PROTOCOL AFM13-203

Protocol Title:	A Phase 2, Open-Label, Multi-Center Study of Innate Cell Engager AFM13 in Combination with Allogeneic Natural Killer Cells (AB-101) in Subjects with Recurrent or Refractory Hodgkin Lymphoma and CD30-Positive Peripheral T-Cell Lymphoma (LuminICE-203)
Protocol No:	AFM13-203
Study Treatments:	AFM13 (anti-human CD30 × anti-human CD16A recombinant antibody) or acimtamig AB-101 (Allogeneic Cord Blood Derived NK Cells) or AlloNK®
Indication(s) Studied:	Recurrent or Refractory Hodgkin Lymphoma and CD30-Positive Peripheral T-Cell Lymphoma
Study Phase:	Phase 2
IND Number:	029407
Sponsor Name:	Affimed GmbH
Sponsor Address	Gottlieb-Daimler-Strasse 2, 68165 Mannheim, Germany
Version No., Date	Version 3.0, 03 July 2024

SPONSOR SIGNATORY

This study will be conducted in compliance with International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements, including data privacy laws.

This protocol, V3.0 dated 03 July 2024, has been approved by Affimed GmbH.

Signature: …… Date: ……

(DD MMM YYYY)

[redacted]

Affimed GmbH
Gottlieb-Daimler-Strasse 2
68165 Mannheim
Germany

[redacted]

COORDINATING INVESTIGATOR

I declare that the protocol contains all the necessary information required for the conduct of the study.

Coordinating Investigator´s Signature	*Date*

INVESTIGATOR'S DECLARATION AND APPROVAL

I have read this protocol and agree that it contains all the necessary details for carrying out this study. I will conduct the study as described in the current, approved protocol. I verify that I am suitably qualified by education, scientific and medical training and experience to conduct the study. Documentation of my qualifications and professional affiliations are contained in my up-to- date curriculum vitae provided to the Sponsor.

I will provide the supplied copies of the protocol, including future protocol amendments, and all information relating to non-clinical and clinical experience when available (eg, in updated editions of the Investigator's Brochure), to all staff involved in the conduct of this study. I will discuss this material with them to ensure that they are fully conversant with the investigational medicinal product and study design, and that they will handle the data and information generated in the study confidentially.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. I acknowledge that the study will be conducted in accordance with the relevant laws and regulations relating to clinical studies and the protection of subjects, including data privacy laws. I confirm it is my duty and the duty of my study staff to ensure participating subjects are informed comprehensively about the nature of the study and will give their written consent to participate before entry into the study. Subjects will be informed that they may withdraw from the study at any time without jeopardizing their future care. I will use only the subject informed consent form approved by the Sponsor and the Ethics Committee/Institutional Review Board for this study. I will supply the Sponsor with any material written prepared by myself or my study staff e.g., summary of study, which is given to the Ethics Committee/Institutional Review Board in support of the application.

Where applicable, the subject information contained in clinic records, reports and manuscripts will be transcribed to the study case report forms. I (or my delegates as described in my Study File) will attest to the authenticity of the data and accuracy and completeness of the transcription by signing the case report forms. I agree to the audit and monitoring procedures to verify study records against original records. Should it be requested by government regulatory agencies, I will make available additional background data from my records and from the hospital or institution where the study was conducted (as permitted by the hospital or institution).

I understand that the case report forms and other data pertinent to this study are the property of Affimed GmbH and are confidential. I agree to only supply Affimed GmbH (or their delegates) with subject study data in such a way that the subject cannot be personally identified.

Investigator: …… ……

Signature Date

Print Name: ……

Institution Name: ……

Institution Address: ……

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LIST OF ABBREVIATIONS

Abbreviation	Definition/Explanation
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
AESI	adverse event of special interest
AITL	angioimmunoblastic T-cell lymphoma
ALC	absolute lymphocyte count
ALCL	anaplastic large-cell lymphoma
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical, Therapeutic, and Chemical
$AUC_{0\text{-}7days}$	area under the concentration-time curve from 0 to 7 days.
$AUC_{0\text{-}\infty}$	area under the concentration-time curve to infinite time
BV	brentuximab vedotin
CAR-T	chimeric antigen receptor T-cell
CBNK	cord blood natural killer
CFR	US Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLL	chronic lymphocytic leukemia
C_{min}	minimum observed plasma concentration
CMR	complete metabolic response
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response/remission

Abbreviation	Definition/Explanation
CRA	clinical research associate
CrCl	creatinine clearance
CRP	C-reactive protein
CRR	complete response rate
CRS	cytokine release syndrome
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
Cy/Flu	cyclophosphamide and fludarabine
DCR	disease control rate
DILI	drug-induced liver injury
DL	dose level
DLCO	diffusing capacity of the lungs for carbon monoxide
DLT	dose-limiting toxicity
DOR	duration of response
DSUR	Development Safety Update Report
EBV	Epstein Barr Virus
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture System
EMA	Europeans Medicines Agency
EOI	end of infusion
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FEV1	forced expiratory volume
FSH	Follicle -stimulating hormone
FVC	forced vital capacity
G-CSF	granulocyte-colony stimulating factor
GCP	Good Clinical Practice

Abbreviation	Definition/Explanation
GVHD	graft versus host disease
Hb	hemoglobin
HCT	hematopoietic cell transplantation
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HNSTD	highest non-severely toxic dose
IA	interim analysis
IB	Investigator's Brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Council on Harmonisation
ID	identification
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IL-2	interleukin-2
IME	important medical event
IMP	investigational medicinal product
IND	Investigational New Drug Application
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Radiology Committee
IRR	infusion-related reaction(s)
ITT	intent-to-treat
i.v.	intravenous(ly)
LPI	last patient in
mAB	monoclonal antibody
MAGIC	Mount Sinai Acute GVHD International Consortium
MedDRA	Medical Dictionary for Regulatory Activities
MRD	measurable residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute

Abbreviation	Definition/Explanation
NHL	non-Hodgkin lymphoma
NK	Natural killer
NOS	not otherwise specified
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PD-1	receptor for programmed death-ligand 1
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMD	progressive metabolic disease
PMR	partial metabolic response
popPK	population PK
PPS	per protocol set
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome measures
PRR	Partial Responses Rate
PS	performance status
PTCL	peripheral T-cell lymphoma
PTCL-NOS	peripheral T-cell lymphoma not otherwise specified
QoL	quality of life
QTcF	QT interval with Fridericia's correction
QW	once weekly
R/R	refractory/relapsed
RO	receptor occupancy
RP2D	recommended Phase 2 dose
RSI	Reference Safety Information
SAE	serious adverse event

Abbreviation	Definition/Explanation
SAP	Statistical Analysis Plan
SAS	safety analysis set
SCT	stem cell transplantation
SD	stable disease
SRC	Safety Review Committee
SRI	safety run-in set
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TMF	Trial Master File
Treg	Regulatory T cells
ULN	upper limit of normal
USPI	United States Prescribing Information
VH/VL	heavy chain/light chain
WHO	World Health Organization

1. STUDY SYNOPSIS

Sponsor	Affimed GmbH
Investigational Products	AFM13 (anti-human CD30 × anti-human CD16A recombinant antibody) or acimtamig AB-101 (Allogeneic Cord Blood Derived NK Cells) or AlloNK®
Title of Study	A Phase 2, Open-Label, Multi-Center Study of Innate Cell Engager AFM13 in Combination with Allogeneic Natural Killer Cells (AB-101) in Subjects with Recurrent or Refractory Hodgkin Lymphoma and CD30-Positive Peripheral T-Cell Lymphoma (LuminICE-203)
Protocol Number	AFM13-203
Study Design	Open-Label, Multicenter, Efficacy, and Safety study
Study Phase	Phase 2
Number of Study Sites	Approximately 35 sites
Subject Population	Adult subjects aged 18 years or older with a confirmed diagnosis of refractory/relapsed (R/R) classical Hodgkin lymphoma (HL) or CD30-positive peripheral T-cell lymphoma (PTCL)
Number of Subjects	Overall, up to 166 subjects are planned for enrollment

Study Objectives and Endpoints (all endpoints will be analyzed for all cohorts and indications separately)

Primary Objective	**Primary Endpoint**
• Assess the antitumor activity of acimtamig in combination with AlloNK® in subjects with R/R classical HL and CD30-positive PTCLs by objective response rate (ORR).	• ORR (complete response (CR) + partial response [PR]) by Independent Radiology Committee (IRC) based on positron emission tomography-computed tomography (PET-CT) as assessed by the Lugano classification
Secondary Objectives	**Secondary Endpoints**
• To assess efficacy of acimtamig in combination with AlloNK® • To assess the incidence of post-treatment transplant • To assess the safety and tolerability of acimtamig in combination with AlloNK® • To assess the immunogenicity of acimtamig in combination with AlloNK®	• Duration of response (DOR) by Investigator and IRC • Complete response rate (CRR) by Investigator and IRC • ORR by Investigator based on PET-CT as assessed by the Lugano classification • Incidence of subjects receiving subsequent transplant • Frequency of subjects with study-drug related treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) (evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0 and American Society for Transplantation and Cellular Therapy [ASTCT] grading for TEAEs related

	to cytokine release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS]) • Frequency of subjects developing anti-drug antibodies (ADAs) against acimtamig or AlloNK® • Progression-free survival (PFS) by IRC • Overall survival (OS)
Exploratory Objectives	**Exploratory Assessments**
• [redacted]	[redacted]

Study Design and Methodology

This is a phase 2, open-label, multi-center, multi-cohort study with a safety run-in followed by expansion cohorts. The study is evaluating the safety and efficacy of AFM13 in combination with AB-101 in subjects with R/R classical HL and CD30-positive PTCL. In this protocol, AFM13 is referred to as acimtamig and AB-101 is referred to as AlloNK®, with exception of the title which was created prior to the change in product names.

The primary aim for this study is to assess the antitumor activity of acimtamig in combination with AlloNK® in four cohorts of subjects:

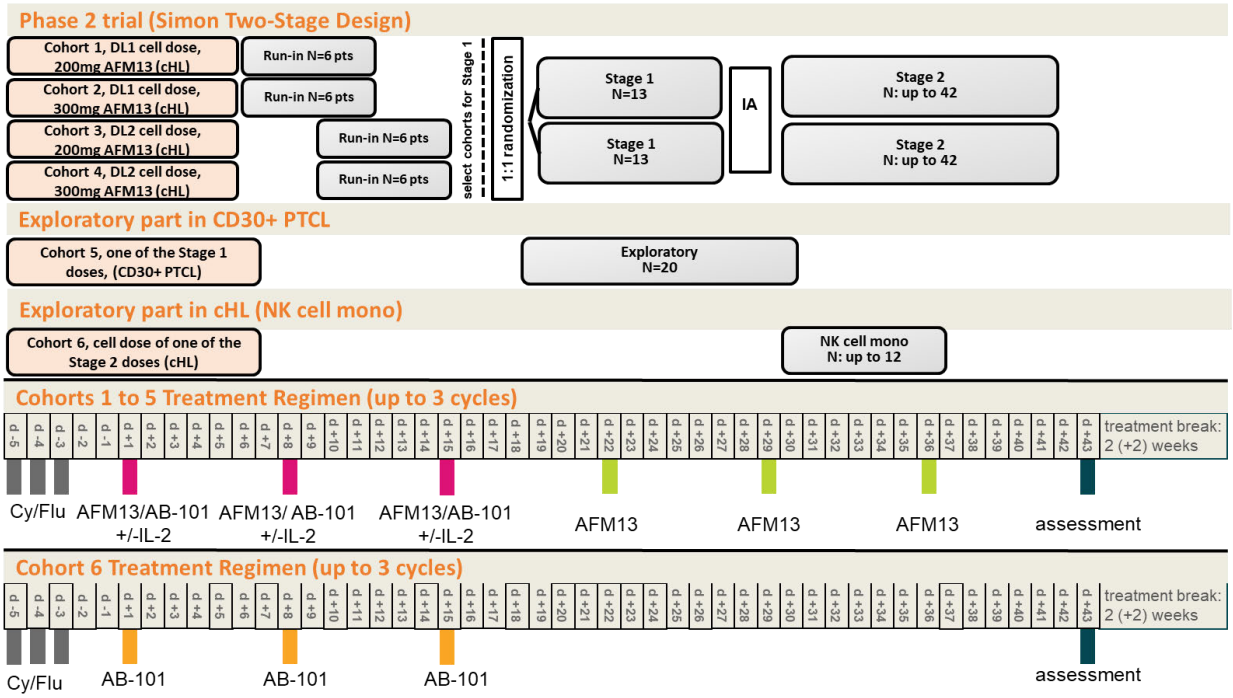
- **Cohort 1:** AlloNK® dose level 1 (DL1) (2×10^9 cells on Day 1, Day 8, Day 15) + 200 mg acimtamig in classical HL (N: 6 to 61)
- **Cohort 2:** AlloNK® DL1 + 300 mg acimtamig in classical HL (N: 6 to 61)
- **Cohort 3**: AlloNK® dose level 2 (DL2) (4×10^9 cells on Day 1; 2×10^9 cells on Day 8, Day 15) + 200 mg acimtamig in classical HL (N: 6 to 61)
- **Cohort 4**: AlloNK® DL2 + 300 mg acimtamig in classical HL (N: 6 to 61)

Two additional exploratory cohorts will be evaluated:

- **Cohort 5:** CD30-positive PTCL (N: 20) (AlloNK® DL1 or DL2 + acimtamig at 200 mg or 300 mg)
- **Cohort 6**: AlloNK® DL1 or DL2 in classical HL (N: up to 12)

A schematic of the study design is provided below. Refer to [redacted].

Overall Study Design



Abbreviations: CD = cluster differentiation; cHL = classical Hodgkin lymphoma; Cy/Flu = cyclophosphamide and fludarabine; IA = interim analysis; IL = interleukin; NK = natural killer; PTCL = peripheral T-cell lymphoma; DL1 = 2×10^9 cells on Day 1, Day 8, and Day 15; DL2 = 4×10^9 cells at Day 1, 2×10^9 cells at Day 8 and Day 15

[redacted]

A safety run-in for the first 6 classical HL subjects in Cohort 1 and Cohort 2 (parallel enrollment) will be implemented, with staggering of at least 12 days between Day -5 (start of lymphodepletion) of one subject to Day -5 (start of lymphodepletion) of the subsequent subject (included as part of the 12-day period is a 7-day observation period following administration of Day 1 treatment). For the first 3 subjects enrolled in each cohort, the safety run-in approach will be utilized to monitor treatment-related toxicities during the safety run-in observation period, defined as the time from the first dose of combination study treatment (acimtamig/AlloNK®) to Day 21 of the treatment cycle (C1D21) for each subject. If a Grade 3 or Grade 4 acimtamig or AlloNK®-related TEAE (meeting criteria as stipulated in Section 10.6) occurs during the safety run-in observation period for the first 3 subjects, then another 3 subjects will be enrolled using the same staggered approach. If no more than one Grade 3 or 4 acimtamig or AlloNK®-related TEAE is observed in the first 6 subjects, then enrollment of the first 3 classical HL subjects in Cohort 3 and Cohort 4 (parallel enrollment) will begin, using the same staggering approach outlined for Cohort 1 and Cohort 2. If Grade 3 or 4 acimtamig or AlloNK®-related TEAEs are not observed in the first 3 subjects, then enrollment in Cohort 1 and Cohort 2 may continue without staggering and enrollment of the first 3 classical HL subjects in Cohorts 3 and 4 (parallel enrollment) will begin, using the same staggering approach as outlined for Cohort 1 and Cohort 2. Backfilling into Cohorts 1 and 2 will be allowed during the safety clearance period for Cohorts 3 and 4.

[redacted]

An independent Safety Review Committee (SRC) will be established prior to the enrollment of the first subject to review at regular intervals the safety data of all subjects throughout the conduct of the study. Further details regarding the constitution of the SRC and its specific roles and responsibilities and timing of reviews will be provided in the SRC charter.

Study Assessments and Procedures

[redacted]

Safety Assessments

Safety and tolerability will be assessed by monitoring and recording of all AEs graded by the NCI CTCAE v.5.0 (including neuro-toxicities that are not considered ICANS) except for CRS and ICANS which will be graded according to the ASTCT grading, tumor lysis syndrome (TLS) will be graded according to the Cairo-Bishop TLS grading system and acute graft versus host disease (GVHD) will be graded according to the Mount Sinai Acute GVHD International Consortium (MAGIC) criteria. For further details on severity grading, please refer to Section 10.2.1. In addition, laboratory assessments (hematology, serum chemistry, coagulation, and urinalysis), vitals, physical examinations, and 12-lead electrocardiograms (ECGs) findings will be used in evaluating the safety of acimtamig in combination with AlloNK®.

Efficacy Assessments

Disease and efficacy assessments will be conducted at Screening and on Day 43 (± 3 days) of each cycle, regardless of any treatment/cycle delays that may occur, as indicated in the Schedule of Assessments ([redacted]). Assessments utilizing PET-CT will be read both locally and centrally. Treatment decisions should be based on the local disease assessment.

Response assessment will follow the Lugano classification (Cheson 2014; [redacted]) for definition of complete metabolic response/complete response (CMR/CR), partial metabolic response/partial response (PMR/PR), no metabolic response, and progressive metabolic disease (PMD). Subjects who achieve a response and proceed to receive subsequent transplant will be followed for progression and survival status.

Note: Should the PET/CT assessment be considered to be "indeterminate" and the subject shows no clinical evidence of progression, at the discretion of the investigator the subject may continue treatment on study pending follow-up evaluation and confirmation of response.

Pharmacokinetic Assessments

All subjects will be required to participate in PK sampling in the study, and serial blood samples will be

collected and analyzed at specified times for measurement of acimtamig and AlloNK®. The PK of acimtamig and AlloNK® will be determined by analyzing samples collected at the time points as indicated in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments ([redacted]).

Pharmacodynamic Assessments

Pharmacodynamic markers evaluation, e.g., immunophenotyping, cytokines, etc., will be collected from all subjects on study to further explore acimtamig and AlloNK® activity and identify potential predictors of response. Pharmacodynamic sampling is performed as indicated in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments ([redacted]). The Sponsor may conduct additional analyses on the PD samples to further evaluate the safety of the study treatment, to better understand the progression of the disease, or to assess response to the study treatment.

Immunogenicity

The development of ADA may impact drug exposure, efficacy and safety in subjects on the study. To assess the immunogenicity of acimtamig and AlloNK®, ADAs will be measured as indicated in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments ([redacted].

Patient Reported Outcomes (PROs)

PROs on QoL will be measured utilizing European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

Criteria for Study Inclusion

Subjects will be considered eligible to be enrolled in the study if ALL of the inclusion and NONE of the exclusion criteria are met as defined below. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Inclusion Criteria

A subject is eligible to be included in the study only if ALL the following criteria apply:

1. Subjects with a diagnosis of FDG-avid relapsed or refractory classical HL OR select subtypes of FDG-avid relapsed or refractory PTCL.

   For subjects with R/R PTCL a pre-enrollment tumor biopsy positive for CD30 locally assessed by Ber-H2 targeted immunohistochemistry at ≥1% is mandatory (Note: Archival tissue may be substituted for a fresh tumor biopsy, please refer to Section 8.1 and the Schedule of Assessments [redacted] for additional details).

   PTCL subtypes

   - Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
   - Angioimmunoblastic T-cell lymphoma
   - Anaplastic large-cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-positive
   - ALCL, ALK-negative

2. Prior treatment for the disease under study consistent with the following:

   - Subjects with R/R classical HL must have received at least two lines of therapy including one prior line of combination chemotherapy. Prior therapy must also

have included brentuximab vedotin and a receptor for programmed death-ligand 1 (PD-1) check point inhibitor.

- Subjects with R/R PTCL must have received at least one prior line of combination chemotherapy. Subjects with ALCL subtype of PTCL must have received or been intolerant to brentuximab vedotin.
- Subjects with R/R classical HL AND R/R PTCL: Prior autologous stem cell transplant (ASCT) is permitted if completed at least 3 months prior to the first dose of study treatment. Prior allogeneic stem cell transplantation will be permitted if completed at least 1 year from study enrollment and there are no signs or symptoms of GVHD. Prior chimeric antigen receptor T-cell (CAR-T) therapy is permitted if last CAR-T dose completed at least 6 months prior to the first dose of study drug (acimtamig and/or AlloNK®).

3. Male or female aged ≥18 years (or as required by local regulation) on the day of signing the informed consent form (ICF).
4. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
5. Absolute neutrophil count (ANC) ≥1000/mm3, hemoglobin ≥7 g/dL, and platelet count ≥50,000/mm^3.

   - Transfusions of packed red blood cells and platelets are allowed up to 2 weeks prior to Day -5 of the first cycle and as needed during the Treatment Period. Growth factors are allowed during Screening up to 2 weeks prior to the first dose of lymphodepleting chemotherapy and as needed during the Treatment Period. All lab parameters should be checked within 2 days of the first dose of lymphodepleting chemotherapy to reassess eligibility.

6. Adequate organ function defined by the following laboratory parameters during screening:

   - Direct (conjugated) bilirubin ≤ 2 × the upper limit of normal (ULN), or total bilirubin ≤ 3 × ULN if considered due to Gilbert's disease.
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × ULN, unless considered due to malignant disease involvement, in which case AST and ALT can be ≤ 5.0 × ULN.
   - Creatinine clearance (CrCl) ≥50 mL/min. Creatinine clearance will be calculated using the Cockcroft and Gault equation.
   - International normalized ratio (INR) <1.5 × ULN and activated partial thromboplastin time (aPTT) <1.5 × ULN (for subjects not receiving therapeutic anticoagulation) (Note: subjects receiving therapeutic anticoagulation may enroll with INR ≥1.5 × ULN).

7. Adequate pulmonary function with forced expiratory volume (FEV1), forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) (corrected for Hgb and volume) ≥50%.
8. Adequate cardiac function with left ventricular ejection fraction ≥50% and no uncontrolled arrhythmias or symptomatic cardiac disease.
9. Capable of giving signed informed consent that includes compliance with the requirements and restrictions listed in the ICF and in the study protocol.

