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Novartis Institutes for BioMedical Research

LFG316

Clinical Trial Protocol CLFG316X2202

# A randomized, open label, controlled, multiple dose study to evaluate the clinical efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of LFG316 in patients with transplant associated microangiopathy after hematopoietic precursor cell transplantation

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## Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

## Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and notify the Clinical Trial Leader).

Contact information is listed in the Site Operations Manual.

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## List of abbreviations

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|---|---|
| aHUS | atypical hemolytic uremic syndrome |
| ACR | albumin-creatinine ratio |
| AE | adverse event |
| AMD | age-related macular degeneration |
| ALT | alanine aminotransferase |
| ALP | alkaline phosphatase |
| ANCOVA | analysis of covariance |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| BMI | Body Mass Index |



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| CD-ROM | compact disc – read only memory |
| CFR | Code of Federal Regulation |
| CTC-AE | Common Terminology Criteria for Adverse Events |
| CTL | clinical trial leader |
| DIC | uncompensated disseminated intravascular coagulation |
| CK | creatinine kinase |
| CNI | calcineurin inhibitors |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| CSR | clinical study report |
| CTC | Common Toxicity Criteria |
| CV | coefficient of variation |
| DBP | diastolic blood pressure |
| DMC | Data Monitoring Committee |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| ELISA | Enzyme-linked immunosorbent assay |
| EMA | European Medicines Agency |

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|---|---|
| EOS | End of study |
| Fc | fragment crystallizable region |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GCS-F | Granulocyte-colony stimulating factor |
| γ-GT | Gamma-glutamyl transferase |
| GvHD | graft versus host disease |
| h | hour |
| HIV | human immunodeficiency virus |
| HPF | high power field |
| HSCT | hematopoietic stem cell transplantation |
| HPCT | hematopoietic precursor cell transplantation |
| IA | Interim analysis |
| IB | Investigators brochure |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IG | Immunogenicity |
| IgG | Immunoglobulin G |
| IN | Investigator's notification |
| IRB | Institutional Review Board |
| IUD | intrauterine device |
| IUS | intrauterine system |
| i.v. | intravenous |
| IVIg | Intravenous immunoglobulin |
| LFT | Liver function test |
| LDH | lactate dehydrogenase |
| LLOQ | lower limit of quantification |
| mAb | Monoclonal antibody |
| MAC | membrane attack complex (C5b-9) |
| MedDRA | Medical dictionary for regulatory activities |
| mg | milligram(s) |

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|---|---|
| mL | milliliter(s) |
| MoA | mode of action |
| NOAEL | non-observed adverse event level |
| PCR | protein/creatinine ratio |
| PD | pharmacodynamic(s) |
| PG | pharmacogenetic(s) |
| PNH | Paroxysmal nocturnal hemoglobinuria |
| PK | pharmacokinetic(s) |
| RBC | red blood cell(s) |
| REB | Research Ethics Board |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SoC | Standard of Care |
| SOM | site operations manual |
| SRGvHD | steroid refractory graft versus host disease |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TAM | transplant associated microangiopathy |
| TBL | total bilirubin |
| TBV | total blood volume |
| TTP | thrombotic thrombocytopenic purpura |
| ULN | upper limit of normal |
| ULQ | upper limit of quantification |
| WBC | white blood cell(s) |
| WHO | World Health Organization |

## Pharmacokinetic definitions and symbols

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| AUC0-t | The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume] |
| AUC/D | Area under the plasma (or serum or blood) concentration-time curve/Dose |
| AUClast | The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume] |
| Cmax | The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume] |
| Cmax/D | The observed maximum plasma (or serum or blood) concentration following drug administration/dose |
| T1/2 | The terminal elimination half-life [time] |
| Tmax | The time to reach the maximum concentration after drug administration [time] |

## Protocol synopsis

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| **Protocol number** | CLFG316X2202 |
| **Title** | A randomized, open label, controlled, multiple dose study to evaluate the clinical efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of LFG316 in patients with transplant associated microangiopathy after hematopoietic precursor cell transplantation |
| **Brief title** | Efficacy and safety of LFG316 in transplant associated microangiopathy (TAM) patients |
| **Sponsor and Clinical Phase** | Novartis<br>Phase II |
| **Intervention type** | Biologic |
| **Study type** | Interventional |
| **Purpose and rationale** | The design of this study addresses the primary objective of establishing efficacy in this indication for both children and adults. The randomized, controlled design allows comparison of LFG316 plus standard of care (excluding prohibited treatment) against Standard of Care (SoC) only. The study will allow inclusion of patients ≥2 years old after safety of LFG316 is demonstrated during interim analysis 1 (IA1) with 5 patients ≥ 12 years old treated with LFG316 for 4 weeks. There are no pediatric data generated so far for LFG316; however eculizumab was administered to pediatric TAM patients. The nonclinical data obtained with LFG316 and the clinical data obtained with eculizumab supports administration of LFG316 to children ≥ 2 years old. The option for patients not responding in either arm to switch to the alternative arm when certain conditions are met allows all patients the opportunity to receive LFG316 treatment in this very rare indication with high unmet medical need and also ensures that patients who fail to improve on LFG316 are not prevented from receiving the SoC treatment. This element of the design does not affect the assessment of efficacy since patients who do switch treatments will be considered to be treatment failures in the comparison of the randomized treatment groups. An open-label design is used instead of a blinded placebo since it is not feasible to blind the treatments used in the SoC arm. |
| **Primary Objective(s)** | To assess the hematological response rate in patients with TAM receiving LFG316 plus standard of care (excluding prohibited treatment) against Standard of Care (SoC) only. |
| **Secondary Objectives** | • To assess the safety and tolerability of LFG316 in patients with TAM<br>• To describe the pharmacokinetics of total LFG316<br>• To evaluate non-relapse mortality in TAM patients treated with LFG316 as compared to patients on SoC<br>• To assess complete response rate at 17 weeks in TAM patients treated with LFG316 compared to patients receiving standard of care |

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| **Study design** | This is a randomized, SoC-controlled, open-label, multi-center study in patients with TAM after hematopoietic precursor cell transplantation (HPCT) from a related or unrelated donor for malignant and nonmalignant disease after myeloablative or non-myeloablative conditioning.<br><br>The study will consist of up to 28 days of screening period, 16 weeks treatment period that can be extended to 45 weeks (in case of ongoing symptoms of TAM), 36 weeks follow up, and end of study visit (EOS) at week 52 (Figure 3-1). Duration of follow up will depend on duration of treatment. Patients who are treated for more than 41 weeks will proceed directly to EOS visit.<br><br>Approximately 40 patients will be randomized to receive SoC alone or LFG316 plus SoC (excluding plasmapheresis and prohibited treatment as per Table 5-1). Patients will be included in the study if they have diagnosis of TAM and poor prognostic markers (Section 4). Corporate Confidential Information<br><br>Patients randomized to LFG316 within 3 age group strata will receive [redacted] on study days 1, 8, and 15 and then weekly doses of [redacted] for remaining treatment duration of total 16 weeks. Patients showing worsening of the disease (definition in Section 3.1) between study week 2 and 3, or no improvement between week 4 and 16, will be considered failures and can be switched to receive the alternative treatment (SoC or LFG316). Patients can only switch treatment arms once. Patients who switch from SoC to LFG316 will need to repeat the visit and dosing schedule starting from visit 3 when first dose of study medication is administered. Patients who change from LFG316 to SoC will continue with their visits as per Assessment schedule. |
| **Population** | Approximately 40 male and female patients ≥ 2 years old undergoing allo-HSCT for malignant and nonmalignant disease with high-risk TAM will be included in the study. The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. |
| **Inclusion criteria** | Key inclusion criteria<br>• Written informed consent/assent before any study-specific screening procedures. For pediatric patients, consent will be obtained from parent(s) or legal guardian(s) and the signature of at least 1 parent or guardian will be required. Investigators will also obtain assent of patients according to local, regional or national guidelines.<br>• Patients after allogeneic stem cell transplantation from a related or unrelated, HLA-matched or mismatched donor with the diagnosis of transplant related microangiopathy. Patients having received any of the following stem cell sources are eligible: G-CSF mobilized peripheral blood stem cells, bone marrow, umbilical cord blood.<br>• Male and female TAM patients ≥ 2 years old at the time of first dose administration. Patients < 12 years old can only be included in the study after first IA has shown that it is safe and well tolerated in patients ≥ 12 years old (Section 3.5).<br>• The presence of TAM as per below diagnostic criteria at baseline (or screening if baseline visit is skipped). All the criteria have to be met for the patients included in the study:<br>- Elevated lactate dehydrogenase (any elevation above normal range) |

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| | - Thrombocytopenia with platelet count < 50x10e9/L or more than 50% decrease in platelet count from the highest value achieved after transplant<br>- Anemia below lower limit of normal or anemia requiring transfusion support as per center standard<br>- Schistocytes on peripheral blood smear (>2 per HPF) OR histologic evidence of microangiopathy<br>- Absence of coagulopathy (no uncompensated disseminated intravascular coagulation, DIC) at screening<br>• The presence of TAM high risk features at baseline (or screening if baseline visit is skipped): Patients ≤ 16 years must have a Lansky score of ≤ 70 and patients > 16 must have Karnofsky score ≤ 70%. and/or proteinuria (> 30 mg/dL) measured in two urine spot analyses.<br>• Hypertension, defined for adults by SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg at baseline (or screening if baseline visit is skipped), and for pediatric patients by blood pressure greater than the 95th percentile for age, sex, and height (see Table 16-1). Additionally, patients who were started on antihypertensive medication after HSCT or who have received additional antihypertensive medication after HSCT will be eligible, even if they don't have elevated blood pressure.<br>• Able to receive antibiotic prophylaxis against N. meningitides for the duration of the study.<br>• Meningococcal vaccine(s) prior to LFG316 treatment if prior vaccination cannot be confirmed. The choice of vaccine(s) should take into account the serotypes prevalent in the geographic areas in which study patients will be enrolled. In case vaccination is not possible or will result in an unfavorable risk benefit ratio as judged by the investigator, vaccination can be postponed until deemed likely to be effective.<br>• Patients <18 years old should receive vaccination for the prevention of S. pneumoniae and H. influenzae type b prior to LFG316 administration. In case vaccination is not possible or will result in an unfavorable risk benefit ratio as judged by the investigator, vaccination can be postponed until deemed likely to be effective.<br>• Weight of at least 10kg. |

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| **Exclusion criteria** | Key exclusion criteria<br>• Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or even longer if required by local regulations. Concomitant investigational treatment, including treatment in the context of a clinical trial with marketed drugs (off-label) may be acceptable but requires approval by the sponsor on the case by case basis.<br>• Known hypersensitivity to any constituent of the study medication<br>• Patients with steroid refractory graft versus host disease (SRGvHD). SRGvHD is defined as progression (=increase in overall grade) after 5 days on ≥2mg/kg methylprednisolone or equivalent OR no improvement (no decrease in overall grade) after 10 days on ≥ 2mg/kg methylprednisolone or equivalent. If patients are receiving steroids for GvHD prophylaxis as per center standard, progression after 5 days and no response after 10 days after doubling the steroid dose will be regarded as steroid refractory.<br>• Patients with ALT > 10x ULN at screening.<br>• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (at screening or baseline).<br>• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 45 days after stopping study medication as specified in Section 4.2.<br>• Sexually active males unwilling to use a condom during intercourse while taking drug and for 45 days after stopping investigational medication. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. Male patients should not father a child in this period<br>• Positive HIV (ELISA and Western blot) test result (checked at screening). Historical local data will be acceptable if it the test was done within one month before start of HSCT conditioning and not more than 3 months before study visit 3.<br>• A positive Hepatitis B surface antigen or Hepatitis C test result at screening. Historical local data will be acceptable if it the test was done within one month before start of HSCT conditioning and not more than 3 months before study visit 3.Patients with any severe, progressive or uncontrolled acute or chronic medical condition (such as uncontrolled infectious disease or sepsis) or clinical laboratory abnormalities that in the investigator's opinion would make the patient inappropriate for entry into this study (at screening or baseline).<br>• Patients with proven TTP as per historical data (as defined by ADAMST13 activity test) and if already available results of ADAMST13 test done at screening<br>• Patients previously treated with eculizumab for TAM<br>• Patients with known or suspected hereditary complement pathway deficiency. This exclusion criterion is not applicable to patients with complement pathway abnormalities/upregulation known to be associated with increased risk of transplant associated microangiopathy |

