STUDY PROTOCOL

Version 6.0

Multicenter, double-blind, placebo-controlled, randomized withdrawal trial with Tadekinig alfa (r-hIL-18BP) in patients with IL-18 driven monogenic autoinflammatory conditions: NLRC4 mutation and XIAP deficiency

SHORT TITLE

THERAPEUTIC USE OF TADEKINIG ALFA IN NLRC4 MUTATION AND XIAP DEFICIENCY

Date:	03 Sep 2021
Version:	6.0
Protocol N°:	NLRC4/XIAP.2016.001
IND N°:	127953
EudraCT No:	2018-003297-27
Sponsor:	AB2 Bio Ltd EPFL Innovation Park Building B, 4th floor CH-1015 Lausanne, Switzerland

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition/Term
ACR20, ACR50	American Score of Rheumatology (score of rheumatoid arthritis improvement by 20%, 50%…)
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ANCOVA	Analysis of covariance
anti-rhIL-18BP	Anti-recombinant Human Interleukin-18 Binding Protein
AOSD	Adult onset Still's Disease
AUC	Area under the concentration-time curve
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German Health Authority)
C	Celsius
CAPS	Cryopyrin-Associated Periodic Syndromes
Cmax	Maximal concentration
CARD	Caspase Recruiting Domain
Con med	Concomitant Medication
CMV	Cytomegalovirus
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Event
DIRA	Deficiency of IL-1 Receptor Antagonist
DMARD	Disease Modifying Anti-rheumatic Drug
DSGCS	Disease Specific Global Composite Score
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr Virus
EC	Ethics Committee
eCCG	eCRF Completion Guidelines
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESR	Erythrocyte Sedimentation Rate
FAS	Full Analysis Set
FDA	Food and Drug Administration
FHL	Familial Hemophagocytic Lymphohistiocytosis
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl Transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HCN	Home Care Nurse
HCV	Hepatitis C virus
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
HLH	Hemophagocytic-Lymphohistiocytosis
i.p.	Intraperitoneal Injection
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFN-Y	Interferon gamma
IL-18	Interleukin-18
IL-18BP	Interleukin-18 binding protein
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IRB	Institutional Review Board

IRR	Incidence Rate Reduction
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
Kd	Dissociation constant
kD	Kilo dalton
Kg	Kilogram
LPLV	Last Patient Last Visit
mAIDAI	Modified Autoinflammatory Disease Activity Index
MAS	Macrophage Activation Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
NCI	National Cancer Institute
ng	Nanogram
NLRC4	Nucleotide-binding oligomerization domain, leucine rich repeat and CARD domain containing 4
MRI	Magnetic Resonance Imaging
NSAID	Non-Steroidal Anti-Inflammatory Drug
pg	Picogram
PBO	Placebo
PD	Pharmacodynamic
PGA	Physician Global Assessment
PK	Pharmacokinetic
PM	Project Manager
PO	Per os (by mouth)
PPS	Per-Protocol dataset
Pso	Psoriasis
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PT	Preferred Term
QOL	Quality of life
RA	Rheumatoid Arthritis
r-hIL-18 BP	Human Recombinant Interleukin-18 Binding Protein
RW	Randomized Withdrawal
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis dataset
SD	Standard Deviation
SDAI	Simple Disease Activity Index
SDV	Source Data Verification
SIV	Site Initiation Visit
SOC	Standard of Care
SUSAR	Serious Unexpected Suspected Adverse Reaction
TB	Tuberculosis
Th1 / Th17 cell	T helper cell type 1 / type 17
Tmax	Time to Maximal Concentration
TNF-α	Tumor Necrosis Factor α
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
V	Visit
WBC	White Blood Cells
XIAP	X-linked inhibitor of apoptosis
µL	Microliter

2 COORDINATING INVESTIGATOR SIGNATURE PAGE

COORDINATING INVESTIGATOR

[redacted]

The Children's Hospital of Philadelphia.
Philadelphia, PA 19107
[redacted]

.....
Date

.....
Signature

By my signature, I agree to supervise and oversee the conduct of this study and to ensure its conduct is in compliance with the protocol, informed consent, IRB/IEC procedures, instructions from AB2 Bio representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines and the applicable local regulations governing the conduct of clinical studies.

3 INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title:	Multicenter, double-blind, placebo-controlled, randomized withdrawal trial with Tadekinig alfa (r-hIL-18BP) in patients with IL-18 driven monogenic autoinflammatory conditions: NLRC4 mutation and XIAP deficiency

Protocol Number: NLRC4/XIAP.2016.001

By my signature, I confirm that my staff and I have carefully read and understand this protocol or protocol amendment, and agree to comply with the conduct and terms of the study specified. For protocol amendments, I agree not to implement the amendment without agreement from the Sponsor and prior submission to and written approval (where required) from the Independent Ethics Committee (IEC), or their equivalent, and regulatory authority, except when necessary to eliminate an immediate hazard to the patients, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

Investigator's Name

Institution Name, Address, Contact Details

Investigator's Signature **Date**

4 SPONSOR TEAM SIGNATURES PAGE

This study protocol was subject to critical review and has been approved by the Sponsor's appropriate protocol review committee. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the study drug.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice (GCP) as described in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events relating to treatment with the investigational product.

MEDICAL DIRECTOR

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[redacted]

.....
Date

.....
Signature

5 STUDY CONTACT INFORMATION

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Home Care Nurse for USA and Canada (Vendor)	[redacted] PCM Trials	1600 Emerson Street Denver, CO 80218 USA [redacted]
Home Care Nurse for Europe (Vendor)	Refer to site binder	Refer to site binder
Investigational Product (IMP) Supplier	Clinigen Clinical Supplies Management GmbH	IMP Labeling and Packaging (and IMP Distribution in Europe) by: Clinigen Clinical Supplies Management Europe GmbH Am Kronberger Hang 3 65824 Schwalbach a.Ts. Germany
	PCI Pharma Services	IMP Distribution (US and Canada) by: PCI Pharma Services 8946 Global Way West Chester, OH 45069 USA
Clinical Research Organization (CRO)	Precision for Medicine (previously Agility Clinical)	6005 Hidden Valley Road, Suite 170 Carlsbad, CA 92011 USA Refer to site binder for contact information

6 SYNOPSIS

NAME OF SPONSOR: AB2 BIO Ltd.

NAME OF STUDY DRUG: TADEKINIG ALFA
Human Recombinant Interleukin-18 Binding Protein (r-hIL-18BP)

PROTOCOL N°: NLRC4/XIAP.2016.001

TITLE OF STUDY
Multicenter, double-blind, placebo-controlled, randomized withdrawal trial with Tadekinig alfa (r-hIL-18BP) in patients with IL-18 driven monogenic autoinflammatory conditions: NLRC4 mutation and XIAP deficiency

DEVELOPMENT PHASE: 3

STUDY DESIGN

This is a Phase 3 study to assess the safety and efficacy of Tadekinig alfa in patients with monogenic, interleukin-18 (IL-18) driven autoinflammation due to Nucleotide-binding oligomerization domain, leucine-rich repeat and caspase recruiting domain (CARD domain) containing 4 (NLRC4) – Macrophage activation syndrome (MAS) mutation (NLRC4-MAS mutation) or X-linked inhibitor of apoptosis (XIAP) deficiency. Because of the likelihood for pathogenic IL-18 in certain monogenic diseases, patients known to harbor deleterious mutations in NLRC4-MAS or XIAP and who have a history of ongoing inflammation will be enrolled if they have ferritin ≥ 500 ng/mL or persistent C-reactive protein (CRP) elevation > 2 times the upper limit of normal (ULN) and the patients should have a Modified Autoinflammatory Disease Activity Index (mAIDAI) ≥ 4.

The study is designed with a single-arm, open-label phase (SAOL) of Tadekinig alfa treatment duration for 18-weeks followed by a 16-week Randomized Withdrawal (RW) phase for efficacy and safety evaluation, with no interruption between the two phases of treatment.

The screening period will occur before the SAOL phase and before the first dose of Investigational Medicinal Product (IMP).

Methodology

- Single-arm, open-label Phase

The Screening visit (V0) will occur before the start of the study treatment. At V0, the patient and/or the patient's legal guardian(s) will sign a Child Assent Form and/or an Informed Consent Form that will be collected by the Investigator. All eligibility criteria will be reviewed during the screening period AND must all be met in order to determine patient eligibility into the study. Eligibility criteria should be confirmed again at the Baseline Visit (V1).

Patients experiencing an active disease will start Tadekinig alfa treatment at V1.

Beginning at V1, Tadekinig alfa (TA) will be administered in addition to the standard of care (SOC) treatment used for the control of the active disease.

In the absence of an approved medication for this disease, the SOC as defined in this protocol consists of glucocorticoids (GC), with a 28-day tapering schedule as follows:

- 28-days (4 weeks): Daily PO/IV Dexamethasone 10 mg/m2 x 7 days, 5mg/m2 x 7 days, 2.5 mg/m2 x 7 days, 1.25 mg/m2 x 7 days

Patients who respond to the initial TA + GC 28-day course (see Definition of Partial and Complete Response to Therapy) will receive Tadekinig alfa for 14 additional weeks.

Patients who responded to TA + SOC initial course and have a disease reactivation again during the course of the study will receive another course of TA + SOC with the same GC dosage and tapering schedule used for the initial treatment of the active disease (see explanations below). Maintenance treatment, with the permitted medications, at stable and at the same doses utilized at study entry are allowed. Dose increments for the permitted co-medications or their introduction after the beginning of the study are not permitted and represent treatment failures and study early termination. If permitted co-medications are weaned off during the course of the study and the investigator decides to re-introduce them, they are permitted as long as the doses are the same or lower than the doses used at study entry.

Upon lack of response to combined treatment after enrollment or upon the occurrence of a disease reactivation during the course of the SAOL after initial response, the investigator may decide to treat the patient with rescue immunosuppressors. This decision results in patient discontinuation for the study.

Tadekinig alfa will be administered at 2 mg/kg subcutaneously (s.c.) for up to approximately 18 weeks.

At V0 and V1, patients will undergo a physical examination, measurement of vital signs, and routine laboratory testing (including hematology, clinical chemistry, urinalysis, erythrocyte sedimentation rate (ESR), CRP, and coagulation panel). Biological evaluation and genetic diagnosis of autoinflammatory conditions (NLRC4-MAS, XIAP deficiency, and other monogenic associations with Macrophage Activation Syndrome [MAS]) will be done at V0. Samples for flow cytometry will be analyzed during the screening period and prior to V1. Complete medical and disease history will also be collected during V0. In addition, prior to initiation of therapy, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) tests, serology tests, and a complete infectious workup will be performed.

Specific laboratory determinations such as total and free IL-18 and IL-18BP will be performed at V1 and subsequent visits.

The global disease activity will be assessed by the mAIDAI. The mAIDAI will be applied at all study visits and will be available for review throughout the study. For the evaluation of response to therapy and disease reactivation, only the objective parameters of the mAIDAI will be taken into consideration. A Physician Global Assessment (PGA) tool will also be applied at all study visits by the physician to assess the global disease status. The patient's or caregiver's evaluation of the health status questionnaire will be applied at V1

and the end of the SAOL phase.

Assessments during the SAOL phase, treatment period of 18 weeks (V1 to V8), will include complete physical examination, review of all adverse events (AEs), and routine and specific laboratory analysis (for further details, refer to the safety and efficacy assessment section).

Samples for anti-drug antibodies (ADAs) will be collected at Baseline of SAOL (V1), Week 2 (V3), Week 4 (V5), Week 12 (V7), and Week 18 (V8).

At the end of the SAOL phase, all patients who completed the phase with a partial or complete response at V8 will be enrolled in the RW phase.

- Randomized Withdrawal (RW) Phase

All patients who have completed 18 weeks of treatment during the SAOL phase and showing a partial or complete response at Week 18 (V8) will be blindly randomized to one of the two treatment arms in a 1:1 ratio to begin treatment in the RW phase. Week 18 will be the baseline of the RW phase.

Experiencing a disease reactivation at any point during the 18-week SAOL phase will not prevent a subject from enrollment into the RW phase; rather, patients are required to meet the criteria for ongoing TA treatment throughout the SAOL phase and show a partial or complete response at Week 18. Patients will receive the study treatment (placebo or TA) for up to additional 16 weeks. Residual components of disease may be present but if they still meet the definition of at least partial response, patients will be enrolled in the RW phase.

Treatment interruption is not recommended between the two phases. Baseline data for the RW phase will be the data collected prior to randomization at the Week 18 (V8) visit.

During the RW phase, visits will be scheduled at Week 20 (V9), Week 22 (V10), Week 26 (V11), Week 30 (V12) and Week 34 (V13/End of Study).

At RW visits, patients will undergo a complete physical examination and laboratory testing (including hematology, clinical chemistry, urinalysis, ESR, CRP, ferritin, and coagulation panel), determinations of total and free IL-18 and of IL-18 BP. The mAIDAI and PGA will be applied at all visits in the RW phase. The patient's or caregiver's evaluation of the health status questionnaire will be applied at the end of the RW phase.

Samples for anti-drug antibodies (ADAs) will be collected at RW Week 22 (V10), Week 26 (V11), and Week 34 (V13).

During the RW phase, patients who develop a partial or full disease reactivation before the 16-week treatment is completed will proceed to the End of Study visit and complete the RW phase. The investigator may also decide to start rescue immunosuppression and discontinue treatment.

If applicable, data on administration of other medications or rescue immunosuppression during both phases (SAOL and RW) will be collected, including the time of treatment start and finish and whether or not there was a response to the rescue treatment.

Patients who discontinue treatment prior to the end of either treatment phase (SAOL or RW) will be followed for all key efficacy and safety assessments.

NOTE: The FDA draft guidance (Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, December 2012) indicates that the RW design should include patients who demonstrated treatment response.

- Additional Standard of Care Cycles or Rescue Immunosuppression in SAOL Phase:

A) If no response after the first combined treatment course (SOC + IMP) at the initiation of the SAOL phase:

If patients do not respond to therapy (see Definition of Partial and Complete Response to Therapy and Disease Improvement) after the initial combined treatment course, they will be treated with rescue immunosuppression or with new/ increased doses of Permitted Concomitant Treatments. Patients treated with rescue immunosuppression or new/ increased doses of Permitted Concomitant Treatments will be considered treatment failures and exit the study

B) Patients with a disease reactivation after having responded to therapy in the SAOL Phase.

If patients show signs of systemic inflammatory reactivation (i.e. partial or full disease reactivation) after having responded to therapy in the SAOL phase, they will receive another cycle of SOC in addition to the IMP.

C) Patients with a disease reactivation during the tapering down of the SOC during the combined treatment in the SAOL Phase:

If, after an initial improvement in response parameters, the patients show again signs of increasing inflammation (i.e. partial or full disease reactivation) during the tapering down of SOC while in combined treatment, another full cycle of extended SOC (4 weeks) in addition to the IMP will be initiated at the original dose.

In the last cases (B or C), the Investigator may also decide to start rescue immunosuppression treatment, and in this case the patient should discontinue study treatment due to treatment failure.

Note to treatment failure:
Any patient starting rescue immunosuppression treatment will be considered a treatment failure and will proceed to the study discontinuation/early termination procedures. Data related to response to the rescue treatment will be collected including all key efficacy and safety assessments.

It is recommended that patients suffering from severe CNS manifestations are put on rescue immunosuppression treatment.

Note to treatment of disease reactivations:
Patients that present a partial or full disease reactivation after previous response to SOC + TA in the SAOL phase can remain in the study, and receive another cycle of SOC in addition to the continuous TA treatment, if according to treating physician, the severity does not require rescue immunosuppression.

Patients that present a partial or full disease reactivation in the RW phase before the 16-week treatment is completed will proceed to the End of Study Visit and complete the RW phase.

Note - normal ranges for ferritin and CRP:
The normal ranges of ferritin and CRP differ per age and respective normal ranges per age at the central or local laboratory will be used as reference.

Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be notified by the contracted Clinical Research Organization (CRO) of clinical or biological worsening of the status of study subjects (i.e., Serious Adverse Events (SAEs)) and also of treatment failures. The DSMB will assess the global safety of Tadekinig alfa and advise whether to continue or discontinue the study. DSMB roles and responsibilities are delineated in the DSMB charter along with the reporting requirements of the Sponsor/CRO to the DSMB. The Investigator will evaluate safety for each individual patient and decide whether to stop or continue treatment, or when to start the rescue immunosuppression.

BACKGROUND (RATIONALE)

Autoinflammatory diseases are caused by innate immune dysregulation and typically present in early childhood with fever and disease-specific patterns of systemic and organ-specific inflammation and dysfunction. Many genetic causes of autoinflammatory diseases have been identified, and associations between specific genes and distinct autoinflammatory conditions have been established. The molecular links between causative genes, specific inflammatory pathways, and defined disease phenotypes represent substantial progress in identifying rational therapies in frequently refractory clinical conditions.

IL-1 blocking therapies have represented an important step forward in the treatment of autoinflammatory conditions. IL-1 blockade in the NLRP3 related Cryopyrin-Associated Periodic Syndromes (CAPS) and Deficiency of IL-1 Receptor Antagonist (DIRA) has been shown to be very efficacious. However, in other autoinflammatory conditions, the response to treatment has been anecdotal and limited to case reports. Thus, the extension of IL-1 blockade from CAPS to other autoinflammatory entities has been largely empiric.

Other auto-inflammatory conditions are related to different genetic defects that trigger other cellular pathways of activation with the production of different mediators. Spontaneous gain-of-function mutations of the NLRC4 inflammasome have been associated with severe early-onset auto-inflammatory conditions with recurrent MAS-like flares, and some patients may present with severe enterocolitis. NLRC4 mutations also result in

constitutive IL-18 hypersecretion.