10. Female subjects must have a negative urine or serum pregnancy test within 7 days prior to first dose of lymphodepletion if of childbearing potential or be of non-childbearing potential. If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as:

    - Postmenopausal, defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Surgically sterile. Surgical sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

11. Females of childbearing potential must agree to sexual abstinence (defined below) or be willing to use a highly effective method of contraception for the course of the study from 14 days prior to the first dose of lymphodepletion through 120 days after the last dose of study drug (acimtamig and/or AlloNK®). Acceptable highly effective birth control methods include:

    - Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
    - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
    - Intrauterine device;
    - Intrauterine hormone-releasing system;
    - Bilateral tubal occlusion;
    - Vasectomized partner (provided that partner is the sole sexual partner of the female of reproductive potential and that the vasectomized partner has received medical assessment of the surgical success); and
    - Sexual abstinence.

      In the context of this study, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 14 days prior to the first dose of lymphodepletion up to 120 days after the last dose of study drug (acimtamig or AlloNK®). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

12. Males who have female partners of childbearing potential must agree to use a highly effective method of contraception as described in inclusion criterion 11, starting with the first dose of lymphodepletion through 120 days after the last dose of study drug (acimtamig and/or AlloNK®).

Exclusion Criteria

A subject is not eligible to enroll into the study if they have ANY of the following:

1. Treatment within prior 3 weeks of Day 1 of treatment schedule (Cycle 1 Day 1) with any anti-cancer agent, investigational or approved.
2. Continued toxicity from prior treatment that has not resolved to Grade ≤ 1, with allowable exceptions (e.g., alopecia).

3. Active central nervous system (CNS) involvement (untreated or uncontrolled parenchymal brain metastasis or positive cytology of cerebrospinal fluid).
4. Previous treatment with acimtamig or cord blood derived NK (CBNK) cells.
5. Known hypersensitivity/allergic reaction ≥Grade 3 to monoclonal antibodies (mAb) or any components used in the acimtamig product preparation, any history of anaphylaxis or uncontrolled asthma.
6. History of a solid organ allograft, or an inflammatory or autoimmune disease likely to be exacerbated by IL-2 or other study specific treatment (including subjects requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease that may require systemic steroids or immunosuppressive agents. Exceptions include any subject on 10 mg or less of prednisone or equivalent, subjects with vitiligo, hypothyroidism stable on hormone replacement, Type I diabetes, Graves' disease, Hashimoto's disease, alopecia areata, eczema, or psoriasis).
7. Treatment with any therapeutic mAb or immunosuppressive medications (such as high-dose steroids defined as ≥10 mg prednisone or equivalent per day) within 4 weeks or 5 half-lives (whichever is shorter) of Day 1 of treatment schedule.

   Exceptions for the use of corticosteroids:

   - Topical (≤20% of the skin surface area), ocular, intra-articular, intranasal, or inhalation corticosteroids with minimal systemic absorption.
   - Short course (≤7 days) of corticosteroids prescribed prophylactically (e.g., for contrast dye allergy or antiemetic therapy for specific chemotherapy) or for treatment of a non-autoimmune causes (e.g., delayed-type hypersensitivity reaction caused by contact allergen) as long as <10 mg prednisone equivalent.
   - Physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency.

8. History of any other systemic malignancy, unless previously treated with curative intent and the subject has been disease free for 2 years or longer. Subjects who meet the above criteria and are on maintenance therapy for prior malignancy may be eligible after discussion and approval from the medical monitor.
9. Live-virus vaccines given within 28 days prior to the initiation of study treatment.
10. Active, uncontrolled infection requiring systemic therapy. If the infection is controlled or has resolved, maintenance and/or prophylactic systemic antimicrobials are permitted.
11. Known active hepatitis B or hepatitis C as defined in the table below. Antiviral prophylaxis for chronic hepatitis B virus infection may be used at the discretion of the Investigator.

    Note: Subjects meeting following criteria are allowed to be enrolled in the study:

	Eligible
HBV	HB sAg (-)
	HB sAg (+) and HBV DNA <500 IU/mL (or 2500 copies/mL)
HCV	HCV Ab (-)
	HCV Ab (+) and HCV RNA (-)

    Abbreviations: HBV = hepatitis B virus; HBs Ag = HBV surface antigen; HCV = hepatitis C virus; HCV Ab = HCV antibody

12. Active HIV infection as evidenced by a positive HIV polymerase chain reaction (PCR) test result.
13. Active acute or chronic GVHD or GVHD requiring immunosuppressive treatment, clinically significant CNS dysfunction (seizure disorder, dementia, cerebellar disease, cerebral edema,

posterior reversible encephalopathy syndrome (PRES), autoimmune disease with CNS involvement).

14. Any uncontrolled medical condition, including but not limited to: unstable angina pectoris, symptomatic congestive heart failure (New York Heart Association [NYHA] II, III, IV;, myocardial infarction ≤6 months prior to first study drug (acimtamig or AlloNK®), uncontrolled cardiac arrhythmia e.g., atrial fibrillation/flutter, cerebrovascular accidents ≤6 months before first dose of study drug (acimtamig and/or AlloNK®).
15. Major surgical procedure (i.e., any open surgical procedure that involves the resection or manipulation of major organ) or significant traumatic injury within 4 weeks before first dose of study drug (acimtamig and/or AlloNK®) or anticipation of need of a major surgical procedure during the course of study.

    Note: Procedures that are considered to be minimally invasive (e.g., peripherally inserted central catheters lines and/or port placements, interventional biopsies) will be exceptions.
16. Pregnant or breastfeeding women. Breastfeeding must be discontinued before onset of and during treatment and should be discontinued for at least 3 months after end of treatment.
17. Substance abuse, medical, psychological, or social conditions that may interfere with the subject's cooperation with the requirements of the study or evaluation of the study results.
18. Any medical, psychological, or social condition that would interfere with the subject's participation in the study.

Study Treatment, Dose, and Mode of Administration

Study treatments will be administered as follows in 48-day cycles, up to 3 cycles in total, with a 2-week (+2 week) rest period between each cycle (refer also to Figure 2):

- **Lymphodepletion**: A standard lymphodepleting regimen of cyclophosphamide 300 mg/m^2/day and fludarabine 30mg/m^2/day intravenously will be administered from Day -5 to Day -3 at the start of each treatment cycle (Section 6.1.1).
    - **Premedication**: Approximately 1 hour prior to acimtamig administration and approximately 30 min prior to AlloNK® administration, a premedication regimen will be administered as follows [redacted]
        - Intravenous (IV) H1 antagonist (e.g., diphenhydramine 50 mg or similar medication as used per local institutional practice) with or without an H2 antagonist (e.g., famotidine or similar medication as used per local institutional practice), and
        - Oral acetaminophen dosage as per local institutional practice (e.g., 650 mg to 1000 mg or equivalent).
- **Acimtamig**: Acimtamig will be administered intravenously at a fixed dose of 200 mg or 300 mg on Day 1, Day 8, and Day 15 of each cycle prior to administration of AlloNK® on these days. Infusions will be administered over approximately 4 hours. Additionally, acimtamig will be administered as the sole therapy (intravenously over approximately 4 hours) on Day 22, Day 29 and Day 36 of each cycle (Section 6.1.3).
- **AlloNK®:** AlloNK® will be administered (as soon as practical after thawing but must be within 90 minutes after thawing) upon completion of administration and observation period for acimtamig. Subjects at DL1 will be administered a fixed dose of 2×10^9 cells IV on Day 1, Day 8 and Day 15 of each cycle. Subjects at DL2 will be administered a fixed dose of 4×10^9 cells IV on Day 1 and a

dose of 2 × 10^9 cells IV on Day 8 and Day 15 in an identical manner and schedule as DL1. (Section 6.1.4).

- **IL-2**: IL-2 will be administered at a dose of 6 × 10^6 IU/dose subcutaneously at least 1 hour after and no more than 4 hours following each AlloNK® dose for all subjects who were initially consented under protocol v2.0 (Section 6.1.5). Those subjects initially consented under protocol v3.0 and later versions will not receive IL-2 following the AlloNK® treatment.

After administration of each acimtamig, AlloNK® and IL-2 (if applicable per consented protocol version) in the treatment regimen, subjects must be observed for at least 1 hour.

Statistical Considerations

Analyses Sets

The **safety analysis set (SAS)** will consist of all subjects who received any amount of any component of the regimen (acimtamig, AlloNK® or any study treatment such as lymphodepletion or IL-2). The SAS will be the primary population for all safety-related endpoints.

Following the intent-to-treat (ITT) principle, the **full analysis set (FAS)** will consist of all subjects enrolled into one of the two selected cHL Cohorts in Stage 1 and Stage 2 or the exploratory PTCL Cohort (Cohort 5), who received at least 1 dose of both acimtamig and AlloNK®. The FAS will be the primary population for all efficacy related endpoints.

Following the ITT principle for analysis of Cohort 6, the **NK full analysis set (NK-FAS)** will consist of all subjects who received at least 1 dose of AlloNK® in Cohort 6. The NK-FAS will be the primary population for all efficacy related endpoints concerning Cohort 6.

The **per protocol set (PPS)** will consist of all subjects in FAS who did not have any major protocol deviations. The primary analysis will be repeated to support the results of the primary analysis on the FAS.

The **safety run-in set (SRI)** consists of all subjects of the 4 safety run-in cohorts who have received at least 66% of the acimtamig and AlloNK® combination dose during Cycle 1.

The **acimtamig PK set** consists of all subjects (except those from Cohort 6) who have received at least 1 dose of acimtamig and have at least 1 post dose acimtamig PK measurement.

The **AlloNK® PK set** consists of all subjects who have received at least 1 dose of AlloNK® and have at least 1 post dose AlloNK® PK measurement.

[redacted]

[redacted]

Secondary Analyses

Efficacy

The following secondary efficacy endpoints will be assessed according to the Lugano classification (Cheson 2014; [redacted]

- DOR by IRC and Investigator
- ORR (CR + PR) by Investigator
- CRR by IRC and Investigator
- PFS by IRC

In addition, incidence of subjects receiving subsequent transplant and OS will be assessed.

Safety

Incidence, severity and relatedness of TEAEs and SAEs. Adverse events will be coded with Medical Dictionary for Regulatory Activities (MedDRA) for regulatory standardization and graded according to the NCI CTCAE v5.0 (including neurotoxicities that are not considered ICANS) except for CRS and ICANS which will be graded according to the ASTCT grading, TLS will be graded according to the Cairo-Bishop TLS grading system and acute GVHD will be graded according to the MAGIC criteria.

Immunogenicity

Immunogenicity parameters will be summarized by descriptive statistics.

[redacted]

[redacted]

2. INTRODUCTION

This clinical study will evaluate acimtamig in combination with AlloNK® in subjects with recurrent or refractory Hodgkin lymphoma and CD30-positive peripheral T-cell lymphoma (PTCL).

2.1. Disease Background

CD30 is a cell membrane protein of the tumor necrosis factor receptor family universally expressed in classical Hodgkin lymphoma (HL) as well as in several sub-types of PTCLs, to varying degrees, including anaplastic large-cell lymphoma (ALCL), peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), and angioimmunoblastic T-cell lymphoma (AITL).

In classical HL, the most common CD30-positive lymphoma, frontline chemotherapy (ABVD or BEACOPP) with or without radiotherapy has demonstrated significant effectiveness. In patients with advanced classical HL, frontline therapy may also include the CD30-targeting antibody drug conjugate brentuximab vedotin with chemotherapy (AVD). However, up to 30% of patients are refractory to frontline treatment or will relapse. For patients with relapsed or refractory classical HL, 50% or fewer can be cured with high-dose chemotherapy and autologous stem cell transplantation (ASCT) (Majhail 2006; Josting 2010; Bartlett 2020). Relapse after ASCT is associated with a poor prognosis with a median survival of 26 months (Voorhees 2020). Systemic treatment options for refractory/relapsed (R/R) patients may also include agents such as brentuximab vedotin either as monotherapy or in combination with another agent, and/or a PD-(L)1 inhibitor. Despite recent advancements that have included promising targeted and immunological agents, there is still an unmet medical need for treatments in the R/R setting that provide a high level of response, longer duration of response, and chance of cure, together with a clinically acceptable safety profile.

With respect to PTCLs, first-line treatment with CHOP or CHOP-like regimens results in poor outcomes, except in the case of *ALK*+ ALCL. Despite intensified approaches in frontline therapy, such as consolidation with ASCT, these patients are still at considerable risk of relapse or early progression. In general, most if not all patients undergoing treatment for PTCL will not achieve remission or will relapse with very poor long-term survival, especially in absence of hematopoietic cell transplantation (HCT), with median progression-free survival (PFS) and overall survival (OS) estimates as low as 3 and 6 months, respectively (Mak 2013; Biasoli 2015; Bellei 2018). Therefore, novel therapeutics and treatment strategies are needed to address the unmet medical needs that exist for patients with PTCL.

2.2. Background of the Study Drugs

2.2.1. Acimtamig

Acimtamig, or AFM13, is a tetravalent bispecific (anti-human CD30 × anti-human CD16A) recombinant antibody construct, which is being investigated for the treatment of HL and other CD30-positive malignancies including PTCL. Acimtamig targets CD30 antigen expressed on malignant lymphoma cells. At the same time, the anti-CD16A domains bind to CD16A (FcγRIIIA) on natural killer (NK) cells and macrophages. Acimtamig forms a bridge between the tumor target cells and innate effector cells, triggering lysis of CD30 antigen-positive cells by NK cells via

antibody-dependent cell-mediated cytotoxicity (ADCC) and macrophage-mediated antibody-dependent cellular phagocytosis (ADCP).

[redacted]

Further nonclinical and clinical data for acimtamig are described in the acimtamig Investigator's Brochure (IB).

2.2.2. AlloNK®

AlloNK® is an allogeneic NK cell product derived from FDA licensed cord blood, specifically designed to treat hematological and solid tumors in combination with therapeutic monoclonal antibodies (mAbs) and bi-specific antibodies. The AlloNK® manufacturing process leads to an NK cell product with the following attributes:

- Consistent NK cell profile. High surface receptor expression of antibody engaging CD16 and tumor antigen-engaging/activating receptors such as NKG2D, NKp46, NKp30 and NKp44.

- KIR-B haplotype. KIR-B haplotype has been associated with improved clinical outcomes in the haploidentical transplant setting and greater therapeutic potential in the allogeneic setting
- CD16 F158V polymorphism. The higher-affinity CD16 F158V variant binding to mAb Fc-domain is seen to facilitate enhanced ADCC.
- Unmodified NK cells. No genetic enhancement or gene editing is required for, or is a part of, the AlloNK® drug product.

AlloNK® has demonstrated direct, specific, and potent killing of multiple tumor cell lines *in vitro* and *in vivo* when combined with tumor targeting monoclonal antibodies and NK cell engaging bi-specific antibodies. AlloNK® has also demonstrated the ability to secrete cytokines such as tumor necrosis TNFα and IFNγ upon activation.

Nonclinical and clinical data for AlloNK® are described in the AlloNK® IB.

2.3. Rationale and Benefit-Risk Conclusion

2.3.1. Overall Rationale for the Study

Natural killer cell populations are absent in the immunosuppressive tumor microenvironment of HL. Furthermore, NK cells from patients with HL are dysfunctional, due in part to an imbalance in activating and inhibitory receptors (Reiners 2022). Because of these limitations in autologous NK cell function, optimal NK immunotherapy for HL likely requires an allogeneic source.

The combination of acimtamig with AlloNK® may prove to be a promising treatment option with the potential to synergistically increase the effect and direct the anti-tumor cytolytic activity of NK cells towards HL and CD30-positive PTCL cells.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.3.2.3. Lymphodepletion

Non-myeloablative lymphodepleting chemotherapy (i.e., Cy/Flu) will be administered prior to the first dose of AlloNK® per cycle to dampen the endogenous T-cell response and provide an improved environment for the activity of AlloNK® (Miller 2005; Dudley 2005; Bachanova 2014; Suen 2018; Grzywacz 2019). Cy/Flu is a standard regimen for the treatment of chronic lymphocytic leukemia (CLL) which has been administered to many subjects every 4 weeks for 6 cycles (Eichhorst 2016).

In this study, subjects will be treated with lymphodepleting doses of fludarabine (30 mg/m^2/day) and cyclophosphamide (300 mg/m^2/day) each cycle for 3 consecutive days (Days -5, -4, and -3) prior to the first acimtamig/AlloNK® dosing. This dose and schedule of lymphodepleting chemotherapy is based on other cell therapy studies that have demonstrated the safety and effectiveness of this regimen, including in the AFM13-104 study of acimtamig precomplexed to CBNK cells followed by three weekly infusions of 200 mg acimtamig monotherapy (Suen 2018; Shimasaki 2020; Nieto 2022).

2.3.2.4. Interleukin-2 (IL-2)

Historically, interleukin-2 (IL-2) in repeated doses ranging from 1×10^6 IU/m^2 to 1×10^7 IU total dose has been administered as a part of standard treatment regimens in NK cell therapy studies (Miller 2005, Shi 2008, Bachanova 2014, Curti 2011, Szmania 2015, Curti 2016). Cytokines, especially IL-2, at the tumor site are key to the cytotoxicity of NK cells when they are under the

influence of the cytokine-deprived tumor microenvironment (Katakam 2006). Therefore, the presence of IL-2 may help to establish a more favorable microenvironment to maintain *in vivo* survival of NK cells. In fact, several clinical studies have demonstrated that low-dose IL-2 given after NK cell infusion can selectively promote NK cell expansion and persistence (Fehniger 2000, Szmania 2015) but the contribution of IL-2 to efficacy is not completely established. Repeated administrations of IL-2 at the planned dose given in this trial are not associated with severe adverse events (e.g., capillary leak syndrome and renal failure in patients) and are not expected to sensitize regulatory T cells (Tregs) that could otherwise out-compete NK cells for IL-2 (Gasteiger 2013) but have a known risk of gastrointestinal, constitutional, and hematological toxicities (Fleming 2002). Thus, in this clinical study, all subjects who have initially consented under protocol v2.0 will receive 6×10^6 IU of IL-2 subcutaneously at least 1 hour but no more than 4 hours after the completion of each weekly dose of AlloNK® for a maximum of 3 weekly doses per cycle. Based on pharmacokinetic data for AlloNK® in NHL (NCT04673617) removal of IL-2 did not lead to meaningful differences in peak level of AlloNK® in peripheral blood. Therefore, all subjects who have initially consented under protocol v3.0 and later versions will not receive IL-2 after AlloNK® treatment to reduce the burden of potential associated adverse events and dosing complexity.

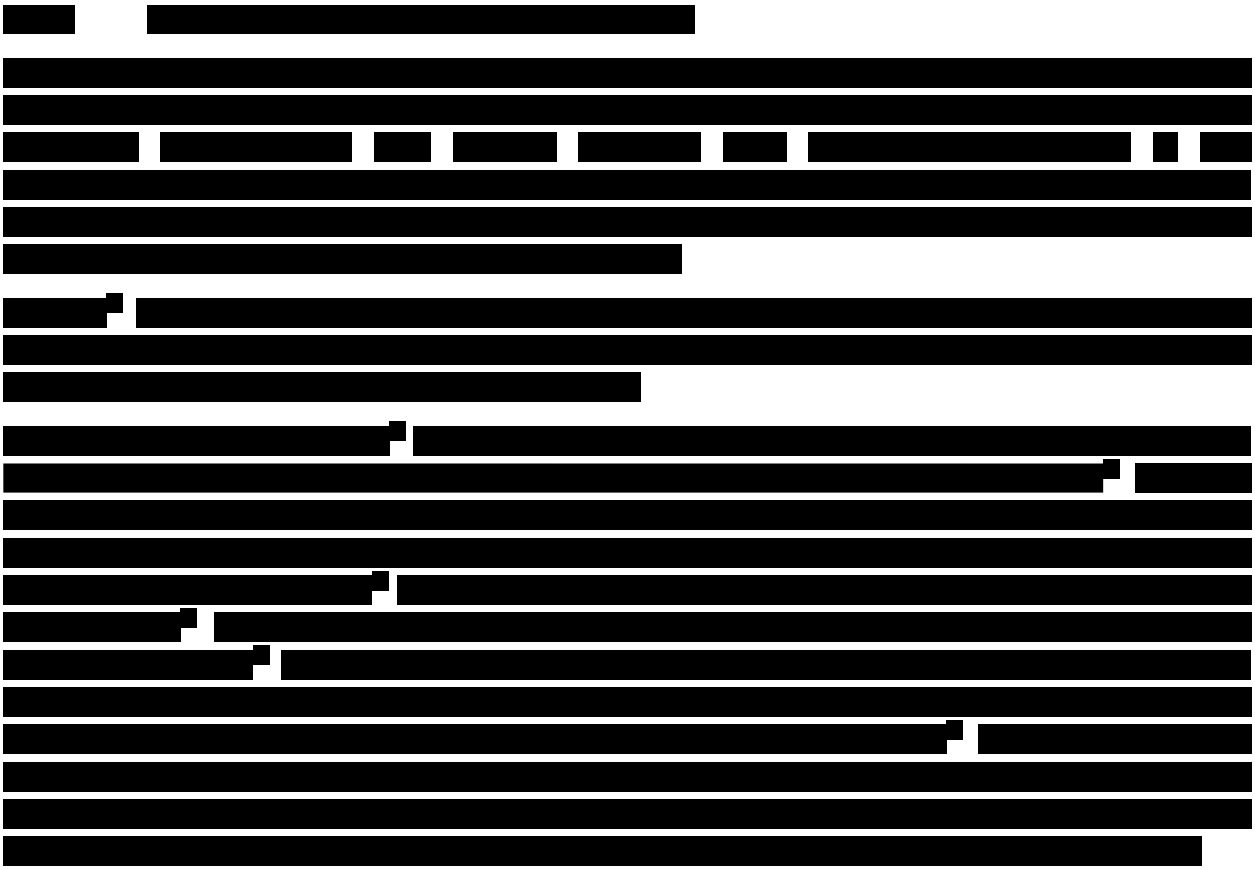


Table 1: Summary of Nonclinical Data: Acimtamig in Combination with AlloNK®

Type of Study	Test system	Noteworthy Findings	Study Number
Assessment of acimtamig binding to AlloNK® cells relative to CD16 expression	NK cells; AlloNK® cells; acimtamig; *in vitro*	The pattern of acimtamig binding to AlloNK® cells was congruent to the frequency of $CD16A^+$ AlloNK® cells, suggesting that acimtamig can saturate CD16A expressed on AlloNK® cells. This robust homogenous binding was observed when acimtamig was pre-complexed with AlloNK® cells prior to cryopreservation and after cryopreservation.	AFM13-AB-101-001
Assessment of acimtamig-mediated cytotoxic activity by AlloNK®	AlloNK® cells; Karpas-299 cells; acimtamig; *in vitro*	The combination of acimtamig with AlloNK® cells demonstrated enhanced cytotoxic activity towards CD30-positive tumor cells. This activity was shown both when acimtamig was pre-complexed with AlloNK® cells prior to cryopreservation and after cryopreservation. Furthermore, the acimtamig-induced cytotoxic activity of AlloNK® was associated with an enhanced functional activation status reflected by increased degranulation/CD107a expression and IFN-γ production by AlloNK® cells in response to Karpas-299 cells	AFM13-AB-101-002
[redacted] on intravenous (i.v.) Karpas-299/Luc cells in IL-15 NOG mice during cotreatment with NK cell product AlloNK® and acimtamig	IL-15 NOG mice; Karpas-299/Luc cells; AlloNK® cells; acimtamig; *in vivo*	The lymphoma cell line Karpas-299/Luc model in IL-15 NOG mice was used to assess the efficacy of AlloNK® in combination with acimtamig. Significant anti-tumor efficacy was observed in groups receiving AlloNK® in combination with acimtamig compared to control groups.	MV17746

Overall, based on preclinical data generated with combining acimtamig with AlloNK®, as well as previous experience of administering acimtamig with a similar CBNK cell product with a positive benefit-risk profile (AFM13-104 study), it is anticipated that acimtamig administered in combination with AlloNK® has the potential to generate a robust ADCC response and clinical activity in subjects with relapsed or refractory HL and CD30-positive PTCL.