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| **Investigational and reference therapy** | • LFG316 [redacted]<br>• LFG316<br>• Site specific SoC |
| **Efficacy/PD assessments** | • Schistocyte count<br>• Incidence of transfusion<br>• Assessment of proteinuria<br>Corporate Confidential Information |
| **Safety assessments** | • blood chemistry, hematology, proteinuria, body height and weight, urinalysis, ECG evaluation, Adverse events, body temperature, blood pressure, physical examination, pulse rate, pregnancy test, Lansky/Karnofsky score |
| **Other assessments** | • PK<br>Corporate Confidential Information<br>• ADAMST13<br>Corporate Confidential Information |
| **Data analysis** | A patient is considered to be a hematological responder at 17 weeks if both of the following criteria are met:<br>1. Schistocytes <2/microscopic high power field (HPF).<br>2. Transfusion independent (no need for TAM-related transfusions (platelets and erythrocytes)<br>Patients who discontinue the randomized treatment before 16 weeks due to lack of efficacy (whether according to the protocol-defined rules allowing a switch to the alternative treatment arm, or not) will be considered non-responders in this analysis. Data from these patients collected after switching treatment will be considered as supportive data but will not be included in the primary analysis.<br>The primary analysis will compare all randomized patients according to the treatment they were assigned. A supportive analysis will compare patients according to the degree of complement blockade achieved.<br>The analysis of hematological response at 17 weeks will present posterior probabilities of meeting the outcome criteria as defined above. The prior distribution for the response rate in each group will be assumed to be a neutral non-informative Beta (1/3, 1/3) distribution. |

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| | The effect of presence/absence of proteinuria at baseline (a key prognostic factor of response) on the response rates in each group will be investigated. The effects of other covariates such as donor type and conditioning regimen will also be investigated.<br><br>Secondary variables supporting the secondary objectives will include:<br><br>Complete response, defined as hematological response and no proteinuria as determined by proteinuria <30mg/dL and eGFR doubled or not less than 0.85 x lower limit of normal<br><br>• Non-relapse mortality<br>• Overall survival<br>• Complete response will be analyzed in the same way as the primary variable of hematological response. Non-relapse mortality and overall survival will be summarized using time to even methods.<br><br>Corporate Confidential Information<br><br>Further details on the analysis and presentation of these variables will be provided in the RAP.<br><br>All other data will be summarized and listed by treatment as appropriate. |
| **Key words** | Transplant associated microangiopathy (TAM); hematopoietic precursor cell transplantation (HPCT), |

# 1 Introduction

## 1.1 Background

Transplant Associated Microangiopathy (TAM; or transplant-associated TA-TAM) is a complication of allogeneic hematopoietic stem cell transplantation (HSCT). TAM is a secondary microangiopathy associated with total body irradiation, high dose chemotherapy, viral reactivation and use of calcineurin inhibitors and rapamycin. TAM does not fall into either major category of thrombotic microangiopathies (TMA), i.e. atypical hemolytic uremic syndrome (aHUS) or thrombotic thrombocytopenic purpura (TTP) (Chapin et al 2014). The exact mechanism of TAM is poorly understood, but is thought to involve initial complement activation and C5-dependent effector mechanisms, which also lead to immunoglobulin consumption. The trigger appears to be endothelial cell damage, leading to a prothrombotic state in the microvasculature. TAM can gives rise to renal, gastrointestinal and neurological dysfunction depending on the area of the vascular bed involved. TAM is associated with high morbidity and mortality, with some estimates of associated mortality as high as 80% (Chapin et al 2014). Complement involvement is suggested by recent clinical data with the C5 targeted antibody eculizumab. Preliminary data indicates that 4 of 6 subjects undergoing HSCT procedures had a beneficial response after eculizumab administration (Jodele et al 2014a). In total as of this writing (March 2015) 25 patients have been reported to have undergone eculizumab treatment with mixed results. Positive response in the published cases seems to be associated with low body weight, high dose per weight and absence of severe acute graft versus host disease.

LFG316 is a fully human monoclonal IgG antibody that targets complement factor 5 (C5). There is experience with the use of LFG316 in intravenous and intravitreal formulations in the clinic (an intravitreal formulation of LFG316 is currently being evaluated for the treatment of age-related macular degeneration (AMD)). However as an intravenous formulation of LFG316 will be used in TAM, the clinical results with intravenous use are considered most relevant and are presented below.

LFG316 will be dosed on a per weight basis for the TAM indication. Therefore, LFG316 dose will be individualized which is expected to result in superior efficacy, especially in dose sensitive indications.

This study is planned in severe TAM which Novartis proposes to define based on the presence of both diagnostic and high risk criteria (please refer to Section 4.1).

Because a high unmet medical need in TAM is in children (Jodele et al 2014b), the study will allow inclusion of pediatric patients after safety of LFG316 has been demonstrated in 5 adult patients who have been treated with LFG316 for at least 4 weeks.

### 1.1.1 Relevant data summary

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## 1.2 Study purpose

The main purpose of the study is to gather preliminary evidence of LFG316 efficacy in treatment of transplant associated microangiopathy (TAM) after hematopoetic precursor cell transplantation.

# 2 Study objectives

## 2.1 Primary objective(s)

| Objective | Endpoint |
|---|---|
| To assess the hematological response rate in patients with TAM receiving LFG316 compared to standard of care (SoC) | Hematological response at 17 weeks where a patient is considered to be a responder if both of the following criteria are met:<br>1. Schistocytes <2/microscopic high power field (HPF).<br>2.Transfusion independent (no need for TAM-related transfusions (platelets and erythrocytes)) |

## 2.2 Secondary objective(s)

| Objective | Endpoint |
|---|---|
| To assess the safety and tolerability of LFG316 in patients with TAM | All safety parameters including: blood chemistry, hematology, proteinuria, body height/weight, urinalysis, ECG evaluation, Adverse events, body temperature, blood pressure, physical examination, pulse rate, Lansky/Karnofsky score |
| To describe the pharmacokinetics of total LFG316 | Serum total LFG316 concentrations |

| Objective | Endpoint |
|---|---|
| To evaluate non-relapse mortality in TAM patients treated with LFG316 as compared to patients on SoC | Non-relapse mortality is any death not considered to be related to a relapse of underlying disease |
| To assess complete response rate at 17 weeks in TAM patients treated with LFG316 compared to patients receiving standard of care | Complete response is defined as hematological response and no proteinuria as determined by<br>• proteinuria <30mg/dL and<br>• eGFR doubled from baseline or not less than 0.85 x lower limit of normal |

# 3 Investigational plan

## 3.1 Study design

This is a randomized, SoC-controlled, open-label, multi-center study in patients with TAM after hematopoietic precursor cell transplantation (HPCT) from a related or unrelated donor for malignant and nonmalignant disease after myeloablative or non-myeloablative conditioning.

The study will consist of up to 28 days of screening period, 16 weeks treatment period that can be extended to maximum of total 45 weeks (in case of ongoing symptoms of TAM ), 36 weeks follow up, and end of study visit (EOS) at week 52 (Figure 3-1). Duration of follow up will depend on duration of treatment. Patients who are treated for more than 41 weeks will proceed directly to EOS visit.

Approximately 40 patients will be randomized to receive standard of care treatment (SoC) (including but not limited to immunosuppressive drugs, such as rituximab, and plasmapheresis) or LFG316 plus SoC (excluding plasmapheresis and prohibited treatment as per Table 5-1). Patients will be included in the study if they have diagnosis of TAM and poor prognostic markers as specified in Section 4.

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Patients randomized to LFG316 will receive [redacted] on study days 1, 8, and 15, followed by weekly doses of [redacted] for remaining treatment duration of total 16 weeks.

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Patients showing worsening disease (definition below) after two weeks of treatment (day 15) or later until visit at week 3, will be considered failures and can be switched to receive the alternative treatment (SoC or LFG316).

- increasing schistocyte count (+50% or more as compared to baseline),
- and/or increase in erythrocyte or platelet transfusion need (increase of 50% or more in number of transfusions during 2 weeks prior to study visit as compared to number of transfusions needed two weeks before treatment initiation),
- and/or increasing proteinuria (+50% or more as compared to baseline)

Patients showing no response (definition below) between visit at week 4 (day 29) and visit at week 16 will be considered to be treatment failures and can be switched to the other treatment arm. Switching the treatment can occur immediately after data is available.

- no decrease in schistocyte count ( as compared to baseline)
- and/or continued erythrocyte or platelet transfusion need (less than 25% improvement in number of transfusions during 2 weeks prior to study visit as compared to number of transfusions needed two weeks before treatment initiation)
- and/or non-responding proteinuria (less than 25% reduction in proteinuria compared to baseline)

Patients can only switch study treatment arms once.

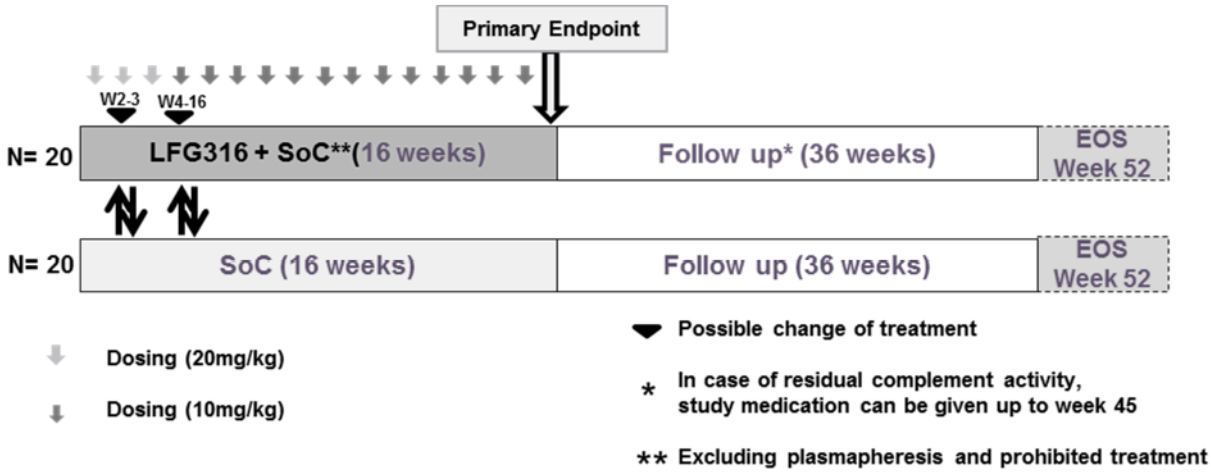
Unscheduled visits will be allowed to check for above parameters in case the data is not available at day 15 or day 29 or at later scheduled visits and there is suspicion of insufficient improvement. Patients who switch from SoC to LFG316 will need to repeat the visit and dosing schedule starting from visit 3 when first dose of study medication is administered. Patients who change from LFG316 to SoC will continue with their visits as per Assessment schedule.

Patients who have ongoing symptoms of TAM may be continued on LFG316 for maximum of total 45 weeks if deemed safe by the investigator. Decision on continuation of the dose after week 16 will be discussed and agreed with the sponsor on a case by case basis.