A patient suffering from NLRC4 mutation was treated with Tadekinig alfa within the frame of an emergency individual patient IND [redacted] approved by the FDA on June 9, 2015. The [redacted] old infant developed generalized, severe, life-threatening MAS with severe enterocolitis, intolerance to enteral feeding, due to an NLRC4 pathogenic mutation (V341A). The patient showed elevated total IL-18 (>50,000 pg/mL) and free IL-18. Aggressive treatment with a combination therapy including steroids, cyclosporine, IL-1β, TNFα, and integrin α4/β7 inhibitors resulted in slight clinical improvement. After receiving a 2-mg/kg dose of Tadekinig alfa, the patient responded immediately to the treatment with rapid improvements in CRP and ferritin, with free-IL-18 levels dropping to below detection levels. Continuous treatment with 2-mg/kg Tadekinig alfa, every other day, resulted in dramatic normalization of disease activity measures such as ferritin and CRP levels and enteropathy. Oral intake was improved. Co-medications, including cyclosporine and corticosteroids, were phased out. The patient was discharged from the hospital after 20 days of treatment. The patient is still on treatment without symptoms or markers of disease activity as of Sep 2021.

X-linked inhibitor of apoptosis (XIAP is frequently associated with Hemophagocytic-Lymphohistiocytosis (HLH), a MAS-like syndrome, but can also have other phenotypes of disease presentation. Similarly to patients with NLRC4-MAS and those with other MAS-prone disorders, patients with XIAP deficiency and a MAS-like phenotype also show high levels of serum IL-18.

AB2 Bio, in collaboration with Dr. [redacted] from Cincinnati Children's Hospital Medical Center, conducted a study in XIAP deficiency pediatric patients to examine the levels of free IL-18 during episodes of active disease and during disease remission. Patients with XIAP deficiency have circulating free IL-18 during active disease and in remission. Higher levels were observed during disease flares. This observation supports the contention that free IL-18 may contribute to the propensity of these patients to develop MAS/HLH.

The constitutive production and secretion of IL-18 by monocytes, macrophages and probably other cell types, and the presence of serum-free IL-18 in both pediatric MAS-like conditions, NLRC4-MAS, and XIAP deficiency, in contrast with other early-onset autoinflammatory conditions such as NOMID, suggests that IL-18 blockade represents not merely another option for the treatment of autoinflammatory diseases, but the most appropriate treatment for this category of patients.

The extremely low incidence of both genetic conditions (1-2 cases per million live births), the common propensity to develop recurrent MAS episodes, and the immunodominant role of IL-18, are factors that have lent support to group the two entities in this trial. This was decided on after consultation with the FDA.

STUDY CENTER (S) / PARTICIPATING COUNTRIES

Approximately 11 clinical sites in the United States, Canada and Germany

OBJECTIVES

Primary Efficacy Objectives

- To assess clinical efficacy of Tadekinig alfa in monogenic autoinflammatory diseases with ongoing inflammation and deleterious mutations of NLRC4-MAS or XIAP
- To assess laboratory/biological evidence of efficacy

Secondary Efficacy Objective

- Main clinical features and laboratory biomarkers (characteristics of each patient profile) will be assessed longitudinally during the SAOL phase for each experimental subject

Secondary Safety Objective

- To assess the safety and tolerability of Tadekinig alfa treatment in monogenic, autoinflammatory disease harboring deleterious mutations of NLRC4-MAS or XIAP

NUMBER OF PATIENTS

An estimated maximum of 15 patients will be enrolled in the study

Note: A maximum of 15 patients enrolled will ensure the randomization of at least 10 patients in the RW phase.

INCLUSION CRITERIA

All entrance criteria must be met in order to enroll;

Eligibility criteria should be evaluated at Screening (V0) prior to V1 and rechecked at Baseline (V1) prior to study treatment.

1. Patients with genetic diagnosis of NLRC4-MAS mutation or XIAP deficiency (caused by BIRC4 gene mutation) as confirmed by analysis performed at the central genetics laboratory. If possible, flow cytometry assay will be performed in parallel to confirm diagnosis of XIAP deficiency. (Note: Previous flow cytometry assay results will be permitted for confirmation of XIAP deficiency diagnosis.) A genetic diagnosis from a local laboratory will be accepted for enrolment and start of treatment, to avoid any treatment delays for these severe conditions. However, the genetic diagnosis has to be confirmed by the central laboratory. If the genetic diagnosis is not confirmed, the patient will discontinue the study.
2. Patients with XIAP deficiency and a previous bone marrow transplantation are allowed, if they show evidence of primary or secondary graft failure, or failure to achieve phenotypic correction with evidence of XIAP-related disease recurrence or clinically significant mixed chimerism. For these patients, genetic diagnosis at the central laboratory may show chimerism; thus, local genetic diagnosis prior to the bone marrow transplantation will be the main source to confirm the genetic diagnosis.
3. Ferritin ≥ 500 ng/mL or persistent elevation of CRP ≥ 2x ULN and mAIDAI ≥ 4
4. Patients receiving corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) or disease modifying anti-rheumatic drugs (DMARDs), and/or

IL-1 blockade with insufficient response to treatment upon enrollment are allowed into the study. Patients not receiving any of these treatments before start of therapy are also allowed.

5. Women of childbearing potential with negative urine pregnancy test (UPT) at all visits (if UPT is positive, a blood test for human chorionic gonadotropin (hCG) to be performed) and who agree to follow highly effective birth control recommendations during the study and until 1 month after the end of the treatment. Birth control methods considered highly effective are: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner or sexual abstinence. In each case of delayed menstrual period (over one month between menstruations, confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles. A post-study contraception duration of 4 weeks is recommended taking into account the median half-life of Tadekinig alfa of almost 40h and 5 half-lives representing a duration of 200 hours.

EXCLUSION CRITERIA

1. Patients with life-threatening co-morbidities not associated with the underlying NLRC4-mutation or XIAP deficiency
2. Positive test for or prior history of HIV, Hepatitis B or Hepatitis C (serology)
3. Presence of active infections or a history of pulmonary TB infection with or without documented adequate therapy (QuantiFERON-TB test)
4. Presence of life-threatening infections (clinically and quantitated PCR if necessary)
5. Oncologic causes of symptoms; current or previous history of malignancy
6. Presence of CNS manifestations (i.e. seizures, altered mental status, signs of increased intracranial pressure, chronic papilledema, loss of vision, other sensorineural deficiencies, etc.)
7. Patients suffering from biallelic mutations in any of the following genes: PRF1/Perforin, UNC13D/Munc 13-4, STX11/Syntaxin11, STXB2/Munc 18-2, RAB27A/Rab27a (Griscelli syndrome type 2), LYST (Chediak-Higashi syndrome), AP3B1, ADTB3A, HPS2 mutations (Hermansky-Pudlak syndrome 2) and X-linked lymphoproliferative syndrome (XLP)-1 with SH2D1A mutation
8. Patients who are pregnant or nursing, women of childbearing potential who are unwilling to use highly effective birth control methods (see definition in Inclusion Criteria above) through 4 weeks after the end of their participation in the study
9. Concomitant use of immunosuppression therapies excluded by the protocol. Note: NSAIDs, glucocorticoids, cyclosporine, tacrolimus, and IL-1 inhibitors (anakinra, canakinumab, or rilonacept, or others) are allowed

10. Patients and/or parents (or legal representative, if applicable) not willing to sign assent/informed consent
11. Hypersensitivity to the active substance or one of the excipients of the investigational product

**** NOTES:***

For Exclusion Criterion 7, lab testing will be performed at Screening (V0). Results should be available for V1 to confirm eligibility. In case treatment is started based on local laboratory genetic results, which don`t include the above listed genes, genetic results have to be confirmed by central laboratory retrospectively as for inclusion criterion 1.

For Inclusion Criterion 1, results from genetic testing will be available prior to treatment initiation.

STUDY DURATION

Approximately 6 years from First-Patient-First-Visit (FPFV) to Last-Patient-Last-Visit (LPLV)

After screening, patients will enter the SAOL phase of 18-weeks duration. Subsequently, eligible patients will enter the 16-week RW phase.

DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

Tadekinig alfa is a soluble glycoprotein of [redacted] amino acids produced from a Chinese Hamster Ovary (CHO) cell line. The polypeptide chain contains [redacted]. The average molecular weight of the full-length polypeptide moiety of r-hIL-18BP calculated on the basis of the amino acid composition is approximately [redacted] kD. The relative molecular mass of the whole molecule is approximately [redacted] kD (including glycans).

Tadekinig alfa is supplied as a colorless to slightly yellow, sterile solution for injection in glass vials containing [redacted] as excipients. It is available in a concentration of 20mg/0.5mL.

The placebo will be supplied in identical volume and aspect.

DOSE/ROUTE/REGIMEN

Patients will receive a dose of 2 mg/Kg (with a maximum of 160 mg) of Tadekinig alfa s.c. every 2 days ± 5 hours for a total treatment duration of 18 weeks in the SAOL phase.
Note: patients with more than 80 kg body weight will receive the maximum dose of 160 mg.

Patients in the RW phase will be treated with the same dosage or volume (2 mg/kg, s.c. every 2 days) of either Tadekinig alfa or equivalent volume of Placebo as randomized. The treatment period in this phase is up to 16 weeks.

CONTROL(S) The isotonic sodium chloride and [redacted] sterile vehicle will be used as placebo.

EFFICACY ASSESSMENT

Efficacy assessment is related to the incidence of disease reactivations and will cover:

Clinical evaluation (mostly captured in the mAIDAI):

- Complete physical examination including: vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, weight, and body temperature)
- All findings should be documented: joint swelling, hepatomegaly and splenomegaly, presence of skin rash, ophthalmic control (presence of uveitis). Ophthalmic examination will be performed to examine the presence/absence of uveitis and, if present, the evolution during the study
- Symptoms should be documented: abdominal pain, diarrhea, nausea, vomiting
- All clinical components (including clinical findings and symptoms) of the disease will be captured in a binary way as either being present or absent. The judgement, of whether an end organ category is affected, is done by the treating physician according to clinical standards, as also previously done for all mAIDAI components.
- Daily weight, stool output, and PO intake measurements including number of emesis episodes will be performed on patients with intestinal dysfunction, only when the patients are hospitalized
- Radiologic findings if assessed as necessary by the treating physician

Maintenance co-treatment:

- Total weekly glucocorticoids
- IL-1 blockers
- Other treatments* (e.g., DMARDs, etc.)

*Refer to Section 11.2.4: Concomitant treatment

Laboratory (see Table 2):

- Serum CRP
- Serum Ferritin
- Complete blood counts
- Serum levels of total IL-18, free IL-18, IL-18BP

Note 1: *Gastrointestinal (GI)-related parameters will be assessed in patients with GI dysfunction*

Note 2: *For outpatient therapy the clinical evaluation will be performed at the monthly visits*

DEFINITION OF ACTIVE DISEASE UPON ENROLMENT

- Increased inflammatory markers, i.e. serum ferritin levels ≥ 500 ng/mL or serum CRP ≥ 2x ULN, and
- Active clinical disease as evidenced by mAIDAI ≥ 4 or CNS manifestations (i.e. seizures, altered mental status, signs of increased intracranial pressure, chronic papilledema, loss of vision, other sensorineural deficiencies, etc.)

For the definition of active disease upon enrolment, all mAIDAI components (subjective and objective) will be evaluated in line with previous protocol versions.

DEFINITION OF RESPONSE TO THERAPY

1. In the 16-week RW phase, response to therapy (as primary endpoint of efficacy) will be assessed by prevention of disease reactivations during the 16-week treatment in the RW phase
2. In the SAOL phase, response to therapy (as secondary endpoint of efficacy) will be assessed through the control of the active disease

For response to therapy, only the objective mAIDAI components will be evaluated as indicated below. Subjective mAIDAI components (see Appendix I) will not be considered to avoid any bias in the efficacy assessment in the open label part of the study. Justification for the revised response to therapy definitions is included in section 8.3.3.

- **Complete response**

  No major end organ damage (=objective mAIDAI components)
  - No fever (body temperature ⩽100.4° F/38° C)
  - No diarrhea
  - No transaminitis and/or hepatomegaly
  - No splenomegaly and/or adenopathy
  - No rash
  - No uveitis
  - No arthritis
  - No radiologic CNS involvement
  - No cytopenia (HgB ⩾ 9.0 and/or PLT ⩾100 and/or WBC ⩾3.0)

  No systemic inflammation
  - No hyperferritinemia (serum level < 500 ng/mL)
  - No increased CRP (serum level < 2x ULN)

  Immunosuppressive therapies
  - Discontinuation of systemic corticosteroids (excluding hydrocortisone for prevention of adrenal insufficiency) or other immunosuppressive therapies including biologics ongoing at baseline
  - No start or dose increase of other immunosuppressive therapies including biologics

- **Partial response**

  At least 50% reduction of the number of affected objective end organ damage categories at baseline and

  - At least 50% of the systemic inflammatory markers (ferritin and/or CRP) increased at baseline reaching levels for complete response or
  - Discontinuation of systemic corticosteroids (excluding hydrocortisone for prevention of adrenal insufficiency) or other immunosuppressive therapies including biologics ongoing at baseline

- **Disease Improvement**

A third response category of Disease Improvement is introduced to be utilized as a description of best response and in order to better describe initial treatment response to therapy and disease evolution over time. This is only used for analysis purposes and will not be evaluated for the decision whether to be eligible for the start of the RW phase. Disease Improvement is defined as:

- Reduction of the number of affected objective end organ damage categories at baseline by at least 1 or
- Normalization (i.e. reaching levels for complete response) or improvement (> 50% change from baseline for laboratory markers but still exceeding levels for complete response) of at least 50% of the systemic inflammatory markers affected at baseline
- Systemic corticosteroids (excluding hydrocortisone for prevention of adrenal insufficiency) or other immunosuppressive therapies including biologics must be at the same or lower doses compared to baseline

DEFINITION OF DISEASE REACTIVATION

For disease reactivation, only the objective mAIDAI components will be evaluated as indicated below. Subjective mAIDAI components (see Appendix I) will not be considered to avoid any bias in the assessment. Justification for the revised disease reactivation definitions is included in section 8.3.3.

During the RW-phase, the reference for a disease reactivation (for the primary endpoint assessment) will be the end of the SAOL phase (V8); for the SAOL phase, reference will the previous visit, as patients enter the SAOL phase with an active disease.

- **Partial disease reactivation ,**
  - Increase in the number of affected objective end organ damage categories by at least 2 or
  - Increase in the number of affected objective end organ damage categories by at least 1 and worsening of at least 1 systemic inflammatory marker (i.e. serum ferritin levels ≥ 500 ng/mL or serum CRP ≥ 2x ULN) that was meeting complete response criteria before

- **Full disease reactivation**
  - Increase in the number of affected objective end organ damage categories to at least the number of affected objective end organ damage categories at baseline (V1) and
  - Exacerbation of at least 1 systemic inflammatory marker (i.e. serum ferritin levels ≥ 500 ng/mL or serum CRP ≥ 2x ULN) that was meeting complete response criteria before

Note: It is recommended that patients suffering from *severe* CNS manifestations are put on rescue immunosuppression treatment.

SAFETY ASSESSMENT

The Investigator will assess patient safety throughout the study. In addition, the DSMB, an independent committee, will analyze clinical or biological worsening of the status of study patients (i.e., SAEs) and also treatment failures and will assess the global safety of Tadekinig alfa (see details in Study Design section of Synopsis).

Safety assessment during the study will include:

- Prior to initiation of therapy, physical examination, vital signs, testing for active and life-threatening infections, complete blood count, clinical chemistry, coagulation and urinalysis.
- During treatment phase, physical examination, including ophthalmic examination, vital signs, routine laboratory (complete blood count, clinical chemistry, urinalysis), AEs, including AEs of Special Interest (AESI), concomitant medications, local tolerability index, immunogenicity, and coagulation tests.
- Regarding immunogenicity, ADAs assessment will be performed at V1, Week 2 (V3), Week 4 (V5), Week 12 (V7), Week 18 (V8), and RW Week 22 (V10), Week 26 (V11) and Week 34 (V13).
- Safety and disease activity labs will be assessed during hospitalization as required, weekly during visits for the first four weeks, then approximately monthly during visits until completion of the study, or at unscheduled visits.

  - weekly from Visit 0 to Visit 5;
  - monthly from Visit 6 to Visit 7;
  - at Visit 9 (2 weeks from Visit 8);
  - at Visit 10 (2 weeks from Visit 9);
  - monthly from Visit 11 to Visit 13.

AEs will be collected from the time of informed consent through the end of the study. Definitions and reporting procedures for AEs and SAEs are provided in Section 16. “Handling of Adverse Events”.

Details on routine safety laboratory assessments, virology, and serology tests, and collection of samples for ADAs (immunogenicity) are provided in Table 2.

Physical examinations and vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, weight and body temperature) will be collected at all visits. Height is collected at Screening.

The Local Tolerability Index is provided in Appendix 2.

**** NOTE:***

Laboratory safety and efficacy endpoints will be studied at the visits by the central lab. For hospitalized patients, local labs will perform, in addition, analyses as required by the standard of care and this information will be entered in the study eCRF.

PRIMARY ENDPOINTS: EFFICACY

- The primary outcome is the time to first occurrence of disease reactivation (including full and partial disease reactivation) during the 16-week RW phase.

