 1 and/or ≤ 0.4 μM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

High-dose Methotrexate Flowchart Guidelines (alternatively, may follow local standards)



++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤ 1 and/or ≤ 0.4 µM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

Attachment 6: The Family of Antihistamine Medications

The following antihistamines may be used for daratumumab preinfusion medication (including, but not limited to):

- Diphenhydramine
- Cetirizine
- Fexofenadine
- Loratadine
- Clemastine
- Dexchlorpheniramine
- Promethazine*

* The IV use of promethazine should be avoided.

Attachment 7: Estimated Total Blood Volume Collected During the Study

Estimated Maximum Volume of Blood to be Collected From Subjects with B-cell ALL/LL

Type of Sample[a,b]	Volume per Sample (mL)	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[c]
Screening			
Blood group and type assessment and IAT assessment	2.0	1	2.0
BCR-ABL (Ph+ subjects only)	2.0	1	2.0
Safety			
Hematology[d]	2.0	1	2.0
Serum chemistry[d]	2.5	1	2.5
Pregnancy[e]	2.0	1	2.0
Hepatitis B serology	5.0	1	5.0
Cycles 1 and 2			
BCR-ABL (Ph+ subjects only)	2.0	2	4.0
Safety			
Hematology[d]	2.0	8	16.0
Serum chemistry[d]	2.5	8	20.0
Pregnancy[e]	2.0	2	4.0
Pharmacokinetic/immunogenicity samples[f]	5.0	4	20.0
Biomarker samples	2.0	2	4.0
Cycles 3 and 4			
BCR-ABL (Ph+ subjects only)	2.0	2	4.0
Safety			
Hematology[d]	2.0	4	8.0
Serum chemistry[d]	2.5	4	10.0
Pregnancy[e]	2.0	2	4.0
Pharmacokinetic/immunogenicity samples[f]	5.0	2	10.0
Cycles 5+			
BCR-ABL (Ph+ subjects only)	2.0	1-3	2.0-6.0
Safety			
Hematology[d]	2.0	2+ (2 per cycle)	4.0+
Serum chemistry[d]	2.5	2+ (2 per cycle)	5.0+
Pregnancy[e]	2.0	1+ (1 per cycle)	2.0+
Pharmacokinetic/immunogenicity samples[f]	5.0	4	20.0
End-of-Treatment Visit			
Safety			
Hematology[d]	2.0	1	2.0
Serum chemistry[d]	2.5	1	2.5
Biomarker samples	2.0	1	2.0
Pharmacokinetic/immunogenicity samples[f]	5.0	1	5.0
Follow-up Period			
Pharmacokinetic/immunogenicity samples[f]	5.0	1	5.0
Approximate Total	**74.5**	**61-63+**	**169.0+**

a. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples but should not exceed allowable daily blood volume limits per local standards.
b. Sample volumes will be adjusted according to standards for pediatric subjects.
c. Calculated as number of samples multiplied by amount of blood per sample.
d. The Monoject pediatric collection containers are a 1.1 mL SST tube for chemistry and a 1.2 mL EDTA tube for hematology.
e. Female subjects of reproductive potential only.
f. Subjects aged 1 to 4 years will have 1.1 mL collected per sample. Subjects aged 5 to 12 years will have 2.5 mL collected per sample.

Estimated Maximum Volume of Blood to be Collected From Subjects with T-cell ALL/LL

Type of Sample[a,b]	Volume per Sample (mL)	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[c]
Screening			
Blood group and type assessment and IAT assessment	2.0	1	2.0
Safety			
Hematology[d]	2.0	1	2.0
Serum chemistry[d]	2.5	1	2.5
Pregnancy[e]	2.0	1	2.0
Hepatitis B serology	5.0	1	5.0
Cycle 1			
Safety			
Hematology[d]	2.0	5	10.0
Serum chemistry[d]	2.5	5	12.5
Pregnancy[e]	2.0	1	2.0
Pharmacokinetic/immunogenicity samples[f]	5.0	2	10.0
Biomarker samples	2.0	1	2.0
Cycle 2			
Safety			
Hematology[d]	2.0	5	10.0
Serum chemistry[d]	2.5	5	12.5
Pregnancy[e]	2.0	1	2.0
Pharmacokinetic/immunogenicity samples[f]	5.0	4	20.0
Biomarker samples	2.0	1	2.0
End-of-Treatment Visit			
Safety			
Hematology[d]	2.0	1	2.0
Serum chemistry[d]	2.5	1	2.5
Biomarker samples	2.0	1	2.0
Pharmacokinetic/immunogenicity samples[f]	5.0	1	5.0
Follow-up Period			
Pharmacokinetic/immunogenicity samples[f]	5.0	1	5.0
Approximate Total	**57.0**	**40**	**113.0**

a. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples but should not exceed allowable daily blood volume limits per local standards.
b. Sample volumes will be adjusted according to standards for pediatric subjects.
c. Calculated as number of samples multiplied by amount of blood per sample.
d. The Monoject pediatric collection containers are a 1.1 mL SST tube for chemistry and a 1.2 mL EDTA tube for hematology.
e. Female subjects of reproductive potential only.
f. Subjects aged 1 to 4 years will have 1.1 mL collected per sample. Subjects aged 5 to 12 years will have 2.5 mL collected per sample.

Attachment 8: Doxorubicin Equivalent Conversion

- Daunorubicin: multiply total dose in m^2 x 1
- Mitoxantrone: multiply total dose in m^2 x 4
- Idarubicin: multiply total dose in m^2 x 5
- Epirubicin: multiply total dose in m^2 x 0.67

For doses in mg/kg, first multiply dose x 30 for mg/m^2 then apply conversion above.

Source: Feijen 2015[13]

INVESTIGATOR AGREEMENT

JNJ-54767414 (daratumumab)
Clinical Protocol 54767414ALL2005 Amendment 3

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 22 January 2019