All patients will receive prophylactic doses of antibiotics active against *N.* meningitidis during the entire LFG316 treatment period and at least 8 weeks after the last treatment with LFG316. The choice of antibiotic medication will be as per hospital standard.

The primary endpoint assessment will be done at week 17 (i.e. 1 week after last dose on week 16).

**Figure 3-1 Study design**




## 3.2 Rationale for study design

The design of this study addresses the primary objective of establishing efficacy in this indication. The randomized, controlled, stratified design allows comparison of LFG316 against SoC.

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There are no pediatric data generated so far for LFG316; however eculizumab was administered to pediatric TAM patients. The published case reports of C5a blockade in TAM comprise 25 patients of whom 16 were pediatric (age range 1.2-11 years) (de Fontebrune et al 2015, Jodele et al 2014a, Jodele et al 2014c, Okano et al 2014). No unexpected safety events related to C5 blockade were reported. No case of invasive

meningitis, a known risk of C5a blockade, was reported in TAM so far. Prophylactic antibiotics active against N. menigitidis will be used to mitigate the risk of the infection.

Based on published information in the Eudract database, studies with eculizumab are ongoing in pediatric subjects (2-17 years of age) with PNH and in pediatric subjects aged 1 month and upwards with atypical hemolytic uremic syndrome (AHUS).

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The nonclinical data obtained with LFG316 and the clinical data obtained with eculizumab supports administration of LFG316 to children ≥12 years old, followed by children ≥ 2 years old. Given the available data and high risk of the disease with standard of care treatment, excluding children from this treatment does not seem to be justifiable.

The option for patients not responding in either arm to switch to the alternative arm when certain conditions are met allows all patients the opportunity to receive LFG316 treatment in this very rare indication with high unmet medical need and also ensures that patients who fail to improve on LFG316 are not prevented from receiving the SoC treatment. This element of the design does not affect the primary assessment of efficacy since patients who do switch treatments will be considered to be treatment failures in the comparison of the randomized treatment groups. An open-label design is used since it is not feasible to blind the treatments used in the SoC arm.

## 3.3 Rationale for dose/regimen, duration of treatment

The dose and dose frequency of LFG316 have been chosen to allow maximal durable complement inhibition throughout the dose interval. Corporate Confidential Information

## 3.4 Rationale for choice of comparator

In severe TAM there is no unified established standard of care treatment. As such, severe TAM is distinct from non-severe TAM where discontinuation of calcineurin inhibitors (CNIs) is the standard of care (as here CNI treatment is thought to be the cause of the disease (Kim et al 2015)). Due to the relative rarity and severity of the disease, physicians often apply multiple (off-label) treatments in parallel. Among the most commonly used treatments are steroids, cyclophosphamide, rituximab and defibrotide. Off-label use of eculizumab is reported increasingly (Kim et al 2015). Although plasmapheresis is widely viewed as being futile in this indication it is still used by some centers as a last line measure in patients who have failed to respond to other treatments. LFG316 will be compared with site specific SoC, since TAM is a potentially fatal disease and placebo treatment is not considered ethically acceptable.

Patients in LFG316 treatment group will not be allowed plasmapheresis because of drug wash-out. All other SoC treatments that do not interfere with the mode of action (MoA) of LFG316 (e.g. corticosteroids, rituximab) are allowed in all patients included in the study. Direct signaling, complement dependent cellular cytotoxicity (CDC) and antibody dependent cellular cytotoxicity all appear to play a role in rituximab efficacy (Weiner 2010). Since LFG316 will suppress free C5 concentrations and hence is likely to reduce CDC, it is possible that the administration of LFG316 may negate some of the mechanisms of efficacy of rituximab. However, the magnitude of this effect is unknown and rituximab remains an allowed concomitant medication. Drugs that have the same mode of action as LFG316 (eculizumab) are prohibited (please refer to Table 5-1 for full list of prohibited treatments).

## 3.5 Purpose and timing of interim analyses/design adaptations

## 3.6 Risks and benefits

TAM is a life-threatening complication after allogeneic hematopoietic stem cell transplantation (HSCT). In surviving patients TAM may be associated with morbidities such as hypertension, chronic kidney disease, pulmonary hypertension gastrointestinal and central nervous system disease. Currently there is no approved and effective therapy for TAM. Classical treatment regimens consist of supportive measures that include withdrawal of triggering agents such as calcineurin inhibitors, treatment of co-existing conditions such as infections that may promote TAM and management of hypertension. Eculizumab was used successfully in a limited number of patients (Jodele et al 2014a).



The prevalence of TAM post-HSCT has recently been reported to be 39% in a prospective cohort study in children (Jodele et al 2014b). The 1-year non relapse mortality was 43.6% in subjects with TAM and 7.8% in HSCT subjects without TAM ($p<0.0001$). A retrospective analysis of 539 adult and pediatric patients reported a cumulative incidence of TAM at five years of 14% with a mortality of 50%. Adults and children were both similarly affected (Uderzo et al 2006). Similar findings were reported in a more recent paper by Cho analyzing outcomes of 672 patients (Cho et al 2010).

The published case reports of C5a blockade with eculizumab in TAM comprise many children and adolescents; in addition there are ongoing studies in pediatric subjects 2-17 years of age in PNH and in pediatric subjects aged 1 month and upwards in the atypical hemolytic uremic syndrome (AHUS) indication.

In a recent report, moderate liver toxicity possibly related to C5 blockade with eculizumab in children with aHUS has been reported (Hayes et al 2014). However, the authors of this report suggest that this observation is more likely disease-related rather than drug-related because liver toxicity has not been observed with an anti-C5 therapy in any other indication. In the proposed study liver function tests will be monitored, therefore, abnormalities in LFTs will be detected and can be acted upon as appropriate. No data is published on liver transaminase elevation specifically in TAM patients. However, there is unequivocal input by physicians treating TAM patients that such elevations are commonly seen and that these elevations can exceed upper level of normal thresholds manifold. There is strong consensus that this should not be viewed as a reason to withhold treatment with C5 blockade.

The main risks of anti-C5 therapies are related to infections. Corporate Confidential Information The most important adverse effect associated with systemic eculizumab, however, is infection by *Neisseria (N). meningitidis* (e.g. meningitis). These infections were so far not reported in TAM patients but are consistent with reports of occasional, but recurrent, meningococcal infections seen in patients with total hereditary C5 deficiency (Haeney et al 1980; Cesbron et al 1985; Sanal et al 1992; Delgado-Cerviño et al 2005; López-Lera et al 2009; Zerzri et al 2010); pneumococcal infections were also reported in hereditary complement deficiency.

The risk to patients in this trial will be minimized by, antibiotics prophylaxis active against *N. meningitidis* mandatory during the entire LFG316 treatment period, adherence to the eligibility criteria, and close clinical monitoring. In addition all patients should be vaccinated against N. and patients <18 year of age should receive vaccination for the prevention of *S. pneumoniae* and *H. influenzae* type b prior to LFG316 administration. In case vaccinations are not possible or will result in an unfavorable risk benefit ratio as judged by the investigator, vaccination can be postponed until deemed useful. For example patients with severe thrombocytopenia might need platelet transfusion support to tolerate s.c. or i.m. injections needed for vaccinations. The inherent risk of platelet infusion might lead to such an unfavorable risk/benefit ratio if a very low efficacy of vaccination is expected.

Although no such events have been reported so far, as with other therapeutic antibodies, LFG316 is expected to carry the risk of anaphylaxis or hypersensitivity reactions. Fluids, vasopressors, antihistamines, bronchodilatators, and oxygen should be available at the clinical site to assure quick administration if needed. Overall, the potential benefits of anti-C5 therapy outweigh the risks in this population of TAM patients.

For adult patients (≥ 18 years) assuming 16 weeks treatment blood volume collected over 52 weeks of the study duration will be approx. up to 800 mL, assuming maximal duration of 45 weeks blood volume during the study will be approx. up to 1050 mL. The maximum blood volume collected from adult patients over consecutive 8 weeks will be up to approximately 450 mL. For the pediatric patient population the maximum blood volume collected will depend on patient weight.

- For children > 20 kg blood volume drawn for analyses is approx. 170 mL for the standard 16 week treatment. In case of treatment extension to maximum allowable treatment duration of 45 weeks this would increase to up to approximately 250 mL.

- For children < 20 kg the maximal blood volume drawn is up to approximately 125 mL and 190 mL respectively. Daily blood collection in children is ≤ 1% of the total blood volume (TBV) and maximum blood collected over 4 week is approximately 5% of TBV (this is only the case for the first 4 weeks of the study). As per EMA guidance the maximum blood volume collected should be < 3% of TBV. However, given the high unmet medical need and the extremely poor prognosis with standard of care the deviation seems to be justifiable.

For the remaining study duration maximal blood volume collected in pediatric patient population over 4 consecutive weeks is less than 3% of the total blood volume.

Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Topical anesthesia might be administered at the site of blood collection in particular in pediatric population.

Women of child bearing potential and sexually active male study participants need to be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, the subject should not be enrolled.

There may be unknown risks of LFG316 which may be serious and unforeseen.

# 4 Population

Approximately 40 male and female patients undergoing allo-HSCT for malignant and nonmalignant disease with high-risk TAM will be included in the study. The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects. Patient selection is to be established by checking through all eligibility criteria at screening or baseline as specified below. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site. Deviation from any entry criterion excludes a patient from enrollment into the study. Patients who drop out from the study for reasons other than lack of efficacy or adverse events considered by Investigator to be related to study treatment may be replaced.

## 4.1 Inclusion criteria

1. Written informed consent/assent before any study-specific screening procedures.
   For pediatric patients, consent will be obtained from parent(s) or legal guardian(s) and the signature of at least 1 parent or guardian will be required. Investigators will also obtain assent of patients according to local, regional or national guidelines.
2. Patients after allogeneic stem cell transplantation from a related or unrelated, HLA-matched or mismatched donor with the diagnosis of transplant related microangiopathy. Patients having received any of the following stem cell sources are eligible: G-CSF mobilized peripheral blood stem cells, bone marrow, umbilical cord blood.

3. Male and female TAM patients ≥ 2 years old at the time of first dose administration. Patients < 12 years old can only be included in the study after first IA has shown that it is safe and well tolerated in patients ≥ 12 years old (Section 3.5).
4. The presence of TAM as per below diagnostic criteria at baseline (or screening if baseline visit is skipped). All the criteria have to be met for the patients included in the study:
   - Elevated lactate dehydrogenase (any elevation above normal range)
   - Thrombocytopenia with platelet count < 50x10e9/L or more than 50% decrease in platelet count from the highest value achieved after transplant
   - Anemia below lower limit of normal or anemia requiring transfusion support as per center standard
   - Schistocytes on peripheral blood smear (>2 per HPF) OR histologic evidence of microangiopathy
   - Absence of coagulopathy (no uncompensated disseminated intravascular coagulation, DIC) at screening
5. The presence of TAM high risk features at baseline (or screening if baseline visit is skipped): Patients ≤ 16 years must have a Lansky score of ≤ 70 and patients > 16 must have Karnofsky score ≤ 70% and/or proteinuria (> 30 mg/dL) measured in two urine spot analyses.
6. Hypertension, defined for adults by SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg at baseline (or screening if baseline visit is skipped), and for pediatric patients by blood pressure greater than the 95th percentile for age, sex, and height (see Table 16-1). Additionally, patients who were started on antihypertensive medication after HSCT or who have received additional antihypertensive medication after HSCT will be eligible, even if they don't have elevated blood pressure.
7. Able to receive antibiotic prophylaxis against N. meningitides for the duration of the study.
8. Meningococcal vaccine(s) prior to LFG316 treatment if prior vaccination cannot be confirmed. The choice of vaccine(s) should take into account the serotypes prevalent in the geographic areas in which study patients will be enrolled. In case vaccination is not possible or will result in an unfavorable risk benefit ratio as judged by the investigator, vaccination can be postponed until deemed likely to be effective.
9. Patients <18 years old should receive vaccination for the prevention of S. pneumoniae and H. influenzae type b prior to LFG316 administration. In case vaccination is not possible or will result in an unfavorable risk benefit ratio as judged by the investigator, vaccination can be postponed until deemed likely to be effective.
10. Weight of at least 10kg.