2.3.4. Benefit-Risk Analysis

Hodgkin lymphoma and PTCL are serious diseases with significant unmet medical need, particularly in the R/R setting, requiring investigation of novel treatment regimens.

Acimtamig is a tetravalent bispecific (anti-human CD30 × anti-human CD16A) recombinant antibody construct which targets the CD30 antigen expressed on malignant lymphoma cells. In addition, the anti-CD16A domains of acimtamig simultaneously bind to CD16A (FcγRIIIA), independent of CD16A genotype, on NK cells and macrophages, leading to lysis of CD30 antigen-positive cells by NK cells via ADCC and ADCP. Acimtamig has demonstrated a toxicity profile that has been generally safe in both the monotherapy and combination therapy setting, with

manageable toxicities including IRRs. To mitigate the risk of developing IRRs due to acimtamig infusion and/or AlloNK®, premedication with intravenous (i.v.) H1 with or without H2 antagonist and oral acetaminophen will be required prior to the infusion (Section 6.1.2). In addition, all subjects who are treated with acimtamig/AlloNK® must be observed for at least 1 hour post-infusion. Other potential risks for acimtamig are serious and opportunistic infections, for which there will be close monitoring with subjects receiving appropriate supportive care as clinically indicated.

AlloNK® is composed of expanded allogeneic NK cells, cryopreserved in an infusion-ready suspension medium. NK cells have been proven to target and kill cancer cells in a manner not dependent on human leukocyte antigen, and, therefore, may have clinical utility in cancer patients (Farag 2002; Moretta 2008; Ruggeri 2002). Based on clinical studies using allogeneic NK cells in oncology treatment as well as clinical data to date, AlloNK® is expected to be well tolerated with few, if any, drug-related adverse events (AEs) (Kim 2006; Ljunggren 2007; Yang 2016). The safety of AlloNK® monotherapy at a dose level of 1 billion cells and 4 billion cells has been shown to be generally safe and well tolerated (Study AB-101-01). To date, risks associated with AlloNK® have been limited to non-serious and non-severe events of CRS. Other potential risks that will be reduced by intensified premedication regimen and monitored throughout the study are risks associated with allergic and infusion reactions, infection, immune effector cell-associated neurotoxicity syndrome, and tumor lysis syndrome (TLS) (refer to the AlloNK® IB). AlloNK® is a commercially scaled and cryopreserved allogeneic NK cell product, derived from cord blood, in an infusion-ready media, which in combination with acimtamig may provide robust anti-tumor activity in subjects with relapsed or refractory HL and CD30-positive PTCL.

Benefits of lymphodepletion include the dampening of the endogenous T-cell response and the provision of an improved environment for the activity of AlloNK® (Section 2.3.2.3). Lymphodepleting chemotherapy (fludarabine and cyclophosphamide) may result in hematologic toxicities that are typically transient and include low white and red blood cell as well as platelet counts. Low absolute neutrophil counts (ANCs) and absolute lymphocyte counts (ALCs), and the extended depression of CD4-lymphocyte counts are also common. Opportunistic infections may occur (Dudley 2005). Study subjects will receive prophylaxis for infection with pneumocystis pneumonia, herpes virus and fungal infections according to National Comprehensive Cancer Network guidelines (NCCN 2022) or standard institutional practice. To lessen these risks, subjects will be monitored closely and receive supportive care as needed.

Potential benefits of IL-2 administration may include the establishment of a more favorable microenvironment to maintain *in vivo* survival of NK cells (Section 2.3.2.4). IL-2 given subcutaneously at the dose administered in this study may result in Grade 1 to 2 side effects, including injection-site pain as well as gastrointestinal, constitutional, and hematological toxicities (Fleming 2002). To lessen these risks and to reduce the dosing complexity, all subjects who are initially consented under protocol v3.0 and later will not receive IL-2 administrations. All subjects with or without IL-2 treatment will be monitored closely and receive supportive care as needed.

The safety profile of acimtamig has been well characterized in clinical studies with IRRs as a known risk and infections as potential risk. IRRs and infections are potential risks associated with NK cell products and cell therapy products in general (refer to the AlloNK® IB, Artiva IND 024149). IRRs are deemed manageable, based on prior clinical experience with interventions for prophylaxis and treatment. Toxicities overall are expected to be manageable, based on the clinical

experience with each drug administered as monotherapy and in combination with other anti-cancer therapies.

Although no CRS cases were reported in monotherapy studies, five CRS events occurred in three subjects during Study AFM13-203, where acimtamig was combined with AlloNK®, an allogeneic, cord blood-derived NK-cell product. Most CRS events were mild to moderate in severity, and only one severe (ASTCT Grade 3) CRS event was reported. All events resolved quickly with standard care, and none resulted in permanent study drug discontinuation. The subject who experienced the Grade 3 event was later re-exposed to acimtamig without any re-occurrence of severe CRS or IRR reactions. The risk of CRS is under observation due to limited available data. Nevertheless, mitigation strategies (see Section 6.3.4) were optimized in this protocol version for the first and subsequent doses of actimtamig and AlloNK® combination to further reduce the risk of immune mediated events (i.e. IRRs or CRS).

In summary, the known clinical safety profile of acimtamig and AlloNK® monotherapy or other NK cell products can be considered tolerable and manageable. The combination of both drugs does not raise the expectation of potential overlapping toxicities, except for IRR/CRS and infections which are considered to be manageable based on available clinical data. This study utilizes a safety run-in for the first 6 subjects with R/R classical HL in each of the 4 cohorts testing the planned doses of acimtamig and AlloNK®, with staggering of 12 days between Day -5 (start of lymphodepletion) of one subject to Day -5 (start of lymphodepletion) of the subsequent subject (includes a 7-day observation period following administration of Day 1 treatment as part of the 12-day period).

Overall, the combination of acimtamig with AlloNK® may prove to be a promising treatment option with the potential to synergistically increase the effect of and direct the anti-tumor cytolytic activity of NK cells towards HL and CD30-positive PTCL. The benefit-risk analysis is considered acceptable for the investigation of acimtamig in combination with AlloNK® in HL and CD30-positive PTCL. On 11-Apr-2024, an independent safety committee reviewed the safety and if available efficacy data from eight subjects (including the first four subjects of each of the first two cohorts) of Study AFM13-203. The committee endorsed the benefit-risk assessment and agreed that enrollment in Cohorts 1 and 2 should continue until fully enrolled. Subsequently, enrollment in Cohorts 3 and 4 will commence.

3. OBJECTIVES AND ENDPOINTS

Table 2: Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
• Assess the antitumor activity of acimtamig in combination with AlloNK® in subjects with R/R classical HL and CD30-positive PTCLs by ORR.	• ORR (CR + PR) by Independent Radiology Committee (IRC) based on positron emission tomography-computed tomography (PET-CT) as assessed by the Lugano classification
Secondary Objectives	**Secondary Endpoints**
• To assess efficacy of acimtamig in combination with AlloNK® • To assess the incidence of post-treatment transplant • To assess the safety and tolerability of acimtamig in combination with AlloNK® • To assess the immunogenicity of acimtamig in combination with AlloNK®	• DOR by Investigator and IRC • Complete response rate (CRR) by Investigator and IRC • ORR by Investigator based on PET-CT as assessed by the Lugano classification • Incidence of subjects receiving subsequent transplant • Frequency of subjects with study-drug related TEAEs and SAEs (evaluated using NCI CTCAE v5.0 and ASTCT grading for TEAES related to CRS and ICANS) • Frequency of subjects developing ADAs against acimtamig or AlloNK® • PFS by IRC • OS
Exploratory Objectives	**Exploratory Assessments**
[redacted]	[redacted]

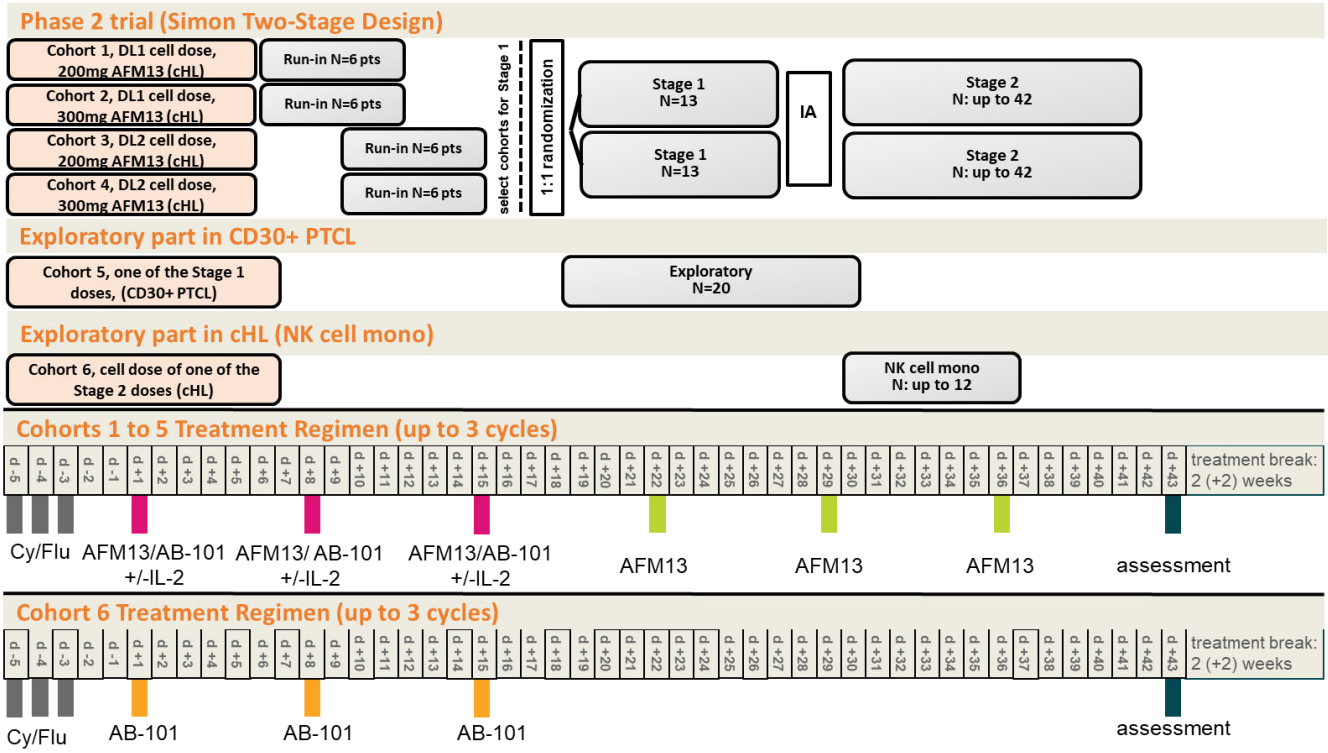
[redacted]

4. OVERALL STUDY DESIGN

This is a phase 2, open-label, multi-center, multi-cohort study with a safety run-in followed by expansion cohorts. The study is evaluating the safety and efficacy of acimtamig in combination with AlloNK® in subjects with R/R classical HL and CD30-positive PTCL.

A schematic of the study design is provided in Figure 2. Refer to the Schedule of Assessments [redacted]) for details of procedures and assessments to be performed.

Figure 2: Overall Study Design



Abbreviations: CD = cluster differentiation; cHL = classical Hodgkin lymphoma; Cy/Flu = cyclophosphamide and fludarabine; IA = interim analysis; IL = interleukin; NK = natural killer; PTCL = peripheral T-cell lymphoma; DL1 = 2×10^9 cells at Day 1, Day 8 and Day 15; DL2 = 4×10^9 cells at Day 1, 2×10^9 cells at Day 8 and Day 15.

The main aim of this study is to assess the antitumor activity of acimtamig in combination with AlloNK® in four cohorts of subjects:

- **Cohort 1**: AlloNK® DL1 (2×10^9 cells on Day 1, Day 8, Day 15) + 200 mg acimtamig in classical HL (N: 6 to 61)
- **Cohort 2**: AlloNK® DL1 + 300 mg acimtamig in classical HL (N: 6 to 61)
- **Cohort 3**: AlloNK® DL2 (4×10^9 cells on Day 1; 2×10^9 cells on Day 8, Day 15) + 200 mg acimtamig in classical HL (N: 6 to 61)
- **Cohort 4**: AlloNK® DL2 + 300 mg acimtamig in classical HL (N: 6 to 61)

Two additional exploratory cohorts will be evaluated:

- **Cohort 5**: CD30-positive PTCL (N: 20) (AlloNK® DL1 or DL2 + acimtamig at 200 mg or 300 mg)
- **Cohort 6**: AlloNK® DL1 or DL2 in classical HL (N: up to 12)

The total number of planned subjects is up to 166. All subjects will receive acimtamig in combination with AlloNK® (Cohorts 1-5) or AlloNK® alone (Cohort 6) up to 3 cycles as described in Section 6.

The main part of the study will include subjects with classical HL and will follow a Simon two-stage design, with two stages designed for each classical HL cohort selected following the safety run-in.

The safety run-in will be utilized for the first 6 classical HL subjects in Cohort 1 and Cohort 2 (parallel enrollment), with staggering of at least 12 days between Day -5 (start of lymphodepletion) of one subject to Day -5 (start of lymphodepletion) of the subsequent subject (included as part of the 12-day period is a 7-day observation period following administration of Day 1 treatment). For the first 3 subjects enrolled in each cohort, the safety run-in approach will be utilized to monitor treatment-related toxicities during the safety run-in observation period, defined as the time from the first dose of combination study treatment (acimtamig/AlloNK®) to Day 21 of the treatment cycle (C1D21). If a Grade 3 or Grade 4 acimtamig or AlloNK®-related treatment-emergent adverse event (TEAE) (meeting criteria as stipulated in Section 10.6) occurs during the safety run-in observation period for the first 3 subjects, then another 3 subjects will be enrolled using the same staggered approach. If no more than one Grade 3 or 4 acimtamig or AlloNK®-related TEAE is observed in the first 6 subjects, then enrollment of the first 3 classical HL subjects in Cohort 3 and Cohort 4 (parallel enrollment) will begin, using the same staggering approach outlined for Cohort 1 and Cohort 2. If no Grade 3 or 4 acimtamig or AlloNK®-related TEAEs are not observed in the first 3 subjects, then enrollment may continue without staggering in Cohort 1 and Cohort 2 and enrollment of the first 3 classical HL subjects in Cohort 3 and Cohort 4 (parallel enrollment) will begin, using the same staggering approach as-outlined for Cohort 1 and Cohort 2. Backfilling into Cohorts 1 and 2 will be allowed during the safety clearance period for Cohorts 3 and 4.

[redacted]

An additional exploratory cohort (Cohort 5) will enroll subjects with CD30-positive PTCL. Cohort 5 will be hypothesis generating only, consisting of one part with a total of N=20 CD30-positive PTCL subjects. This cohort will start enrollment after all classical HL cohorts have cleared the safety run-in (i.e., each subject enrolled in Cohort 1 to Cohort 4 have completed the safety run-in observation period). The planned dose level will be chosen from the two regimens selected for Stage 1 evaluation after analysis of the benefit-risk profile for each regimen.

Another additional exploratory cohort (Cohort 6) will consist of up to 12 subjects with R/R HL for exploratory investigation of AlloNK® monotherapy in cHL. The planned dose of AlloNK® will be chosen from the regimen(s) selected for Stage 2. As such, this cohort will start enrollment at the

time of Stage 2 of the trial. [redacted]

An independent Safety Review Committee (SRC) will be established prior to the enrollment of the first subject. The independent SRC will be responsible for reviewing at regular intervals the safety data of all subjects throughout the conduct of the study. Detailed recruitment status and interim safety reports will be provided to the SRC on a regular basis. Further details regarding the constitution of the SRC and its specific roles and responsibilities and timing of reviews will be provided in the SRC charter.

4.1. Study Periods

This multi-center study will include a Screening Period, a Treatment Period, End of Treatment (EOT) visit, a Safety Follow-up visit, and a Long-Term Follow-Up Period.

4.1.1. Screening Period

The Screening Period lasts up to 28 days prior to Cycle 1 Day -5 (from Day -34 up to Day -5). The Screening Period begins when the Informed Consent Form (ICF) is signed and ends on the day before the first dose of lymphodepletion on Cycle 1 Day -5. Before entering the study, all study procedures and possible risks will be explained to each subject who is asked to participate in the study. After provision of written informed consent for the study, screening assessments will include a careful review of the subject's medical history, assessment of Eastern Cooperative Oncology Group (ECOG) performance status (PS), physical examination, electrocardiogram (ECG), echocardiography, laboratory, and disease assessment, as specified in the Schedule of Assessments [redacted]). For subjects with the diagnosis of PTCL a fresh tumor biopsy should be obtained during the Screening Period for retrospective confirmation of CD30 status, unless archival tissue/slides will be substituted (the specimen must be 90 days or younger from Cycle 1 Day -5), refer to Section 8.2 for further details. Subject's laboratory assessments to confirm eligibility criteria (Section 5.1) must be confirmed before D-5 of the treatment cycle (start of lymphodepletion). The assessments for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) do not need to be repeated for re-screened subjects if performed within 3 months before first dose of lymphodepletion (i.e., on Cycle 1 Day -5). Please review the inclusion criteria (Section 5.1) and exclusion criteria (Section 5.2) to see allowed time periods of screening assessments.

4.1.2. Treatment Period

Upon confirmation of study eligibility, the subjects will be defined as enrolled, and they will enter the Treatment Period which starts with the day of first dose of lymphodepletion on Cycle 1 Day-5 and will receive study drugs according to their assigned dose level. Day 1 of every Cycle is the anchor for all timepoints in the specific cycle.

The study drugs will be administered in 48-day cycles up to 3 cycles total as detailed in Section 6.1.

Please refer to [redacted] detailing all assessments and procedures to be completed during the Treatment Period throughout the study.

4.1.3. End of Treatment Visit

The EOT visit will be performed up to 14 to 21 days from the last dose of study drug (acimtamig and/or AlloNK®) or before the start of any new anti-cancer treatment; whichever is sooner. For subjects who discontinue treatment for reasons other than disease progression, the EOT visit must be performed as the last visit. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the electronic case report form (eCRF). The subject should be encouraged to return for the follow-up visit.

[redacted]

4.1.5. Long-Term Follow-Up Period

After the Safety Follow-up visit, subjects will enter the Long-term Follow-Up Period where they will continue to be followed for progression (if discontinued prior to documented disease progression, subjects should receive a PET/CT every 3 months [± 1 month] for the first 12 months and then every 6 months [± 1 month] until disease progression, start of a new treatment (exception: auto/allo stem cell transplantation [SCT]: If a subject discontinues prior to documented disease progression due to receiving a SCT as consolidation of the documented response in this trial, the subject will remain in long-term follow-up, SCT includes the conditioning regimen and subsequent immunosuppressive therapy) or end of follow-up period, (whichever is sooner) or survival (if discontinued with documented disease progression) every three months up to 18 months from the last dose of study drug (acimtamig and/or AlloNK®).

4.2. Study Duration

Study duration for each participant will be as follows:

- Screening Period within 28 days (Day -34 up to Day -5) prior to first dose of lymphodepletion on Cycle 1 Day -5
- 24-week Treatment Period of up to 3 cycles (average estimate; includes 2-week rest intervals between treatment cycles)
- EOT up to 14-21 days after last dose of study treatment (acimatmig and/or AlloNK®)
- Safety Follow-Up 30 days (± 5 days) from the last dose of any study treatment (acimatmig and/or AlloNK®)
- Long-Term Follow-Up Period: Every 3 months (Progression/Survival Status) up to 18 months from the last dose of study drug (acimtamig and/or AlloNK®). Collection of this information may cease prior to 18 months from the last dose of

study drug (acimtamig and/or AlloNK®) if the subject withdraws their consent or the Sponsor decides to stop collecting this information.

4.3. Study Initiation and Completion

The start of this clinical study is defined as the first act of recruitment for a potential subject.

The end of the study is defined as when the last subject ending treatment has completed the last visit, withdrawn consent, has been lost to follow-up, or has died.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects will be considered eligible to be enrolled in the study if ALL the inclusion criteria and NONE of the exclusion criteria are met as defined below. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

A subject is eligible to be included in the study only if ALL the following criteria apply:

1. Subjects with a diagnosis of FDG-avid relapsed or refractory classical HL OR select subtypes of FDG-avid relapsed or refractory PTCL.

   For subjects with R/R PTCL a pre-enrollment tumor biopsy positive for CD30 locally assessed by Ber-H2 targeted immunohistochemistry at ≥1% is mandatory (Note: Archival tissue may be substituted for a fresh tumor biopsy, please refer to Section 8.1 and the Schedule of Assessments ([redacted]) for additional details).

   PTCL subtypes

   - PTCL-NOS
   - Angioimmunoblastic T-cell lymphoma
   - ALCL, anaplastic lymphoma kinase (ALK)-positive
   - ALCL, ALK-negative

2. Prior treatment for the disease under study consistent with the following:

   - Subjects with R/R classical HL must have received at least two lines of therapy including one prior line of combination chemotherapy. Prior therapy must also have included brentuximab vedotin and a PD1 check point inhibitor.
   - Subjects with R/R PTCL must have received at least one prior line of combination chemotherapy. Subjects with ALCL subtype of PTCL must have received or been intolerant to brentuximab vedotin.
   - Subjects with R/R classical HL AND R/R PTCL: Prior ASCT is permitted if completed at least 3 months prior to the first dose of study treatment (acimtamig and/or AlloNK®). Prior allogeneic stem cell transplantation will be permitted if completed at least 1 year from study enrollment and there are no signs or symptoms of GVHD. Prior CAR-T therapy is permitted if last CAR-T dose completed at least 6 months prior to the first dose of study drug (acimtamig and/or AlloNK®).