SECONDARY ENDPOINTS

Key Secondary Efficacy Endpoint

- Response to therapy (including complete response and partial response) in the SAOL phase from Week 10 onwards and observed at least at 2 consecutive visits at least 2 weeks apart during the SAOL phase

Other Secondary Efficacy Endpoints

- Best response to therapy during the SAOL phase (including complete response and partial response and disease improvement)
- Duration of response to therapy (including complete response and partial response) during the SAOL phase
- Disease reactivation rate for individual subjects (number of disease reactivations experienced per week while each subject is on the study treatment during the SAOL phase).
- Treatment failures (i.e. patients who experience at least one disease reactivation)
- Intensity of disease reactivations (defined by the level of activity given by the mAIDAI – both objective and subjective criteria)
- Serum CRP
- Serum Ferritin
- Improvement of fevers (if present at Baseline)
- Improvement of hepato/splenomegaly (if present at Baseline)
- Improvement in serum albumin and liver transaminases, anemia and/or platelet count (if present at Baseline)

- Hospital length of stay
- Physician Global Assessment
- Patient`s/Caregiver`s qualitative evaluation of health status
- Presence of skin rash (evolution if present at Baseline or appearance during the study)
- Tolerance to oral/enteral nutrition for hospitalized patients if intestinal dysfunction was present at Baseline
- Improvement of stool output for hospitalized patients if intestinal dysfunction was present at Baseline

During the SAOL phase, patient evolution will be described by plotting over time the mAIDAI, PGA, Ferritin, and CRP as well as the most prominent clinical features according to the individual patient profiles. Absolute and percentage of change from baseline will be calculated for continuous variables. Response to treatment in the initial active disease, number, frequency and severity of disease reactivations during the study will be compared to incidence and severity described in the medical history of individual patients.

- Secondary Safety and Tolerability Endpoints

- Adverse events [including AESI] will be reported
- Physical examination findings: clinically significant changes from Baseline
- Vital signs: clinically significant changes from Baseline
- Laboratory assessments (*): including clinically significant changes from Baseline in hematology with platelet counts, CRP, ESR, ferritin, fibrinogen, D-dimer, liver enzymes, (Note: all clinically significant abnormal laboratory results or assessments must be followed until they resolve (i.e., return to normal or Baseline values) or stabilize, or until they are judged by the Investigator to be no longer clinically significant)
- Immunogenicity evaluation: Generation of anti-recombinant human IL-18BP (anti-rhIL-18BP) antibodies
- Local tolerability at the injection site (evaluated by a standardized assessment)

(*) NOTE:

Laboratory safety and efficacy endpoints will be studied at the visits by the central lab. For hospitalized patients, local labs will perform, in addition, analyses as required by the standard of care and this information will be entered in the study eCRF.

CHARACTERIZATION OF THE PHARMACOKINETIC (PK) PROFILE OF TADEKINIG ALFA AFTER REPEATED S.C. INJECTIONS

Enrolled patients will be assessed for PK at V1 (week1) and V5 (week4). Additional sample for PK study will be collected at V1 and V5 prior to treatment and at 2 h, 4 h, 6 h and 24h post treatment (with a +/- 30 minute window at each sample collection). Trough levels are calculated based on blood samples used for lab testing taken at every visit prior to treatment administration (no extra sample needed). Patients who are not hospitalized will require separate study

visits at Week 0 / Day 2, and Week 4 / Day 29, and will need to present to the site 24 hours post-treatment for final PK sample collections, as well as AE and concomitant medication assessments.

PK Endpoints - Time to maximal concentration (T_{max}), the maximal concentration (C_{max}), trough concentration, area under the curve during the first 24 hours of treatment (AUC_{t0-24}) and the elimination half-life will be determined in serum. The steady state concentration will be explored at V5 (week 4).

STOPPING RULE (S) FOR DISCONTINUING TREATMENT IN INDIVIDUAL PARTICIPANT

Patient withdrawal/Physician discontinuation

The physicians and the patients (or legal representative) will have the option to discontinue the treatment if they feel that pursuing the treatment is not appropriate.

The physician can decide anytime to start rescue immunosuppression and therefore discontinue the patient from the study*.

* All key safety and efficacy outcomes will be followed up. Patients will continue to come to the scheduled visits for safety and efficacy assessments.

Treatment discontinuation

The occurrence of adverse events of grades 3 and 4 of severity (section 16) may result in transient or permanent treatment discontinuation. If treatment interruption is more than 3 weeks, the subject will be permanently discontinued from the study.

Study discontinuation

Stopping of the study will be strictly determined for safety concerns.

At any time, the DSMB may recommend to the Sponsor the early termination of the study after reviewing study safety data including AEs, SAEs, and suspected unexpected serious adverse reactions (SUSARs).

At any time, the Sponsor may recommend terminating the study.

Conduct of telemedicine study visits

In order to protect the patient's and caregiver's safety and welfare during the COVID-19 pandemic, conduction of on-site study visits may not be considered appropriate; most patients have to travel to their study site and on-site study visits may expose both the patients and caregivers as well as study site personnel to an increased risk of infection.

Moreover, due to the ultra-rare indication of this study, conducting on-site study visits at sites often located far away from the patient`s home has made study conduct challenging.

Thus, in an effort to accommodate the patients and their families while ensuring the relevant study data is collected, scheduled study visits (except for the Baseline visit) may be conducted as telemedicine visits involving the use of electronic communications (for example, live interactive video and

audio) to enable site staff to conduct “virtual” (not in-person) visits with their patients. These visits may be supported by home health nurses assisting in physical examination or performance of blood draws. Laboratory assessments may be also performed at qualified local laboratories. The study site may also utilize a physical examination from the patient’s most recent standard of care visit conducted by the local treating physician, for the purpose of the study.

Patients and/or parents (or legal representative, if applicable) will sign a respective assent/informed consent prior to the conduct of such telemedicine visits.

Further details about the different possibilities for the conduct of telemedicine visits are described in section 14.1.

STATISTICAL ANALYSIS

Statistical analysis:

Data will be analyzed on an intent-to-treat basis. Baseline patient and disease characteristics according to treatment arm will be presented using standard descriptive statistics.

Comparative statistical analyses will be performed on data collected during the RW phase. The primary endpoint is time to first occurrence of disease reactivation (including full and partial disease reactivation) during the RW phase. Tadekinig alfa will be compared to placebo using the log rank test at the alpha = 0.05 level of significance (2-sided). Kaplan-Meier estimates of the distribution of time-to-event will be summarized and graphed by treatment group.

To test the efficacy of Tadekinig alfa on secondary outcomes during the RW, Fisher's exact test will be utilized for binary outcomes (i.e. treatment failure rate) and a non-parametric, Mann–Whitney–Wilcoxon test will be utilized for continuous outcomes (i.e. change in the mAIDAI). To assess the impact of possible variation in baseline measures, an analysis of covariance (ANCOVA) model with covariate adjustment for Baseline may be considered as a sensitivity analysis, or alternative non-parametric approaches if normality assumptions are not met.

If the primary analysis is statistically significant ($p<0.05$), the following secondary endpoints measured during the RW phase will be analyzed using a fixed-sequence testing procedure in the order specified below to control the overall level of significance:

- Treatment failure rate;
- Change from RW baseline to Week 34 (i.e. Week 16 of the RW phase) or End of Study Visit in the mAIDAI total score; and
- Change from RW baseline to Week 34 or End of Study Visit in the PGA symptom severity score.

For each of these endpoints, the treatment groups will be compared using a two-sided test at alpha = 0.05 level of significance. However, once a non-significant result (i.e. $p > 0.05$) occurs, the results of all subsequent analyses will be exploratory rather than confirmatory.

In addition, all endpoints will be evaluated descriptively including 95% confidence intervals for the mean and proportions.

Analysis of data collected during the SAOL phase will be descriptive in nature, to include 95% CIs around select mean estimates and proportions of interest. Absolute and percentage of change from baseline will be calculated for continuous variables. Response to treatment in the initial active disease, number, frequency and severity of disease reactivations during the study will be compared to incidence and severity described in the medical history of individual patients.

Individual subject's raw data will be captured with data listings and individual patient plots at each time point to visualize the different responses (e.g. in terms of mAIDAI, PGA, Ferritin and CRP as well as the most prominent

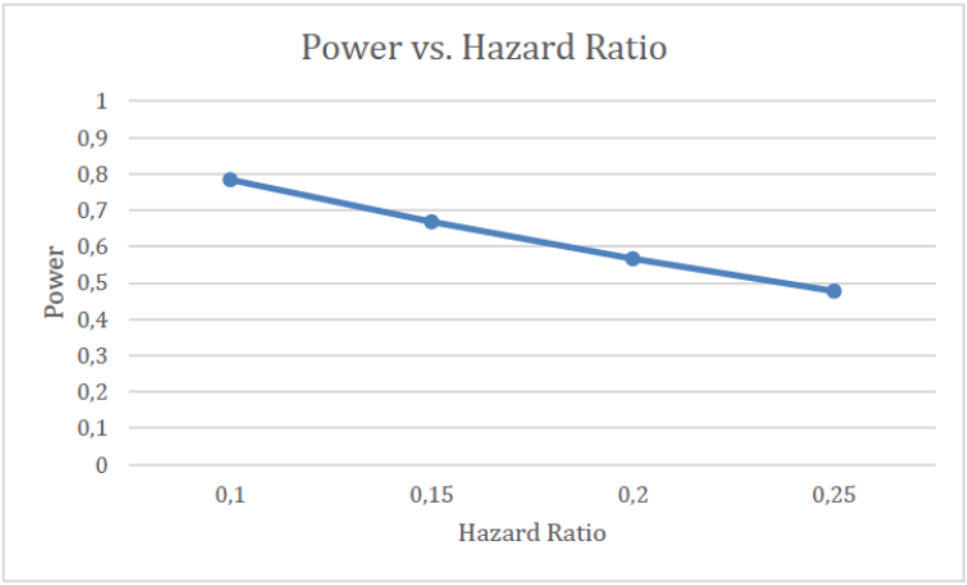
clinical features and results from patient`s/caregiver`s qualitative evaluation of health status) at each time point to the assigned treatment in a descriptive manner.

Power Calculations

The primary endpoint of the study is time to first occurrence of disease reactivation (including full and partial disease reactivation) during the RW phase of the study. There is limited historical data for this disease condition, for either a control or an experimental test product. The frequent recurrence of disease reactivation was expected in the control arm (Wada 2014). An 8-week event rate was assumed to be 90% in the placebo group and a considerable reduction in disease reactivations for subjects receiving Tadekinig alfa was expected. However, a lower event was observed from the currently enrolled (still blinded) patients. Thus, the RW phase is prolonged to a maximum of 16 weeks to better assess the effect of Tadekinig alfa withdrawal. The power calculations below will assume the same 90% event rate in the SOC arm at 16 weeks.

The figure below displays the power achieved for a two-arm study with a 1:1 randomization of 10 subjects, based on two-sided alpha=0.05, a 16-week event rate of 90% in the control arm, and assumed hazard ratios that vary from 0.1, 0.15, 0.2, and 0.25.

Figure 1: *Power vs. Hazard Ratio*



A hazard ratio of 0.1 equates to an assumed 16-week event rate in the Tadekinig alfa group of 20.6% (i.e., a survival event-free rate of 79.4%). These assumptions achieve 78.4% power based on a two-sided log rank test with an overall sample size of 10 patients to be randomized in the RW phase (5 in the placebo group and 5 in the Tadekinig alfa group). A hazard ratio of 0.1 results in an assumed number of total events among 10 patients to be 6.7, with 4.9 occurring in the placebo group and 1.8 occurring in the Tadekinig alfa group.

No power calculations were performed for the SAOL phase of the study, as analysis will be descriptive in nature.

7 SCHEDULE OF EVENTS

Table 1: *Schedule of Events -- Note: Flexibility in the visit scheduling is allowed (± 3 days) for V2 through V13 – The table shows week numbers approximately*

	SAOL Phase [h]									**RW Phase**				
	Prior to V1 V0 **Screening Visit**	W 0 V1/ Day0 **Baseline**	W1 V2/ Day7 *SOC Taper*	W2 V3/ Day14 *SOC Taper*	W3 V4/ Day21 *SOC Taper*	W4 V5/ Day 28 *SOC Taper*	W 8 V6/ Day 56	W 12 V7/ Day 84	W18 V8/ Day 126	W20 V9/ Day 140	W22 V10/ Day 154	W26 V11/ Day 182	W30 V12/ Day 210	W34 V13/ Day 238 **Study completion**
Review and signing of Child Assent and Informed Consent Form (ICF)	X													
Demographics and medical history (previous treatments and comorbidities)	X													
Ophthalmic examination		X												
Inclusion/exclusion criteria review	X	X[a]												
Physical exam with specific assessment of hepatosplenomegaly and vital signs	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization to Tadekinig alfa or placebo (applicable for the RW phase only)		N/A							X					
Standard of Care (SOC) Tapering[f]		X	X	X	X	X								
Treatment with Tadekinig alfa (SAOL phase only)		X	X	X	X	X	X	X	X					
Treatment with Tadekinig alfa or placebo as randomized in the double blind RW phase (s.c. every 2days)[b]									X[i]	X	X	X	X	X
Review of adverse events (AEs, AESIs) & concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local Tolerability Index assessment[e]		X	X	X	X	X	X	X	X	X	X	X	X	X
Physician global clinical evaluation: mAIDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician Global Assessment (PGA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient`s/caregiver`s evaluation of health status		X							X					X
Genetic evaluation, infection evaluations (CMV, EBV, etc.), and serology (HIV, HCV, HBV),	X													
Hematology, clinical chemistry, ESR (at local lab), urinalysis, CRP and Ferritin, coagulation (platelets, fibrinogen, D-dimer, PTT, PT) -- (***sample taken prior to treatment***), pregnancy test[g] [l] TB blood test[d] [l]	X[l] X[d] [l]	X	X	X	X	X	X	X	X[l]	X	X	X	X	X

Flow Cytometry[m]	X													
Serum: Total IL-18, free IL-18, IL-18BP (***sample taken prior to treatment***)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-Tadekinig alfa antibodies (***sample taken prior to treatment***)		X		X		X		X	X		X	X		X
PK study measurements [e]		X[e]				X[e]								

CMV = cytomegalovirus; CRP = C-reactive protein; EBV = Epstein-Barr Virus; ESR = erythrocyte sedimentation rate; FU = Follow up; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = Human Immunodeficiency Virus; ICF = Informed Consent Form; IL-18 = interleukin-18; IL-18 BP = interleukin-18 binding protein; mAIDAI = Modified Autoinflammatory Disease Activity Index; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RW = Randomized Withdrawal phase; SAOL phase = Single arm open label phase; s.c. = subcutaneous; TB = tuberculosis

a Reassessment of inclusion/exclusion criteria prior to treatment start

b Investigational product (Tadekinig alfa or placebo) will be administered every 2 days ± 5 hours to the patient. If the patient is located within close vicinity to the site, s/he has the option to go to the site for treatment administration or a Home Care Nurse may administer the treatment at the patient's residence. At V1 (Week 0), the first dose will be administered at the study center and the patient will remain at the site for a 2-hour observation.

c Local Tolerability Index will be assessed by the Investigator or study nurse at the in-clinic visits including Week 0/Visit 1 when patient is at site under observation after first dose, and by the home care nurse on the subject's dose administration days, approximately every other day.

d TB blood testing (QuantiFERON TB test) should be done at the local (hospital) lab or central lab, prior to treatment initiation

e Additional sample for PK study will be collected at V1 and V5 prior to treatment and at 2 h, 4 h, 6 h and 24h post treatment (with a +/- 30 minutes window at each sample collection). Trough levels are calculated based on blood samples used for lab testing (no extra sample needed). Patients who are not hospitalized will need to present to the site 24h post-treatment for final PK sample collection, as well as AE and concomitant medication assessments.

f If the patient has a disease reactivation during the tapering down, 28-day (4-week) SOC tapering cycles may be used and can be repeated during the 18-week SAOL study period.

g A urine pregnancy test will be performed at each study visit on all females of childbearing potential. If the urine pregnancy test is positive, a serum pregnancy test will be performed.

h W18/Visit 8 will serve as the End of the SAOL period visit for those patients who discontinued treatment during the SAOL phase (an early termination form should be completed for these patients). These patients will not continue into the RW phase of the study.

i Treatment of study drug administered to patients at W18/Visit 8 would be determined by randomization into RW phase. Final dose of treatment under the SAOL phase of the study will occur 2 days prior to W18/Visit 8. All W18 assessments must be performed prior to administration of study drug at W18/Visit 8.

k Height collected at screening

l Collection of Baseline lab samples may occur up to 3 days prior to the scheduled Week 0/Day 0 and Week 18/ Day 126 visit in order to have results available to confirm patient eligibility prior to study treatment.

m Flow cytometry studies are necessary when a XIAP genetic abnormality has been found in the genetic testing. It is not required for patients with NLRC4 genetic mutations.

8 INTRODUCTION

8.1 Background Information

Interleukin 18 (IL-18) is a member of the IL-1 superfamily of cytokines and was initially described as an IFN-γ-inducing factor produced by activated macrophages subsequent to microbial stimulation {Nakamura et al., 2000}. Macrophages and dendritic cells are important sources of IL-18 but IL-18 expression has been also described in: keratinocytes, osteoblasts, intestinal epithelial cells, adrenal cortex cell, microglial, and synovial fibroblasts {Gracie et al., 2003}. IL-18 is considered an important mediator of inflammatory responses and a central player in pathophysiological conditions such as autoinflammatory and autoimmune diseases {Akira, 2000}. Similarly to IL-1 β, IL-18 is first synthesized as an inactive precursor without a signal peptide, remaining as an intracellular cytokine {Dinarello et al., 2013}. The *IL-18* gene is constitutively active resulting in continuous expression of IL-18 mRNA {Tone et al., 1997}. TLR and IFN-γ signaling and NF-kB activation have been also recognized as enhancers of IL-18 gene expression, {Gracie et al., 2003}.

The intracellular IL-18 precursor is cleaved by caspase-1 to form active IL-18 that is secreted to the extracellular compartment. Caspase-1 requires, in turn, activation by the inflammasome/apoptosis-associated Speck-like protein with a caspase-recruitment domain (ASC) complex. The leaderless secretion of IL-1β and IL-18 is independent of the endoplasmic reticulum/Golgi pathway and is dependent on caspase 1 activation {Rathinam and Fitzgerald, 2016}.

IL-18 signals through the IL-18 receptor complex, a heterodimer of IL-18Rα and IL-18Rβ. IL-18Rα is the binding site of IL-18, whereas IL-18Rβ is a signaling molecule. IL-18R is expressed on lymphocytes, monocytes, dendritic cells, and other cell types such as endothelium and epithelium. {Smeltz et al., 2001} {TUCCI et al., 2007}.