## 4.2 Exclusion criteria

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or even longer if required by local regulations. Concomitant investigational treatment, including treatment in the context of a clinical trial with marketed drugs (off-label) may be acceptable but requires approval by the sponsor on the case by case basis.
2. Known hypersensitivity to any constituent of the study medication.
3. Patients with steroid refractory graft versus host disease (SRGvHD). SRGvHD is defined as progression (=increase in overall grade) after 5 days on ≥2mg/kg methylprednisolone or equivalent OR no improvement (no decrease in overall grade) after 10 days on ≥ 2mg/kg methylprednisolone or equivalent. If patients are receiving steroids for GvHD prophylaxis as per center standard, progression after 5 days and no response after 10 days after doubling the steroid dose will be regarded as steroid refractory.
4. Patients with ALT > 10x ULN at screening.
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (at screening or baseline).
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 45 days after stopping study medication. Highly effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (i.e., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilization (at least 6 m prior to screening). The vasectomized male partner should be the sole partner for that subject.
   - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
   - In case of use of oral contraception women should have been stabile on the same pill for a minimum of 3 months before taking study treatment.
7. Sexually active males unwilling to use a condom during intercourse while taking drug and for 45 days after stopping investigational medication. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. Male patients should not father a child in this period.
8. Positive HIV (ELISA and Western blot) test result (checked at screening). Historical local data will be acceptable if it the test was done within one month before start of HSCT conditioning and not more than 3 months before study visit 3.

9. A positive Hepatitis B surface antigen or Hepatitis C test result at screening. Historical local data will be acceptable if it the test was done within one month before start of HSCT conditioning and not more than 3 months before study visit 3.
10. Patients with any severe, progressive or uncontrolled acute or chronic medical condition (such as uncontrolled infectious disease or sepsis) or clinical laboratory abnormalities that in the investigator's opinion would make the patient inappropriate for entry into this study (at screening or baseline).
11. Patients with proven TTP as per historical data (as defined by ADAMST13 activity test) and if already available results of ADAMST13 test done at screening.
12. Patients previously treated with eculizumab for TAM.
13. Patients with known or suspected hereditary complement pathway deficiency. This exclusion criterion is not applicable to patients with complement pathway abnormalities/upregulation known to be associated with increased risk of transplant associated microangiopathy

# 5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the restrictions as defined in Section 5.1 and Section 5.2.

## 5.1 Contraception requirements

Please refer to exclusion criteria (Section 4.2) for details of contraception requirements for the study.

## 5.2 Prohibited treatment

Use of treatments specified in Table 5-1 is NOT allowed after start of the treatment.

**Table 5-1 Prohibited treatment**

| Medication | Wash-out | Action to be taken |
|---|---|---|
| Eculizumab in either treatment arm | NA | Discontinue study treatment |
| High dose IVIg in the LFG316 treatment arm** | NA | To be discussed with Sponsor on case by case basis |
| Plasmapheresis in the LFG316 treatment arm | NA | To be discussed with Sponsor on case by case basis |
| Live vaccinations* in LFG316 treatment arm | NA | To be discussed with Sponsor on case by case basis |

*not allowed to be administered during the LFG316 treatment period and 2 months after last dose of LFG316.

** In case of IgG levels below age specific normal ranges (as specified by local laboratories) the use of Intravenous immunoglobulins (IVIg) up to 0.5g/kg/BW with the intention to substitute IgG to reach a low-normal age adjusted blood levels is acceptable. Administration of IVIg should be timed to be spaced at least 36 hours before or after administration of LFG316 (Section 6.10).

## 5.3 Dietary restrictions and smoking

No restrictions.

# 6 Treatment

## 6.1 Study treatment

Details on the storage and management of study medication, and instructions for prescribing and taking study treatment are outlined in Section 3 of the SOM. Instruction on preparation of study medication will be included in the Pharmacy manual.

LFG316 will be administered weekly as intravenous injection (i.v.) for total of 16 weeks (can be prolonged to maximum total 45 weeks as described in Section 3.1):

- days 1, 8, and 15: [redacted]
- day 22 up to end of treatment (week 16): [redacted]

There will be no placebo in the study. Reference therapy will be a standard of care of each clinical center.

Topical anesthesia might be administered at the site of the i.v. catheter.

### 6.1.1 Investigational treatment

The investigational drug, LFG316, will be prepared by Novartis and supplied to the Investigator. For details regarding LFG316 preparation and administration, please refer to Pharmacy manual.

## 6.2 Treatment arms

Patients will be assigned to one of the following two treatment arms in a ratio of 1:1

A: LFG316 administered weekly as described in Section 6.1 plus SoC (excluding prohibited treatment as per Table 5-1)

B: SoC (excluding prohibited treatment as per Table 5-1)

## 6.3 Permitted dose adjustments and interruptions of study treatment

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If per judgment of Investigator, patients need continuation of the therapy based on the presence of TAM symptoms, LFG316 can be administered weekly up to week 45.

## 6.4 Treatment assignment

Randomization numbers will be assigned in ascending, sequential order to eligible subjects (see Site Operations Manual for details) within the three age groups. This study is stratified for randomization by age group based on the age at the day of randomization. The three strata are adult patients ≥ 18 years old, youth patients 12-17 years old inclusive, and children patients less than 12 years old. Any replacement patients will be within the same age group.

The investigator will enter the randomization number on the CRF. The randomization numbers will be generated to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff until after study enrollment. A randomization list will be

produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio within the three strata defined by age. The randomization scheme for subjects will be reviewed and approved by a member of the Novartis IIS Randomization Group. For details regarding randomization process refer to SOM-Section 3.4.

## 6.5 Treatment blinding

This is an open label study; however the allocation of patients to treatment will be performed in a blinded manner such that treatment allocation is known to the investigator, patient and Novartis study team only after enrollment (randomization) into the study.

Additionally schistocyte count should be performed by a person blinded to study treatment.

## 6.6 Emergency breaking of assigned treatment code

Not applicable

## 6.7 Treatment exposure and compliance

LFG316 will be administered via intravenous infusion by the Investigator or designated study staff over a maximum of 2 hours. For details please refer to the Pharmacy manual provided separately. Compliance will be assured by close medical supervision of the study personnel and study Monitors. Serum concentrations of total LFG316 (measure of treatment exposure) will be determined in all subjects treated with LFG316, as detailed in Section 8.5.

## 6.8 Recommended treatment of adverse events

Treatment of AEs should follow standard practice. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

As with other therapeutic antibodies, LFG316 is expected to carry the risk of anaphylaxis or hypersensitivity reactions. Fluids, vasopressors, antihistamines, bronchodilatators, and oxygen should be available at the clinical site to assure quick administration if needed.

## 6.9 Rescue medication

Please refer to Section 3.1 for description of the treatment switch in case no improvement is observed after treatment with LFG316 or SoC. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF after start of study drug.

## 6.10 Concomitant treatment

All prescription medications, over-the-counter drugs and significant non-drug therapies (including blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy. In case of IgG levels below age specific normal ranges (as specified by local laboratories) the

use of Intravenous immunoglobulins (IVIg) up to 0.5g/kg/BW with the intention to substitute IgG to reach a low-normal age adjusted blood levels is acceptable. Administration of IVIg should be timed to be spaced at least 36 hours before or after administration of LFG316. Administration of high dose IVIg (2 g/kg BW or higher) in single doses is not acceptable in LFG316 treatment arm during the study duration.

Meningococcal vaccine(s) should be administered prior to LFG316 treatment according to recommendations for patients with complement deficiencies if prior vaccination cannot be confirmed. The choice of vaccine(s) should take into account the serotypes prevalent in the geographic areas in which study patients will be enrolled. Based on recommendations, revaccination at the start of LFG316 therapy should be considered for previously vaccinated subjects as well as during LFG316 therapy for subjects who will receive prolonged treatment. Whenever possible, meningococcal vaccine(s) should be administered at least two weeks prior to starting LFG316. In addition, patients < 18 years old should receive vaccination for the prevention of *S. pneumoniae* and *H. influenzae* type b prior to LFG316 treatment. In case vaccinations are not possible or will result in an unfavorable risk benefit ratio as judged by the Investigator, vaccination can be postponed until it is likely to be effective.

If patients are not already on antibiotic prophylaxis or treatment active against local strains of *N. meningitis* and *S. pneumoniae* during any time during the treatment with LFG316 or 8 weeks after last dose, penicillin V 500 mg twice a day or erythromycin 500 mg (or equivalently effective doses in pediatric patients) twice a day must be given to patients in LFG316 treatment arm. If local strains of either of these bacteria are resistant to either of these or the patient is allergic or cannot otherwise tolerate the standard prophylactic treatment, the choice of antibiotic will be made upon local guidelines or the recommendation of the local ID consultant.

# 7 Discontinuation and study completion

## 7.1 Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment for any reason at any time.

The investigator must discontinue study treatment for a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

Study treatment **must** be discontinued under the following circumstances:

- Subject withdraws consent.
- Patients showing worsening disease between week 2 and 3, or absence of response at week 4 or anytime thereafter (as defined in the study Section 3.1) will be considered a failure and can be switched to receive the alternative treatment (SoC or LFG316).
- Patients on LFG316 that as per judgment of Investigator require plasmapheresis or prohibited medication as per Section 5.2.
- Patients with confirmed TTP (as per ADAMST13 test result).
- Treatment discontinuation and switch to SoC might also occur after consultation with Sponsor in case of treatment related SAE, or any other AE that in judgment of Investigator warrants LFG316 treatment discontinuation.

Patients who wish to discontinue either study treatment, whether initially allocated or subsequently switched, but who did not withdraw their consent, will be asked to continue with study visits as per assessment schedule if possible. Every effort will be made to assess the parameters required for assessment of hematological and complete response at the time of discontinuation (i.e., schistocytes, transfusion independence, proteinuria <30mg/dL and eGFR). In case patient withdraws consent, the procedure described in Section 7.3 needs to be followed.

## 7.2 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last subject completes their End of Study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early total study termination decision, the date of that decision.

At a minimum, subjects will be contacted for safety evaluations during the 30 days following the Study Completion visit, including a final post-study safety contact at the 30-day point. Documentation of attempts to contact the subject should be recorded in the source documentation.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

### 7.2.1 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

## 7.3 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject does not want to participate in the study anymore **and** does not want any further visits or assessments **and** does not want any further study related contact **and** does not allow analysis of already obtained biologic material. If not all above criteria are met, please refer to procedure outline in Section 7.1.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

## 7.4 Study stopping rules

The study may be put on hold pending full safety data review done by the Data Monitoring Committee (DMC) if one or more of the following criteria are met:

- Two or more investigational drug (LFG316) related SAEs are reported
- Other clinically significant events that in the opinion of the investigator or sponsor preclude continuation of dosing (especially events that are suspected to be drug related).

A DMC will also review available safety data after the first 5 patients complete 4 weeks of LFG316 treatment and approximately every 3 months thereafter during the study. When possible, DMC meetings will be aligned with planned IAs. In the case of any safety concerns identified during the study (as described above) or faster than anticipated recruitment, DMC meetings might happen more regularly.

## 7.5 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, subjects should be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests.

The Investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

# 8 Procedures and assessments

## Table 8-1 Assessment schedule for adult patients (greater or equal 18 years old)

| Study Phase | Screening | Baseline (2) | Treatment (11) | | | | | | | | | | | | | | | | | | | | | | | | Follow up | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Numbers (1) | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 | V14 | V15 | V16 | V17 | V18 | V19 | V20 | V21 | V22 | V23 | V24 | V25 | V26-V54 (9) | V501 | V502 | V503 | V777 |
| Study Day(s)* | -28 to -4 | -3 to -1 | 1 | 2 | 5 | 8 | 9 | 12 | 15 | 16 | 19 | 22 | 23 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 78 | 85 | 92 | 99 | 106 | 113-309 | 113 | 182 | 293 | 364 |
| Week | | | w 1 | | | w 2 | | | w 3 | | | w 4 | | w 5 | w 6 | w 7 | w 8 | w 9 | w 10 | w 11 | w 12 | w 13 | w 14 | w 15 | w 16 | W17-45 | w 17 | w 26 | w 42 | w 52 |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical history/current medical conditions (16) | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatitis and HIV Screen | S | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion / Exclusion | S | S | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Activated partial thromboplastin time | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy test (3) | X | X | | | | | | | | | | | | X | | | | X | | | | | X | | | X (12) | X | X | X | X |
| FSH (4) | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lansky/Karnofsky score | X | | | | | | | | | | | | | X | | | | X | | | | | X | | | X (12) | | | | X |
| Dose administration | | | X | | | X | | | X | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| Adverse events*** | as required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| GvHD | as required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical examination | S | S | S(7) | | | S(7) | | | S(7) | | | S(7) | | S(7) | S(7) | S(7) | S(7) | S | S | S | S | S | S | S | S | S | S | S | S | S |
| Height/weight (5) | X | X | X | | | X | | | X | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body temperature** | X | X | X(7) | | | X(7) | | | X(7) | | | X(7) | | X(7) | X(7) | X(7) | X(7) | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pulse rate** | X | X | X(7) | | | X(7) | | | X(7) | | | X(7) | | X(7) | X(7) | X(7) | X(7) | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood pressure** | X | X | X(7) | | | X(7) | | | X(7) | | | X(7) | | X(7) | X(7) | X(7) | X(7) | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECG evaluation** | X | X | X | | | X | | | X | | | X | | X | | | | X | | | | | X | | | X (12) | X | X | X | X |
| Hematology/blood chemistry/urinalysis (13)** | X | X | X | | | X | | | X | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X(14) | X | X | X | X |
| Schistocyte count** | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Spot urine analysis | X | X | | | | X | | | X | | | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Corporate Confidential Information | X | X | X(7) | X | X | X(7) | X | X | X(7) | X | X | X(7) | X | X(7) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X | X | X | X |
| | X | X | X(7) | X | X | X(7) | X | X | X(7) | X | X | X(7) | X | X(7) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(14) | X | X | X | X |
| Incidence of transfusion (6) | recorded for entire study duration | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Corporate Confidential | | | X(8) | | | | | | | | | | | X(8) | | | | X(8) | | | | X(8) | | | | X(14) | X | X | X | X |
| PK blood collection (15) | | | X(7) | X | x | X(7) | X | x | X(7) | X | x | X(7) | X | X(7) | | X(8) | | X(8) | | X(8) | | X(8) | | X(8) | | X(14) | X | X | X | X |
| Corporate Confidential Information | X | X | X(7) | X | X | X(7) | X | X | X(7) | X | X | X(7) | X | X(7) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(14) | X | X | X | X |
| Corporate Confidential Information | X | X | X(7) | X | X | X(7) | X | X | X(7) | X | X | X(7) | X | X(7) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(14) | X | X | X | X |
| ADAMST13 in plasma | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Corporate Confidential | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Corporate Confidential Information | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant therapies | as required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Comments | as required | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Study completion info | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X |

*Allowed visit windows: +/-1 day for visits at days 2-29 (except for visits 5, 8, and 11when +1/-2 days visit window is allowed);
+/-2 day for visit at days 36-106 (or until LFG316 is administered), +/-15 days after day 106 until EOS. After visit 3 merging of the visits is not allowed
** If not specified otherwise all safety assessments should be performed pre-dose
*** SAE to be reported until 30 days after the last study visit
S- collected only as source data
(1) Visit structure given for internal programming purpose only
(2) If Screening visit is conducted within 3 days prior to planned dosing Baseline visit is not required
(3) For all women, serum pregnancy testing is required at screening and EOS regardless of reported reproductive/menopausal status. Urine pregnancy tests at remaining visits need to be performed only in women of child-bearing potential.
(4) For postmenopausal women, FSH is measured at Screening to assist in confirming menopausal status.
(5) body height will be checked only at screening
(6) Erythrocyte and platelet transfusions will be recorded separately
(7) Done pre and post-dose in LFG316 treatment group and only once (if applicable pre-dose) in SoC treatment group
(8) Done pre-dose in LFG316 treatment arm and (if applicable) in SoC treatment arm
(9) Weekly LFG316 injections at weeks17- 45 are allowed as per Section 3.1

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(11) For patients who switch from SoC to LFG316 dosing schedule starts from visit 3. Patients who change from LFG316 to SoC will continue with their visits as per assessment schedule.
(12) done every 4 weeks

Corporate Confidential Information

(14) Done pre-dose, every four weeks
(15) collected only in LFG316 treatment group
(16) Including GvHD

Corporate Confidential Information

## Table 8-2 Assessment schedule for children (less than 18 years old)

| Study Phase | Screening | Baseline (2) | Treatment (11) | | | | | | | | | | | | | | | | | | | | Follow up | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Numbers (1) | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 | V14 | V15 | V16 | V17 | V18 | V19 | V20 | V21 | V22-V50 (9) | V501 | V502 | V503 | V777 |
| Study Day(s)* | -28 to -4 | -3 to -1 | 1 | 5 | 8 | 12 | 15 | 19 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 78 | 85 | 92 | 99 | 106 | 113-309 | 113 | 182 | 293 | 364 |
| Week | | | w 1 | | w 2 | | w 3 | | w 4 | w 5 | w 6 | w 7 | w 8 | w 9 | w 10 | w 11 | w 12 | w 13 | w 14 | w 15 | w 16 | W17-45 | w 17 | w 26 | w 42 | w 52 |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical history/current medical conditions (18) | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatitis and HIV Screen | S | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion / Exclusion | S | S | | | | | | | | | | | | | | | | | | | | | | | | |
| Activated partial thromboplastin time | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy test (3) | X | X | | | | | | | | X | | | | X | | | | | X | | | X (12) | X | X | X | X |
| Lansky/Karnofsky score | X | | | | | | | | | X | | | | X | | | | | X | | | X (12) | | | | X |
| Dose administration | | | X | | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| Adverse events*** | as required | | | | | | | | | | | | | | | | | | | | | | | | | |
| GvHD | as required | | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical examination** | S | S | S(7) | | S(7) | | S(7) | | S(7) | S(7) | S(7) | S(7) | S(7) | S | S | S | S | S | S | S | S | S(7) | S | S | S | S |
| height/weight (5)** | X | X | X | | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body temperature** | X | X | X(7) | | X(7) | | X(7) | | X(7) | X(7) | X(7) | X(7) | X(7) | X | X | X | X | X | X | X | X | X(7) | X | X | X | X |
| Pulse rate** | X | X | X(7) | | X(7) | | X(7) | | X(7) | X(7) | X(7) | X(7) | X(7) | X | X | X | X | X | X | X | X | X(7) | X | X | X | X |
| Blood pressure** | X | X | X(7) | | X(7) | | X(7) | | X(7) | X(7) | X(7) | X(7) | X(7) | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECG evaluation** | X | X | X | | X | | X | | X | X | | | | X | | | | X | | | | X (12) | X | X | X | X |
| Hematology/blood chemistry/urinalysis (13)** | X | X | X | | X | | X | | X | X | | | | X | | | | X | | | | X (12) | X | X | X | X |
| Schistocyte count** | X | X | X | | X | | X | | X | X | | | | X | | | | X | | | | X (12) | X | X | X | X |
| Spot urine analysis | X | X | | | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Corporate Confidential Information | X | | X(8) | | X(8) | | X(8) | | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X(8) | X | X | X | X |
| Corporate Confidential Information | X | | X(8) | | X(8) | | X(8) | | X(8) | X(8) | | | | X(8) | | | | X(8) | | | | X(14) | X | X | X | X |
| Incidence of transfusion (6) | recorded for entire study duration | | | | | | | | | | | | | | | | | | | | | | | | | |
| Corporate Confidential Information | | | X(8) | | | | | | | X(8) | | | | X(8) | | | | X(8) | | | | X(14) | X | X | X | X |
| PK blood collection (15, 17) | | | X(7) | X | X(7) | X | X(7) | X | X(7) | X(7) | | X(8) | | X(8) | | X(8) | | X(8) | | X(8) | | X(14) | X | X | X | X |
| Corporate Confidential Information | X | | X(7) | X | X(7) | X | X(7) | X | X(7) | X(7) | | X(8) | | X(8) | | X(8) | | X(8) | | X(8) | | X(14) | X | X | X | X |
| Corporate Confidential Information | X | | X(7) | X | X(7) | X | X(7) | X | X(7) | X(7) | | X(8) | | X(8) | | X(8) | | X(8) | | X(8) | | X(14) | X | X | X | X |
| ADAMST13 in plasma | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Corporate | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Corporate Confidential Information | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant therapies | as required | | | | | | | | | | | | | | | | | | | | | | | | | |
| Comments | as required | | | | | | | | | | | | | | | | | | | | | | | | | |
| Study completion info | | | | | | | | | | | | | | | | | | | | | | | | | | X |

*Allowed visit windows: +/-1 day for visits at days 2-29 (except for visits 4,6, and 8 when +1/-2 days visit window is allowed);
+/-2 day for visit at days 36-106 (or until LFG316 is administered), +/-15 days after day 106 until EOS. After visit 3 merging of the visits is not allowed
** If not specified otherwise all safety assessments should be performed pre-dose
*** SAE to be reported until 30 days after the last study visit
S- collected only as source data
(1) Visit structure given for internal programming purpose only
(2) If Screening visit is conducted within 3 days prior to planned dosing Baseline visit is not required
(3) only for menstruating females, serum pregnancy testing is required at screening and EOS, urine pregnancy tests at remaining visits
(5) body height will be checked only at screening, v21 and EOS
(6) Erythrocyte and platelet transfusions will be recorded separately
(7) Done pre and post-dose in LFG316 treatment group and only once (if applicable pre-dose) in SoC treatment group
(8) Done pre-dose in LFG316 treatment arm and (if applicable) in SoC treatment arm
(9) Weekly LFG316 injections at weeks17- 45 are allowed as per Section 3.1

Corporate Confidential Information

(11) For patients who switch from SoC to LFG316 dosing schedule starts from visit 3. Patients who change from LFG316 to SoC will continue with their visits as per assessment schedule.
(12) done every 4 weeks starting from visit 23

Corporate Confidential Information

(14) Done pre-dose, every four weeks
(15) collected only in LFG316 treatment group
(16) sample collected only in patients >20kg

Corporate Confidential Information

(18) Including GvHD

Corporate Confidential Information

## 8.1 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent (assent in case of children).

All subjects must be counseled about the risk of meningococcal infections as well as other infections, such as those caused by *S. pneumoniae*, *H. influenzae* type b, and *Aspergillus* spp as a part of the informed consent process.

If incapable of doing so, in cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

The date of signing off the informed consent form (and the date of withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.





A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

## 8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

Investigators have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

## 8.3 Efficacy

Efficacy assessments are specified below, with the methods for assessment and recording specified in the SOM. Assessments will be performed/samples collected at the timepoint(s) defined in the Assessment schedule.