3. Male or female aged ≥18 years (or as required by local regulation) on the day of signing the ICF.
4. ECOG Performance Status (PS) 0 or 1.

5. Absolute neutrophil count ≥1000/mm^3, hemoglobin ≥7 g/dL, and platelet count ≥50,000/mm^3.
    - Transfusions of packed red blood cells and platelets are allowed up to 2 weeks prior to Day -5 of the first cycle and as needed during the Treatment Period. Growth factors are allowed during Screening up to 2 weeks prior to the first dose of lymphodepleting chemotherapy and as needed during the Treatment Period. All lab parameters should be checked within 2 days of the first dose of lymphodepleting chemotherapy to reassess eligibility.
6. Adequate organ function defined by the following laboratory parameters during screening:
    - Direct (conjugated) bilirubin ≤2 × the upper limit of normal (ULN), or total bilirubin ≤3 × ULN if considered due to Gilbert's disease AST and alanine aminotransferase (ALT) ≤3.0 × ULN, unless considered due to malignant disease involvement, in which case AST and ALT can be ≤ 5.0 × ULN.
    - Creatinine clearance (CrCl) ≥50 mL/min. Creatinine clearance will be calculated using the Cockcroft and Gault equation.
    - International normalized ratio (INR) <1.5 × ULN and activated partial thromboplastin time (aPTT) <1.5 × ULN (for subjects not receiving therapeutic anticoagulation) (Note: subjects receiving therapeutic anticoagulation may enroll with INR ≥1.5 × ULN).
7. Adequate pulmonary function with forced expiratory volume (FEV1), forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) (corrected for Hgb and volume) ≥50%.
8. Adequate cardiac function with left ventricular ejection fraction ≥50% and no uncontrolled arrhythmias or symptomatic cardiac disease.
9. Capable of giving signed informed consent that includes compliance with the requirements and restrictions listed in the ICF and in the study protocol.
10. Female subjects must have a negative urine or serum pregnancy test within 7 days prior to first dose of lymphodepletion if of childbearing potential, or be of non-childbearing potential. If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as:
    - Postmenopausal, defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Surgically sterile. Surgical sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
11. Females of childbearing potential must agree to sexual abstinence (defined below) or be willing to use a highly effective method of contraception for the course of the study from 14 days prior to the first dose of lymphodepletion through 120 days after the last dose of

study drug (acimtamig and/or AlloNK®). Acceptable highly effective birth control methods include:

- Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
- Intrauterine device;
- Intrauterine hormone-releasing system;
- Bilateral tubal occlusion;
- Vasectomized partner (provided that partner is the sole sexual partner of the female of reproductive potential and that the vasectomized partner has received medical assessment of the surgical success); and
- Sexual abstinence.

  In the context of this study, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 14 days prior to the first dose of lymphodepletion up to 120 days after the last dose of study drug (acimatamig and/or AlloNK®). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

12. Males who have female partners of childbearing potential must agree to use a highly effective method of contraception as described in inclusion criterion 11, starting with the first dose of lymphodepletion through 120 days after the last dose of study drug (acimatamig and/or AlloNK®).

5.2. Exclusion Criteria

A subject is not eligible to enroll into the study if they have ANY of the following:

1. Treatment within prior 3 weeks of Day 1 of treatment schedule (Cycle 1 Day 1) with any anti-cancer agent, investigational or approved.
2. Continued toxicity from prior treatment that has not resolved to Grade ≤ 1, with allowable exceptions (e.g., alopecia).
3. Active central nervous system (CNS) involvement (untreated or uncontrolled parenchymal brain metastasis or positive cytology of cerebrospinal fluid).
4. Previous treatment with acimtamig or CBNK cells.
5. Known hypersensitivity/allergic reaction ≥Grade 3 to monoclonal antibodies or any components used in the acimtamig product preparation, any history of anaphylaxis or uncontrolled asthma.
6. History of a solid organ allograft, or an inflammatory or autoimmune disease likely to be exacerbated by IL-2 or other study specific treatment (including subjects requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease that may require systemic steroids or immunosuppressive agents. Exceptions include any subject on 10 mg or less of prednisone or equivalent, subjects with vitiligo, hypothyroidism stable on hormone replacement, Type I diabetes, Graves' disease, Hashimoto's disease, alopecia areata, eczema, or psoriasis).

7. Treatment with any therapeutic mAb or immunosuppressive medications (such as high-dose steroids defined as ≥10 mg prednisone or equivalent per day) within 4 weeks or 5 half-lives (whichever is shorter) of Day 1 of treatment schedule.

   Exceptions for the use of corticosteroids:

   - Topical (≤20% of the skin surface area), ocular, intra-articular, intranasal, or inhalation corticosteroids with minimal systemic absorption.
   - Short course (≤ 7 days) of corticosteroids prescribed prophylactically (e.g., for contrast dye allergy or antiemetic therapy for specific chemotherapy) or for treatment of a non-autoimmune causes (e.g., delayed-type hypersensitivity reaction caused by contact allergen) as long as <10 mg prednisone equivalent.
   - Physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency.

8. History of any other systemic malignancy, unless previously treated with curative intent and the subject has been disease free for 2 years or longer. Subjects who meet the above criteria and are on maintenance therapy for prior malignancy may be eligible after discussion and approval from the medical monitor.
9. Live-virus vaccines given within 28 days prior to the initiation of study treatment.
10. Active, uncontrolled infection requiring systemic therapy. If the infection is controlled or has resolved, maintenance and/or prophylactic systemic antimicrobials are permitted.
11. Known active hepatitis B or hepatitis C as defined in the table below. Antiviral prophylaxis for chronic hepatitis B virus infection may be used at the discretion of the Investigator.

    Note: Subjects meeting following criteria are allowed to be enrolled in the study:

	Eligible
HBV	HB sAg (-)
	HB sAg (+) and HBV DNA <500 IU/mL (or 2500 copies/mL)
HCV	HCV Ab (-)
	HCV Ab (+) and HCV RNA (-)

    Abbreviations: HBV = hepatitis B virus; HBs Ag = HBV surface antigen; HCV = hepatitis C virus; HCV Ab = HCV antibody

12. Active HIV infection as evidenced by a positive HIV polymerase chain reaction (PCR) test result.
13. Active acute or chronic GVHD or GVHD requiring immunosuppressive treatment, clinically significant central nervous system (CNS) dysfunction (seizure disorder, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome (PRES), autoimmune disease with CNS involvement).
14. Any uncontrolled medical condition, including but not limited to: unstable angina pectoris, symptomatic congestive heart failure (New York Heart Association [NYHA] II, III, IV;, myocardial infarction ≤6 months prior to first dose of study drug (acimtamig and/or AlloNK®), uncontrolled cardiac arrhythmia e.g., atrial fibrillation/flutter, cerebrovascular accidents ≤6 months before first dose of study drug (acimtamig and/or AlloNK®).
15. Major surgical procedure (i.e., any open surgical procedure that involves the resection or manipulation of major organ) or significant traumatic injury within 4 weeks before first

dose of study drug (acimtamig and/or AlloNK®) or anticipation of need of a major surgical procedure during the course of study.

Note: Procedures that are considered to be minimally invasive (e.g., peripherally inserted central catheters lines and/or port placements, interventional biopsies) will be exceptions.

16. Pregnant or breastfeeding women. Breastfeeding must be discontinued before onset of and during treatment and should be discontinued for at least 3 months after end of treatment.
17. Substance abuse, medical, psychological, or social conditions that may interfere with the subject's cooperation with the requirements of the study or evaluation of the study results.
18. Any medical, psychological, or social condition that would interfere with the subject's participation in the study.

5.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently confirmed as eligible to participate in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Subjects who do not meet the criteria for participation in this study for reversible reasons may be rescreened. A new subject number will be assigned upon screening (**Note**: Screening assessments that have not been performed within 28 days of Cycle 1 Day -5 for subjects who are rescreened must be repeated. The assessments for hepatitis B, hepatitis C, and HIV do not need to be repeated for re-screened subjects if performed within 3 months).

5.4. Withdrawal of Subjects in the Study

5.4.1. Withdrawal of Consent

A subject may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the subject is otherwise entitled. When a subject wishes to withdraw consent, it is important to distinguish between withdrawing his/her consent for a particular study procedure or visit versus withdrawing his/her consent from the study entirely (i.e., premature discontinuation).

When a subject withdraws consent from the study (or study procedure), the reason(s) for withdrawal will be recorded by the Investigator or designee on the relevant page of the eCRF.

5.4.2. Premature Discontinuation

All subjects have the right to refuse further participation in the study at any time and for any reason. A subject's participation must, therefore, be terminated immediately upon his/her request.

Subjects can withdraw from treatment or participation in this study at any time, for any reason, specified or unspecified, and without prejudice. The reasons for study drug (acimtamig and/or AlloNK®) discontinuation or study withdrawal may include the following reasons:

- Radiographic or symptomatic disease progression or disease relapse

- Unacceptable toxicity or any study treatment-related event that is deemed life-threatening, regardless of grade
- Investigator decision
- Significant non-compliance with the study procedures by the subject, or the Investigator
- Sponsor terminates the study
- Pregnancy

Subjects who are withdrawn from study treatment should complete the EOT visit, Safety Follow-up visit and will enter into long-term follow-up for progression and survival status ([redacted].

5.5. Lost to Follow-up

Study subjects will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. The following actions must be taken if a study subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a registered letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record; and
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Situations of non-compliance will be reviewed on a case-by-case basis with the Sponsor and the site will be provided guidance on subject withdrawal from treatment and/or the study, where appropriate.

5.6. Replacement of Subjects

During the safety run-in, subjects will be replaced if they have not received at least 66% of the AlloNK® and acimtamig combination during cycle 1.

For the randomized stage 1 and stage 2 part of the study, replacement of a subject may be permitted only if a subject discontinues or withdraws prior to receiving both study drugs (i.e., acimtamig and AlloNK®). The same rule applies for the exploratory PTCL cohort (Cohort 5).

For Cohort 6, subjects will be replaced if they have not received at least 66% of AlloNK® during cycle 1.

6. STUDY TREATMENTS

6.1. Overview of Study Treatments and Administration

The Investigator shall take responsibility for the study treatments and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study treatments in accordance with the clinical study protocol and any applicable laws and regulations.

Study treatments described in the sections below will be administered in 48-day cycles, up to 3 cycles in total, with a 2-week rest period (+ 2 week) between each cycle as indicated in the Schedule of Assessments [redacted] refer also to Figure 2). On treatment days, after administration of all study drugs in the treatment regimen, subjects must be observed for at least 1 hour.

6.1.1. Lymphodepletion

Prior to the administration of the first acimtamig and AlloNK® infusions in each cycle, a standard lymphodepleting regimen will be administered.

Within 2 days prior to the start of each lymphodepletion regimen of each cycle, the absolute neutrophil count, hemoglobin, platelet count, bilirubin, AST, ALT, and creatinine clearance should be assessed for suitability to proceed:

- Absolute neutrophil count ≥1000/mm^3, hemoglobin ≥7 g/dL, and platelet count ≥50,000/mm^3.
- Direct (conjugated) bilirubin ≤2 × ULN, or total bilirubin ≤3 × ULN if considered due to Gilbert's disease, AST and ALT ≤3.0 × ULN, unless considered due to malignant disease involvement, in which case AST and ALT can be ≤ 5.0 × ULN.
- CrCl ≥50 mL/min. Creatinine clearance will be calculated using the Cockcroft and Gault equation.

NOTE: If a subject does not meet the minimum laboratory values for absolute neutrophil count, platelet count, bilirubin, AST, ALT, and creatinine clearance stated above, please refer to Section 6.3 for allowed dose delays and allowed supportive concomitant medications in Section 6.4.1.

Intravenous cyclophosphamide (300 mg/m^2/day) and fludarabine (30 mg/m^2/day) will be administered daily for 3 consecutive days, starting 5 days before the first dose of acimtamig and AlloNK® (i.e., from Day -5 through Day -3). Lymphodepleting therapy may only be started if the laboratory values for hematology, renal and liver function meet the requirements of the inclusion criteria. Pre-medication should be administered per institutional guidelines but should not include steroids.

[redacted]

Subjects may also be administered prophylactic antiemetic medications as indicated.

6.1.3. Acimtamig

Acimtamig will be administered intravenously at a fixed dose of 200 mg or 300 mg on Day 1, Day 8, and Day 15 of each cycle prior to administration of AlloNK®. Additionally, acimtamig will be administered as the sole therapy at a dose of 200 mg or 300 mg intravenously on Day 22, Day 29 and Day 36 of each cycle.

On the days that acimtamig is given in combination with AlloNK®, it will be given first, followed by a one-hour observation period. All doses of acimtamig will be infused at an initial infusion rate of 50 mg/h (level 1).[redacted]

6.1.4. AlloNK®

AlloNK® will be administered (as soon as practical after thawing but must be within 90 minutes after thawing) upon completion of administration and observation period for acimtamig. Subjects at DL1 will be administered a fixed dose of 2×10^9 cells IV on Day 1, Day 8 and Day 15 of each cycle. Subjects at DL2 will be administered a fixed dose of 4×10^9 cells IV on Day 1, then 2 x 10^9 cells/dose on Days 8 and 15. Those subjects who initially consented under protocol v3.0 and later versions and thus will not receive IL-2 after the AlloNK® treatment, the observation period will end 1-hour after the AlloNK® infusion on Day 1, Day 8, or Day 15 of every Cycle if AlloNK® is given.

Refer to the AB-101 Storage, Preparation, and Administration Manual for additional information on storage, preparation, and administration.

6.1.5. IL-2

IL-2, dosed at 6×10^6 IU, will be administered to all subjects who initially consented under protocol v2.0 subcutaneously, at least 1 hour and no more than 4 hours following the conclusion of each AlloNK® dose. IL-2 administration is followed by a 1-hour observation period. Those subjects who initially consented under protocol v3.0 and later versions will not receive IL-2 after the AlloNK® treatment. For subjects under treatment with IL-2 experiencing IL-2 related adverse events, subsequent IL-2 administrations can be stopped.

Refer to the PROLEUKIN® (aldesleukin) USPI for additional information on storage, preparation, and administration.

6.2. Assignment of a Study Number and Dose Level

6.2.1. Assignment of a Subject Number

At the Screening Visit, each subject will have a unique subject identification (ID) number assigned for subject identification.

For subjects that are rescreened (Section 5.3), a new subject number will be assigned upon rescreening.

6.2.2. Assignment to a Cohort and Dose Level

Once eligibility has been confirmed by the Investigator, sites must submit a subject eligibility packet to the Medical Monitor for review. After Medical Monitor approval to proceed with enrollment, subjects will be enrolled first into Cohorts 1 and 2 in parallel (alternating between Cohort 1 and Cohort 2). Upon safety clearance of Cohorts 1 and 2, subjects will be enrolled in parallel into Cohorts 3 and 4 (alternating between Cohort 3 and Cohort 4). Backfilling into cohorts 1 and 2 will be allowed during the safety clearance period for Cohorts 3 and 4. After the safety run-in is completed for Cohorts 1 to 4, classical HL subjects will be randomized thereafter into the two selected cohorts for further evaluation in the Simon two-stage design part of the study (refer to Section 4 and Figure 2). After the safety run-in is completed for Cohorts 1 to 4, CD30-positive PTCL subjects will be enrolled sequentially into the exploratory Cohort 5. Cohort 6 will be started during Stage 2 of the trial.

6.3. Dose Modification, Delays, or Interruptions

Permitted windows for study specific treatment administration are provided in the Schedule of Assessments ([redacted]

Study drug dosing delays may be permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation and/or holidays) after obtaining approval from the Sponsor.

Dose management may be required for subjects to recover from treatment-emergent toxicities and return to baseline or Grade 2 and are permitted as specified in Section 6.3.1 for acimtamig and Section 6.3.2 for AlloNK®. Management and grading of IRRs and CRS events and provided in Section 6.3.4.

A maximum of 3 days is allowed for a treatment/dose delay of acimtamig, AlloNK® or the combination during an individual cycle. If the dose delay is 3 days or less, then the individual cycle should continue as scheduled with the appropriate intervals between subsequent doses should clinical status allow. If the dose delay is 4 or more days, then the dose should be omitted and the subsequent doses/treatment should be administered per the individual cycle plan if clinical status allows. The re-initiation of study drugs after a treatment delay of > 7 days will require prior authorization from the Medical Monitor.

A two-week rest period is planned between each treatment cycle. In general, dose delays of up to an additional 2 weeks (≤14 days) are allowed between completion of one cycle and start of the next cycle, for subjects to recover from any AE and return to baseline or ≤Grade 2. Re-initiation of study treatment should be discussed with and approved by the Medical Monitor.

6.3.1. [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

6.3.3. IL-2 Dose Management Guidance for Treatment -Emergent Toxicities

Administration of IL-2 should be withheld if AlloNK® is not administered.

Administration of IL-2 should also be withheld for AEs considered to be related to IL- 2 per Investigator decision.

6.3.4. Grading and Management of IRRs and CRS Treatment-Emergent Adverse Events

IRRs are defined according to the NCI CTCAE v5.0 definition (Table 3). CRS and ICANS events are defined according to the ASTCT CT grading system (Table 4). PLEASE NOTE: Neurotoxicity/ICANS should be evaluated and managed according to institutional Standard of Care.

In the case of an IRR which occurs during study drug infusion, rate and/or dose interruptions or delays along with any medical interventions as indicated may be utilized according to the guidance described in [redacted] If an IRR occurred due to acimtamig, AlloNK® can be administered after all IRR related symptoms have improved to ≤ Grade 1, even if acimtamig has been omitted the same day.

In the case of CRS events, study drug infusion, rate and/or dose interruptions or delays along with any medical interventions as indicated may be utilized according to the guidance described in [redacted]

Table 3: Grading System for IRR and related Events

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances. Clinically it presents with tachypnea, headache, tachycardia, hypotension, rash, chills, fever and/or hypoxia					
Navigational Note: - If related to infusion, use Injury, poisoning, and procedural complication: Infusion related reaction. Do not report both					
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy related edema/angioedema; hypotension	Life-threatening consequences; urgent interventions indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness, and may lead to death.					

Table 4: Grading System for CRS and Neurotoxicity (ASTCT Grading and ASTCT ICANS Grading)

ASTCT Grading Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cytokine release syndrome: Fever with,	Temperature ≥38 C,	Temperature ≥ 38 °C	Temperature ≥ 38 C	Temperature ≥ 38 C	Death
Hypotension and/or	No Hypotension	Hypotension responding to fluids;	Hypotension managed with one vasopressor with or without vasopressin;	Requiring multiple vasopressors (excluding vasopressin)	
Hypoxia	No hypoxia	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.					
Navigational Note: Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading. Fever is defined as temperature 38 °C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5 °C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS. Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute					

ASTCT ICANS Grading **NOTE: ICANS/Neurotoxicity should be evaluated and managed according to institutional Standard of Care**					
Neurotoxicity Domain	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
ICE score	7-9	3-6	0-2	0 (Subject is unarousable and unable to perform ICE)	Death
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma	
Seizure	Not applicable	Not applicable	Any clinical seizure focal or generalized that resolve rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life threatening prolonged seizure (>5min); or repetitive clinical or electrical seizures without return to baseline in between	
Motor findings	Not applicable	Not applicable	Not applicable	Deep focal motor weakness such as hemiparesis or paraparesis	
Elevated ICP/ cerebral edema	Not applicable	Not applicable	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing´s triad	
Definition: Psychiatric disorders: Hallucinations or Confusions; Nervous system disorders: Seizure, Dysphasia, Headache					
Definition of ICE score as Encephalopathy assessment Tool: Orientation: 4 points; Naming: 3 points; Following commands: 1 point; Writing a standard sentence: 1 point; Attention/Counting backwards: 1 point Scoring: 10, no impairment; 7-9, Grade 1 ICANS; 3-6, Grade 2 ICANs;0-2, Grade 3 ICANS; 0, Grade 4 ICANS Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication). Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.					

Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy ; ICP = intracranial pressure.