The broad spectrum of immunoregulatory activities of IL-18 is related to pleiotropic effects dependent on signaling cascades set into motion within various target cells {Carroll et al., 2008}. IL-18 induces IFN-γ synthesis and synergizes with IL-12 in Th1 cells {Xu et al., 1998}. IL-18 also induces IFN-γ through NK cell activation {Akira, 2000}, and potentiates the action of other cytokines on innate and adaptive NK functions {Nielsen et al., 2016}.

IL-18 signal transduction is primarily mediated by the MYD88-dependent pathway with the result of NF-kB translocation to the nucleus for proinflammatory gene activation {Sacre et al., 2007}. In addition to the MYD88/IRAK//TRAF6 signaling a role for mitogen-activated protein kinases (MAPK) have been described for IL-18 signaling {Gracie et al., 2003}. Moreover, IL-18 enhances the IFN-γ-induced mRNA expression and secretion of CXCL9, CXCL10 and CXCL11 in parallel to the activation of NF-kB, STAT1 and IFN-regulatory factor (IRF)-1{Kanda et al., 2007}.

IL-18 biological activity needs a tight regulation. Intracellular pro-IL-18 is converted into the active mediator subsequent to inflammasome activation and caspase-1 processing. In the extracellular environment IL-18 binding protein (IL-18BP) binds IL-18 with high affinity and inhibits IL-18 proinflammatory activity. Soluble IL-18Rs, α and β, can inhibit IL-18 induced IFN-Y production {Reznikov et al., 2002}.

IL-18BP is a circulating inhibitor of IL-18. The *IL-18BP* gene is constitutively expressed in mononuclear cells and IFN-Y induces its enhanced expression {Hurgin et al., 2002} establishing a negative feedback loop. The *IL-18BP* gene encodes 4 different isoforms of IL-18BP, a, b, c, and d. IL-18BP isoforms a and c neutralize the biological activity of IL-18, while isoforms b and d lack this biological activity. IL-18BP a neutralizes the activity of IL-18 by binding to it with a slow dissociation rate (6.43 + 0.4 sec-4) and a high affinity constant (Kd = 400 pM) ({Kim et al., 2000

Many inflammatory conditions are associated with elevated serum levels of total IL-18 as compared to healthy controls ({Gracie et al., 1999, #73659}, {Kawashima et al., 2001}, {Maeno et al., 2002}, {Maeno et al., 2004}). Certain conditions, prone to the development of Macrophage Activation

Syndrome (MAS), such as systemic juvenile idiopathic arthritis (SJIA), AoSD, NLRC4-associated autoinflammation, and X-linked inhibitor of apoptosis protein (XIAP) deficiency are associated with extraordinary high serum levels of IL-18, ({Wada et al., 2014}, {Shimizu et al., 2015}), and concomitant elevation of free IL-18 (AB2 Bio Ltd. Unpublished data). In the later, approximately half of 23 patients suffering from various autoinflammatory diseases show elevated serum free-IL18 levels. These patients specifically presented with MAS, NLRC4-associated MAS, SJIA, and XIAP deficiency.

Severe, systemic inflammatory diseases modulated by IL-18, including MAS and MAS-like disorders, lead to the excessive activation and proliferation of T-lymphocytes and macrophages and lead to hemophagocytosis and overproduction of cytokines. The disease manifestations are: high fever, pancytopenia, hepatitis, hyperferritinemia, and neurologic symptoms {Ravelli, 2002}. If left untreated the clinical conditions can progress to coagulopathy, organ failure, and death. These can appear during the evolution of a rheumatic condition, such as SJIA and ASD, triggered by infections or malignancies, or as a result of certain genetic mutations. For example, the protein NLRC4 is a NOD-like receptor whose stimulation recruits and proteolytically activates caspase-1 ({Canna et al., 2014} {Romberg et al., 2014}). Active caspase-1 cleaves the precursors of IL-1β and IL-18 to their active forms and induces pyroptotic cell death. Two mutations have been identified in the gene coding for NLRC4, which result in increased NLRC4 inflammasome spontaneous activity and NLRC4-mediated severe systemic inflammation with cases evolving into NLRC4-mediated MAS. In two recent case studies, such mutations resulted in early-onset enterocolitis and recurrent episodes of fever and splenomegaly distinctive for MAS, over time resulting in stunted growth ({Canna et al., 2014}, {Romberg et al., 2014}). Similarly, mutations resulting in deficiency of the XIAP protein are linked with a high susceptibility to develop recurrent HLH, a MAS-like condition involving systemic dysregulation of the immune response in the form of macrophage activation and hemophagocytosis as well as enterocolitis. Patients with XIAP deficiency also show very high IL-18 levels during HLH episodes {Wada et al., 2014}.

Tadekinig alfa is a recombinant form of human, soluble IL-18BP isoform a (r-hIL-18BP) that binds to and neutralizes IL-18 with high affinity. The average molecular weight of the full-length polypeptide moiety, calculated per the [redacted] amino acid composition, is approximately [redacted] kDa. The relative molecular mass of the glycosylated molecule is estimated to be approximately [redacted] kDa. The primary structure and N-glycan forms of Tadekinig alfa have been shown to be comparable to the natural protein purified from urine.

Although there is scant epidemiological evidence on these conditions, severe, systemic, autoinflammatory monogenic disorders are very rare, with an estimated prevalence of less or equal to 1 in 1 million in the pediatric population based on a recent literature report of a database of orphan diseases (http://www.orpha.net/consor/cgibin/OC_Exp.php?lng=en&Expert=2442, {Latour and Aguilar, 2015}).

Five clinical studies have been performed with Tadekinig alfa in Europe, which show the drug is safe and well tolerated. Two double blind, randomized, placebo-controlled Phase 1 studies (single and repeat dose, IMP 23344 and IMP 23728 respectively) were performed in healthy adult volunteers to assess the safety, pharmacokinetics and pharmacodynamics of Tadekinig alfa. Two other multi-center, randomized, parallel, double blind, placebo-controlled Phase 1b studies were performed in patients with autoinflammatory diseases to assess the safety, tolerability, and efficacy of Tadekinig alfa: one in 35 patients with psoriasis/psoriatic arthritis (Study 24318), and the other in 36 patients with rheumatoid arthritis (Study 24611). An additional Phase 2 study, AOSD-2014-001 was conducted in Europe to test the safety and efficacy of Tadekinig alfa in 23 patients with Adult onset Still's Disease (AoSD). In the United Sates, an emergency, individual patient Investigational New Drug Application (IND) was approved on June 9, 2015 (IND [redacted]) for the compassionate use of Tadekinig alfa in a [redacted] old infant with an NLRC4 mutation, elevated total IL-18 (>50,000 pg/mL) and presenting general, severe, life-threatening systemic inflammation, particularly colitis. The infant received her initial dose on June 18, 2015 and responded immediately to treatment, with free IL-18 levels below detection, CRP levels normalizing, and ferritin decreasing to the patient's reported

minimum level within 18 days. The colitis resolved, and co-medications, including cyclosporine and methylprednisolone, were phased out. By July 8, 2015, after 20 days of treatment, the patient remained afebrile, progressed to full breast milk feeds, had normal stool output, and was discharged from the hospital on August 6, 2015. Compassionate treatment of Tadekinig alfa has continued for the infant as of Sep 2021.

AB2 Bio, in collaboration Dr. [redacted] from Cincinnati Children's Hospital Medical Center, has conducted a study in XIAP deficiency pediatric patients to examine the levels of free IL-18 during episodes of active disease and during disease remission. Patients with XIAP deficiency have circulating free IL-18 during active disease and in remission. Higher levels were observed during disease flares. This observation supports the contention that free IL-18 may contribute to the propensity of these patients to develop MAS/HLH.

It is hypothesized that inhibition of free IL-18 by Tadekinig alfa would serve as a disease-modifying therapeutic in these conditions.

The aim of AB2 Bio is to develop Tadekinig alfa in the US for the treatment of a cluster of rare pediatric diseases, namely, MAS and MAS-like disorders dominated by the activation of the IL-18 pathway.

8.2 Summary of Risks and Benefits (R/B assessment)

It is hypothesized that disease modification by therapeutic targeting of IL-18 with Tadekinig alfa may offer significant benefit in patients suffering from mutations in NLRC4 and XIAP deficiency, due to IL-18 neutralization together with blocking downstream cytokines such as IL-6 and tumor necrosis factor–α (TNF-α).

A female infant presented at [redacted] of age (IND #[redacted]) with an unremarkable upper respiratory infection associated with positive Polymerase Chain Reaction testing positive for parainfluenza type 3. Cough and coryza improved and viral RNA cleared, but hectic fevers and erythroderm rash persisted for several weeks. After three weeks of fever, she acutely developed oral intolerance and severe secretory diarrhea that persisted despite cessation of oral intake. Her condition worsened with acute rise in inflammatory markers, relative thrombocytopenia, and rising ferritin all consistent with a MAS-like syndrome. Upper and lower endoscopy showed severe mucosal inflammation extending from the stomach through large intestine. Functional assessment for impaired cytotoxicity, which causes a similar phenotype known as familial Hemophagocytic Lymphohistiocytosis (FHL), was normal. The patient's presentation was reminiscent of recent reports of early-onset enterocolitis with MAS associated with mutations in *NLRC4*. A de novo heterozygous mutation in *NLRC4* (c.1022T>C, p.Val341Ala) was confirmed by Sanger sequencing and previously associated with a similar, but ultimately fatal, presentation {Romberg et al., 2014}.

The patient was treated aggressively with corticosteroids and IL-1β blockade with minimal response. The addition of maximal doses of TFNα-blockade (infliximab), cyclosporine, and $\alpha_4\beta_7$-integrin inhibition (vedolizumab) succeeded in stabilizing the patient's fevers and coagulopathy but did not improve the anemia, hyperferritinemia, or enterocolitis. The patient's serum was assessed for total IL-18, as well as free IL-18 and both were found to be extraordinarily elevated. Under a compassionate-use IND authorization, the patient was given Tadekinig alfa at a dose of 2 mg/kg subcutaneously (s.c.) every 48 hours. Within the first two doses, the patient improved rapidly in association with acute drop in free IL-18. Her remaining inflammatory features, including enterocolitis, also improved steadily and allowed weaning of other immunosuppression and reintroduction of enteral feeding.

After more than 3 months of combined IL-1β and IL-18 blockade, the patient stopped all other immunomodulation and made a full recovery. Importantly, no adverse events (AEs), opportunistic infections, or loss of efficacy have been observed.

X-linked lymphoproliferative syndrome 2 or XIAP deficiency is a form of familial or primary HLH caused by loss-of-function or inactivating XIAP mutations. XIAP deficiency is mostly a pediatric condition with HLH as a frequent clinical presentation (54%) and recurrent splenomegaly (57%) and IBD (26%) as other frequent phenotypes (Latour et al. 2015). IL-18 is strikingly elevated in XIAP-HLH patients; it remains high at recovery but increases significantly during disease activation (Wada et al. 2014). Many immunomodulatory functions have been ascribed to XIAP. Among other functions, XIAP is a negative regulator of inflammasomes including NLRC4. Although no clinical evidence for the efficacy of IL-18 blockade exist so far for XIAP deficiency it is highly plausible that IL-18 is the common dominant immune mediator in both monogenic conditions, NLRC4-MAS and XIAP deficiency.

Together, the PK and toxicological evaluation of Tadekinig alfa assessed in animals and the data obtained with single and repeated SC administration of doses up to 320 mg in humans, the ongoing Phase II clinical study and case report of the NLRC4 mutation, have so far demonstrated a favorable safety and tolerability profile, supporting the initiation of the planned phase 3 study.

The slight and reversible safety findings previously identified during the nonclinical and clinical program will be closely monitored through the collection of AEs, including the evaluation of immunogenicity, follow-up. The Data Safety Monitoring Board (DSMB) will perform a safety evaluation.

In conclusion, inhibiting IL-18 in these patients may bring a therapeutic solution that is not offered by existing treatments. The collected data suggest that Tadekinig alfa displays a favorable safety profile at the doses to be tested.

In addition, measures are in place as in a First-in-Human setup, in case of emergencies (i.e. see example patient emergency card, appendix 5).

8.3 Primary Objectives – Efficacy

The primary objectives of the study will be to:

1. Assess clinical efficacy of Tadekinig alfa in monogenic autoinflammatory diseases with ongoing inflammation and deleterious mutations of NLRC4-MAS or XIAP
2. Assess laboratory/biological evidence of efficacy

8.3.1 Primary Efficacy Endpoints

- The primary outcome is the time to first occurrence of disease reactivation (including full and partial disease reactivation) during the 16-week RW phase.

Efficacy assessment is related to the incidence of disease reactivations and will cover:

i) Clinical evaluation (captured mostly in the mAIDAI)

- Complete physical examination including: vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, weight, and body temperature)
- All findings should be documented: joint swelling, hepatomegaly and splenomegaly, presence of skin rash, ophthalmic control (presence of uveitis). Ophthalmic examination will be performed for assessment of uveitis.
- Symptoms should be documented: abdominal pain, diarrhea, nausea, vomiting
- All clinical components (including clinical findings and symptoms) of the disease will be captured in a binary way as either being present or absent. This binary system is considered the most stringent tool to describe a clinically relevant level of improvement and control of the severe clinical

manifestations in the patients treated with Tadekinig alfa. The judgement, of whether an end organ category is affected, is done by the treating physician according to clinical standards, as also previously done for all mAIDAI components.

- Daily weight, stool output, and PO intake measurements including number of emesis episodes will be performed on patients with intestinal dysfunction, only when the patients are hospitalized
- Radiologic findings if assessed as necessary by the treating physician

ii) Maintenance of co-treatment

- Total weekly glucocorticoids
- IL-1 blockers
- Other treatments* (i.e. DMARDs, etc.)

* Refer to Section 11.2.4: Concomitant treatment

iii) Laboratory assessments:

- Serum CRP
- Serum Ferritin
- Complete blood counts
- Serum levels of total IL-18, free IL-18, IL-18BP

8.3.2 *Secondary Efficacy Endpoints*

Key Secondary Efficacy Endpoint

- Response to therapy (including complete response and partial response) in the SAOL phase from Week 10 onwards and observed at least at 2 consecutive visits at least 2 weeks apart during the SAOL phase

Other Secondary Efficacy Endpoints

- Best response to therapy during the SAOL phase (including complete response and partial response and disease improvement)
- Duration of response to therapy (including complete response and partial response) during the SAOL phase
- Disease reactivation rate for individual subjects (number of disease reactivations experienced per week while each subject is on the study treatment during the SAOL phase).
- Treatment failures (i.e. patients who experience at least one disease reactivation)
- Intensity of disease reactivations (defined by the level of activity given by the mAIDAI – both objective and subjective criteria)
- Serum CRP
- Serum Ferritin
- Improvement of fevers (if present at Baseline)
- Improvement of hepato/splenomegaly (if present at Baseline)
- Improvement in serum albumin and liver transaminases, anemia and/or platelet count (if present at Baseline)
- Hospital length of stay
- Physician Global Assessment

- Patient's or caregiver's qualitative evaluation of health status
- Presence of skin rash (evolution if present at Baseline or appearance during the study)
- Tolerance to oral/enteral nutrition for hospitalized patients with intestinal dysfunction was present at Baseline
- Improvement of stool output for hospitalized patients if intestinal dysfunction was present at Baseline

During the SAOL phase, patient evolution will be described by plotting over time the mAIDAI, PGA, Ferritin, and CRP as well as the most prominent clinical features according to the individual patient profiles. Absolute and percentage of change from baseline will be calculated for continuous variables. Response to treatment in the initial active disease, number, frequency and severity of disease reactivations during the study will be compared to incidence and severity described in the medical history of individual patients.

Notes:
- GI related parameters will be assessed in subjects with GI dysfunction
- For outpatient therapy the clinical evaluation will be performed at the visits
- *Laboratory safety and efficacy endpoints will be studied at the visits by the central lab. For hospitalized patients, local labs will perform, in addition, analyses as required by the standard of care and this information will be entered in the study eCRF.*

Active disease upon enrolment is defined as:

- Increased inflammatory markers, i.e. serum ferritin levels ≥ 500 ng/mL or serum CRP ≥ 2x ULN, and
- Active clinical disease as evidenced by mAIDAI ≥ 4 or CNS manifestations (i.e. seizures, altered mental status, signs of increased intracranial pressure, chronic papilledema, loss of vision, other sensorineural deficiencies, etc.)

For the definition of active disease upon enrolment, all mAIDAI components (subjective and objective) will be evaluated in line with previous protocol versions.

Response to Therapy is defined as:

1. In the 16-week RW phase, response to therapy (as primary endpoint of efficacy) will be assessed by prevention of disease reactivations during the 16-week treatment in the RW phase.
2. In the SAOL phase, response to therapy (as secondary endpoint of efficacy) will be assessed through the control of the active disease

For response to therapy, only the objective mAIDAI components will be evaluated as indicated below. Subjective mAIDAI components (see Appendix I) will not be considered to avoid any bias in the efficacy assessment in the open label part of the study.

- **Complete response**

  No major end organ damage (=objective mAIDAI components)
  - No fever (body temperature ⩽100.4° F/38° C)
  - No diarrhea
  - No transaminitis and/or hepatomegaly
  - No splenomegaly and/or adenopathy
  - No rash

- No uveitis
- No arthritis
- No radiologic CNS involvement
- No cytopenia (HgB ⩾ 9.0 and/or PLT ⩾100 and/or WBC ⩾3.0)

No systemic inflammation

- No hyperferritinemia (serum level < 500 ng/mL)
- No increased CRP (serum level < 2x ULN)

Immunosuppressive therapies

- Discontinuation of systemic corticosteroids (excluding hydrocortisone for prevention of adrenal insufficiency) or other immunosuppressive therapies including biologics ongoing at baseline
- No start or dose increase of other immunosuppressive therapies including biologics

- **Partial response**

At least 50% reduction of the number of affected objective end organ damage categories at baseline and

- At least 50% of the systemic inflammatory markers (ferritin and/or CRP) increased at baseline reaching levels for complete response or
- Discontinuation of systemic corticosteroids (excluding hydrocortisone for prevention of adrenal insufficiency) or other immunosuppressive therapies including biologics ongoing at baseline

Partial response is thus a measure of the complete resolution of clinical manifestations in at least 50% of involved specific organ classes together with a reduction of the systemic inflammatory markers most relevant for this disease or the possibility to reduce other immunosuppressive therapies.