### 8.3.1 Schistocyte count

Blood samples will be collected to evaluate schistocyte count at time points specified in the Assessment schedule. Schistocyte assessment will be part of the blood hematology panel. Person performing schistocyte count will be blinded to treatment received by the patient. Details regarding sample processing will be provided in the laboratory manual. Schistocyte count will be performed at central laboratory.

### 8.3.2 Proteinuria

Urine samples will be collected at time points specified in the Assessment schedule to evaluate proteinuria using spot urine analysis. Concentration of protein in the urine will be compared to the creatinine level (protein/creatinine ratio; PCR). Details regarding sample processing will be provided in the laboratory manual. Assessment of PCR will be performed at central laboratory.

### 8.3.3 Incidence of transfusion

Site will record incidence of both erythrocyte and platelet transfusion during entire study. In addition history of transfusion from time of transplant will be recorded in CRF.

## 8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Laboratory manual provided separately, with the Assessment Schedule detailing when each assessment is to be performed.

### 8.4.1 Performance status

Performance status will be scored using the Karnofsky (for patients older than 16 years) or Lansky (for patients less than or equal to 16 years old) performance scales, depending on the patient's age (Section 15). For patients that have their 17th birthday during the study, performance status will continue to be assessed by the Lansky scale, in order to preserve continuity.

### 8.4.2 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Detailed procedure for physical examination is provided in the Site Operations Manual.

### 8.4.3 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

### 8.4.4 Height and weight

- Height
- Body weight
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]$^2$)

### 8.4.5 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported in CRF and can be discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted. Central laboratory will be used in the study but in exceptional cases local laboratory tests can be used in case patients need immediate treatment. In this case site should still collect sample for central laboratory analysis and provide GCP-required local laboratory documentation in advance. Also date of the local laboratory assessments should be within allowed window for screening or baseline visit as defined by inclusion/exclusion criteria. Detailed procedure for collection and preparation of the samples will be provided in Laboratory Manual.

#### Hematology

Hemoglobin, hematocrit, red blood cell count, reticulocytes, white blood cell count with differential and platelet count will be measured. In addition schistocytes will be measured as described in Section 8.3.1.

#### Clinical chemistry

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, γGT, AST, ALT, aPTT, PT/INR, CK, glucose, total cholesterol, triglycerides, haptoglobin. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. In addition blood concentrations of IgG will be determined.

### Urinalysis

Urine test by dipstick e.g. Combur9: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/ hemoglobin. In addition to urine dipstick, spot urine will be done as described in Section 8.3.2.

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

### Test to detect medications

Blood sample will be taken to check serum levels of medications frequently administered to patients after HSCT. Level of the tacrolimus, sirolimus and cyclosporine will be checked at the same timepoints when blood hematology/chemistry is being done by central laboratory.

### 8.4.6 Electrocardiogram (ECG)

PR interval, QRS duration, heart rate, RR, QT, QTc.

The Fridericia QT correction formula (QTcF) should be used for drug development decisions.

### 8.4.7 Pregnancy and assessments of fertility

All females that had their first menstruation will need to have serum pregnancy test at Screening and EOS. For postmenopausal women, FSH is measured at screening to assist in confirming menopausal status. Urine pregnancy tests need to be performed at remaining visits only in women of child-bearing potential.

### 8.4.8 Vaccination(s)

Please refer to Section 6.10.

### 8.4.9 GvHD

The medical history and the presence of the graft versus host disease (GvHD) will be monitored during the study and recorded in CRF.

## 8.5 Pharmacokinetics

PK samples will be collected at the timepoints defined in the Assessment schedule. Further details on sample collection, numbering, processing and shipment can be found in the in SOM and/or Laboratory Manual.

Determination of the concentration of total LFG316 in serum will be performed using an ELISA or LC/MS assay. A detailed description of the method used to quantify the concentration of total LFG316 will be included in the bioanalytical raw data of the study and in the bioanalytical data report. The lower limit of quantification (LLOQ) will be specified in the total LFG316 bioanalytical report. Pharmacokinetic (PK) samples will be obtained and evaluated in all subjects treated with LFG316. Total LFG316 concentrations will be expressed as µg/mL. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification

will be treated as zero in summary statistics for concentration data only. They will not be considered for calculation of PK Parameters. PK samples remaining after completion of the determination of total LFG316 may be used for exploratory assessments or other bioanalytical purposes (e.g. cross check between different sites, stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated.

The following pharmacokinetic parameters will be determined (if feasible) using non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): AUC (0-tlast), AUC(0-t) , Cmax , tmax , Cmax/D, AUC/D. The linear trapezoidal rule will be used for AUC calculation.

## 8.6 Pharmacodynamics markers

PD samples will be collected at the timepoints defined in the Assessment schedule. Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual and/or SOM.

## 8.7 Other assessments

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### 8.7.2 ADAMST13

ADAMST13 activity will be evaluated to rule out Thrombotic Thrombocytopenic Purpura (TTP). Details on sample collection and processing will be provided in SOM and/or Laboratory Manual. Patients lacking ADAMST13 activity will be discontinued and replaced (only in case ADAMST13 data not available prior to V3).

### 8.7.3 Exploratory Biomarker assessments

Corporate Confidential Information

# 9 Safety monitoring

## 9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver related events are included in Section 9.3.

Adverse events must be recorded on the Adverse Events CRF for subjects that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. Adverse events will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTC-AE grading does not exist for an adverse event, use:
   - 1=mild,
   - 2=moderate,
   - 3=severe
   - 4=life threatening.

CTC-AE grade 5 (death) is not used, but is collected in other CRFs (e.g. Study Completion, Death/Survival).

2. its relationship to the study treatment (no/yes), or investigational treatment (no/yes), or other study treatment (non-investigational) (no/yes), or both or indistinguishable,
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE) See Section 9.2 for definition of SAE
5. action taken regarding [study/investigational] treatment(select as appropriate).

   All adverse events should be treated appropriately. Treatment may include one or more of the following:
   - no action taken (i.e. further observation only)
   - study treatment dosage adjusted/temporarily interrupted
   - study treatment permanently discontinued due to this adverse event
   - concomitant medication given
   - non-drug therapy given
   - subject hospitalized/subject's hospitalization prolonged

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or Core Data Sheet (for marketed drugs) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

The investigator should also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

## 9.2 Serious adverse event reporting

### 9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to DS&E as per Section 9.2.2.

### 9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit. must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several drugs) complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department, notifying the Clinical Trial Leader. Contact information is listed in the Site Operations Manual.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

## 9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation and follow-up

Please refer to Table 9-1 and Table 9-2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in Table 9-2.

**For the liver laboratory trigger**:

- Repeating the liver function test (LFT) within the next week to confirm elevation

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible.

**For the liver events:**

- Repeating the LFT to confirm elevation as appropriate
- Hospitalization of the subject if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- If liver safety events are possibly related to the study drug and are unlikely to be part of the TAM presentation, discontinuation of the investigational drug may be considered after consultation with Sponsor.
- An investigation of the liver event which needs to be followed until resolution

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF.

**Table 9-1 Liver event and laboratory trigger definitions**

| | Definition/ threshold |
|---|---|
| Liver laboratory triggers | >5 x ULN < ALT / AST |
| Liver events | ALT or AST > 10 × ULN |
| | ALP > 5 × ULN (in the absence of known bone pathology) |
| | TBL > 5 × ULN (in the absence of known Gilbert syndrome, unless elevation attributed to PNH hemolysis, e.g. unconjugated fraction) |
| | ALT or AST > 5 × ULN and INR > 1.5 |
| | Any adverse event potentially atypical for TAM and indicative of a liver toxicity * |

**Table 9-2 Follow up requirements for liver events and laboratory triggers**

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| ALT or AST | | |
| > 5 × ULN | Establish causality and define if likely caused by TAM or likely other reason for abnormality | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 10 × ULN | Establish causality and define if likely caused by TAM or likely other reason for abnormality. If change persists over 2 visits inform sponsor and consider presenting to DMC for discussion. | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| ALP (isolated) | | |
| > 5 × ULN (in the absence of known bone pathology) | Repeat LFT if elevation persists. Establish causality and define if likely caused by TAM or likely other reason for abnormality. If change persist over 2 visits inform sponsor and consider presenting to DMC for confirmation | Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit |

## 9.4 Renal safety monitoring

Because renal events are defined as inclusion and response criteria, renal safety events may trigger AE reports but if deemed consistent with TAM presentation will not lead to study drug discontinuation. If renal safety events are deemed related to study drug they will be presented to the DMC to decide if further action is needed

## 9.5 Pregnancy reporting

To ensure patient safety, each pregnancy in a subject on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments. Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on an SAE Report Form.

## 9.6 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

# 10 Data review and database management

## 10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis. Additionally, a central analytics organization may analyse data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

## 10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

CRO working on behalf of Novartis review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO working on behalf of Novartis who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

## 10.3 Data Monitoring Committee

A Data Monitoring Committee (DMC) will monitor subjects for early symptoms and signs of meningococcal infection. The DMC will review available safety data after the first 5 patients ≥ 12 years old randomized to LFG316 completed 4 weeks of treatment and approximately every 3 months thereafter during the study. Other safety, dosing and treatment duration questions regarding individual patients may be also brought to the DMC if requested by the Investigator and/or the Sponsor. If possible, DMC meetings will be aligned with planned IAs. In case of any safety concerns identified during the study (as described above) or faster than anticipated recruitment (especially in pediatric patient population), DMC meetings might happen more regularly.

Further details will be provided in Data Monitoring Committee charter.

## 10.4 Adjudication Committee

Not required.

# 11 Data analysis

## 11.1 Analysis sets

For the safety, PK and PD analysis sets, subjects will be analyzed according to the study treatment(s) received.

The full analysis set will include all subjects that received any study drug.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with available PD and mode-of-action biomarker data and no protocol deviations with relevant impact on PD data. Patients who switch treatments according to the protocol defined rules will be indicated as having received two treatments in the listings, and data from the period after switching will in general be summarized separately. Thus in general there may be four treatment groups in the summary tables:

- LFG316
- SoC
- LFG316 then SoC (in case of switch in treatment as described in Section 3.1)
- SoC then LFG316 (in case of switch in treatment as described in Section 3.1)

## 11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

## 11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration, standard of care therapy and concomitant therapies will be listed by treatment group and subject.

## 11.4 Analysis of the primary variable(s)

### 11.4.1 Variable(s)

The primary efficacy variable is hematological response.

A patient is considered to be a hematological responder at 17 weeks if both of the following criteria are met:

1. Schistocytes <2/microscopic high power field (HPF).
2. Transfusion independent (no need for TAM-related transfusions (platelets and erythrocytes)

Patients who discontinue the randomized treatment before 16 weeks due to lack of efficacy (whether according to the protocol-defined rules allowing a switch to the alternative treatment arm, or not) or due to treatment-related safety reasons will be considered non-responders in this analysis. Data from these patients collected after switching treatment will be considered as supportive data but will not be included in the primary analysis.

### 11.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will compare all randomized patients according to the treatment they were assigned.

Results for hematological response will be categorized as providing evidence of good, satisfactory or poor efficacy as defined by the rules below.

- Good efficacy: $Pr(\Delta > 30\% | \text{data}) \geq 0.5$ and $Pr(\Delta > 0 | \text{data}) \geq 0.9$
- Satisfactory efficacy: $Pr(\Delta \geq 10\% | \text{data}) \geq 0.5$ and $Pr(\Delta > 0 | \text{data}) \geq 0.9$
- Poor efficacy: $Pr(\Delta \geq 10\% | \text{data}) < 0.5$ or $Pr(\Delta > 0 | \text{data}) < 0.9$

where $\Delta$ is the difference in percentage points in response rates (LFG316 - control).

The analysis of hematological response at 17 weeks will present posterior probabilities of meeting the outcome criteria as defined above. The prior distribution for the response rate in each group will be assumed to be a neutral non-informative Beta (1/3, 1/3) distribution.