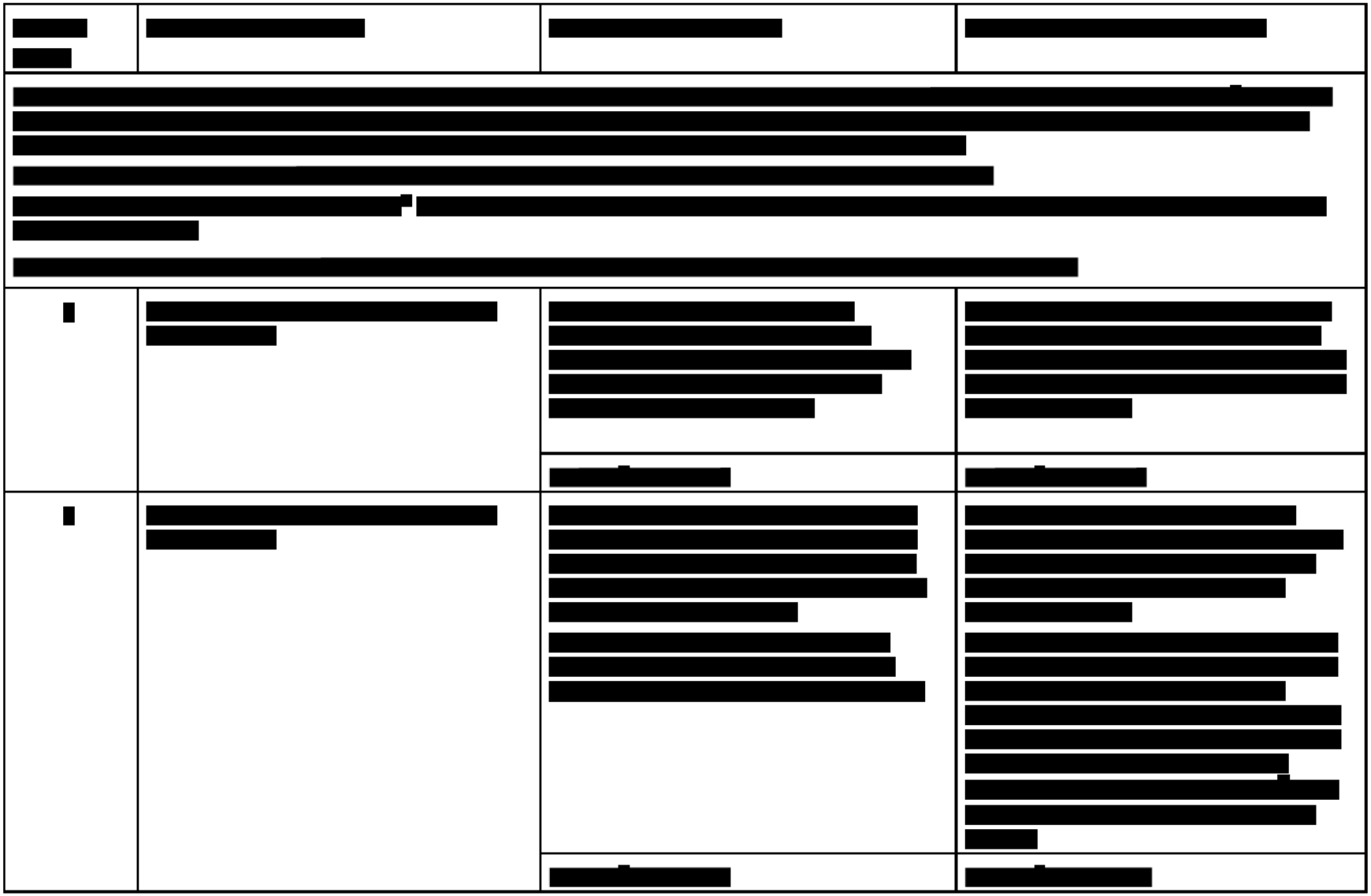
Table 5: Clinical Grading of Acute GVHD (MAGIC Criteria)

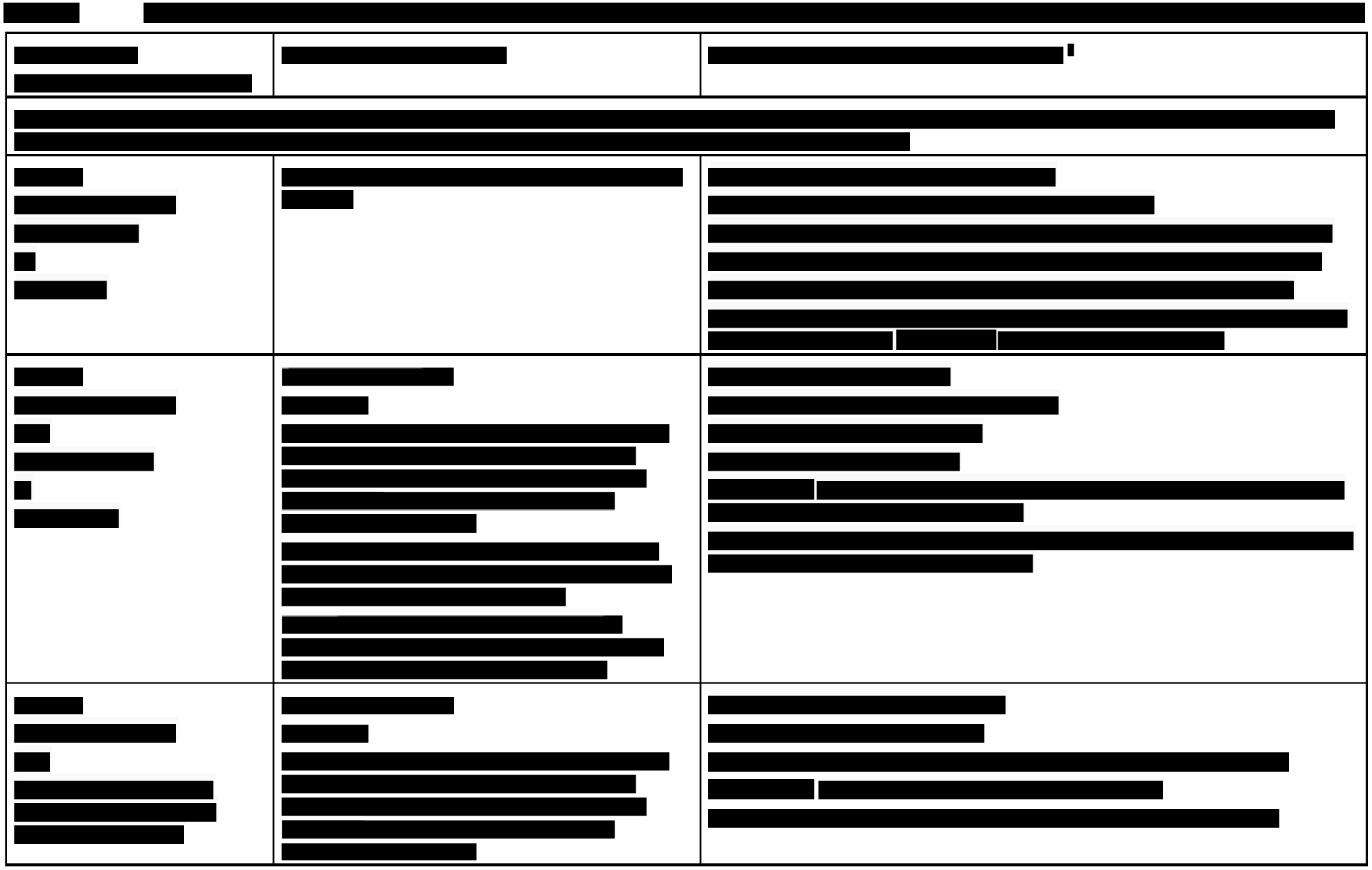
Overall clinical grade (based upon most severe target organ involvement):	
Grade 0	No stage 1–4 of any organ
Grade 1	Stage 1–2 skin without liver, upper GI or lower GI involvement
Grade 2	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI
Grade 3	Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI
Grade 4	Stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI

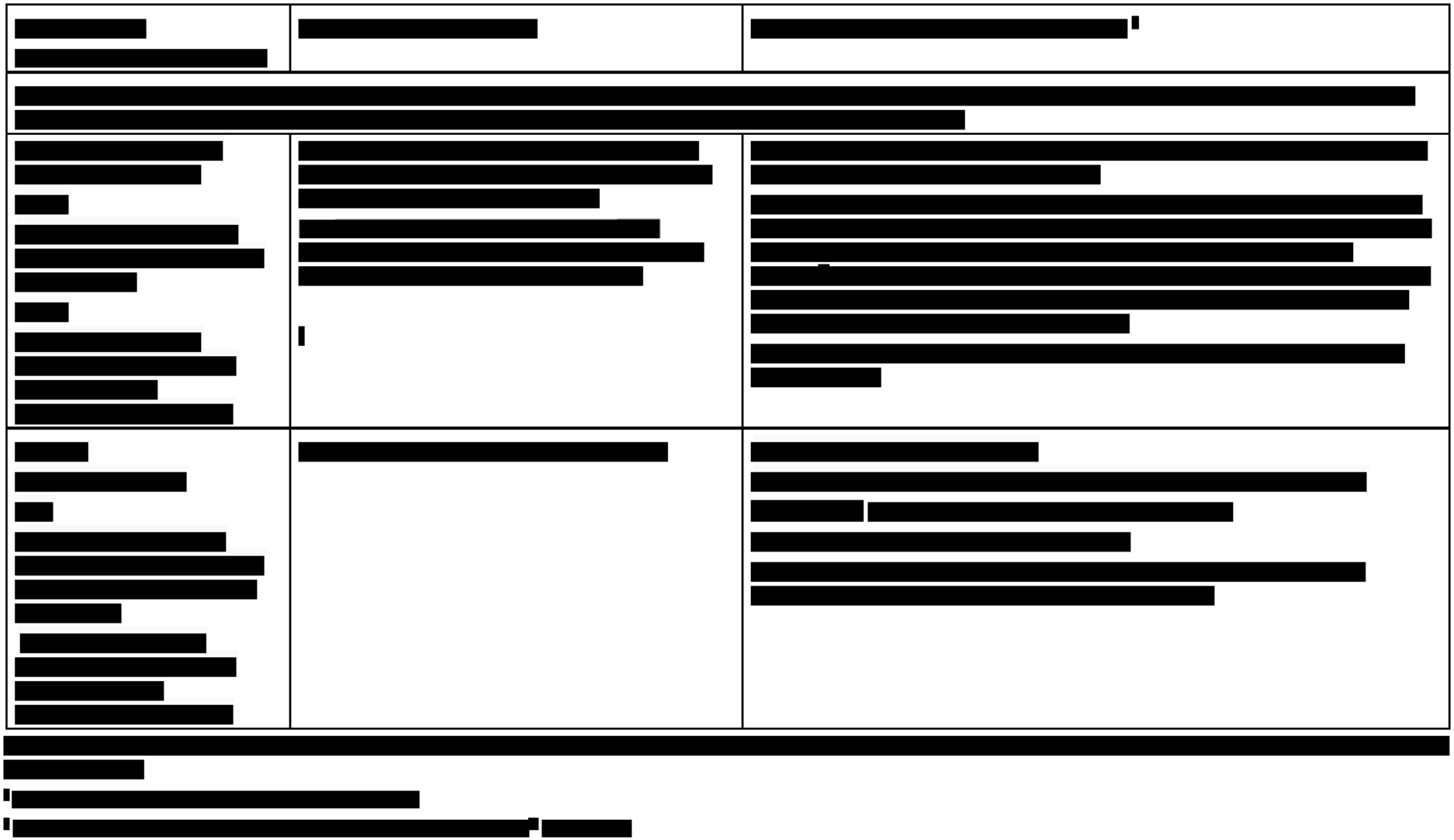
Stage	**Skin (active erythema only)**	**Liver (bilirubin)**	**Upper GI**	**Lower GI (stool output/day)**
0	No active (erythematous) GVHD rash	< 2 mg/dl	No or intermittent nausea, vomiting or anorexia	Adult: < 500 ml/day or <3 episodes/day
				Child: < 10 ml/kg/day or <4 episodes/day
1	Maculopapular rash	2–3 mg/dl	Persistent nausea, vomiting or anorexia	Adult: 500–999 ml/day or 3–4 episodes/day
	<25% BSA			Child: 10–19.9 ml/kg/day or 4–6 episodes/day
2	Maculopapular rash	3.1–6 mg/dl	-	Adult: 1000–1500 ml/day or 5–7 episodes/day
	25 – 50% BSA			Child: 20 – 30 ml/kg/day or 7–10 episodes/day
3	Maculopapular rash	6.1–15 mg/dl	-	Adult: >1500 ml/day or >7 episodes/day
	> 50% BSA			Child: > 30 ml/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation > 5% BSA	>15 mg/dl	-	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

Abbreviations: BSA = body surface area; GI = gastrointestinal; GVHD = graft versus host disease.
Source: Adapted from the Mount Sinai Acute GVHD International Consortium (MAGIC) criteria (Harris 2016).

[redacted]







6.4. Concomitant Medications

Any medication (other than those excluded by the study protocol) that is considered necessary for the subjects' welfare may be given at the Investigator's discretion. Supportive medications will be reported in the eCRF with their reason for prescription, start and end date, route of administration, and daily dose. If a subject requires treatment with a prohibited medication (Section 6.4.2), this should be discussed with the Medical Monitor.

6.4.1. Permitted Medications

- Short term treatment (i.e., <1 week) with low doses (e.g., <10 mg prednisone equivalent) of systemic corticosteroids when medically necessary for the control of acute symptoms
- Red blood cell and platelet transfusions per institutional guidelines.
- Growth factors (e.g., granulocyte-colony stimulating factor [G-CSF]) may be considered during study treatment for subjects who develop neutropenia along with fever and/or infection, or who are considered at high risk of developing a life-threatening infection, according to the institutional standard of care. Growth factors and pegylated G-CSF must be stopped 7 and 14 days, respectively, prior to the bone marrow aspiration in the absence of an urgent medical need for continuing G-CSF administration.
- Antibiotics (e.g., quinolone), antifungals, and antivirals may be used as standard of care for the prevention or treatment of infections.
- Immunoglobulins should be administered with caution at the discretion of the Investigator. Immunoglobulins should not be administered within 3 days of any study drug (acimtamig and/or AlloNK®) administration.
- Palliative radiotherapy for emergency treatment of complications of the disease under study is allowed provided the irradiated tumor site is not the only tumor manifestation. However, may not be given concomitantly with study treatments.

6.4.2. Prohibited Medications

- Subjects may not receive concomitant chemotherapy, immunotherapy, non-emergent radiotherapy, transplant, or any ancillary therapy that is not specified in the protocol, or that is considered to be investigational (i.e., used for non-approved indications(s) and in the context of a research investigation) while on study treatment.
- [redacted]
- [redacted]
- [redacted]

[redacted]

6.5. Blinding and Procedures for Unblinding the Study

This is an open-label study; there are no procedures for blinding and unblinding.

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. Study Drug Materials

Acimtamig and AlloNK® are investigational medicinal products, the storage, preparation, and administration of which are summarized in the section below and will be described in more detail in their respective pharmacy manuals.

The other study drugs (see Section 6.1) will be supplied from commercial sources or provided by the Sponsor. The Investigators should refer to the respective package inserts for information on use and administration.

7.1.1. Acimtamig Investigational Product, Labeling, Storage, and Handling

Acimtamig drug product is an injection intended to be used for i.v. infusion.

The Sponsor will supply acimtamig study drug as a sterile lyophilized powder for reconstitution for intravenous (IV) infusion.

Acimtamig study drug will be labeled as required per country requirement. Acimtamig vials containing drug product must be stored at 2 °C to 8 °C (36 °F – 46 °F). Acimtamig will be shipped to the site and must be stored at the site in a secure location under controlled conditions and in the required temperature range.

Acimtamig infusions should be prepared on the day of dosing and used immediately after preparation. If not administered immediately, the acimtamig infusions (diluted drug product) should be stored ≤24 hours at 2 °C to 8 °C (36 °F – 46 °F). If necessary, the infusion solution is stable for up to 24 hours at room temperature (≤ 25°C / ≤77°F), however the accumulated time for storage, warm-up and infusion must not exceed 24 hours. In case of cold storage, a warm-up time of at least 30 minutes should be allowed before the start of infusion.

Please refer to the current version of the acimtamig IB for information on the physical, chemical, and pharmaceutical properties of acimtamig.

7.1.2. AlloNK® Investigational Product, Labeling, Storage, and Handling

AlloNK® drug product is an injection intended to be used for i.v. infusion.

AlloNK® is comprised of *ex vivo*-expanded allogeneic CBNK cells cryopreserved in an infusion-ready suspension medium.

[redacted]

[redacted]

7.2. Accountability

The Investigator is obliged to keep sufficient documentation of the delivery, use, and destruction or return of unused, used, or partially used study drug. The documentation must include dates, quantities, subject numbers, batch numbers, or other identification number. The Investigator may assign some or all of the Investigator's duties for drug accountability to an appropriate pharmacist. Roles and responsibilities of site staff will be recorded in the Investigator Site File.

The Investigator should maintain records that document adequately that the subjects were administered the doses specified in the protocol and reconcile all study drug received for the study. The local Clinical Research Associate (CRA) will be responsible for checking the drug accountability records maintained by the site during study monitoring visits.

Study drug provided for this study is for use only as directed in the protocol. It is the Investigator and their institution's responsibility to establish a system for handling study drug so as to ensure that:

- Deliveries of study drug are correctly received by a responsible person;
- Such deliveries are recorded;
- Study drug is handled and stored safely and properly as stated on the label;
- Study drug is only dispensed to study subjects in accordance with the protocol; and
- Any unused study drug is destroyed locally or returned for destruction in liaison with the CRA after written approval by the Sponsor.

Certificates of delivery and return must be signed by the responsible pharmacist or delegate and copies retained in the Pharmacy File. Throughout the study, it must be possible to reconcile delivery records with records of usage and any destroyed/returned stock of study drug. To help

with compliance checks, records of usage should include an appropriate form of identification of the subject to whom the study treatment was dispensed (using an indirect form to allow cross reference to the subjects' identity), plus the quantity and date of dispensing.

The return or destruction of unused drug will be conducted after written approval by the Sponsor, with appropriate documentation and drug accountability procedures completed following destruction.

7.3. Treatment Compliance

Administration of study drug will be supervised by the Investigator or sub-Investigator. Any delegation of this responsibility must follow the standard operating procedures.

All subjects will be dosed at the site; thus, they will receive study drug directly from the Investigator or designee, under medical supervision. The date, time, and total amount delivered of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. Should the total amount of study drug not be delivered or there is an interruption to dosing, the reason(s) and any associated AEs will be recorded in the source documents and recorded in the eCRF.

8. STUDY ASSESSMENTS AND PROCEDURES

The planned application of the study medication, the study procedures and study evaluations for efficacy, safety and tolerability assessments as well as translational research evaluations are summarized in the Schedule of Assessments [redacted]

8.1. Confirmation of CD30-positive PTCL

Histological confirmation of CD30-positive PTCL by locally assessed Ber-H2 targeted IHC is required for study participation (Section 5.1). In addition, CD30-positive PTCL will be assessed centrally for retrospective confirmation of CD30-positivity using Ber-H2 targeted IHC.

The following criteria must be met to confirm CD30-positivity:

- CD30 detected in ≥1% of neoplastic cells;
- Total lymphocytes may be used only if enumeration of neoplastic cells is not feasible; this must be clearly documented by the local pathologist;
- CD30 staining at any intensity above background; and membranous, cytoplasmic, and/or Golgi pattern of expression of the CD30 antigen.

8.2. PTCL Tumor Procurement

Four to ten (4-10) unstained slides from a fresh tumor biopsy will be required (mandatory) to be submitted to the Sponsor, or their selected vendor, for CD30 expression confirmation in PTCL subjects (Section 8.1). If archival tissue/slides will be substituted for a biopsy, the specimen must be collected not more than 90 days before Cycle 1 Day -5 and must be from a malignant node or extra-nodal tissue (including bone marrow) obtained by excisional/incisional or core biopsy. Fine needle aspirate or cytology samples will not be acceptable. Cutaneous biopsies will not be accepted.

During the study, new lesions suspicious for relapse or progression will be considered in all subjects for biopsy as clinically indicated or to confirm response. Biopsies will be used for the below-mentioned analyses (Section 8.6.1), to better understand resistance mechanism related to the drug treatments after obtaining subject consent for optional analysis.

Residual blood and biopsy samples will be stored to enable investigational research questions that may arise in the future to help gain information in understanding the cancer and/or the actions of the study treatments.

The Sponsor may decide at any point during the trial to suspend or terminate exploratory biomarker assessments.

8.3. Efficacy Assessments

Disease and efficacy assessments will be conducted at Screening and on Day 43 (± 3 days) of each cycle, regardless of any treatment/cycle delays that may occur, as indicated in the Schedule of Assessments [redacted]

Response assessment will follow the Lugano classification (Cheson 2014; [redacted] for definition of CR, complete metabolic response (CMR), PR, partial metabolic response (PMR),

progressive disease , and progressive metabolic disease (PMD). Subjects who achieve a response and proceed to receive subsequent transplant will be followed for progression and survival status.

Assessments utilizing PET-CT will be performed both locally and centrally. Treatment decisions should be based on the local disease assessment.

At the discretion of the investigator, subjects with the assessment of "indeterminate" response on PET/CT and no clinical evidence of progression, may continue to receive treatment on study pending further evaluation to confirm true progression versus pseudoprogression.

8.4. Safety and Tolerability Assessments

Safety and tolerability will be assessed by monitoring and recording of all AEs graded by the NCI CTCAE v.5.0 (including neurotoxicities that are not considered ICANS) except for CRS and ICANS which will be graded according to the ASTCT grading (Table 4), TLS will be graded according to the Cairo-Bishop TLS grading system (Appendix H) and acute GVHD will be grading according to the MAGIC criteria (Table 5). For further details on severity grading, please refer to Section 10.2.1. The time points for the different study assessments related to safety and tolerability are listed in the Schedule of Assessments ([redacted]

8.4.1. Medical History

There will be a baseline assessment of relevant medical history conducted at Screening to confirm eligibility and to record significant medical history and concurrent illnesses in the eCRF. Concurrent illnesses recorded at Screening (excluding the primary disease under evaluation), that worsen in severity or frequency from this baseline assessment during the study, should be reported as AEs (see Section 10).

8.4.2. Pregnancy and Follicle Stimulating Hormone Tests

Female subjects of reproductive potential will be required to have a pregnancy testing during study participation. The first pregnancy test must be carried out within 7 days prior to the first dose of lymphodepletion. Subsequent tests are required for each cycle within 7 days before the start of lymphodepletion, on Day 1 and Day 29 of each cycle during the Treatment Period, and at the EOT visit [redacted] A urine test is acceptable; however, where a urine test is equivocal, a blood test must be performed to confirm the result. Subjects confirmed as pregnant will be excluded from participation in the clinical study.

Female subjects who require documented confirmation of post-menopausal status will have their FSH levels assessed at Screening. A urine test is acceptable; however, where a urine test is equivocal, a blood test must be performed to confirm the result. Where post-menopausal status is not confirmed, subjects will be required to undergo pregnancy testing per protocol to confirm suitability to proceed.

8.4.3. Eastern Cooperative Oncology Group Performance Status

ECOG PS will be assessed at the times given in Schedule of Assessments [redacted] Details of the ECOG PS categories are presented in [redacted] Subjects must be confirmed as ECOG PS 0 or 1 at Screening to be eligible for study participation (Section 5.1).

8.4.4. Vital Signs

Vital sign parameters will be taken at the times given in Schedule of Assessments ([redacted] The date and time of collection will be recorded in the source data and in the eCRF.

Vital sign parameters will consist of measurements of temperature, resting heart rate, seated blood pressure (systolic/diastolic) and respiratory rate.

If any clinically significant findings are identified during the study, the Investigator will record these as an AE, where the finding represents a change from baseline.

8.4.5. Physical Examinations

A physical examination, including measurement of weight, will be taken at the times given in Schedule of Assessments [redacted] The subject's height will be measured at Screening. The subject's weight will also be assessed at Screening and prior to each acimtamig administration.

Height and body weight will be obtained while the subject is wearing light clothing (without shoes).