- **Disease Improvement**

A third response category of Disease Improvement is introduced to be utilized as a description of best response and in order to better describe initial treatment response to therapy and disease evolution over time. This is only used for analysis purposes and will not be evaluated for the decision whether to be eligible for the start of the RW phase. Disease Improvement is defined as:

- Reduction of the number of affected objective end organ damage categories at baseline by at least 1 or
- Normalization (i.e. reaching levels for complete response) or improvement (> 50% change from baseline for laboratory markers but still exceeding levels for complete response) of at least 50% of the systemic inflammatory markers affected at baseline
- Systemic corticosteroids (excluding hydrocortisone for prevention of adrenal insufficiency) or other immunosuppressive therapies including biologics must be at the same or lower doses compared to baseline

A Disease reactivation occurs if:

For disease reactivation, only the objective mAIDAI components will be evaluated as indicated below. Subjective mAIDAI components (see Appendix I) will not be considered to avoid any bias in the assessment.

During the RW-phase, the reference for a disease reactivation (for the primary endpoint assessment) will be the end of the SAOL phase (V8); for the SAOL phase, reference will the previous visit, as patients enter the SAOL phase with an active disease.

- **Partial disease reactivation**
  - Increase in the number of affected objective end organ damage categories by at least 2 or
  - Increase in the number of affected objective end organ damage categories by at least 1 and worsening of at least 1 systemic inflammatory marker (i.e. serum ferritin levels ⩾ 500 ng/mL or serum CRP ⩾ 2x ULN) that was meeting complete response criteria before
- **Full disease reactivation**
  - Increase in the number of affected objective end organ damage categories to at least the number of affected end organ damage categories at baseline (V1) and
  - Exacerbation of at least 1 systemic inflammatory marker (i.e. serum ferritin levels ⩾ 500 ng/mL or serum CRP ⩾ 2x ULN) that was meeting complete response criteria before

Note: It is recommended that patients suffering from *severe* CNS manifestations are put on rescue immunosuppression treatment.

8.3.3 Justification for revised Efficacy Endpoints

The changes in the definitions of response to therapy (complete and partial) and flare/disease reactivation (full and partial) with protocol version 6 take into consideration the newly gained disease information since the initial study design. In the previous clinical protocol versions, a fix mAIDAI of 4 was considered the cut-off to determine whether a patient has an active disease or disease reactivation throughout the study together with a simultaneous increase in inflammatory markers. This fix mAIDAI cut-off did not take into consideration the individual disease severity of each patient and heterogeneity of the disease, which has been observed both in the enrolled patients as well as patients described in the literature. To demonstrate a clinically meaningful improvement for the patient, the clinical end organ damage as a major criterion is assessed separately from the laboratory systemic inflammatory markers. In addition, a discontinuation of broad-spectrum immunosuppressive therapy is added to the evaluation, as this represents a major clinical meaningful achievement for these patients. By using the above definitions of full and partial disease reactivation, the re-occurrence of the inflammation will be evaluated in a more sensitive way taking into account the observed disease heterogeneity.

Complete and partial response to therapy from week 10 onwards was added as new key secondary endpoint. The evidence provided in the open label part to control the disease after the patients have entered the study in a status of high inflammatory activity is a crucial part to provide evidence of the efficacy of Tadekinig alfa treatment. The 10-week time point to begin assessing the response to therapy was chosen based on the timeline for steroid discontinuation and the need for the residual effect of steroids to no longer be present. Per the protocol, patients may receive Tadekinig alfa in addition to standard of care systemic steroids. The steroids are tapered down by day 28 after study initiation. However, a patient may receive another 28 day cycle of steroids upon initial disease reactivation, which is expected to occur during or shortly after the first steroid tapering. This results in a total expected time of 8 weeks of steroid taper. If patients are not stabilized after the second steroid taper, they are expected to start rescue immunosuppression and discontinue study treatment. Therefore, at week 10, patients are expected to no longer require steroids and any residual effects will not be present.

A patient's or caregiver's qualitative evaluation of health status was added with protocol version 6. Given the heterogeneous patient population (age range, disease symptom and impacts) and regulatory concerns that generic validated quality of life questionnaires would not be fit-for-purpose for use in this trial to support regulatory decisions, a non-validated questionnaire specifically designed for this patient population and study design is used. It captures the patient's or caregiver's qualitative evaluation of health status similar to the physician global assessment (PGA), the severity of individual symptoms and the perceived change in symptoms at the end of the SAOL and RW phase.

8.4 Secondary Objective – Efficacy

The secondary efficacy objective is to assess the main clinical features and laboratory biomarkers (characteristics of each patient profile) longitudinally during the SAOL phase for each experimental subject.

8.4.1 Efficacy Endpoints in the SAOL phase

Efficacy endpoints evaluated during the SAOL phase will include response to therapy, best response to therapy, duration of response, as well as plotting over time the mAIDAI, PGA, Ferritin, and CRP as well as the most prominent clinical features according to the individual patient profiles. Absolute and percentage of change from baseline will be calculated for continuous variables. Number, frequency and severity of disease reactivations during the study will be compared to incidence and severity of disease reactivations described in the medical history of individual patients.

8.5 Secondary Objective – Safety and Tolerability

The secondary objective is to assess the safety and tolerability of Tadekinig alfa treatment in monogenic, autoinflammatory disease harboring deleterious mutations of NLRC4-MAS or XIAP.

8.5.1 Safety and Tolerability Endpoints

- Adverse events [including AESI] will be reported
- Physical examination findings: clinically significant changes from Baseline
- Vital signs: clinically significant changes from Baseline
- Laboratory assessments (*): including clinically significant changes from Baseline in hematology with platelet counts, CRP, ESR, ferritin, fibrinogen, D-dimer, liver enzymes, creatinine and glomerular filtration rate (note: all clinically significant abnormal laboratory results or assessments must be followed until they resolve (return to normal or Baseline values) or stabilize, or until they are judged by the Investigator to be no longer clinically significant)
- Immunogenicity evaluation: Generation of anti-rh-IL-18BP antibodies
- Local tolerability at the injection site (evaluated by a standardized assessment)

(*) NOTE: *Laboratory safety (and efficacy) endpoints will be studied at the visits by the central lab. For hospitalized patients, local labs will perform, in addition, analyses as required by the standard of care and this information will be entered in the study eCRF.*

9 STUDY DESIGN

9.1 Type of Trial

This is a Phase 3 study to assess the safety and efficacy of Tadekinig alfa in patients with monogenic, interleukin-18 (IL-18) driven autoinflammation due to Nucleotide-binding oligomerization domain, leucine rich repeat and CARD domain containing 4 – Macrophage activation syndrome (NLRC4-MAS mutation) or X-linked inhibitor of apoptosis (XIAP) deficiency. Because of the likelihood for pathogenic IL-18 in certain monogenic diseases, patients known to harbor deleterious mutations in NLRC4-MAS or XIAP and who have a history of ongoing inflammation will be enrolled if they have ferritin >= 500 ng/mL or persistent C-reactive protein (CRP) elevation ≥ 2 times the upper limit of normal (ULN) and the patients have a mAIDAI ≥ 4.

The study is designed with single-arm, open-label phase (SAOL) of Tadekinig alfa treatment duration for 18-week followed by a 16-week Randomized Withdrawal (RW) phase for efficacy and safety evaluation, with no interruption between the two phases of treatment.

Single-arm, open-label Phase (SAOL)

The Screening visit (V0) will occur before the start of the study treatment. At V0, the patient and/or the patient's legal guardian(s) will sign a Child Assent Form and/or an Informed Consent Form that will be collected by the Investigator. All eligibility criteria will be reviewed during the screening period AND must all be met in order to determine patient eligibility into the study. Eligibility criteria should be confirmed again at the Baseline Visit (V1).

Patients experiencing active disease will start Tadekinig alfa treatment at V1.

Beginning at V1, Tadekinig alfa (TA) will be administered in addition to the standard of care (SOC) treatment used for the control of the active disease. In the absence of an approved medication for this disease, the SOC as defined in this protocol consists of glucocorticoids (GC), with a 28-day tapering schedule as follows

- 28-days (4 weeks): Daily PO/IV Dexamethasone 10 mg/m^2 x 7 days, 5mg/m^2 x 7 days, 2.5 mg/m^2 x 7 days, 1.25 mg/m^2 x 7 days

Patients who respond to the initial TA + GC 28-day course (see Definition of Partial and Complete Response to Therapy) will receive Tadekinig alfa for 14 additional weeks.

Patients who responded to TA + SOC initial course and have a disease reactivation again during the SAOL phase will receive another course of TA + SOC with the same GC dosage and tapering schedule used for the initial treatment of the active disease (see explanations below). Maintenance treatment, with the permitted medications, at stable and at the same doses utilized at study entry are allowed. Dose increments for the permitted co-medications or their introduction after the beginning of the study are not permitted and represent treatment failures and study early termination. If permitted co-medications are weaned off during the course of the study and the investigator decides to re-introduce them, they are permitted as long as the doses are the same or lower than the doses used at study entry.

Upon lack of response to combined treatment after enrollment or upon the occurrence of a disease reactivation during the course of the SAOL after initial response, the investigator may decide to treat the patient with rescue immunosuppressors. This decision results in patient discontinuation from the study.

Tadekinig alfa will be administered at 2 mg/kg (with a maximum of 160 mg) subcutaneously (s.c.) for up to approximately 18 weeks.

At V0 and V1, patients will undergo a physical examination, measurement of vital signs, and routine laboratory testing (including hematology, clinical chemistry, urinalysis, erythrocyte sedimentation rate (ESR), CRP, and coagulation panel). Biological evaluation and genetic diagnosis of autoinflammatory conditions (NLRC4-MAS, XIAP deficiency, and other monogenic associations with Macrophage Activation Syndrome [MAS]) will be done at V0. Samples for flow cytometry will be analyzed during the screening period and prior to V1. Complete medical and disease history will also be collected during V0. In addition, prior to initiation of therapy, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) tests, serology tests, and a complete infectious workup will be performed.

Specific laboratory determinations such as total and free IL-18 and IL-18BP will be performed at V1 and subsequent visits.

The global disease activity will be assessed by the mAIDAI. The mAIDAI will be applied at all study visits and will be available for review throughout the study. For the evaluation of response to therapy and disease reactivation, only the objective parameters of the mAIDAI will be taken into consideration. A Physician Global Assessment (PGA) tool will also be applied at all study visits by the physician to assess the global disease status. The patient's or caregiver's evaluation of the health status questionnaire will be applied at V1 and the end of the SAOL phase.

Assessments during the SAOL phase, treatment period of 18 weeks (V1 to V8), will include complete physical examination, review of all adverse events (AEs), and routine and specific laboratory analysis (for further details, refer to the safety and efficacy assessment section).

Samples for anti-drug antibodies (ADAs) will be collected at Baseline of SAOL (V1), Week 2 (V3), Week 4 (V5), Week 12 (V7), and Week 18 (V8).

At the end of the SAOL phase, all patients who completed the phase with a partial or complete response at V8 will be enrolled in the RW phase.

Randomized Withdrawal (RW) Phase

All patients who have completed 18 weeks of treatment during the SAOL phase and showing a partial or complete response at Week 18 (V8) will be randomized to one of the two treatment arms in a 1:1 ratio to begin treatment in the RW phase (**Baseline of the RW phase**). Experiencing a disease reactivation at any point during the 18-week SAOL phase will not prevent a subject from enrollment into the RW phase; rather, patients are required to meet the criteria for ongoing Tadekinig alfa treatment throughout the SAOL phase and show a partial or complete response at Week 18. Patients will receive the study treatment (placebo or Tadekinig alfa) for up to additional 16 weeks. Residual components of the disease may be present but if they still meet the definition of at least partial response, patients will be enrolled in the RW phase.

Treatment interruption is not recommended between the two phases. Baseline data for the RW phase will be the data collected prior to randomization at the Week 18 (V8) visit.

During the RW phase, visits will be scheduled at Week 20 (V9), Week 22 (V10), Week 26 (V11), Week 30 (V12) and Week 34 (V13/End of Study).

At RW visits, patients will undergo a complete physical examination and laboratory testing (including hematology, clinical chemistry, urinalysis, ESR, CRP, ferritin, and coagulation panel), determinations of total and free IL-18 and of IL-18 BP. The mAIDAI and PGA will be applied at all visits in the RW phase. The patient's or caregiver's evaluation of the health status questionnaire will be applied at the end of the RW phase.

Samples for anti-drug antibodies (ADAs) will be collected at RW Week 22 (V10), Week 26 (V11) and Week 34 (V13).

During the RW phase, patients who develop a partial or full disease reactivation before the 16-week treatment is completed will proceed to the End of Study visit and complete the RW phase. The investigator may also decide to start rescue immunosuppression and discontinue treatment.

If applicable, data on administration of other medications or rescue immunosuppression during both phases (SAOL and RW) will be collected, including the time of treatment start and finish and whether or not there was a response to the rescue treatment.

Patients who discontinue treatment prior to the end of either treatment phase (SAOL or RW) will be followed for all key efficacy and safety assessments up to the End of Study visit.

NOTE: The FDA draft guidance (Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, December 2012) indicates that the RW design should include patients who demonstrated treatment response.

Additional Standard of Care Cycles or Rescue Immunosuppression in SAOL Phase:

A) If no response after the first combined treatment course (SOC + IMP) at the initiation of the SAOL phase:

If patients do not respond to study treatment (see Section 12.1 Definition of Partial and Complete Response to Therapy and Disease Improvement) after the initial combined treatment course, they will be treated with rescue immunosuppression or with new/ increased doses of Permitted Concomitant Treatments. These cases will be considered treatment failures and will exit the study.

B) Patients with a disease reactivation after having responded to therapy in the SAOL Phase:

If patients show signs of systemic inflammatory reactivation (i.e. partial or full disease reactivation after having responded to therapy in the SAOL phase, they will receive another cycle of SOC in addition to the IMP.

C) Patients with a disease reactivation during the tapering down of the SOC during the combined treatment in the SAOL Phase:

If after an initial improvement in response parameters , the patients show again signs of increasing inflammation (i.e. partial or full disease reactivation) during the tapering down of SOC while in combined treatment, another full cycle of extended SOC (4 weeks) in addition to the IMP, will be initiated at the original dose.

In the last cases (B or C), the Investigator may also decide to start rescue immunosuppression treatment, and in this case the patient should discontinue study treatment due to treatment failure.

Note to treatment failure:
Any patient starting rescue immunosuppression treatment or treated with new/ increased doses of Permitted Concomitant Treatments will be considered a treatment failure and will proceed to the study discontinuation/early termination procedures. Data related to response to the rescue treatment will be collected including all key efficacy and safety assessments.

It is recommended that patients suffering from severe CNS manifestations are put on rescue immunosuppression treatment.

Note to treatment of disease reactivations:

Patients that present a partial or full disease reactivation after previous response to SOC + TA in the SAOL phase can remain in the study, and receive another cycle of SOC in addition to the continuous TA treatment, if according to treating physician, the severity does not require rescue immunosuppression.

Patients that present a partial or full disease reactivation in the RW Phase before the 16-week treatment is completed will proceed to the End of Study Visit and complete the RW Phase.

Note - normal ranges for ferritin and CRP:
The normal ranges of ferritin and CRP differ per age and respective normal ranges per age at the central or local laboratory will be used as reference.

Data Safety Monitoring Board
The Data Safety Monitoring Board (DSMB) will be notified by the contracted Clinical Research Organization (CRO) of clinical or biological worsening of the status of study subjects (i.e., Serious Adverse Events (SAEs)) and also of treatment failures. The DSMB will assess the global safety of Tadekinig alfa and advise whether to continue or discontinue the study. DSMB roles and responsibilities are delineated in the DSMB charter along with the reporting requirements of the Sponsor/CRO to the DSMB. The Investigator will evaluate safety for each individual patient and decide whether to stop or continue treatment, or when to start the rescue immunosuppression.

Conduct of telemedicine study visits

In order to protect the patient`s and caregiver`s safety and welfare during the COVID-19 pandemic, conduction of on-site study visits may not be considered appropriate; most patients have to travel to their study site and on-site study visits may expose both the patients and caregivers as well as study site personnel to an increased risk of infection. Moreover, due to the ultra-rare indication of this study, conducting on-site study visits at sites often located far away from the patient`s home has made study conduct challenging.

Thus, in an effort to accommodate the patients and their families while ensuring the relevant study data is collected, scheduled study visits (except for the Baseline visit) may be conducted as telemedicine visits involving the use of electronic communications (for example, live interactive video and audio) to enable site staff to conduct “virtual” (not in-person) visits with their patients. These visits may be supported by home health nurses assisting in physical examination or performance of blood draws. Laboratory assessments may be also performed at qualified local laboratories. The study site may also utilize a physical examination from the patient’s most recent standard of care visit conducted by the local treating physician, for the purpose of the study.

Patients and/or parents (or legal representative, if applicable) will sign a respective assent/informed consent prior to the conduct of such telemedicine visits. Further details about the different possibilities for the conduct of telemedicine visits are described in section 14.1.

9.2 Patients, Groups and Centers

A maximum of 15 patients will be enrolled in this study.

Study Centers:

Approximately 11 clinical sites in the United States, Canada and Germany.