### 11.4.3 Handling of missing values/censoring/discontinuations

Patients who discontinue treatment due to lack of efficacy (defined as either meeting the criteria defined in Section 3.1 for switching treatments or having reason for discontinuation marked as "lack of efficacy" at the study completion visit) are defined to be non-responders. Other patients, for whom hematological response cannot be assessed due to discontinuation for treatment-related safety reasons, will be considered to be non-responders. Hematological response for patients who discontinue for any other reason will be determined based on their available data at the time of discontinuation.

Given the severe nature of the indication and the need for close monitoring of these patients it is expected that there will be very little truly missing data.

### 11.4.4 Supportive analyses

A supportive analysis will compare patients according to the degree of complement blockade achieved. And given schistocyte counts, erythrocytes, platelets, and proteinuria are involved in definitions of treatment failure or success each will be summarized and plotted over time, with the possibility of further analyses.

The effect of presence/absence of proteinuria at baseline (a key prognostic factor of response) on the response rates in each group will be investigated. Corporate Confidential Information

## 11.5 Analysis of secondary and exploratory variables

### 11.5.1 Efficacy / Pharmacodynamics

Secondary variables supporting the secondary objectives will include:

- Complete response, defined as hematological response and no proteinuria as determined by proteinuria <30 mg/dL and eGFR doubled or not less than 0.85 x lower limit of normal
- Number of patients switching treatment and time at which the switch occurred
- Non-relapse mortality
- Overall survival

Complete response will be analyzed in the same way as the primary variable of hematological response. The number of patients switching treatment will be summarized. Time to treatment switch, non-relapse mortality and overall survival will be summarized using time to event methods. Further details will be provided in the Reporting and Analysis Plan (RAP).

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Further details on the analysis and presentation of these variables will be provided in the RAP.

### 11.5.2 Safety

#### Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

#### ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

#### Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

#### Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

#### Other evaluations



### 11.5.3 Pharmacokinetics

Total LFG316 serum concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. Pharmacokinetic parameters will be calculated as described in Section 8.5 and will be listed by treatment and subject.

### 11.5.4 Pharmacokinetic / pharmacodynamic interactions

The relationship of PD, mode-of-action, and efficacy biomarkers with the exposure to LFG316 will be explored.

### 11.5.5 Other assessments

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Corporate Confidential Information

## 11.6 Sample size calculation

At least 40 TAM patients are planned to be included in the study initially. Patients will be randomized to either SoC (n=20) or LFG316 (n=20) treatment arm. Results for hematological response will be categorized as providing evidence of good, satisfactory or poor efficacy as defined by the rules in Section 11.4.2.

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## 11.7 Power for analysis of key secondary variables

Not applicable

## 11.8 Interim analyses

# 12 Ethical consideration

## 12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

## 12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

## 12.3 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

# 13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

## 13.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the CTL should be informed and (serious) adverse event reporting requirements (Section 9) followed as appropriate.

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Available upon request

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# 15 Appendix 1: Lansky/Karnofsky scores

## 15.1 Karnofsky Performance Status Scale (for patients greater than 16 years old)

| | | |
|---|---|---|
| Able to carry on normal activity and work; no special care needed | 100% | Normal; no complaints |
| | 90% | Able to carry on normal activity; minor signs or symptoms of disease |
| | 80% | Normal activity with effort; some signs or symptoms of disease |
| Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed | 70% | Cares for self; unable to carry on normal activity or work |
| | 60% | Requires occasional assistance; able to care for most personal needs |
| | 50% | Requires considerable assistance and frequent medical care |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly | 40% | Disabled; requires special care and assistance |
| | 30% | Severely disabled; hospitalization is indicated though death not imminent |
| | 20% | Very sick; hospitalization necessary; active supportive treatment necessary |
| | 10% | Moribund; fatal processes progressing rapidly |
| | 0 | Dead |

## 15.2 Lansky Score (for patients less than or equal to 16 years old)

| | |
|---|---|
| 100 | Fully active, normal |
| 90 | Minor restrictions in physically strenuous activity |
| 80 | Active, but tires more quickly |
| 70 | Both greater restriction of play and less time spent in play activity |
| 60 | Up and around, but minimal active play; keeps busy with quieter activities |
| 50 | Gets dressed but lies around much of the day; no active play but able to participate in all quiet play and activities |
| 40 | Mainly in bed; participates in quiet activities |
| 30 | Bed-bound; needs assistance even for quiet play |
| 20 | Often sleeping; play entirely limited to very passive activities |
| 10 | No play; does not get out of bed |
| 0 | Unresponsive |

# 16 Appendix 2: vital signs in children

## Table 16-1 Vital signs in children

### Blood Pressure Levels for Boys by Age and Height Percentile

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) ← Percentile of Height → | | | | | | | Diastolic BP (mmHg) ← Percentile of Height → | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 50th | 80 | 81 | 83 | 85 | 87 | 88 | 89 | 34 | 35 | 36 | 37 | 38 | 39 | 39 |
| | 90th | 94 | 95 | 97 | 99 | 100 | 102 | 103 | 49 | 50 | 51 | 52 | 53 | 53 | 54 |
| | 95th | 98 | 99 | 101 | 103 | 104 | 106 | 106 | 54 | 54 | 55 | 56 | 57 | 58 | 58 |
| | 99th | 105 | 106 | 108 | 110 | 112 | 113 | 114 | 61 | 62 | 63 | 64 | 65 | 66 | 66 |
| 2 | 50th | 84 | 85 | 87 | 88 | 90 | 92 | 92 | 39 | 40 | 41 | 42 | 43 | 44 | 44 |
| | 90th | 97 | 99 | 100 | 102 | 104 | 105 | 106 | 54 | 55 | 56 | 57 | 58 | 58 | 59 |
| | 95th | 101 | 102 | 104 | 106 | 108 | 109 | 110 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 99th | 109 | 110 | 111 | 113 | 115 | 117 | 117 | 66 | 67 | 68 | 69 | 70 | 71 | 71 |
| 3 | 50th | 86 | 87 | 89 | 91 | 93 | 94 | 95 | 44 | 44 | 45 | 46 | 47 | 48 | 48 |
| | 90th | 100 | 101 | 103 | 105 | 107 | 108 | 109 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 95th | 104 | 105 | 107 | 109 | 110 | 112 | 113 | 63 | 63 | 64 | 65 | 66 | 67 | 67 |
| | 99th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 71 | 71 | 72 | 73 | 74 | 75 | 75 |
| 4 | 50th | 88 | 89 | 91 | 93 | 95 | 96 | 97 | 47 | 48 | 49 | 50 | 51 | 51 | 52 |
| | 90th | 102 | 103 | 105 | 107 | 109 | 110 | 111 | 62 | 63 | 64 | 65 | 66 | 66 | 67 |
| | 95th | 106 | 107 | 109 | 111 | 112 | 114 | 115 | 66 | 67 | 68 | 69 | 70 | 71 | 71 |
| | 99th | 113 | 114 | 116 | 118 | 120 | 121 | 122 | 74 | 75 | 76 | 77 | 78 | 78 | 79 |
| 5 | 50th | 90 | 91 | 93 | 95 | 96 | 98 | 98 | 50 | 51 | 52 | 53 | 54 | 55 | 55 |
| | 90th | 104 | 105 | 106 | 108 | 110 | 111 | 112 | 65 | 66 | 67 | 68 | 69 | 69 | 70 |
| | 95th | 108 | 109 | 110 | 112 | 114 | 115 | 116 | 69 | 70 | 71 | 72 | 73 | 74 | 74 |
| | 99th | 115 | 116 | 118 | 120 | 121 | 123 | 123 | 77 | 78 | 79 | 80 | 81 | 81 | 82 |
| 6 | 50th | 91 | 92 | 94 | 96 | 98 | 99 | 100 | 53 | 53 | 54 | 55 | 56 | 57 | 57 |
| | 90th | 105 | 106 | 108 | 110 | 111 | 113 | 113 | 68 | 68 | 69 | 70 | 71 | 72 | 72 |
| | 95th | 109 | 110 | 112 | 114 | 115 | 117 | 117 | 72 | 72 | 73 | 74 | 75 | 76 | 76 |
| | 99th | 116 | 117 | 119 | 121 | 123 | 124 | 125 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| 7 | 50th | 92 | 94 | 95 | 97 | 99 | 100 | 101 | 55 | 55 | 56 | 57 | 58 | 59 | 59 |
| | 90th | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 70 | 70 | 71 | 72 | 73 | 74 | 74 |
| | 95th | 110 | 111 | 113 | 115 | 117 | 118 | 119 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 99th | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 82 | 82 | 83 | 84 | 85 | 86 | 86 |
| 8 | 50th | 94 | 95 | 97 | 99 | 100 | 102 | 102 | 56 | 57 | 58 | 59 | 60 | 60 | 61 |
| | 90th | 107 | 109 | 110 | 112 | 114 | 115 | 116 | 71 | 72 | 72 | 73 | 74 | 75 | 76 |
| | 95th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| | 99th | 119 | 120 | 122 | 123 | 125 | 127 | 127 | 83 | 84 | 85 | 86 | 87 | 87 | 88 |
| 9 | 50th | 95 | 96 | 98 | 100 | 102 | 103 | 104 | 57 | 58 | 59 | 60 | 61 | 61 | 62 |
| | 90th | 109 | 110 | 112 | 114 | 115 | 117 | 118 | 72 | 73 | 74 | 75 | 76 | 76 | 77 |
| | 95th | 113 | 114 | 116 | 118 | 119 | 121 | 121 | 76 | 77 | 78 | 79 | 80 | 81 | 81 |
| | 99th | 120 | 121 | 123 | 125 | 127 | 128 | 129 | 84 | 85 | 86 | 87 | 88 | 88 | 89 |
| 10 | 50th | 97 | 98 | 100 | 102 | 103 | 105 | 106 | 58 | 59 | 60 | 61 | 61 | 62 | 63 |
| | 90th | 111 | 112 | 114 | 115 | 117 | 119 | 119 | 73 | 73 | 74 | 75 | 76 | 77 | 78 |
| | 95th | 115 | 116 | 117 | 119 | 121 | 122 | 123 | 77 | 78 | 79 | 80 | 81 | 81 | 82 |
| | 99th | 122 | 123 | 125 | 127 | 128 | 130 | 130 | 85 | 86 | 86 | 88 | 88 | 89 | 90 |

## Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) ← Percentile of Height → | | | | | | | Diastolic BP (mmHg) ← Percentile of Height → | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 11 | 50th | 99 | 100 | 102 | 104 | 105 | 107 | 107 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 90th | 113 | 114 | 115 | 117 | 119 | 120 | 121 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 117 | 118 | 119 | 121 | 123 | 124 | 125 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 99th | 124 | 125 | 127 | 129 | 130 | 132 | 132 | 86 | 86 | 87 | 88 | 89 | 90 | 90 |
| 12 | 50th | 101 | 102 | 104 | 106 | 108 | 109 | 110 | 59 | 60 | 61 | 62 | 63 | 63 | 64 |
| | 90th | 115 | 116 | 118 | 120 | 121 | 123 | 123 | 74 | 75 | 75 | 76 | 77 | 78 | 79 |
| | 95th | 119 | 120 | 122 | 123 | 125 | 127 | 127 | 78 | 79 | 80 | 81 | 82 | 82 | 83 |
| | 99th | 126 | 127 | 129 | 131 | 133 | 134 | 135 | 86 | 87 | 88 | 89 | 90 | 90 | 91 |
| 13 | 50th | 104 | 105 | 106 | 108 | 110 | 111 | 112 | 60 | 60 | 61 | 62 | 63 | 64 | 64 |
| | 90th | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 75 | 75 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 124 | 126 | 128 | 129 | 130 | 79 | 79 | 80 | 81 | 82 | 83 | 83 |
| | 99th | 128 | 130 | 131 | 133 | 135 | 136 | 137 | 87 | 87 | 88 | 89 | 90 | 91 | 91 |
| 14 | 50th | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 60 | 61 | 62 | 63 | 64 | 65 | 65 |
| | 90th | 120 | 121 | 123 | 125 | 126 | 128 | 128 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| | 95th | 124 | 125 | 127 | 128 | 130 | 132 | 132 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| | 99th | 131 | 132 | 134 | 136 | 138 | 139 | 140 | 87 | 88 | 89 | 90 | 91 | 92 | 92 |
| 15 | 50th | 109 | 110 | 112 | 113 | 115 | 117 | 117 | 61 | 62 | 63 | 64 | 65 | 66 | 66 |
| | 90th | 122 | 124 | 125 | 127 | 129 | 130 | 131 | 76 | 77 | 78 | 79 | 80 | 80 | 81 |
| | 95th | 126 | 127 | 129 | 131 | 133 | 134 | 135 | 81 | 81 | 82 | 83 | 84 | 85 | 85 |
| | 99th | 134 | 135 | 136 | 138 | 140 | 142 | 142 | 88 | 89 | 90 | 91 | 92 | 93 | 93 |
| 16 | 50th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 63 | 63 | 64 | 65 | 66 | 67 | 67 |
| | 90th | 125 | 126 | 128 | 130 | 131 | 133 | 134 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 95th | 129 | 130 | 132 | 134 | 135 | 137 | 137 | 82 | 83 | 83 | 84 | 85 | 86 | 87 |
| | 99th | 136 | 137 | 139 | 141 | 143 | 144 | 145 | 90 | 90 | 91 | 92 | 93 | 94 | 94 |
| 17 | 50th | 114 | 115 | 116 | 118 | 120 | 121 | 122 | 65 | 66 | 66 | 67 | 68 | 69 | 70 |
| | 90th | 127 | 128 | 130 | 132 | 134 | 135 | 136 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| | 95th | 131 | 132 | 134 | 136 | 138 | 139 | 140 | 84 | 85 | 86 | 87 | 87 | 88 | 89 |
| | 99th | 139 | 140 | 141 | 143 | 145 | 146 | 147 | 92 | 93 | 93 | 94 | 95 | 96 | 97 |

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

## Blood Pressure Levels for Girls by Age and Height Percentile

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) ← Percentile of Height → | | | | | | | Diastolic BP (mmHg) ← Percentile of Height → | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 50th | 83 | 84 | 85 | 86 | 88 | 89 | 90 | 38 | 39 | 39 | 40 | 41 | 41 | 42 |
| | 90th | 97 | 97 | 98 | 100 | 101 | 102 | 103 | 52 | 53 | 53 | 54 | 55 | 55 | 56 |
| | 95th | 100 | 101 | 102 | 104 | 105 | 106 | 107 | 56 | 57 | 57 | 58 | 59 | 59 | 60 |
| | 99th | 108 | 108 | 109 | 111 | 112 | 113 | 114 | 64 | 64 | 65 | 65 | 66 | 67 | 67 |
| 2 | 50th | 85 | 85 | 87 | 88 | 89 | 91 | 91 | 43 | 44 | 44 | 45 | 46 | 46 | 47 |
| | 90th | 98 | 99 | 100 | 101 | 103 | 104 | 105 | 57 | 58 | 58 | 59 | 60 | 61 | 61 |
| | 95th | 102 | 103 | 104 | 105 | 107 | 108 | 109 | 61 | 62 | 62 | 63 | 64 | 65 | 65 |
| | 99th | 109 | 110 | 111 | 112 | 114 | 115 | 116 | 69 | 69 | 70 | 70 | 71 | 72 | 72 |
| 3 | 50th | 86 | 87 | 88 | 89 | 91 | 92 | 93 | 47 | 48 | 48 | 49 | 50 | 50 | 51 |
| | 90th | 100 | 100 | 102 | 103 | 104 | 106 | 106 | 61 | 62 | 62 | 63 | 64 | 64 | 65 |
| | 95th | 104 | 104 | 105 | 107 | 108 | 109 | 110 | 65 | 66 | 66 | 67 | 68 | 68 | 69 |
| | 99th | 111 | 111 | 113 | 114 | 115 | 116 | 117 | 73 | 73 | 74 | 74 | 75 | 76 | 76 |
| 4 | 50th | 88 | 88 | 90 | 91 | 92 | 94 | 94 | 50 | 50 | 51 | 52 | 52 | 53 | 54 |
| | 90th | 101 | 102 | 103 | 104 | 106 | 107 | 108 | 64 | 64 | 65 | 66 | 67 | 67 | 68 |
| | 95th | 105 | 106 | 107 | 108 | 110 | 111 | 112 | 68 | 68 | 69 | 70 | 71 | 71 | 72 |
| | 99th | 112 | 113 | 114 | 115 | 117 | 118 | 119 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| 5 | 50th | 89 | 90 | 91 | 93 | 94 | 95 | 96 | 52 | 53 | 53 | 54 | 55 | 55 | 56 |
| | 90th | 103 | 103 | 105 | 106 | 107 | 109 | 109 | 66 | 67 | 67 | 68 | 69 | 69 | 70 |
| | 95th | 107 | 107 | 108 | 110 | 111 | 112 | 113 | 70 | 71 | 71 | 72 | 73 | 73 | 74 |
| | 99th | 114 | 114 | 116 | 117 | 118 | 120 | 120 | 78 | 78 | 79 | 79 | 80 | 81 | 81 |
| 6 | 50th | 91 | 92 | 93 | 94 | 96 | 97 | 98 | 54 | 54 | 55 | 56 | 56 | 57 | 58 |
| | 90th | 104 | 105 | 106 | 108 | 109 | 110 | 111 | 68 | 68 | 69 | 70 | 70 | 71 | 72 |
| | 95th | 108 | 109 | 110 | 111 | 113 | 114 | 115 | 72 | 72 | 73 | 74 | 74 | 75 | 76 |
| | 99th | 115 | 116 | 117 | 119 | 120 | 121 | 122 | 80 | 80 | 80 | 81 | 82 | 83 | 83 |
| 7 | 50th | 93 | 93 | 95 | 96 | 97 | 99 | 99 | 55 | 56 | 56 | 57 | 58 | 58 | 59 |
| | 90th | 106 | 107 | 108 | 109 | 111 | 112 | 113 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| | 95th | 110 | 111 | 112 | 113 | 115 | 116 | 116 | 73 | 74 | 74 | 75 | 76 | 76 | 77 |
| | 99th | 117 | 118 | 119 | 120 | 122 | 123 | 124 | 81 | 81 | 82 | 82 | 83 | 84 | 84 |
| 8 | 50th | 95 | 95 | 96 | 98 | 99 | 100 | 101 | 57 | 57 | 57 | 58 | 59 | 60 | 60 |
| | 90th | 108 | 109 | 110 | 111 | 113 | 114 | 114 | 71 | 71 | 71 | 72 | 73 | 74 | 74 |
| | 95th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| | 99th | 119 | 120 | 121 | 122 | 123 | 125 | 125 | 82 | 82 | 83 | 83 | 84 | 85 | 86 |
| 9 | 50th | 96 | 97 | 98 | 100 | 101 | 102 | 103 | 58 | 58 | 58 | 59 | 60 | 61 | 61 |
| | 90th | 110 | 110 | 112 | 113 | 114 | 116 | 116 | 72 | 72 | 72 | 73 | 74 | 75 | 75 |
| | 95th | 114 | 114 | 115 | 117 | 118 | 119 | 120 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| | 99th | 121 | 121 | 123 | 124 | 125 | 127 | 127 | 83 | 83 | 84 | 84 | 85 | 86 | 87 |
| 10 | 50th | 98 | 99 | 100 | 102 | 103 | 104 | 105 | 59 | 59 | 59 | 60 | 61 | 62 | 62 |
| | 90th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 73 | 73 | 73 | 74 | 75 | 76 | 76 |
| | 95th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| | 99th | 123 | 123 | 125 | 126 | 127 | 129 | 129 | 84 | 84 | 85 | 86 | 86 | 87 | 88 |

## Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) ← Percentile of Height → | | | | | | | Diastolic BP (mmHg) ← Percentile of Height → | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 11 | 50th | 100 | 101 | 102 | 103 | 105 | 106 | 107 | 60 | 60 | 60 | 61 | 62 | 63 | 63 |
| | 90th | 114 | 114 | 116 | 117 | 118 | 119 | 120 | 74 | 74 | 74 | 75 | 76 | 77 | 77 |
| | 95th | 118 | 118 | 119 | 121 | 122 | 123 | 124 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| | 99th | 125 | 125 | 126 | 128 | 129 | 130 | 131 | 85 | 85 | 86 | 87 | 87 | 88 | 89 |
| 12 | 50th | 102 | 103 | 104 | 105 | 107 | 108 | 109 | 61 | 61 | 61 | 62 | 63 | 64 | 64 |
| | 90th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 119 | 120 | 121 | 123 | 124 | 125 | 126 | 79 | 79 | 79 | 80 | 81 | 82 | 82 |
| | 99th | 127 | 127 | 128 | 130 | 131 | 132 | 133 | 86 | 86 | 87 | 88 | 88 | 89 | 90 |
| 13 | 50th | 104 | 105 | 106 | 107 | 109 | 110 | 110 | 62 | 62 | 62 | 63 | 64 | 65 | 65 |
| | 90th | 117 | 118 | 119 | 121 | 122 | 123 | 124 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 80 | 80 | 80 | 81 | 82 | 83 | 83 |
| | 99th | 128 | 129 | 130 | 132 | 133 | 134 | 135 | 87 | 87 | 88 | 89 | 89 | 90 | 91 |
| 14 | 50th | 106 | 106 | 107 | 109 | 110 | 111 | 112 | 63 | 63 | 63 | 64 | 65 | 66 | 66 |
| | 90th | 119 | 120 | 121 | 122 | 124 | 125 | 125 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| | 95th | 123 | 123 | 125 | 126 | 127 | 129 | 129 | 81 | 81 | 81 | 82 | 83 | 84 | 84 |
| | 99th | 130 | 131 | 132 | 133 | 135 | 136 | 136 | 88 | 88 | 89 | 90 | 90 | 91 | 92 |
| 15 | 50th | 107 | 108 | 109 | 110 | 111 | 113 | 113 | 64 | 64 | 64 | 65 | 66 | 67 | 67 |
| | 90th | 120 | 121 | 122 | 123 | 125 | 126 | 127 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| | 95th | 124 | 125 | 126 | 127 | 129 | 130 | 131 | 82 | 82 | 82 | 83 | 84 | 85 | 85 |
| | 99th | 131 | 132 | 133 | 134 | 136 | 137 | 138 | 89 | 89 | 90 | 91 | 91 | 92 | 93 |
| 16 | 50th | 108 | 108 | 110 | 111 | 112 | 114 | 114 | 64 | 64 | 65 | 66 | 66 | 67 | 68 |
| | 90th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 78 | 78 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 128 | 130 | 131 | 132 | 82 | 82 | 83 | 84 | 85 | 85 | 86 |
| | 99th | 132 | 133 | 134 | 135 | 137 | 138 | 139 | 90 | 90 | 90 | 91 | 92 | 93 | 93 |
| 17 | 50th | 108 | 109 | 110 | 111 | 113 | 114 | 115 | 64 | 65 | 65 | 66 | 67 | 67 | 68 |
| | 90th | 122 | 122 | 123 | 125 | 126 | 127 | 128 | 78 | 79 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 129 | 130 | 131 | 132 | 82 | 83 | 83 | 84 | 85 | 85 | 86 |
| | 99th | 133 | 133 | 134 | 136 | 137 | 138 | 139 | 90 | 90 | 91 | 91 | 92 | 93 | 93 |

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.