A full physical examination will include assessment of the following categories: head, eyes, ears, nose, throat, heart, lungs, abdomen, skin, musculoskeletal, extremities, neurological, lymph nodes, and 'other'. After the Screening assessment, the physical examination may be reduced to a symptom-directed assessment.

If any clinically significant findings are identified during the study, the Investigator will record these as an AE, where the finding represents a change from baseline.

8.4.6. Clinical Chemistry, Hematology, Coagulation, and Urinalysis

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis parameters will be taken at the times given in Schedule of Assessments ([redacted] and recorded in the source data and in the eCRF. Coagulation will be assessed at Screening and EOT visit only and may be assessed from the hematology sample.

The laboratory variables to be measured are described in [redacted]

Copies of laboratory accreditation certificates and reference ranges will be obtained from each study site prior to analysis of their first subject sample and maintained over the course of the study.

If any clinically significant findings are identified during the study, the Investigator will record these as an AE, where the finding represents a change from baseline.

8.4.7. Electrocardiogram

A resting 12-lead ECG will be performed at the times given in Schedule of Assessments [redacted]

All 12-lead ECGs should be recorded while the subject is in the supine position. ECGs will be recorded at 25 mm/sec. All efforts should be made to ensure that an identical ECG machine is used to collect traces for individual subjects. The Investigator or designated physician will review the ECG results. If any clinically significant findings are identified during the study, the Investigator will record these as an AE, where the finding represents a change from baseline.

8.5. Pharmacokinetic Sampling

All subjects will be required to participate in PK sampling in the study, and serial blood samples will be collected and analyzed at specified times for measurement of acimtamig and AlloNK®

The nominal PK blood sampling times requested should be adhered to as closely as possible. It is essential that the actual date and time of collection of each blood sample is recorded in the subject's records and in the eCRF.

8.6. Additional Assessments

8.6.2. Anti-drug Antibodies

All subjects will have blood samples taken to assess anti-drug antibodies (ADAs) at the time points described in Schedule of Assessments).

8.6.3. Quality of Life Assessment

Evaluation of QoL parameters will be performed at the time points described in Schedule of Assessments ( ).

Subjects will be evaluated utilizing EORTC QLQ-C30, an example is provided in

8.7. Volume of Blood Sampling

Total blood volumes required during study participation will be provided in the ICF provided to each subject. Efforts will be made to limit blood sampling and to avoid any redundancy.

Residual blood samples may be stored and used as the basis for additional exploratory analysis after the study to help gain information in understanding HL, PTCL or other hematological malignancies and/or the actions of the study treatments.

9. STATISTICAL METHODS AND DATA ANALYSIS

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock. This section is a summary of the planned statistical analyses. Detailed statistical analysis information will be provided separately in the SAP, which will also outline protocol deviation criteria. Any deviations to the planned analyses specified or populations defined within the SAP will be justified in writing and presented within the final clinical study report (CSR).

The clinical database lock will occur after all data are reconciled (i.e., "cleaned") for all subjects who receive at least one dose of acimtamig and AlloNK®. A single CSR will be generated for this study.

An addendum (or addenda) to the CSR will be generated as required to report any data obtained during the Follow-up Assessments.

The study will have six separate cohorts, which will be analyzed independently as described below. Those subjects who initially consented under protocol v3.0 and later versions, and thus will not receive IL-2 after the AlloNK® treatment, will be analysed separately.

9.1. Analysis Sets

The **safety analysis set (SAS)** will consist of all subjects who received any amount of any component of the regimen (acimtamig, AlloNK® or any study treatment such as lymphodepletion or IL-2). The SAS will be the primary population for all safety-related endpoints.

Following the ITT principle, the **full analysis set (FAS)** will consist of all subjects enrolled into one of the two selected cHL Cohorts in Stage 1 and Stage 2 or the exploratory PTCL Cohort (Cohort 5), who received at least 1 dose of both acimtamig and AlloNK®. The FAS will be the primary population for all efficacy related endpoints.

Following the ITT principle for analysis of Cohort 6, the **NK full analysis set (NK-FAS)** will consist of all subjects who received at least 1 dose of AlloNK® in Cohort 6. The NK-FAS will be the primary population for all efficacy related endpoints concerning Cohort 6.

The **per protocol set (PPS)** will consist of all subjects in FAS who did not have any major protocol deviations. The primary analysis will be repeated to support the results of the primary analysis on the FAS.

The **safety run-in set (SRI)** consists of all subjects of the 4 safety run-in cohorts who have received at least 66% of the acimtamig and AlloNK® combination dose during Cycle 1.

The **acimtamig PK set** consists of all subjects (except those from Cohort 6) who have received at least 1 dose of acimtamig and have at least 1 post dose acimtamig PK measurement.

The **AlloNK® PK set** consists of all subjects who have received at least 1 dose of AlloNK® and have at least 1 post dose AlloNK® PK measurement.

Subjects who were screened and have signed the informed consent but did not receive any treatment will be listed including reason for screening failure and any SAE that is related to study procedure. These subjects will not be part of any summary table except for summarizing disposition.

Further populations might be explored and the final populations for analyses will be specified in the SAP.

9.2. Sample Size Determination

After the exhaustion of initial chemo, brentuximab vedotin (BV) and PD1 inhibitor (pembrolizumab, nivolumab) therapies, options for the heavily pretreated cHL patients are limited and largely palliative in nature and therefore patients should be included into clinical trials (Hanel 2022).

Single agent or combination chemotherapy regimens recommended by the NCCN guideline Version 2.2013, such as bendamustine (Moskowitz 2013), gemcitabine + oxaliplatin (Gutierrez 2014), or bendamustine + carboplatin + etoposide (Budde 2018), as well as non-chemotherapeutic targeted options such as lenalidomide (Fehninger 2011) and everolimus (Johnston 2010) have shown activity in r/r cHL patients.

All studies cited above were uncontrolled Phase 1/ 2 or 2 studies with small sample size. Importantly, patients had not been pretreated with BV and PD1 inhibitor, thus do not reflect the target population of the proposed study AFM13-203.

The Phase 1/2 single-center study AFM13-104 enrolled subjects with r/r cHL (n=41) that were treated with multiple lines of systemic therapy including BV and PD1 inhibitor – a study population that is comparable to that of AFM13-203. The study reported no responses to the immediate prior therapy before study inclusion (Nieto ASH 2022).

Cohort 5 (CD30-Positive PTCL)

Due to the exploratory nature of Cohort 5, a sample size of N=20 is planned, to assess preliminary efficacy, safety and PD data and allow for hypotheses generation for follow up studies.

Cohort 6 (cHL)

Due to the exploratory nature of Cohort 6, a sample size of up to 12 subjects is planned to assess the efficacy and safety of AlloNK® given as monotherapy.

9.3. Randomization

The two selected cHL Cohorts in Stage 1 and Stage 2 of the trial will be randomized. The details about the randomization will be described in a separate document. Cohorts 5 and 6 will not be randomized.

9.4. Demographic, Medical History, Prior Medication and Other Baseline Characteristics

Demographic and tumor characteristics, prior anti-cancer therapies and surgeries, medical history, prior medication and other baseline data will be listed and summarized using descriptive statistics for continuation data and contingency tables for categorical data. Prior medication/Prior anti-cancer therapies will be coded by World Health Organization (WHO) Anatomical, Therapeutic, and Chemical (ATC) terms. Medical history will be coded utilizing corresponding Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) and PTs.

9.5. Study Drug

The number of doses of acimtamig and AlloNK® administered over the entire study period will be listed and summarized using descriptive statistics. The time on acimtamig or AlloNK® until last treatment received will be listed and presented by descriptive statistics.

9.6. Concomitant Medication

Concomitant medication and significant non-drug therapies after the start of acimtamig or AlloNK® will be listed and summarized by WHO ATC terms in contingency tables.

[redacted]

[redacted]

9.7.1. ORR by IRC for Cohort 6

The ORR by IRC for Cohort 6 is based on the ORR (CR + PR) assessed by IRC according to the Lugano classification (Cheson 2014; [redacted] and will be analyzed in a similar way as described above, but on the NK-FAS. Furthermore, subjects who do not develop a response (at least PR) after cycle 1 (i.e., after the first assessment) will be counted as treatment failures.

The ORR will be presented as percentage rate including the 95% confidence interval. In addition to the ORR, the CRR and PRR will be provided, calculated as the proportion of subjects having a best response of CR or PR, respectively.

9.8. Secondary Analyses

9.8.1. Secondary Efficacy Analyses

Secondary efficacy analyses will be performed based on IRC assessment and/or Investigator assessment of disease response as specified below. Consequently, endpoints using IRC assessments will be derived using only responses provided by IRC regardless of Investigator responses. Similarly, endpoints using Investigator assessments will be derived using only responses provided by Investigator regardless of IRC responses. The following secondary efficacy endpoints will be assessed according to the Lugano classification (Cheson 2014; [redacted]):

- DOR by IRC and Investigator
- CRR by IRC and Investigator
- ORR (CR + PR) by Investigator
- PFS by IRC

In addition, incidence of subjects receiving subsequent transplant and OS will be assessed.

9.8.1.1. Duration of Response by IRC and Investigator

The DOR defined as time from first assessment of PR or CR to the first assessment of progressive disease will be summarized by descriptive statistics including median DOR and respective 95% CIs and Kaplan-Meier estimates. DOR will also be listed.

Subjects who started a new anti-lymphoma therapy prior to a documented progressive disease will be censored at the last disease assessment prior to initiation of new anti-lymphoma therapy. Detailed censoring rules will be described in the SAP.

9.8.1.2. CRR by IRC and Investigator

The CRR will be calculated as the proportion of subjects having CR as best response.

9.8.1.3. ORR by Investigator

The primary analysis will be repeated using the local Investigator assessments.

9.8.1.4. Progression-free Survival by IRC and Overall Survival

Time from first treatment (acimtamig/AlloNK®) received until PFS/OS will be summarized by Kaplan-Meier estimates, median PFS/OS and respective 95% CIs. Subjects with no event will be censored at the last available disease assessment for PFS and at the last time point known alive for OS. A detailed censoring rule table will be presented in the SAP.

9.8.1.5. Subsequent Transplant

The incidence of subjects receiving subsequent transplant will be assessed and summarized by percentage rates and 95% CIs.

Additional efficacy parameters may be defined in the SAP.

9.8.2. Safety Analyses

Treatment-emergent adverse events are those events with onset at/or after the first administration of any study drug of the regimen (acimtamig, AlloNK® or any study treatment such as lymphodepletion or IL-2) until 30 days after last administration of any study drug. TEAEs and SAEs will be coded using MedDRA and graded using NCI CTCAE v5.0 (including neurotoxicities that are not considered ICANS) except for CRS and ICANS, which will be graded according to the ASTCT grading, TLS will be graded according to the Cairo-Bishop TLS grading system and acute GVHD will be grading according to the Mount Sinai Acute GvHD International Consortium (MAGIC) criteria.

Incidence, relatedness, and severity of TEAEs and SAEs will be tabulated and listed. Deaths within 30 days after the last dose and the corresponding reasons will be summarized. Also, overall mortality will be summarized.

Safety laboratory results will be graded by NCI CTCAE v5.0 if no grading exists values will be classified into low/normal/high based on laboratory normal ranges. All laboratory values will be listed. A separate listing for abnormal lab values (Grade 3 and higher, and low/high values) will be presented.

Vital Signs will be summarized by descriptive statistics at each visit including change from baseline. All values will also be listed.

9.8.3. Immunogenicity Analyses

Immunogenicity parameters, including frequency of subjects developing ADAs against acimtamig or AlloNK®, will be summarized by descriptive statistics and listed for both acimtamig and AlloNK®.

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10. SAFETY MANAGEMENT

10.1. Safety Definitions

10.1.1. Adverse Event

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal (investigational) product or study procedure, whether assessed as related or unrelated.

During clinical studies, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs. Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the start of the study;
- Intercurrent illness;
- Drug interactions;
- Any safety events resulting from procedures required by the protocol.
- Experiences related or possibly related to concomitant medications;
- Clinically significant abnormal laboratory values or shifts from baseline;
- Clinically significant abnormalities in physical examination, vital signs, weight, or ECG; and
- An accident or injury.

10.1.2. Special Considerations Related to AE Reporting

The Investigator shall record in the eCRF all AEs, and special situations including Misuse, Medication error, Overdose (refer to Section 10.1.5) or a new cancer that is not a condition of the study, after the subject signs the ICF until 30 days after the last administration or before start of any new anti-cancer treatment whichever is sooner, regardless of causal relationship to the investigational medicinal product (IMP).

The term “disease progression” alone should not be used when reporting AEs or SAEs. Additionally, death that occurs as consequence of disease progression is an outcome, and NOT an AE.

Example, a subject died due to a pulmonary hemorrhage secondary to tumor progression; a SAE report with the event pulmonary hemorrhage should be notified as a Grade 5 (fatal).

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.

Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation and did not worsen during study. In the latter case, the condition should be reported as medical history.

Pregnancy is not considered an AE, although a subject will be withdrawn from the study if a pregnancy occurs (please refer to Section 5.4.2 for more details). The pregnancy must be reported as instructed in Section 10.3.2 and will be followed for at least 8 weeks after delivery.

10.1.3. Adverse Events of Special Interest

An AE of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor are necessary.

In order to increase the understanding of infusion-related reaction (IRR) and CRS, these events are considered to be AESIs and must be reported by the Investigator within **24 hours** as per the instructions outlined in Section 10.3.1. All symptoms suggesting an IRR or CRS should be mentioned in the report. Information related to the timely development of symptoms relative to dose per time, actions taken as well as outcome of events are of particular interest and shall be reported to the Sponsor or delegate for proper case evaluation.

Infusion related reactions can manifest with allergic or anaphylactic symptoms, including but not limited to chills, flushing, hypotension, fever, hypoxia, loss of consciousness, bronchospasm and even with cardiac arrest. Although the majority of such IRRs are mild to moderate, in some rare cases these can be life threatening or even fatal. Most of the IRRs are associated with the first infusion (during or shortly after the infusion); however, IRRs can happen during or after any infusion, despite the lack of previous signs or symptoms. Infusion related reaction severity shall be graded using the classifications of NCI CTCAE v5.0

Cytokine release syndrome occurring during or following infusion of study treatment can be further defined by symptoms such as fever, hypotension, and/or hypoxia as described in the ASTCT grading system.

10.1.4. Serious Adverse Event

An SAE is any AE, occurring at any dose and regardless of causality that is defined as any untoward medical occurrence that at any dose causes or qualifies as the following:

- Fatal;
- Results in death;
- Life-threatening; "Life-threatening" means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization. – This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the SAE or that they occurred as a consequence of the event.

Note :

- Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfills any other of the serious criteria.
- Hospitalization for elective treatment or diagnostic procedure of a pre-existing condition that did not worsen from baseline (including study disease) is NOT considered an SAE.
- Hospitalization and pre-planned admission to hospital for administration of chemotherapy, AlloNK®, IL-2 (if applicable), acimtamig, or other protocol-mandated procedures (i.e., lymphodepletion or biopsy) do NOT qualify as serious unless a new AE occurs that results in prolongation or meets any of the other "seriousness" criteria.

- Results in persistent or significant disability or incapacity – "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect; and/or
- Is an important medical event – An ***important medical event*** is a serious event that may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may **jeopardize the subject** or may **require medical intervention** to prevent one or more outcomes listed in the definition of serious. Examples of such events include potential drug induced liver injury (DILI), graft versus host disease (GVHD), multiple organ dysfunction syndrome, mucosal necrosis, intensive treatment (in an emergency room or at home) for allergic bronchospasm, convulsions that do not result in hospitalization, or the development of drug dependency or abuse, overdose or misuse. For more examples refer to the latest IME list released by EMA.For more examples refer to the latest IME list released by EMA.

All SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the event is otherwise explained, or the subject is lost to follow-up or withdraws consent.

10.1.5. Overdose, Medication Error, and Misuse

Overdose is defined as: >10% above the intended study drug daily dose is given or a dose interval <4 days between two consecutive doses. If the pharmacy discovers that an overdose has or may have been administered, they should contact the Investigator and Sponsor (or their delegate) immediately.

Medication error is defined as: an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the subject.

Misuse is defined as: situations where an investigational medicinal product is intentionally and inappropriately used not in accordance with the terms of the current protocol.

10.2. Evaluation and Classification

Following the subject's written consent to participate in the study, all AEs will be collected. Pre-existing conditions that are detected prior to the subjects written consent will be recorded as part of the medical history.

For all subjects, the AE reporting period will start with signing the informed consent form (ICF) for all AEs and continue until 30 days after the last dose study treatment (acimtamig and/or AlloNK®) or before initiation of subsequent anticancer therapies. (Note: any SAEs that occur prior to the first dose of lymphodepletion will still be reported according to the instructions provided on reporting of SAEs in Section 10.3.1). Where known, the diagnosis of the underlying illness or disorder should be recorded, rather than listing individual symptoms.

The following Information should be captured for all AEs: date of onset and resolution, severity of the event, assessment as to whether the event was serious or non-serious, Investigator's opinion of the relationship to study drug(s), treatment required for the AE, action taken with study drug(s), and information regarding resolution/outcome.

10.2.1. Severity Assessment

All AEs (including SAEs) are to be accurately recorded on the AE page of the subject's eCRF. Each event will be graded for severity using the classifications of NCI CTCAE v5.0 (including neuro-toxicities that are not considered ICANS) except for CRS and ICANS, which will be graded according to the ASTCT grading (Table 4), TLS will be graded according to the Cairo-Bishop TLS grading system (Appendix H), and acute GVHD will be grading according to the MAGIC criteria (Table 5). For events not addressed in the NCI CTCAE v5.0, ASTCT grading classifications, the Cairo-Bishop TLS grading system, or MAGIC criteria, the following grading will apply:

- Mild (Grade 1) – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2) – Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activity of daily living.
- Severe (Grade 3) – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living.
- Life-threatening (Grade 4) – Life-threatening consequences; urgent intervention indicated.
- Fatal (Grade 5) – Related to AE.

During initial dosing and its respective post-observation period, any clinical finding despite its severity that represents a change from baseline (e.g., mild skin reaction, fatigue, myalgia, etc.) should be recorded and followed until resolution. Likewise, any clinically significant finding identified during the remaining course of the study, which represents a change from baseline would be required to be recorded by the Investigator.

10.2.2. Expectedness Assessment

The Sponsor will assess all SAEs whether they are expected or unexpected. An unexpected AE is any adverse drug event, the outcome, specificity, or severity of which is not listed in the current Reference Safety Information (RSI) of the IB.

10.2.3. Causality Assessment

All AEs (including SAEs) will be assessed by the Investigator and Sponsor for the causal relationship of the AE to the study drug(s) using the following definitions described in Table 8.

For reporting and data analysis purposes, AEs reported with a causality assessment of "Definitely", "Probably", and "Possibly" are to be considered as "having a reasonable causal relationship" to study drug. In case of disagreement between the Investigator and the Sponsor, the more conservative assessment will determine the reportability of the case.

Table 8: Relationship to Study Drug

	Relationship	Description
1	Not related	This category applies to those AEs which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
2	Unlikely (must have 2)	In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug. An AE may be considered unlikely if or when: 1. It does not follow a reasonable temporal sequence from administration of the test drug. 2. It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It does not follow a known pattern of response to the test drug. 4. It does not reappear or worsen when the drug is re-administered.
3	Possibly (must have 2)	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It follows a known pattern of response to the test drug.
4	Probably (must have 3)	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug. An AE may be considered probably related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia). 4. It follows a known pattern of response to the test drug.
5	Definitely (must have all)	This category applies to those AEs which, the Investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

	Relationship	Description
		3. It disappears or decreases on cessation or reduction in dose with re-exposure to drug. (Note: this is not to be construed as requiring re-exposure of the subject, however, a category of definitely related can only be used when a recurrence is observed.) 4. It follows a known pattern of response to the test drug.
Abbreviations: AE = adverse event		

10.3. Safety Reporting

Timely and complete reporting of safety information is very important to assist in the identification of any untoward medical occurrence, thereby ensuring:

- The safety of study subjects;
- A greater understanding of the overall safety profile of the investigational drug;
- Recognition of any dose-related investigational drug toxicity;
- Appropriate modification of study protocols;
- Improvements in study design or procedures as required; and
- Adherence to required ethical and regulatory requirements for clinical study conduct.

10.3.1. Safety Reporting of Serious Adverse Events and Adverse Events of Special Interest

Investigators must report SAEs/AESIs to the Sponsor or delegate within **24 hours** of becoming aware of the event, by entering all required information into the Electronic Data Capture (EDC) system by completing an electronic Case Report Form (eCRF) in accordance with the eCRF completion guidelines.

Upon completion of the eCRF and submission of the eCRF, an automated notification will be triggered to the sponsor (or delegate). The investigator will receive an acknowledgement of receipt within one business day of submitting the report.

[redacted]

Other supporting documentation of the event may be requested by the Sponsor or delegate and should be provided as soon as possible in an anonymized manner. Follow-up information about a previously reported SAE/AESI must be reported within the same applicable timeframe of receiving it. Serious AEs/AESIs will be followed up until resolution or stabilization at a level acceptable to the Investigator and/or the Sponsor.

The Investigator is not responsible for actively seeking new SAEs/AESIs after the safety follow-up period. However, if the Investigator becomes aware of an SAE/AESI that is reasonably associated

[redacted]

10.3.2. Exposure During Pregnancy or Lactation

Although pregnancy and lactation are not considered AEs, they are considered an exclusion criterion for this study (Section 5.2).

Any pregnancy or lactation in a subject, or pregnancy in a subject's partner that occurs after the ICF is signed through 60 days following cessation of study drug treatment shall be recorded by the Investigator on the Pregnancy Form provided by the sponsor (or delegate) as soon as possible but no later than 14 days of being made aware of the pregnancy. [redacted] Any events (including congenital anomalies/birth defects) that meet the definition of a SAE would need to be notified to the Sponsor as per Section 10.3.1. The Investigator must also ensure that any pregnancy is followed up until outcome, i.e., the health of the infant will be queried by the Sponsor or delegate. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. Off-spring should be followed up for at least 8 weeks after delivery. Longer observation periods may be determined by the Sponsor or delegate if an adverse outcome of the pregnancy was observed.

A congenital anomaly will only need to be expedited to competent authorities and ECs/IRBs if it meets the definition of a suspected unexpected serious adverse reaction (SUSAR). In addition, pregnancy case(s) will be reported as part of the annual Development Safety Update Report (DSUR).