9.3 Expected Study Duration

Approximately 6 years from First-Patient-First-Visit (FPFV) to Last-Patient-Last-Visit (LPLV).

After screening, patients will enter the SAOL phase of 18-weeks duration. Subsequently, eligible patients will enter the 16-week RW phase.

10 STUDY POPULATION

A maximum of 15 eligible male or female patients, suffering from NLRC4-MAS or XIAP deficiency will be enrolled in the study. Eligible patients will enter the SAOL phase. All patients who complete the 18 weeks of treatment with a partial or complete response at V8 will be enrolled in the RW phase for up to extra 16-week treatment period. Patients will be allowed to receive maintenance (permitted) treatment at stable doses.

Patients should meet all inclusion and exclusion criteria (Sections 10.2 and 10.3).

10.1 Description

10.2 Patient Inclusion Criteria

All entrance criteria must be met in order to enroll;

Eligibility criteria should be evaluated at Screening V0 prior to V1 and rechecked at V1 prior to study treatment initiation in the SAOL phase.

1. Patients with genetic diagnosis of NLRC4-MAS mutation or XIAP deficiency (caused by BIRC4 gene mutation) as confirmed by analysis performed at the central genetics' laboratory. If possible, flow cytometry assay will be performed in parallel to confirm diagnosis of XIAP deficiency. (Note: Previous flow cytometry assay results will be permitted for confirmation of XIAP deficiency diagnosis.) A genetic diagnosis from a local laboratory will be accepted for enrolment and start of treatment, to avoid any treatment delays for these severe conditions. However, the genetic diagnosis has to be confirmed by the central laboratory. If the genetic diagnosis is not confirmed, the patient will discontinue the study.
2. Patients with XIAP deficiency and a previous bone marrow transplantation are allowed, if they show evidence of primary or secondary graft failure, or failure to achieve phenotypic correction with evidence of XIAP-related disease recurrence or clinically significant mixed chimerism. For these patients, genetic diagnosis at the central laboratory may show chimerism; thus, local genetic diagnosis prior to the bone marrow transplantation will be the main source to confirm the genetic diagnosis.
3. Ferritin ≥ 500 ng/mL or persistent elevation of CRP ≥ 2x ULN and mAIDAI ≥ 4
4. Patients receiving corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) or disease modifying anti-rheumatic drugs (DMARDs), and/or IL-1 blockade with insufficient response to treatment upon enrollment are allowed into the study. Patients not receiving any of these treatments before start of therapy are also allowed
5. Women of childbearing potential with negative urine pregnancy test (UPT) at all visits (if UPT is positive, a blood test for human chorionic gonadotropin (hCG) to be performed) and who agree to follow highly effective birth control recommendations during the study and until 1 month after the end of the treatment. Birth control methods considered highly effective are: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner or sexual abstinence. In each case of delayed menstrual period (over one month between

menstruations, confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles. A post-study contraception duration of 4 weeks is recommended taking into account the median half-life of Tadekinig alfa of almost 40h and 5 half-lives representing a duration of 200 hours.

10.3 Patient Exclusion Criteria

Subjects representing one or more of the following criteria are excluded from participation in the study:

1. Patients with life-threatening co-morbidities not associated with the underlying NLRC4-mutation or XIAP deficiency
2. Positive test for or prior history of HIV, Hepatitis B or Hepatitis C (serology)
3. Presence of active infections or a history of pulmonary TB infection with or without documented adequate therapy (QuantiFERON-TB test)
4. Presence of life-threatening infections (clinically and quantitated PCR if necessary)
5. Oncologic causes of symptoms; current or previous history of malignancy
6. Presence of CNS manifestations (i.e. seizures, altered mental status, signs of increased intracranial pressure, chronic papilledema, loss of vision, other sensorineural deficiencies, etc.)
7. Patients suffering from biallelic mutations in any of the following genes: PRF1/Perforin, UNC13D/Munc 13-4, STX11/Syntaxin11, STXB2/Munc 18-2, RAB27A/Rab27a (Griscelli syndrome type 2), LYST (Chediak-Higashi syndrome), AP3B1, ADTB3A, HPS2 mutations (Hermansky-Pudlak syndrome 2) and X-linked lymphoproliferative syndrome (XLP)-1 with SH2D1A mutation
8. Patients who are pregnant or nursing, women of childbearing potential who are unwilling to use highly effective birth control methods (see definition in Inclusion Criteria above) through 4 weeks after the end of their participation in the study
9. Concomitant use of immunosuppression therapies excluded by the protocol. Note: NSAIDs, glucocorticoids, cyclosporine, tacrolimus, and IL-1 inhibitors (anakinra, canakinumab, or rilonacept, or others) are allowed
10. Patients and/or parents (or legal representative, if applicable) not willing to sign assent/informed consent
11. Hypersensitivity to the active substance or one of the excipients of the investigational product.

**** NOTES:***

For Exclusion Criterion 7, lab testing will be performed at Screening (V0). Results should be available for V1 to confirm eligibility prior to study treatment. In case treatment is started based on local laboratory genetic results, which don`t include the above listed genes, genetic results have to be confirmed by central laboratory retrospectively as for inclusion criterion 1.

For Inclusion Criterion 1, results from genetic testing will be available prior to study treatment initiation.

10.4 Patient Withdrawal Criteria

A patient may be withdrawn from the study at any time for reasons including, but not limited to, the following:

1. The patient will stop the study for safety concerns in the opinion of the Investigator
2. Stopping for ineffectiveness should only be related to serious manifestations (i.e., MAS) uncontrolled by the drug. In the case of study discontinuation for lack of response to treatment and start of rescue immunosuppression, all key safety and efficacy outcomes will be followed up throughout the double-blind period on all randomized patients
3. Physician decision due to safety concerns or lack of efficacy
4. The patient withdraws consent
5. If IMP has been administered and the patient experiences intolerance (i.e. manifestations of hypersensitivity) that cannot be controlled despite the best efforts of the physician
6. Participation in the study is no longer in the best interests of the patient, in the judgment of the managing clinician or the Sponsor
7. The study is terminated prior to the end of the patient's participation.
8. The patient is unwilling or unable to adhere to protocol requirements or requires a concomitant medication prohibited by the protocol

If a patient is discontinued prematurely from the study, the Investigator must provide an explanation in the Additional Comments section and complete the Early Termination page of the electronic case report form (eCRF). If IMP has been administered, the Investigator should make every effort to perform scheduled evaluations prior to discharge, provided the evaluations do not jeopardize the safety or on-going medical care of the patient (i.e., physical examination, vital signs, clinical laboratory tests, immunologic assessments, and AE assessments). All key efficacy and safety endpoints will be collected for the length of the study.

In the event that a patient discontinues prematurely due to an SAE, the patient will be followed until resolution, until the condition stabilizes, or until the patient is lost to follow-up. See Section 20 for discussion of management of subjects who discontinue prematurely because of an AE or SAE.

The physicians and the patient will have the option to discontinue the treatment if they feel that pursuing the treatment is not appropriate. In case of discontinuation and start of another medication, it is important to capture this information too, and also to report whether a response was observed in case of change. All key efficacy and safety endpoints will also be collected for the length of the study.

A patient who discontinues prematurely after one or more treatments will not be replaced.

10.5 Blinding/unblinding Arrangements

Sponsor, patients, investigators, investigator staff, persons performing the assessments, and data analysts will remain blinded to the identity of the assigned study treatment from the time of randomization into the RW phase until the final database lock, using the following methods:

1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the treatment administration, treatment outcome assessment or data collection or analysis, with the exception of the DSMB members as described in the DSMB Charter.
2) The identity of the treatments will be concealed by the use of study drugs (Tadekinig alfa and Placebo) that are all identical in packaging, labeling, schedule of administration, appearance and odor.
3) The randomization code for an individual patient may only be unblinded in emergency situations, where the investigator decides that a patient cannot be adequately treated without knowing the identity of their treatment allocation. To break the randomization code, the investigator must open the emergency unblinding envelopes provided. If any unblinding envelope is opened, the time, date, subject number and reason for opening must be documented.

The primary endpoint, time to first disease reactivation, is a parameter which is objectively assessed by reporting a time and measuring serum ferritin levels, serum CRP and assessing mAIDAI. mAIDAI is comprised of 14 items of which 4 symptoms could be considered subjective and thus are excluded from the definition of response to therapy and disease reactivation (see Appendix I). All 14 items will continue to be collected and will be plotted over time in the descriptive analysis.

11 STUDY PRODUCT

11.1 Study Product Description

Tadekinig alfa is a soluble glycoprotein of [redacted] amino acids produced from Chinese Hamster Ovary cell line. The polypeptide chain contains [redacted] The average molecular weight of the full-length polypeptide moiety of recombinant human IL-18BP (r-hIL-18BP), calculated on the basis of the aminoacid composition, is approximately [redacted] kD. The relative molecular mass of the whole molecule is approximately [redacted] kD (including glycans).

Tadekinig alfa is supplied as a colorless to slightly yellow, sterile solution for injection in glass vials containing [redacted] as excipients. It is available in a concentration of 20mg/0.5mL.

A sodium chloride [redacted] will be used as placebo. To ensure that the IMP remains blinded for the entire study period, both the actual drug and the placebo solutions will be supplied in identical vials and similar labeling and will be indistinguishable in terms of their texture, color, and smell.

11.1.1 Composition

The drug product formulation r-hIL-18BP has a strength of 20mg per vial, and is prepared as a sterilized solution for injection containing [redacted] to adjust to pH [redacted], water for injection up to 0.5 mL

The placebo drug product formulation has an identical composition apart from no drug being present.

Glass vials containing 0.5 mL of the injection volume and 20mg of the recombinant molecule.

Vials with placebo will be supplied in identical volume and aspect.

11.1.2 Quality Control

Quality control of the products will be performed at the production stage, on product release, and during the study. The study product is manufactured in compliance with GMP.

11.1.3 Packaging and Labelling

The IMP will be contained in a single-use glass vial with rubber stopper. The IMP will be labelled for use by trial subjects and will have the study designation, and other identifying codes as required by the local regulatory authority.

Labelling and packaging will be blinded with regard to study treatment (Tadekinig alfa / placebo)

11.2 Study Product Administration

11.2.1 Amount, Dose, Concentration, Frequency

Patients will receive the treatments of r-hIL-18BP at a dose of 2 mg/kg s.c. every 2 days ± 5 hours for a total treatment period of 18 weeks in the SAOL phase. The maximum dose is 160 mg (note: patients with more than 80 kg body weight will receive the maximum dose of 160 mg).

Patients in the RW phase will be treated with the same dosage or volume (2 mg/kg, s.c. every 2 days) of either Tadekinig alfa or equivalent volume of Placebo as randomized. The treatment period in this phase is up to 16 weeks.

The volume for injection will need to be individually calculated on the basis of the weight of the patient collected at least weekly for patients weighing less or equal to 15 Kg, or in the more recent or current study visit for patients weighing more than 15 Kg. This, corresponds to a dose of 2mg/Kg (or 0.05mL of investigational product per kg patient weight). The required volume will be withdrawn from the vial

using a sterile, single use syringe. Before treatment, the vials will be brought to room temperature (18 – 25°C) by removing them from the refrigerator 15 min prior to administration. The IMP will be withdrawn into a sterile syringe and administered without delay.

Further instructions on IMP handling and storage will be provided by the Sponsor/CRO.

Note: more than 1 vial might be required to deliver the calculated dose.

Drug product selected dose: The safety and tolerability of Tadekinig alfa has been studied in adult human volunteers following single s.c. injections with doses ranging from 20mg to 350mg and repeated s.c. doses (35mg and 175mg) administered on alternate days. In addition, 6 weeks duration Phase Ib studies (three administrations per week) have been completed in Rheumatoid Arthritis (RA) (n=35) subjects and Psoriasis (Pso) (n=36) subjects with doses ranging from 20mg to 160mg in the former, and 20mg to 320mg in the latter. No SAEs were observed in any of the studies and the most frequent AE (mild to moderate) were injection site reactions (with a causality described as “probably related” to Tadekinig alfa).

A phase II Clinical Trial in Adult Onset Still’s Disease (AOSD) subjects (n=23) is completed. 10 subjects were treated with 80 mg and 13 subjects were treated with 160mg for 12 weeks (three administrations per week). One patient in the 80 mg cohort suffered from a gastroenteritis that required hospitalization, SAE (grade 3) not related to the IMP as per Investigator. A patient of the 160 mg cohort suffered from Toxic Opticus Neuropathy that required hospitalization, SAE (grade 3) and was considered possibly related to the IMP by the physician.

Under a compassionate-use IND, a patient suffering from a severe neonatal autoinflammatory condition caused by an NLRC4 mutation, was given r-hIL-18BP at a dose of 2 mg/kg s.c. every 48 hours. Within the first two doses, the patient’s overall status improved rapidly in correlation with acute drop (non-detectable) in free IL-18. All remaining inflammatory features, including enterocolitis, also improved steadily and allowed weaning of other immunosuppression and reintroduction of enteral feeding. The treatment has continued for more than 6 years, at the same dose, with clinical and biological remission and without observed side effects. Therefore, from a safety point of view, the collected human data supports the selected dose range of the study.

From a clinical efficacy point of view, it is important to underline that doses of 20 mg 3 times a week showed no efficacy in RA and Pso adult subjects. Those doses will be likely also ineffective in AoSD subjects considering that blood levels of IL-18 in AoSD are higher than those reported in the two conditions noted above

In conclusion, based on preclinical and previous human studies performed with Tadekinig alfa and in order to avoid providing inefficient doses to patients suffering from NLRC4 mutation and XIAP deficiency the selected dose is of 2 mg/kg.

11.2.2 Route of Administration

The product comes as a solution to be administered by the s.c. route. Glass vials contain 0.5mL corresponding to a dose of 20mg of the active product, and a 0.12mL overfill is included.

The site of the s.c. injection should be alternated e.g. the outside of the thighs, arms and the various quadrants of the anterior abdominal wall. The personnel of the participating sites shall give instructions for proper injection procedures to the study nurse (home care nurse or site nurse) in order to minimize injection site reactions due to poor injection procedure. AB2 Bio will provide written s.c. injection instructions. Used syringes and needles will be disposed of in a puncture-resistant container. Used glass vials will be disposed of at the site, per the site’s IMP destruction policy, after IMP accountability and reconciliation is performed. However, unused vials will be returned to the drug supplier for destruction.

11.2.3 Patient Compliance

In order to enhance subjects' compliance, local skin treatment will be proposed to the parents/patients to mitigate local inflammatory reactions.

After patient discharge from the hospital the parents/patient will complete a daily diary recording current health status including body temperature, skin rash, vomiting, diarrhea, changes in concomitant medication, and any other unusual, remarkable symptoms.

NOTE: Temporary Stop of Treatment

Temporary treatment interruptions will be allowed in case the patient shows fever or any sign of undergoing an infection process unrelated to the treated condition. For the injections done by the home care nurse (HCN) every 2 days, the HCN should contact the Investigator for advice on treatment continuation or stopping. In case of any doubt, the treatment may be discontinued temporarily.

In case of treatment stop of more than 3 weeks the effect of the investigational drug is lost and the case will be considered a dropout (discontinuation).

11.2.4 Concomitant Treatment

All concomitant medications (together with route of administration) and treatment initiated during the period of the study between screening and end of the study will be recorded in the concomitant treatment section of the eCRF.

Permitted Concomitant Treatments

Patients can maintain treatment with stable doses of Non-Steroidal anti-inflammatory Drugs (NSAIDs), cyclosporine, tacrolimus and IL-1 inhibitors (anakinra, canakinumab, or rilonacept, or others). Dose increments for the permitted co-medications or their introduction after the beginning of the study are not permitted and represent treatment failures and study early termination. For cyclosporine and sirolimus treatments, the physician may need to change the dose slightly to readjust serum levels. Dose adjustments for keeping stable serum levels is acceptable during the study. The weaning of permitted co-medications after the beginning of the study are permitted and are evaluated as additional parameter for response to therapy; the decision for weaning other immunosuppressive therapies other than the SOC steroids is at the discretion of the treating physician and should be based on the individual patient's disease status. If permitted co-medications are weaned off during the course of the study and the investigator decides to re-introduce them, they are permitted as long as the doses are the same or lower than the doses that were administered at study entry.

Unauthorized Concomitant Treatments

The study-assigned treatments (Tadekinig alfa or placebo as randomized, plus SOC) are, in addition to the permitted concomitant medications if prescribed by the treating physician, the only treatment allowed during the study treatment period.

The need to use rescue immunosuppression will be considered as treatment failure and the patient will discontinue study treatment.

They include cytoablative drugs as **etoposide**, **cyclophosphamide**, etc. Specific cell-depleting agents such as **alemtuzumab**, **rituximab**, **anti-thymocyte globulin**. I**mmunosuppressive antimetabolites such as 6-mercaptopurine and azathioprine** and **mycophenolate mofetil** that inhibits the proliferation of immune cells**.** Other biologics different to IL-1 blockers will also be considered as rescue immunosuppression, i.e. anti-TNF antibodies, **tocilizumab**, **vedolizumab**.

If the Investigator feels the clinical situation of the patient is likely to require any of the above rescue immunosuppression medications, the patient will be considered a treatment failure and discontinue study treatment. If the investigators consider necessary the introduction of another medication that is not included in the list or category above, the Investigator should contact the Medical Monitor.

11.3 Study Product Handling

11.3.1 Storage and Distribution

The Sponsor will supply the IMP. The transport of the drug product to the clinical supply vendor will be performed under controlled temperature conditions (between 2-8 °C). The storage of the bulk material at the clinical supply vendor will be performed under controlled temperature conditions (2-8°C). The clinical supply vendor will prepare treatment kits containing 20mg vials or placebo vials in kit cartons with carton labels, and vial labels. Syringes and needles will be provided separately for treatment administration. The kits and supplies will be shipped from the clinical supply vendor (central storage) to the hospital pharmacy or patient's home after once a patient has been screened, signed the ICF and all required documentation are available at the site. The Project Manager (PM), or designee, at the CRO will be in charge of the communication to the central vendor for product shipment to the sites. Initial IMP release to sites is approved by the Sponsor PM or designee upon timely receipt of all required documents from the CRO.

The kits will contain either the active substance or placebo.

The kits will be stored at the hospital pharmacy or patient's home under controlled temperature conditions (2-8°C).

For ambulatory patients, if the patient's home is located near the hospital, and causes no major inconveniences to the patient, the patient will go to the hospital every 2 days for the treatment administration by the site nurse.

For any patient who cannot attend the hospital for the injections every 2 days, a study home care nurse may be involved. The site will discuss with the patient and request HCN in advance to allow timely training and logistic set up at patient home (e.g. locked fridge, IMP shipment to patient home).

If patient home is close by the site, the HCN will go to the hospital pharmacy to recover the IMP for the treatment of the day, in validated cooling bags. The maximum duration allowed for IMP transport under 2-8°C is 4 hours in a validated cooling bag. The HCN will go from the site to the patient home for the IMP administration and will document any observations (even if no major observations) during IMP transit, and before IMP administration.

A courier may be involved for IMP shipment from site/IMP depot to patient home if distance is too far away.

Further instructions and adjustments to this logistic will be provided in a separate manual to the site.

11.3.2 Study Product Accountability and Reconciliation

All IMP received and dispensed by the Investigators/pharmacists of each site will be inventoried and accounted for throughout the trial period by the Investigators/pharmacists on the corresponding "Master IMP Accountability Log" and "Subject IMP Accountability Log" (to be provided prior to the Site Initiation Visit (SIV).

The Investigators agree not to supply the IMP to any person except to study staff, the HCN or courier service if involved to ship IMP to patient home.

Unused IMP must not be traded. Used and unused IMP at completion of the study should be returned to the IMP depot for destruction. Used vials may be destroyed at the site, according to the site's procedures, after completion of IMP accountability. Used vials will be destroyed only at the drug supplier premises according to their own procedures.

12 ASSESSMENT OF EFFICACY

Efficacy assessment is related to the incidence of disease reactivations and will cover:

Clinical evaluation (mostly captured in the mAIDAI):

- Complete physical examination including: vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, weight, and body temperature)
- All findings should be documented: joint swelling, hepatomegaly and splenomegaly, presence of skin rash, ophthalmic control (presence of uveitis). Ophthalmic examination will be performed to examine the presence/absence of uveitis and, if present, the evolution during the study.
- Symptoms should be documented: abdominal pain, diarrhea, nausea, vomiting
- All clinical components (including clinical findings and symptoms) of the disease will be captured in a binary way as either being present or absent. The judgement, of whether an end organ category is affected, is done by the treating physician according to clinical standards, as also previously done for all mAIDAI components.
- Daily weight, stool output, and PO intake measurements including number of emesis episodes will be performed on patients with intestinal dysfunction, only when the patients are hospitalized
- Radiologic findings if assessed as necessary by the treating physician

Maintenance co-treatment:

- Total weekly glucocorticoids
- IL-1 blockers
- Other treatments * (e.g., DMARDs…etc.)

  * Refer to Section 11.2.4: Concomitant treatment

Laboratory (see Table 2):

- Serum CRP
- Serum Ferritin
- Complete blood counts
- Serum levels of total IL-18, free IL-18, IL-18BP

Note 1: *GI-related parameters will be assessed in patients with GI dysfunction*

Note 2: *For outpatient therapy the clinical evaluation will be performed at the monthly visits*

12.1 DEFINITION OF RESPONSE TO THERAPY

1. In the 16-week RW phase, response to therapy (as primary endpoint of efficacy) will be assessed by prevention of disease reactivations during the 16-week treatment in the RW phase
2. In the SAOL phase, response to therapy (as secondary endpoint of efficacy) will be assessed through the control of the active disease

For response to therapy, only the objective mAIDAI components will be evaluated as indicated below. Subjective mAIDAI components (see Appendix I) will not be considered to avoid any bias in the efficacy assessment in the open label part of the study. Justification for the revised response to therapy definitions is included in section 8.3.3.

- **Complete response**

  No major end organ damage (=objective mAIDAI components)
  - No fever (body temperature ⩽100.4° F/38° C)
  - No diarrhea
  - No transaminitis and/or hepatomegaly
  - No splenomegaly and/or adenopathy
  - No rash
  - No uveitis
  - No arthritis
  - No radiologic CNS involvement
  - No cytopenia (HgB ⩾ 9.0 and/or PLT ⩾100 and/or WBC ⩾3.0)

  No systemic inflammation
  - No hyperferritinemia (serum level < 500 ng/mL)
  - No increased CRP (serum level < 2x ULN)

  Immunosuppressive therapies
  - Discontinuation of systemic corticosteroids (excluding hydrocortisone for prevention of adrenal insufficiency) or other immunosuppressive therapies including biologics ongoing at baseline
  - No start or dose increase of other immunosuppressive therapies including biologics

- **Partial response**

  At least 50% reduction of the number of affected objective end organ damage categories at baseline and
  - At least 50% of the systemic inflammatory markers (ferritin and/or CRP) increased at baseline reaching levels for complete response or
  - Discontinuation of systemic corticosteroids (excluding hydrocortisone for prevention of adrenal insufficiency) or other immunosuppressive therapies including biologics ongoing at baseline

- **Disease Improvement**

A third response category of Disease Improvement is introduced to be utilized as a description of best response and in order to better describe initial treatment response to therapy and disease evolution over time. This is only used for analysis purposes and will not be evaluated for the decision whether to be eligible for the start of the RW phase. Disease Improvement is defined as:
- Reduction of the number of affected objective end organ damage categories at baseline by at least 1 or
- Normalization (i.e. reaching levels for complete response) or improvement (> 50% change from baseline for laboratory markers but still exceeding levels for complete response) of at least 50% of the systemic inflammatory markers affected at baseline
- Systemic corticosteroids (excluding hydrocortisone for prevention of adrenal insufficiency) or other immunosuppressive therapies including biologics must be at the same or lower doses compared to baseline

12.2 DEFINITION OF DISEASE REACTIVATION

For disease reactivation, only the objective mAIDAI components will be evaluated as indicated below. Subjective mAIDAI components (see Appendix I) will not be considered to avoid any bias in the assessment. Justification for the revised disease reactivation definitions is included in section 8.3.3.

During the RW-phase, the reference for a disease reactivation (for the primary endpoint assessment) will be the end of the SAOL phase (V8); for the SAOL phase, reference will the previous visit, as patients enter the SAOL phase with an active disease.

- **Partial disease reactivation**
  - Increase in the number of affected objective end organ damage categories by at least 2 or
  - Increase in the number of affected objective end organ damage categories by at least 1 and worsening of at least 1 systemic inflammatory marker (i.e. serum ferritin levels ≥ 500 ng/mL or serum CRP ≥ 2x ULN) that was meeting complete response criteria before
- **Full disease reactivation**
  - Increase in the number of affected objective end organ damage categories to at least the number of affected end organ damage categories at baseline (V1) and
  - Exacerbation of at least 1 systemic inflammatory marker (i.e. serum ferritin levels ⩾ 500 ng/mL or serum CRP ⩾ 2x ULN) that was meeting complete response criteria before

Note: It is recommended that patients suffering from *severe* CNS manifestations are put on rescue immunosuppression treatment.

13 ASSESSMENT OF SAFETY

The Investigator will assess patient safety throughout the study. In addition, the DSMB, an independent committee, will analyze clinical or biological worsening of the status of study patients (i.e., SAEs) and also treatment failures and will assess the global safety of Tadekinig alfa (see details in Study Design section).

Safety assessment during the study will include:

- Prior to initiation of therapy, physical examination, vital signs, testing for active and life-threatening infections, complete blood count, clinical chemistry, coagulation and urinalysis.
- During treatment phase, physical examination, including ophthalmic examination, vital signs, routine laboratory (complete blood count, clinical chemistry, urinalysis), AEs, including AEs of Special Interest (AESI), concomitant medications, local tolerability index, immunogenicity, and coagulation tests.
- Regarding immunogenicity, ADAs assessment will be performed at Baseline V1, Week 2 (V3), Week 4 (V5), Week 12 (V7), Week 18 (V8), and RW Week 22 (V10), Week 26 (V11) and Week 34 (V13).
- Safety and disease activity labs will be assessed during hospitalization as required, weekly during visits for the first four weeks, then approximately monthly during visits until completion of the study, or at unscheduled visits.
  - weekly from Visit 0 to Visit 5;
  - monthly from Visit 6 to Visit 7;
  - at Visit 8 (6 weeks from Visit 7);
  - at Visit 9 (2 weeks from Visit 8);
  - at Visit 10 (2 weeks from Visit 9);
  - monthly from Visit 11 to Visit 13.

AEs will be collected from the time of informed consent through the end of the study. Definitions and reporting procedures for AEs and SAEs are provided in Section 16. “Handling of Adverse Events”.

Details on routine safety laboratory assessments, virology, and serology tests, and collection of samples for ADAs (immunogenicity) are provided in Table 2.

Physical examinations and vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, weight and body temperature) will be collected at all visits. Height is collected at Screening.

The Local Tolerability Index is provided in Appendix 2.

**** NOTE:***

Laboratory safety and efficacy endpoints will be studied at the visits by the central lab. For hospitalized patients local labs will perform, in addition, analyses as required by the standard of care and this information will be entered in the study eCRF.

14 CONDUCT OF THE STUDY

14.1 Schedule of Events

See section 7, Table 1.

In order to protect the patient`s and caregiver`s safety and welfare during the COVID-19 pandemic, on-site study visits may not be considered appropriate; most patients have to travel to their study site and on-site study visits may expose both the patients and caregivers as well as study site personnel to an increased risk of infection. Moreover, due to the ultra-rare indication of this study, conducting on-site study visits at sites often located far away from the patient`s home has made study conduct challenging.

Thus, in an effort to accommodate the patients and their families while ensuring the relevant study data is collected, scheduled study visits (except for the Baseline visit) may be conducted as telemedicine visits involving the use of electronic communications (for example, live interactive video and audio) to enable site staff to conduct "virtual" (not in-person) visits with their patients. These visits may be supported by home health nurses assisting in physical examination (by performing a body assessment supporting the physical examination done by the investigator via telemedicine), collection of vital signs or performance of central laboratory blood draws. Laboratory assessments may be also performed at qualified local laboratories. The study site may also utilize a physical examination from the patient's most recent standard of care visit conducted by the local treating physician, for the purpose of the study.

Patients and/or parents (or legal representative, if applicable) will sign a respective assent/informed consent prior to the conduct of such telemedicine visits.

It is expected that the Baseline Visit will be conducted as an on-site visit, as patients are having an active disease at that time and eligibility needs to be confirmed during an on-site visit. For the Screening visit, eligibility may be evaluated during a telemedicine visit. This visit shall be based on local laboratory results and standard of care physical examination, including vital signs, conducted by the local treating physician. This may be permitted in order to avoid long-distance travel for the patients with uncertainties whether they meet the protocol definitions for an active disease status.

For all visits after the Screening and Baseline visits, the risks and burden of travel to the study site versus the requirement for a close patient follow-up in line with protocol requirements will be evaluated for each individual patient. Aspects to consider include the disease severity of each patient, the distance from the patient`s home to the study site, the patient`s local situation of the COVID-19 pandemic and the possibilities and local regulatory requirements for telemedicine visits at the study sites.

SAOL Phase

14.2 Patient Recruitment - Screening Visit (before treatment start at V1)

- Review and signing of Child Assent and/or Informed Consent Form (ICF)
- Collection of AEs starts after signing ICF
- Demographics and medical history
- Completion of the Inclusion/exclusion checklist by the physician
- Physical examination with specific assessment of hepatosplenomegaly and vital signs (including height)
- Clinical evaluation by the physician using the mAIDAI (Appendix 1)
- Physician Global Assessment (PGA) (Appendix 3)
- Lab testing
    - Genetic evaluations

- Infection evaluations (CMV, EBV, etc.)
- Serology (HIV, HCV, HBV)
- Pregnancy test (UPT and/or hCG as applicable)
- Hematology, clinical chemistry, ESR (at local lab), urinalysis, CRP, Ferritin, TB blood testing (Note: QuantiFERON-TB testing should be done either at central lab or local [hospital] lab, prior to treatment initiation)
- Flow cytometry
- Coagulation (Thrombocytes, Fibrinogen, D-dimer, PTT, PT)

- Specialized lab testing
  - Serum: Total IL-18, free IL-18, IL-18BP

14.3 Baseline visit at Week 0 (V1- Treatment Initiation) – SAOL Phase

- Reassessment of inclusion and exclusion criteria prior to treatment with Tadekinig alfa start
  - Physical examination with specific assessment of hepatosplenomegaly and vital signs
  - Treatment start with Tadekinig alfa
  - Review of AEs and concomitant medications
  - Clinical evaluation by the physician using the mAIDAI
  - Physician Global Assessment (PGA)
  - Patient` s/caregiver`s qualitative evaluation of health status (study specific questionnaire for all patients implemented in protocol version 6)
  - Local Tolerability Index Assessment by Investigator
  - Ophthalmic examination will be performed for the diagnosis (presence/absence), severity and evolution of uveitis and occurrence of ophthalmic adverse events (i.e. toxic neuropathy)
  - Lab testing (Samples taken prior to treatment)
    - Hematology, clinical chemistry, ESR (at local lab), urinalysis, CRP, Ferritin,
    - Coagulation (Thrombocytes, Fibrinogen, D-dimer, PTT, PT)
    - Urine pregnancy test, as applicable
  - Specialized lab testing
    - Serum: Total IL-18, free IL-18, IL-18BP (Samples taken prior to treatment)
    - Serum: Anti-Tadekinig alfa antibodies (measurement performed on blood drawn before Tadekinig alfa administered for all patients)
    - Additional sample for PK study will be collected at 2 h, 4 h, 6 h and 24h post treatment. Trough levels are calculated based on blood samples used for lab testing (no extra sample needed)
- Treatment initiation

- Two-hour patient observation after first treatment

14.4 Visits at Weeks 1, 2, 3 (V2/Day 7, V3/Day 14, V4/Day 21)

- Physical examination with specific assessment of hepatosplenomegaly and vital signs
- Treatment with Tadekinig alfa (every 2d)
- Review of AEs and concomitant medications
- Clinical evaluation by the physician using the mAIDAI
- Physician Global Assessment (PGA)
- Local Tolerability Index Assessment by Investigator
- Lab testing (Samples taken prior to treatment)
    - Hematology, clinical chemistry, ESR (at local lab), urinalysis, CRP, Ferritin
    - Coagulation (Thrombocytes, Fibrinogen, D-dimer, PTT, PT)
    - Urine pregnancy test, as applicable
- Specialized lab testing
    - Serum: Total IL-18, free IL-18, IL-18BP (Samples taken prior to treatment)
    - Serum: Anti-Tadekinig alfa antibodies (measurement performed on blood drawn before Tadekinig alfa administered for all patients) will be performed at V3

14.5 Visit at Week 4 (V5/Day 28)

- Physical examination with specific assessment of hepatosplenomegaly and vital signs
- Treatment with Tadekinig alfa (every 2d)
- Review of AEs and concomitant medications
- Clinical evaluation by the physician using the mAIDAI
- Physician Global Assessment (PGA)
- Local Tolerability Index Assessment by Investigator
- Lab testing (Samples taken prior to treatment)
    - Hematology, clinical chemistry, ESR (local lab), urinalysis, CRP, Ferritin
    - Coagulation (Thrombocytes, Fibrinogen, D-dimer, PTT, PT)
    - Urine pregnancy test, as applicable
- Specialized lab testing
    - Serum: Total IL-18, free IL-18, IL-18BP (Samples taken prior to treatment)

- Serum: Anti-Tadekinig alfa antibodies (measurement performed on blood drawn before Tadekinig alfa administered for all patients)
- PK assessment - Additional sample for PK study will be collected at at 2 h, 4 h, 6 h and 24h post treatment. Trough levels are calculated based on blood samples used for lab testing (no extra sample needed)

14.6 Visits at Week 8, 12 (V6/Day 56, V7/Day 84) – Monthly Visits

- Physical examination with specific assessment of hepatosplenomegaly and vital signs
- Treatment with Tadekinig alfa (every 2d)
- Review of AEs and concomitant medications
- Clinical evaluation by the physician using the mAIDAI
- Physician Global Assessment (PGA)
- Local Tolerability Index Assessment by Investigator
- Lab testing (Samples taken prior to treatment)
  - Hematology, clinical chemistry, ESR, urinalysis, CRP, ferritin
  - Coagulation (Thrombocytes, Fibrinogen, D-dimer, PTT, PT)
  - Urine pregnancy test, as applicable
- Specialized lab testing
  - Serum: Total IL-18, free IL-18, IL-18BP (Samples taken prior to treatment)
  - Serum: Anti-Tadekinig alfa antibodies (measurement performed on blood drawn before Tadekinig alfa administered for all patients) at Week 12 (V7)

14.7 Visit at Week 18 (V8/Day 126): End of SAOL Phase/Start of RW Phase

- Physical examination with specific assessment of hepatosplenomegaly and vital signs
- Review of AEs and concomitant medications
- Clinical evaluation by the physician using the mAIDAI
- Physician Global Assessment (PGA)
- Patient` s/caregiver`s qualitative evaluation of health status
- Local Tolerability Index Assessment by Investigator
- Lab testing (Samples taken prior to treatment)
  - Hematology, clinical chemistry, ESR, urinalysis, CRP, ferritin
  - Coagulation (Thrombocytes, Fibrinogen, D-dimer, PTT, PT)
  - Urine pregnancy test, as applicable
- Specialized lab testing

- Serum: Total IL-18, free IL-18, IL-18BP (Samples taken prior to treatment)
- Serum: Anti-Tadekinig alfa antibodies (measurement performed on blood drawn before Tadekinig alfa or placebo administered for all patients) at Week 18 (V8)

- Treatment with Tadekinig alfa or placebo (every 2 days) ***as randomized for RW phase***
  - **Note:** Study drug administration should occur after all V8 assessments have been performed

14.8 Visits at Weeks 20, 22, 26, 30 (V9/Day 140, V10/Day 154, V11/Day 182, V12/Day 210)

- Physical examination with specific assessment of hepatosplenomegaly and vital signs
- Treatment with Tadekinig alfa or placebo (every 2 days) as randomized for RW phase
- Review of AEs and concomitant medications
- Clinical evaluation by the physician using the mAIDAI
- Physician Global Assessment (PGA)
- Local Tolerability Index Assessment by Investigator
- Lab testing (Samples taken prior to treatment)
  - Hematology, clinical chemistry, ESR, urinalysis, CRP, ferritin
  - Coagulation (Thrombocytes, Fibrinogen, D-dimer, PTT, PT)
  - Urine pregnancy test, as applicable
- Specialized lab testing
  - Serum: Total IL-18, free IL-18, IL-18BP (Samples taken prior to treatment)
  - Serum: Anti-Tadekinig alfa antibodies (only at Weeks 22 (V10) and 26 (V11))

14.9 Study Completion Visit at Week 34 (V13/Day 238)/Study Completion for Patients experiencing disease reactivations during RW/ Early Termination for Discontinued Patients:

- Physical examination with specific assessment of hepatosplenomegaly, vital signs
- Review of AEs and concomitant medications
- Clinical evaluation by the physician using the mAIDAI
- Physician Global Assessment (PGA)
- Patient` s/caregiver`s qualitative evaluation of health status
- Local Tolerability Index Assessment by Investigator
- Lab testing

  - Hematology, clinical chemistry, ESR (at local lab), urinalysis, CRP, Ferritin
  - Coagulation (Thrombocytes, fibrinogen, D-dimer, PTT, PT)
  - Urine pregnancy test, if applicable
- Recording other medications given to the patient after study treatment stop, and if (or not) any response to new medication
- Specialized lab testing
  - Serum: Total IL-18, free IL-18, IL-18BP (Samples taken prior to treatment)
  - Serum: Anti-Tadekinig alfa antibodies

Note: A patient experiencing a partial or full disease reactivation during the 16 week RW phase and thus proceeding to the End of Study Visit will not be considered as having early terminated from the study.