10.3.3. Other Reporting Obligations

Special situations including misuse, medication error, overdose, or a new cancer that is not a condition of the study, shall be recorded in the eCRF. Those events shall be collected from the time the subject signs the ICF until 30 days after the last administration or before start of any new anti-cancer treatment whichever is sooner, regardless of causal relationship to the IMP.

If the special situation results in an adverse event that meets any of the seriousness criterion defined in Section 10.1.4, the case qualifies for immediate reporting and has to be reported within 24 hours using the instructions for SAE reporting stated in Section 10.3.1.

10.4. Follow-Up Information on Reported Events

The Sponsor (or their delegate) will review SAE reports for missing information and send queries to the site for resolution as appropriate.

An SAE is followed until it is considered resolved, returns to baseline, is chronically ongoing, stabilized, or is otherwise explained by the Investigator.

Collection of complete information concerning reported events is extremely important. Thus, follow-up information that becomes available as the event evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently if not available at the time of the initial report and immediately uploaded to the eCRF.

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out by the Investigator (or designee).

10.5. Reporting of Serious Adverse Events to Regulatory Authorities

In accordance with the 21 CFR Part 312.32 and the International Council for Harmonization (ICH) Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the Sponsor must submit written documentation in the form of an IND Safety Report or SUSAR reports, respectively. The Sponsor should submit to the regulatory authority all safety updates and periodic reports, as required by applicable regulatory requirements. The IND Safety Reports/SUSARs are required to be reported within 7 calendar days for fatal and life-threatening events and/or 15 calendar days for all other SUSARs. These timeframes begin with the date when the Sponsor or their delgate becomes aware of the IND Safety Reports/SUSARs.

The Sponsor (or their delegate) will determine whether expedited reporting is necessary for SAEs depending on the assessment of seriousness, expectedness, and causal relationship. In case of disagreement between the Investigator and the Sponsor regarding causal relationship, the more conservative assessment will determine the reportability of the case.

The Investigator must ensure they are aware and comply with any additional local reporting requirements. For all SAEs regardless of expectedness and causal relationship, the Sponsor (or their delegate) will assign a case number/ID to be used in all case-related correspondence regarding the event and can provide a MedWatch or Council for International Organizations of Medical Sciences (CIOMS I) form describing the event, for the Investigators to report to their local Institutional Review Board (IRB)/Ethics Committee (EC) or other committee. Other SAEs (e.g., expected or unrelated SAEs) should be reported per the relevant institution's procedures (if required).

Where required, submission of Safety Updates by the Investigator to local regulatory agencies should be handled according to local regulations. Otherwise, periodic safety reports to the regulatory agencies will be handled by the Sponsor (or their delegate). These safety updates will also include SAEs that do not require expedited reporting to the authorities.

Periodically (at least annually), the IB will be updated to include new and relevant safety information. Expectedness assessment shall be based on the RSI section approved by regulatory agencies at the onset of the event.

10.6. Study Interruption or Stopping Criteria for Safety Concerns

Stopping rules for safety concerns include any of the following:

1. Any Grade 5 TEAE at least possibly related to acimtamig and/or AlloNK® and clearly unrelated to either underlying HL/PTCL or disease progression.
2. Any unexpected, significant or unacceptable risk to subjects as determined by the independent SRC
3. Any Grade 3 or 4 TEAE at least possibly related to acimtamig and/or AlloNK® and clearly unrelated to either underlying HL/PTCL, disease progression occurring in ≥33%

of subjects with at least 6 subjects enrolled in the safety-run-in or ≥33% of subjects in the main study with the following exceptions:

- ASTCT Grade 3 CRS or CTCAE Grade 3 IRR related toxicity that improve to Grade 2 or lower within 72 hours of adequate medical support
- CTCAE Grade 3 fever, neutropenic fever, or infections that improve to Grade 2 or lower within 72 hours
- CTCAE Grade 3 fatigue that improves to Grade 2 or lower within 10 days
- CTCAE Grade 3 nausea, vomiting, or diarrhea that does not result in hospitalization, total parenteral nutrition, or tube feeding
- CTCAE Grade 3 ALT, AST, alkaline phosphatase (ALP) (>5 × ULN) or bilirubin (>3 × ULN) resolving to Grade 1 or baseline within 7 days;
- CTCAE Grade 3 electrolyte abnormalities that can be corrected with supportive therapy within 72 hours
- CTCAE Grade 3 laboratory abnormality unless confirmed with a repeat test and considered clinically significant
- QT interval with Fridericia's correction (QTcF) prolongation (>500 msec or >60 msec change from baseline) must be confirmed by 2 separate ECGs at least 6 hours apart or must be associated with arrhythmias in order to be considered a study interruption criterion

If at least one of the stopping rules is met, subject recruitment will be paused and the safety data will be reviewed by the independent SRC (additional details will be provided in a separate charter). If the new safety findings are considered treatment related by the independent SRC, subjects who are already receiving study treatment and are deriving clinical benefit may continue study treatment at the discretion of the Investigator only after reconsenting a second informed consent that has been updated with the new safety information.

11. QUALITY, CONTROL, AND QUALITY ASSURANCE

This study will be conducted under GCP and all applicable regulatory requirements. To ensure data accuracy, completeness, and compliance, the study center should have processes in place for data review and quality control. Sponsor (or delegate) may also conduct a quality assurance audit.

11.1. Data Recording, Monitoring of the Study, and Regulatory Compliance

The project manager, or their designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the initiation site visit, the eCRF and other pertinent study materials will be reviewed with the Investigator's research staff. During the course of the study, the CRA will make regular site visits in order to review protocol compliance, examine CRFs and individual subject's medical records, and assure that the study is being conducted according to pertinent regulatory requirements including ICH-GCP. Sites should ensure that source documentation is available to enable verification of all eCRF data entries. The review of medical records will be done in a manner to ensure that subject confidentiality is maintained.

All data will be collected using an eCRF within a fully validated and 21 CFR Part 11 compliant EDC system. All data will be entered into the eCRF by the site staff. These data will then be source-data verified and reviewed by the CRAs before data cleaning by data management is performed. All queries will be raised and resolved within the EDC system. During entry, programmatic checking of the data will be performed, and, once saved into the database, more complex programmatic checks will also be performed. During the conduct of the study, all system users will have real-time access to the data. The level of access to the data and study privileges will be determined by their user role.

After all queries have been resolved, the SAP approved and signed, and any summary/analysis populations approved, the database will be locked, and the data released for summary and analysis. All summary and analysis of the data will be performed using appropriate versions of SAS® and WinNonLin Pro, or equivalent.

11.2. Study Monitoring

Clinical Research Associates will be responsible for the monitoring of the study. The CRA will review the progress of the study on a regular basis to ensure adequate and accurate data collection. Monitoring site visits to review the eCRF, subject case notes, administrative documentation including the Investigator Site File, and frequent telephone/e-mail communications with site will be performed throughout the study.

At each study monitoring visit, the Investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the CRA, monitoring visits will be confirmed in advance of planned visits.

The process for study monitoring and source data verification requirements for the study will be specified in the Monitoring Plan (or equivalent).

11.3. Clinical Study Audit

The Sponsor, Sponsor representative, or external regulatory agency may at any time during or after completion of the study conduct a GCP audit. Prior notice will be given to each site selected for audit in advance of a planned audit.

11.4. Clinical Study Report

The results of the study will be presented in a Clinical Study Report according to ICH guidelines. The CSR will be written once all enrolled cohorts reached the primary endpoint assessment.

In case subjects are still being treated with study medication at the final data cut-off date for this study, such subjects will be kept on treatment in the study and data collected will then be reported in an addendum to the final CSR. It will be noted in the final CSR that such a revised report may be provided.

11.5. Data Availability

The Investigator is required to maintain copies of all essential study documentation, including the Site Study File, all eCRF data (including the full audit trail and all data queries), signed ICFs, and records for the receipt and disposition of study drug.

During the study, the Investigator must make study data accessible to the CRA, the Sponsor (or a third-party auditor assigned by the Sponsor), and relevant IRB/EC and regulatory agencies. A file (or appropriate records) for each subject must be maintained that includes the signed ICF and all source documentation related to that subject. The Investigator must ensure the availability of source documents from which the information in the eCRF was derived.

Please refer to Section 13.2 for details of required record retention for the study.

11.6. Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 (or accepted equivalent), and a financial disclosure statement. All Sub-investigators will be required to provide a current curriculum vitae and a financial disclosure statement.

11.7. Protocol Modifications

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

11.8. Study or Site Termination

If the Sponsor or their representatives, Investigator, or Competent Authority discover conditions during the study that indicate that the study or site involvement should be terminated, this action

may be taken after appropriate consultation with the Sponsor and the Investigator. Conditions that may warrant termination of the study or a study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study;
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug;
- Failure of an Investigator(s) to comply with pertinent clinical study regulations;
- Submission of knowingly false information from the study site to the Sponsor, CRA, or Competent Authority; and
- Insufficient adherence to protocol requirements.

Study termination and/or site close out will be performed in accordance with applicable local regulations.

12. ETHICAL CONSIDERATIONS

The Investigator will obtain written informed consent from each subject, or their authorized representative, participating in the study. The form must be signed, witnessed and dated. The ICF will contain all the Essential Elements of Informed Consent set forth in 21 CFR Part 50, the ICH Guideline for GCP, and the terms of the Declaration of Helsinki. Copies of the signed document should be given to the subject and filed in the Investigator's Study File, as well as the subject's medical record if in conformance with the institution's Standard Operating Procedures.

The final study protocol and subject ICF will be approved by the appropriate IRB/EC for each investigational site. Approval will be received in writing before initiation of the study.

Changes to the protocol during the study will be documented as amendments. Depending on the contents of the amendments and local legal requirements, the amendment will be submitted for approval to the relevant IRB/EC and to the relevant competent authorities prior to implementation. Exceptions are cases of changes made to protect subject safety, which will be implemented immediately.

If an amendment substantially alters the study design, increases the potential risk to the subjects, affects the treatment of the subject, or might otherwise influence the willingness of the subject to participate in the study, then the ICF must be revised and submitted to the relevant IRB/EC and, where necessary, to the relevant competent authorities, for review and approval. When a subject is currently undergoing study procedures and is affected by the amendment, then the subject must be asked to consent again using the new ICF.

12.1. Ethical Conduct of the Study

The study will be conducted in accordance with ICH GCP, the Declaration of Helsinki, the Clinical trials – Regulation EU No 536/2014, the GCP Directive 2005/28/EC, the requirements of local IRBs/ECs, and the 21 CFR Part 50.

12.2. Informed Consent

The principles of informed consent in the Declaration of Helsinki and GCP guidelines will be implemented before any protocol-specific procedures or interventions are carried out.

All subjects will be informed that participation is voluntary and that they can cease participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled.

With the help of the ICF, the subject will be informed about the study treatments and anticipated effects and the reason, design, and implication of the study. The subject must give consent to participate prior to enrollment in the study. This consent must be given in writing. The Investigator who conducts the informed consent discussion must also sign. The Investigator may delegate this responsibility to a suitably qualified member of the study team (e.g., Sub-Investigator) if permitted by local regulations. This delegation of responsibility must be recorded in the Study File. By giving signed consent, the subject will confirm that his or her participation is voluntary and that he or she will follow the instructions of the Investigator and answer the questions asked. Signatures must be personally dated.

The signed and dated consent form will be kept by the Investigator. Prior to participation in the study, the subject should receive a copy of the signed and dated written ICF.

The ICF must include all elements required by law, local regulations, GCP and ICH guidelines including consent to allow the Sponsor, Sponsor representative, or external regulatory auditor to review the subject's medical records. This gives permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study.

Any party with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the subjects' identities and Sponsor's proprietary information. It is the CRA's responsibility to verify that each subject has consented, in writing, to direct access.

12.3. Subject Participation Card

A study participation card will be provided to subjects where required by local regulations or IRB/EC. The card will indicate that he or she is participating in a clinical study and give the name and contact details of the Sponsor and the Investigator/study site. The subject will be asked to retain this card while participating in the study and show it to any other medical practitioners consulted during this time. Subjects will be advised to contact the Investigator/study site if there are any questions.

12.4. Insurance

Appropriate insurance for this study will be arranged by Affimed (or their delegate), as Sponsor of the clinical study, in accordance with the regulatory requirements of the countries involved. A copy of the country-specific insurance certificate will be held in the Trial Master File (TMF) and in the Investigator Site File.

12.5. Institutional Review Board/Independent Ethics Committee

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

12.6. Subject Privacy

The Investigator must ensure that subject privacy is maintained. On the eCRF or other documents submitted to the Sponsor, subjects will be identified by a subject number only. Clinical study documents that are not submitted to the Sponsor (e.g., signed ICF) should be kept in a confidential file by the Principal Investigator.

In accordance with local, national, or federal regulations, the Investigator will allow the Sponsor or their designee personnel access to all pertinent medical records to verify the data gathered on the CRFs and to audit the data collection process. Regulatory agencies such as the FDA may also

request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the subject as outlined in the subject consent form.

13. DATA HANDLING AND RECORDKEEPING

13.1. Recording of Data

The Investigator will be responsible for the recording of all data on the CRFs provided, as certified by the Investigator's signature and date on the designated pages. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the CRFs.

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

13.2. Study Record Retention

All clinical study documents must be retained by the Investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e., US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator must retain all clinical study documents until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, or by local regulations.

Subjects' medical files should be retained in accordance with applicable legislation and with the maximum period permitted by the hospital, institution, or private practice.

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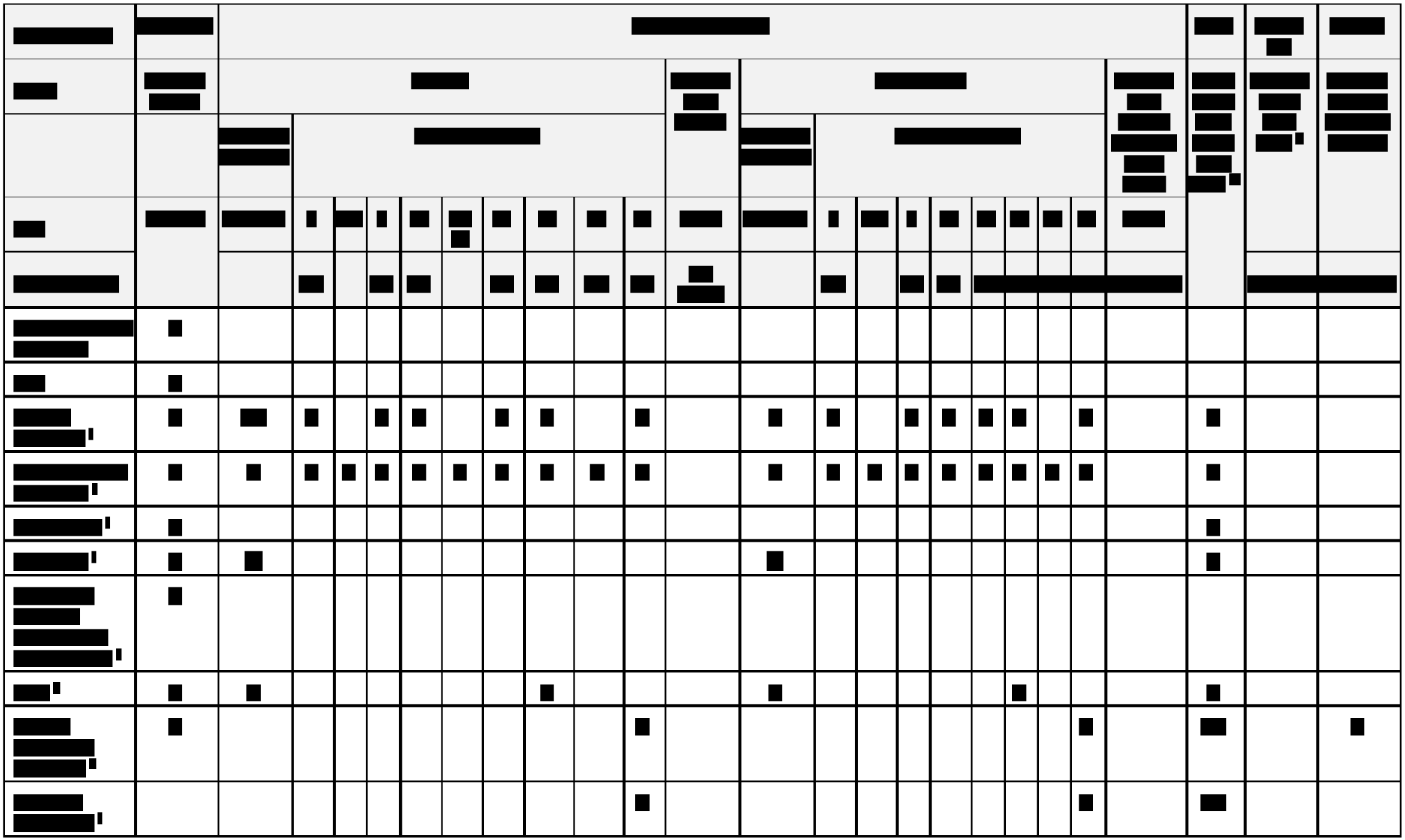

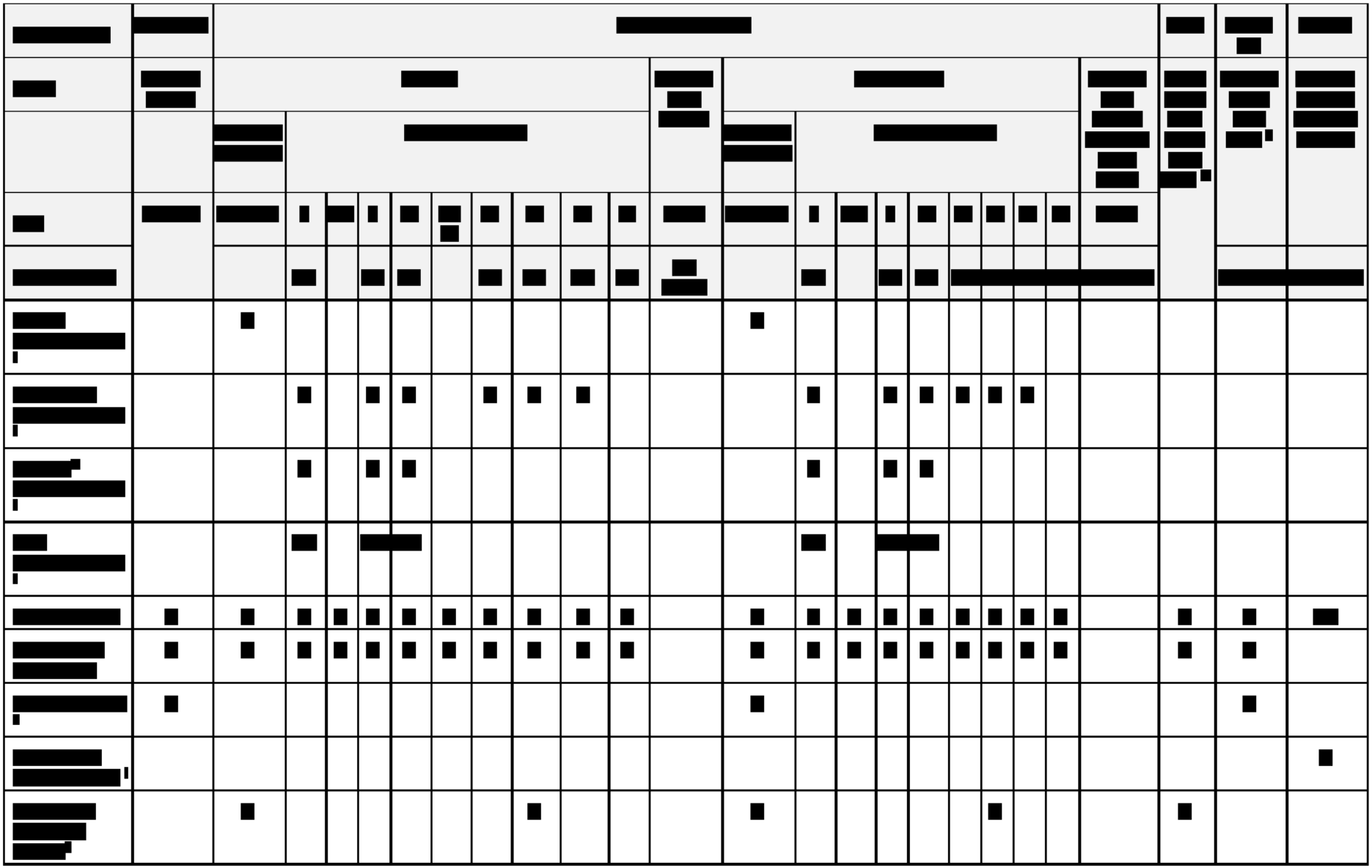

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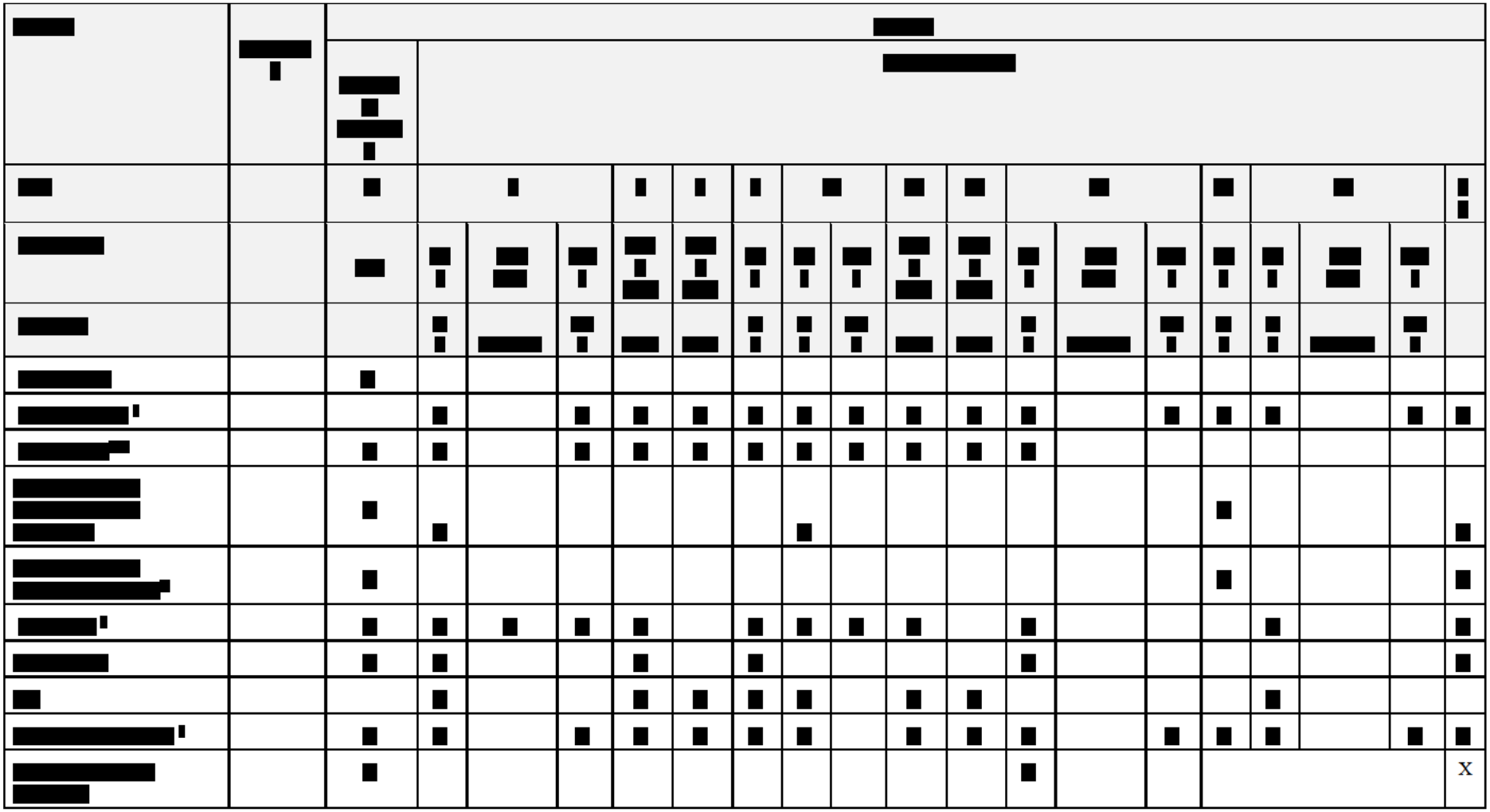

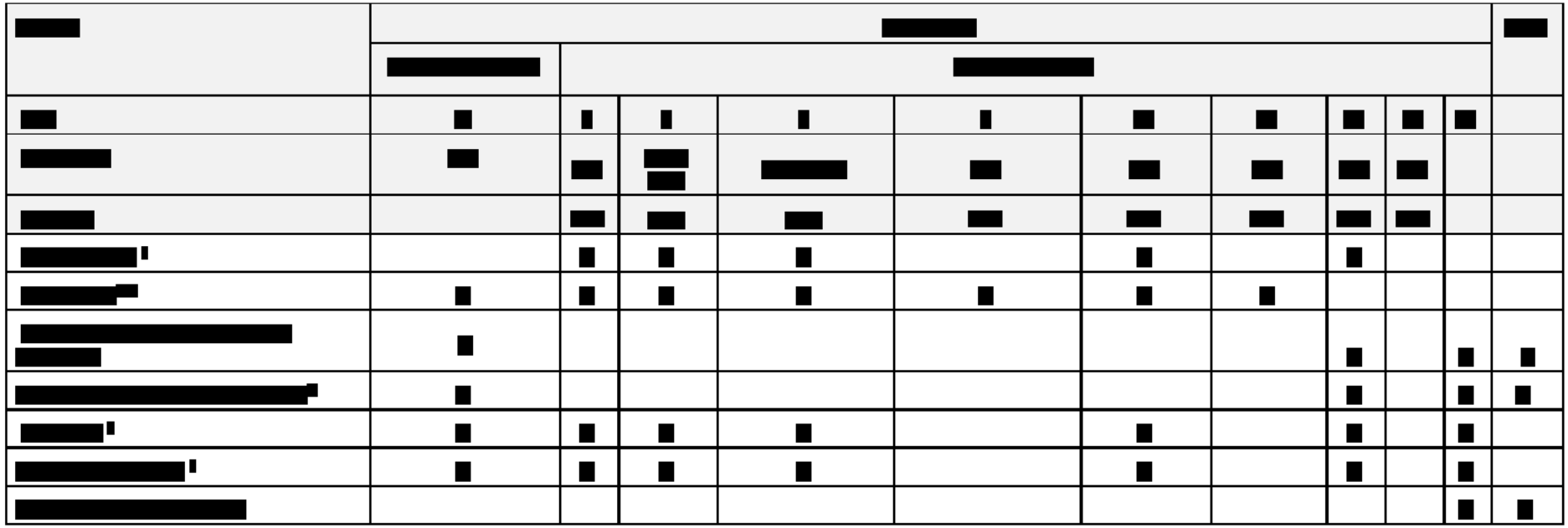

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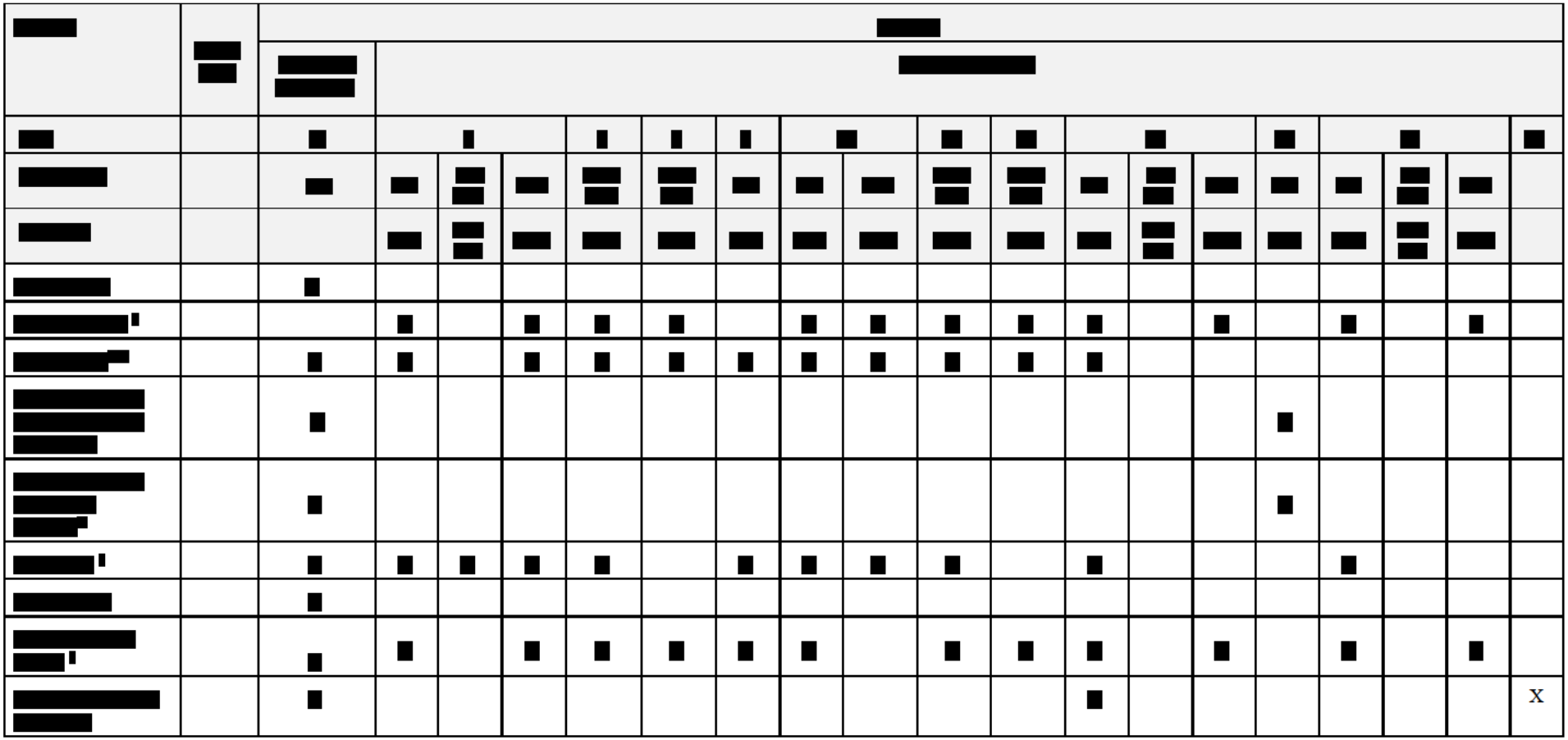

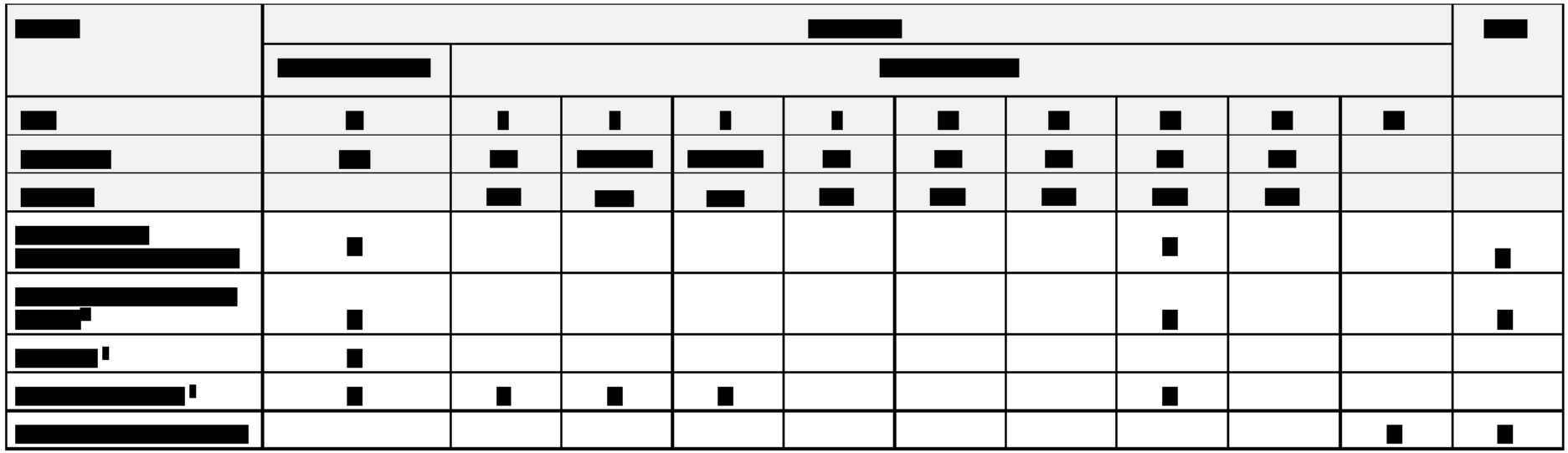

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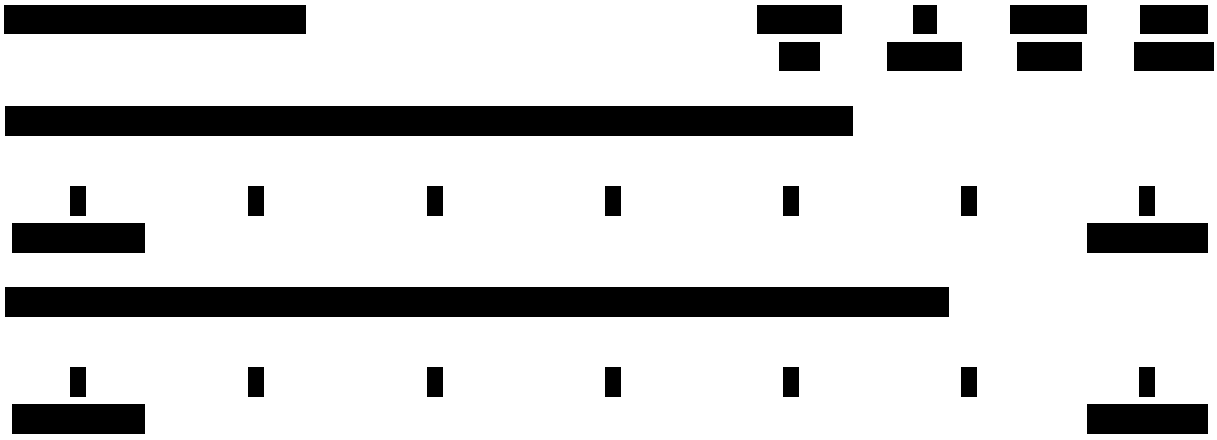

APPENDIX E. CONTRACEPTIVE GUIDANCE

Section E.1. Female Participants

Females of childbearing potential must agree to sexual abstinence (defined below) or be willing to use a highly effective method of contraception for the course of the study from 14 days prior to the first dose of lymphodepletion through 120 days after the last dose of study drug (acimtamig and/or AlloNK®). Acceptable highly effective birth control methods include:

- Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
- Intrauterine device;
- Intrauterine hormone-releasing system;
- Bilateral tubal occlusion;
- Vasectomized partner (provided that partner is the sole sexual partner of the female of reproductive potential and that the vasectomized partner has received medical assessment of the surgical success); and
- Sexual abstinence.

  In the context of this study, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 14 days prior to the first dose of lymphodepletion up to 120 days after the last dose of study drug (acimtamig and/or AlloNK®). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

Section E.2. Male Participants

Male subjects are eligible to participate if they agree to the following, starting with the first dose of lymphodepletion through 120 days after the last dose of study drug (acimtamig and/or AlloNK®)

- Refrain from donating sperm

AND

- Female partners must agree to use contraception/barrier as detailed below

Section E.3. Collection of Pregnancy Information

Male subjects with partners who become pregnant:

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the

Sponsor. Generally, the follow-up will be at least 8 weeks following the delivery. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

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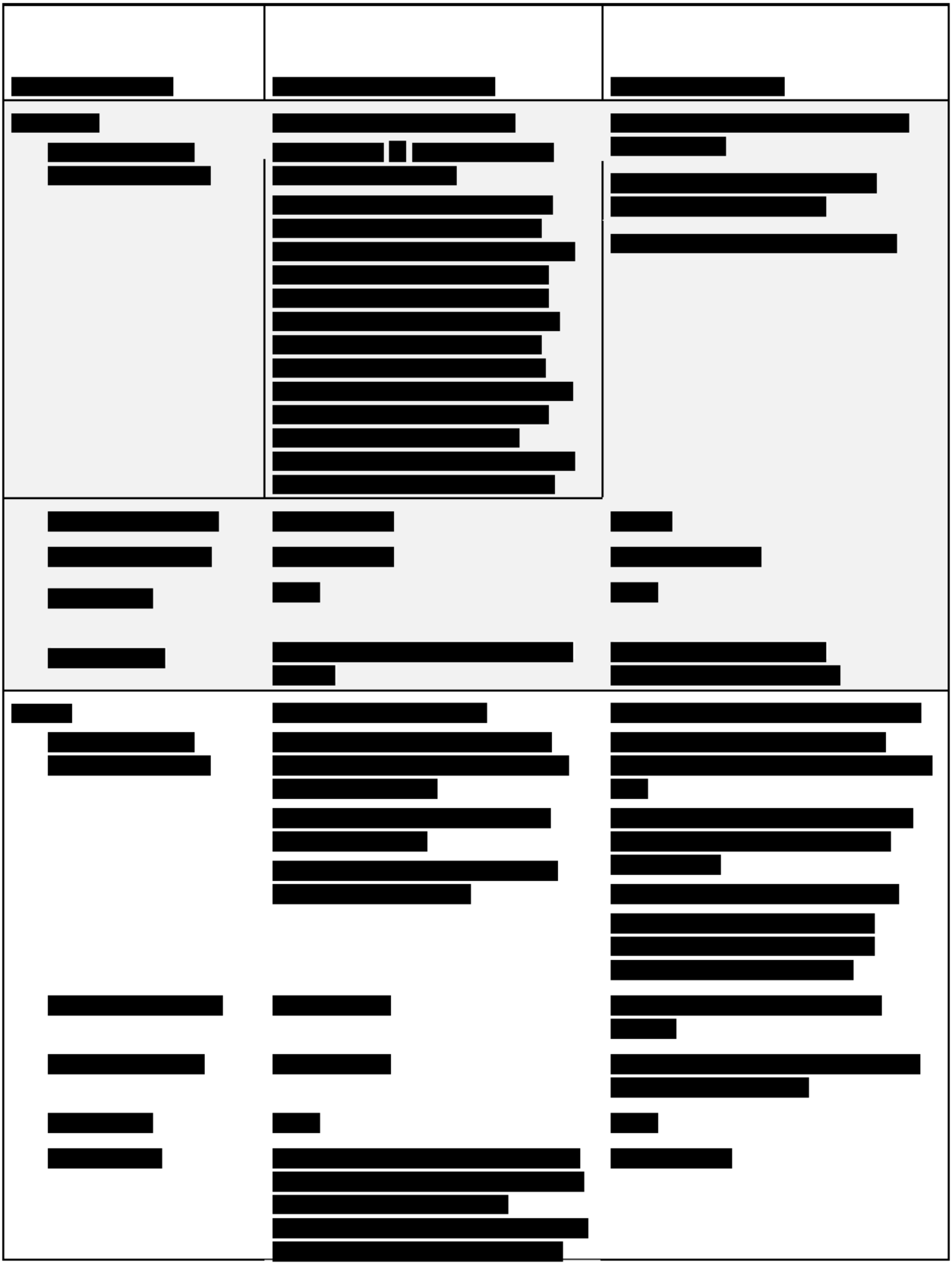

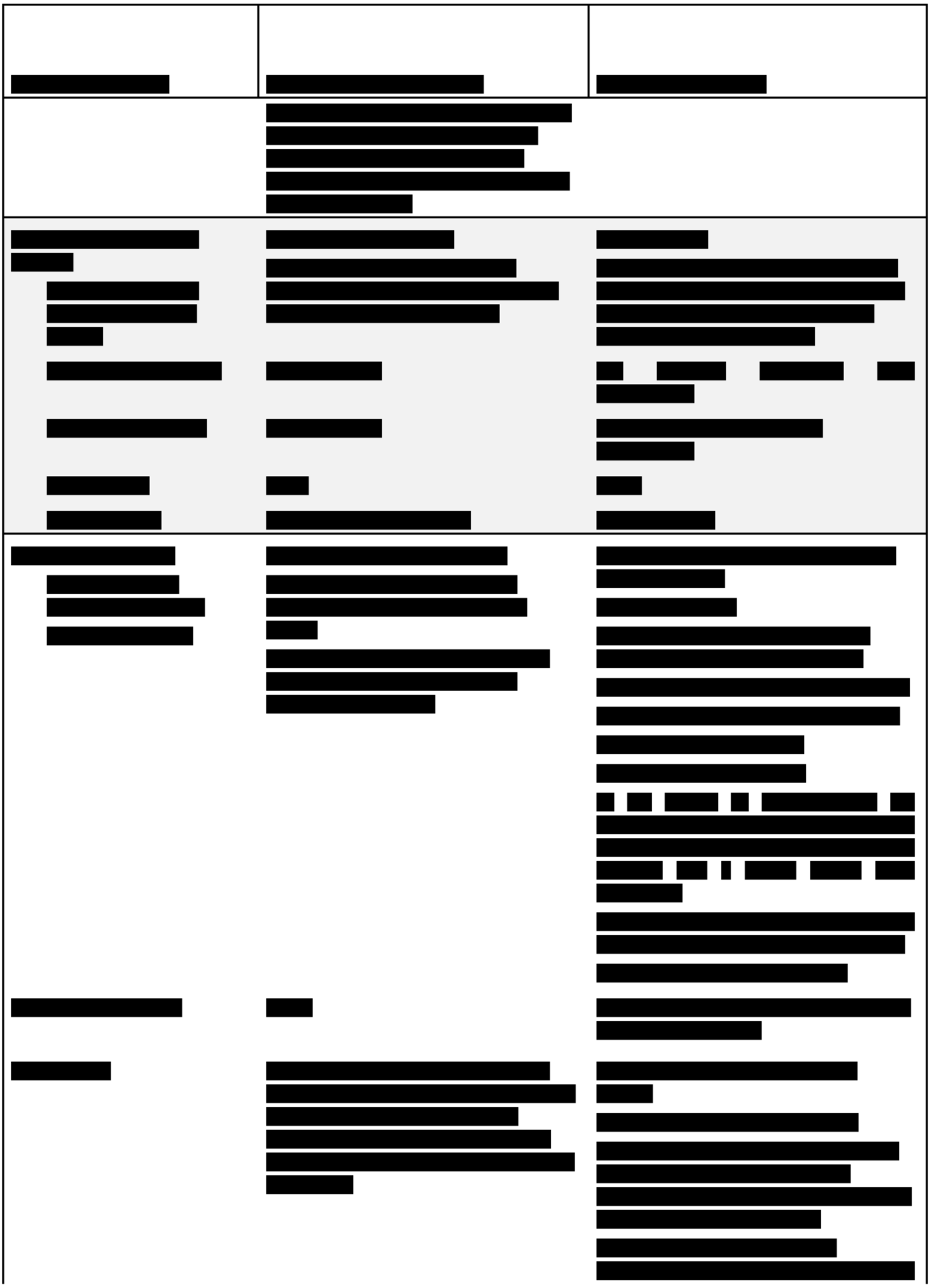

APPENDIX H. CAIRO-BISHOP DEFINITION AND GRADING OF TUMOR LYSIS SYNDROME

Table 14: Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Uric acid	x ≥ 476 µmol/L or 25% increase from baseline
Potassium	x ≥ 6.0 mmol/L or 25% increase from baseline
Phosphorous	x ≥ 1.45 mmol/L or 25% increase from baseline
Calcium	x ≤ 1.75 mmol/L or 25% decrease from baseline

Source: Cairo and Bishop 2004

Table 15: Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome

(1) Creatine: x ≥ 1.5 ULN (age >12 years or age adjusted)
(2) Cardiac arrhythmia/sudden death
(3) Seizure

Source: Cairo and Bishop 2004

Table 16: Cairo-Bishop Grading Classification of Tumor Lysis Syndrome

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
LTLS	–	+	+	+	+	+
Creatinine	≤ 1.5 × ULN	1.5 × ULN	> 1.5 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN	Death
Cardiac Arrhythmia	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure	None	-	One brief generalized seizure; seizure(s) well controlled by anti-convulsant(s) or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

Notes: Clinical tumor lysis syndrome (CTLS) requires one or more clinical manifestations (Table 14) along with criteria for laboratory tumor lysis syndrome (LTLS) (Table 15).
Maximal CTLS manifestation (renal, cardiac, neuro) defines the grade.
Source: Cairo and Bishop 2004