14.10 CLINICAL LABORATORY TESTS

Sample analysis will be performed in the central lab and local labs (as applicable). A list of all samples collected and associated laboratory assessments is provided in **Table 2**. Approximately 10-20 ml of blood will be taken at visits when laboratory tests are required, the actual volume will depend on the patient weight. Due to sample volume limitations duplication of determinations between the central and the local labs will be avoided when possible.

Other clinical laboratory tests may be performed locally by the Investigator, as deemed necessary, to ensure patient safety.

Table 2: *Clinical Laboratory Tests*

Biochemistry	**Haematology**
GOT/AST	Hematocrit
GPT/ALT	Haemoglobin
Gamma-glutamyl transferase (GGT)	Red blood cell (RBC) count
	Complete blood count, White Blood Cell (WBC) count
Alkaline phosphatase (ALP)	
Total bilirubin	Neutrophils
BUN	Lymphocytes
LDH	Monocytes
Creatinine	Eosinophils
Uric acid	Basophils
Potassium	Platelets
Sodium	MCC
Chloride	MCHC
Calcium	MCV
Total protein Serum albumin Glucose	**Coagulation**
Total cholesterol	PT
Triglycerides	PTT, D-Dimer and Fibrinogen
CRP	
ESR (Erythrocyte Sedimentation Rate)	
Viral Infection – CMV, EBV	**Cytokines and inflammatory mediators**
Genetic Analysis –	IL-18 total
Flow Cytometry	IL-18 free IL-18BP
Serology	
HIV (anti-HIV1 and anti-HIV2 antibodies,	
HIV1 Ag)	**PK study**
Hepatitis C Hepatitis B	IL-18BP
Pregnancy Test (UPT and/or hCG as applicable)	**Ferritin system**
	Ferritin
Urinalysis	
Dipstick: protein, erythrocytes (blood), leukocytes, nitrite, bilirubin, urobilinogen, glucose, ketone bodies, pH, specific gravity	**Anti-drug antibodies**

15 DATA MANAGEMENT

15.1 Data Collection

- Patient data will be collected on eCRFs and will be substantiated by source documents at the clinical site. Laboratory results from outside laboratories will be received by the site and entered from hard copy print-outs into the eCRF.
- Prior to the start of the study, the Investigator will complete a Registry of Signatures / Delegation of Responsibility Log showing the signatures and handwritten initials of all site staff individuals who are authorised to make or change entries on eCRFs. The eCRFs will be completed according to the eCRF Completion Guidelines (eCCGs) provided by the CRO in writing and/or verbally.
- Data will be collected using, a web-based electronic data capture (EDC) system. The Study Monitor will review all eCRF data to 100% source data verification (SDV) to ensure adequate quality control and complete patient data. Any discrepancies found during the eCRF review will be clarified by the Investigator (or his/her designated staff). This includes eCRF reviews at the site by the Sponsor or its designee, or during quality assurance review of the data or audits.
- The Investigator or designee must record all required patient data using the eCRFs. The Investigator must electronically sign and date a declaration on the eCRF attesting to his/her responsibility for the quality of all data recorded, and that the data represent a complete and accurate record of each patient's participation in the study. All Investigators authorized to approve eCRFs will sign a declaration stating that their handwritten signature is the legal equivalent of an electronic signature. Each patient eCRF will be retained by the Investigator.
- A patient diary will be completed by/for patients dosed at home. The diary does not need to be completed if the patient is hospitalized. The diary may be provided electronically or in hard copy booklets to be completed by the subjects or by another person other than the patient (e.g., Caregiver).
- Data will be collected to the extent possible for subjects who discontinue the treatment. In case of such discontinuation and start of another medication, it is important to capture this information too and also to report whether a response was observed in case of change.
- All DM activities are done according to CRO SOPs.

16 STATISTICS

16.1 General Considerations

The statistical analysis will be conducted by the assigned CRO. Statistical methods will be pre-specified and documented in detail in a Statistical Analysis Plan (SAP) to be finalized before database lock and breaking the treatment blind on all subjects. Any deviations from the analysis pre-planned in the protocol or the SAP will be described and justified in the final study report. All statistical analyses will be generating using validated Base SAS® software, Version 9 or higher.

16.2 Interim Analysis

No interim analysis will be performed at this stage.

16.3 Sample Size Calculations

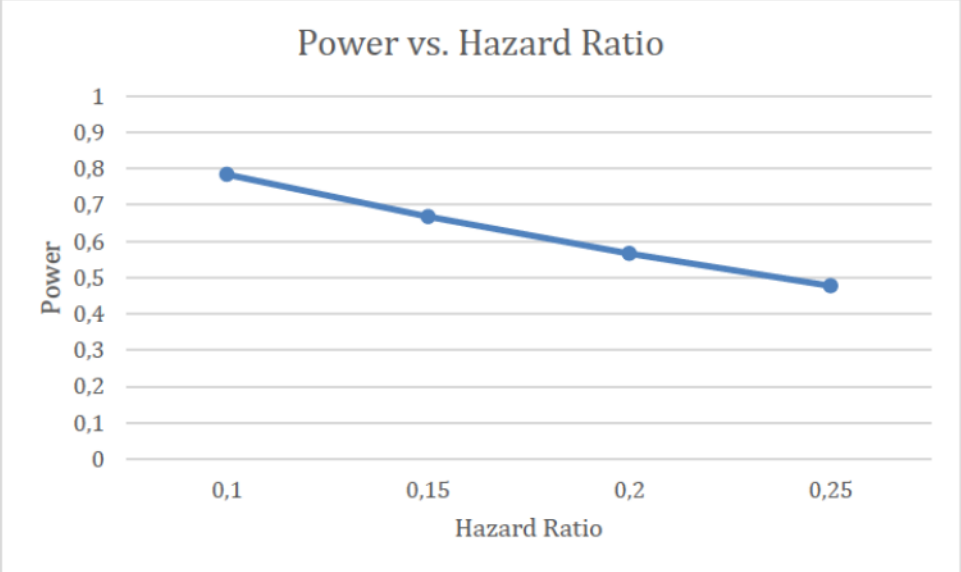
Power Calculations

The primary endpoint of the study is time to first occurrence of disease reactivation (including full and partial disease reactivation) during the RW phase of the study. There is limited historical data for this disease condition, for either a control or an experimental test product, however the frequent recurrence of disease reactivations was expected in the control arm (Wada 2014). Originally, an 8-week event rate was assumed to be 90% and a considerable reduction in disease reactivations for subjects receiving Tadekinig alfa was expected. However, a lower event was observed from the currently enrolled (still blinded) patients. Thus, the RW phase is prolonged to a maximum of 16 weeks to better assess the effect of Tadekinig alfa withdrawal. The power calculations below will assume the same 90% event rate in the SOC arm at 16 weeks.

Figure 2 below displays the power achieved for a two-arm study and assumes the following:

- Two-sided log-rank test, with input based on the proportion of patients surviving (i.e., event-free) at 16 weeks;
- Two-sided alpha = 0.05;
- A 1:1 randomization of 10 patients (i.e., 5 patients per arm);
- The proportion of patients surviving (i.e., event-free) in the control arm at Week 16 of the RW phase is 0.1, which equates to a 90% event rate;
- No patients in either group drop out of the study prior to experiencing a disease reactivation or completing the 16-week treatment period as planned;
- Total study time is 32 weeks including a 16 week accrual period and a 16 week follow-up time;
- Varying levels of a hazard ratio, from 0.1 to 0.25 in 0.05 increments.

Figure 2 *Power vs. Hazard Ratio*



A hazard ratio of 0.1 equates to an assumed 16-week event rate in the Tadekinig alfa group of 20.6% (i.e., a survival event-free rate of 79.4%). These assumptions achieve 78.4% power based on a two-sided log rank test with an overall sample size of 10 subjects to be randomized in the RW phase (5 in the placebo group and 5 in the Tadekinig alfa group). A hazard ratio of 0.1 results in an assumed number of total events among the 10 subjects to be 6.7, with 4.9 occurring in the placebo group and 1.8 occurring in the Tadekinig alfa group.

No power calculations were performed for the SAOL phase of the study, as analysis will be descriptive in nature.

16.4 Patient Treatment Randomization

Randomization to Tadekinig alfa or Placebo concerns only the RW phase of the study.

Patients who will be eligible to enter the RW phase of the study will be randomized to one of the two treatment arms (Tadekinig alfa / Placebo) in a 1:1 ratio at Week 18 (V8). The randomization will be stratified by disease condition at RW phase entry (NLRC4-MAS mutation or XIAP deficiency). The randomization will be designed to be dynamic yet non-deterministic such that subjects are randomized in a 1:1 ratio within each disease condition, while also ensuring that the overall allocation is exactly balanced if the total number of subjects randomized is an even number and different by no more than one if odd.

16.5 Datasets for Analysis

For the statistical analysis the patients will be divided up into the following datasets:

The following definitions are applicable:

SAOL Full Analysis Set (SAOL-FAS)	All patients who are eligible and received at least one dose of investigational medicinal product at V1.
SAOL PK Analysis Set (SAOL-PKAS)	All patients in the SAOL-FAS who have sufficient plasma concentration data to calculate PK parameters.
RW Full Analysis Set (RW-FAS)	All patients who meet the criteria for randomization and receive at least one dose of blinded study treatment during the RW phase
RW Per-Protocol Analysis Set (RW-PPAS)	All patients in the RW-FAS who compete the RW phase up through Week 22 (V10) for whom no relevant protocol deviations were documented

The analysis of safety and efficacy during the RW phase will be based on the RW-FAS. Additionally, exploratory analysis of efficacy on the RW-PPAS may be done.

Safety and efficacy analysis during the SAOL phase will be based on the SAOL-FAS.

The decision whether a protocol deviation is relevant or not for the exclusion of subjects from the RW-PPAS will be made on a case-by-case basis in a blind data review meeting.

16.6 Statistical Analysis

16.6.1 Randomized withdrawal phase

Data will be analyzed on an intent-to-treat basis. Baseline patient and disease characteristics according to treatment arm will be presented using standard descriptive statistics.

Comparative statistical analyses will be performed on data collected during the RW phase. The primary endpoint is time to first occurrence of disease reactivation (including full and partial disease reactivation) during the RW phase. Tadekinig alfa will be compared to placebo using the log rank test at the alpha = 0.05 level of significance (2-sided). Kaplan-Meier estimates of the distribution of time-to-event will be summarized and graphed by treatment group.

To test the efficacy of Tadekinig alfa on secondary outcomes during the RW phase, Fisher's exact test will be utilized for binary outcomes (i.e. treatment failure rate) and a non-parametric, Mann–Whitney–Wilcoxon test will be utilized for continuous outcomes (i.e. change in the mAIDAI). To assess the impact of possible variation in baseline measures, an analysis of covariance (ANCOVA) model with covariate adjustment for Baseline may be considered as a sensitivity analysis, or alternative non-parametric approaches if normality assumptions are not met.

If the primary analysis is statistically significant ($p<0.05$), the following secondary endpoints measured during the RW phase will be analyzed using a fixed-sequence testing procedure in the order specified below to control the overall level of significance:

- Treatment failure rate;
- Change from RW baseline to Week 34 (i.e. Week 16 of the RW phase) or End of Study Visit in the mAIDAI total score; and
- Change from RW baseline to Week 34 or End of Study Visit in the PGA symptom severity score.

For each of these endpoints, the treatment groups will be compared using a two-sided test at alpha = 0.05 level of significance. However, once a non-significant result (i.e. $p > 0.05$) occurs, the results of all subsequent analyses will be exploratory rather than confirmatory.

In addition, all endpoints will be evaluated descriptively including 95% confidence intervals for the mean and proportions.

16.6.2 SAOL Phase

Analysis of data collected during the SAOL phase will be descriptive in nature, to include 95% CIs around select mean estimates and proportions of interest. Absolute and percentage of change from baseline will be calculated for continuous variables. Response to treatment in the initial active disease, number, frequency and severity of disease reactivations during the study will be compared to incidence and severity described in the medical history of individual patients.

Individual subject's raw data will be captured with data listings and individual patient plots at each time point to visualize the different responses (e.g. in terms of mAIDAI, PGA, Ferritin and CRP as well as the most prominent clinical features and results from patient`s/caregiver`s qualitative evaluation of health status) at each time point to the assigned treatment in a descriptive manner.

16.7 Subgroup Analysis

No subgroup analysis is planned.

16.8 Withdrawals, Drop-outs, Missing Values

The analysis of the primary endpoint, time to first disease reactivation (including full and partial disease reactivation), will be based on KM survival analysis techniques, where patients who do not experience a disease reactivation during the RW phase will be censored at date of their last assessment for disease symptoms.

Details to account for missing data in the analysis of secondary efficacy endpoints will be described in the statistical analysis plan.

17 HANDLING OF ADVERSE EVENTS

17.1 Non-Serious and Serious Adverse Events

An adverse event (AE) is any undesirable sign, symptom, or medical condition occurring after signing the Informed consent form (ICF) through the end of study at follow up (V13).
Information about all AEs, whether volunteered by the subject, discovered by questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the AE CRF page and followed as appropriate.
All relevant medical conditions present prior to study entry will be documented in the Medical History CRF. However, medical conditions occurring after signing the ICF are to be recorded as AEs. This includes worsening of a pre-existing condition. AEs occurring prior to administration of study drug will be considered non-treatment emergent, and those occurring after the start of study drug will be considered treatment emergent.
Adverse events will be monitored and recorded from the time the informed consent is signed. The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE, an SAE and an AE of special interest (AESI) as provided in this protocol (see Sections 17.2 and 17.3). All AEs (including AESIs) and SAEs will be recorded in the source documents. AEs will be entered on the appropriate eCRF page from the time of signing informed consent until completion of the study (Visit 13) or premature withdrawal.

Throughout the study, during clinic visits, home visits and other contacts, after the patient has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. The HCN will inquire about potential AEs at the moment of treatment administration. If an AE is reported, the nurse will communicate to the site responsible physician. The following are examples of open-ended questions that may be used to obtain this information at the sites during the programmed visits or by the home care nurse:

- “How are you feeling?”
- "Have you had any medical problems since your last visit/assessment?"
- "Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?"

17.2 Definition of an Adverse Event (AE)

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose

All AEs must be documented and assessed for:

- Duration (start and end dates)
- Severity grade
- Frequency
- Relationship to the study product.
- Action(s) taken
- Outcome

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity (severity) of the condition.
    - This excludes disease reactivations of the condition under study being collected as study endpoints. According to the FDA Guidance (Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies; CDER, CBER, December 2012), reactivations of the condition under study would not ordinarily be reported as AEs and/or IND safety reports, except when there is evidence suggesting a causal relationship between the drug and the event (21 CFR 312.32(c)(5).
- A new condition detected or diagnosed after study treatment initiation even though it may have been present prior to the start of the study.
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concurrent medication ("overdose" per se, should not be reported as an AE/SAE).
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (e.g. invasive protocol-defined procedures, modification of a patient's previous drug treatment regimen).

An AE does not include:

- Medical or surgical procedures (e.g., colonoscopy, biopsy). The medical condition that leads to the procedure may be an AE unless the medical or surgical procedure was pre-planned (prior to commencement of study, and the medical condition that led to the procedure did not worsen after Baseline).
- Social or convenience hospital admissions where an untoward medical occurrence did not occur. Hospitalization of subjects may be considered based on the course of the disease and the patient accessibility to the site.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.

All relevant medical conditions present prior to study entry will be documented in the Medical History eCRF (including co-morbidities). Medical conditions occurring after signing the ICF are to be recorded as AEs.

AEs occurring prior to administration of study drug will be considered non-treatment emergent, while those occurring after the start of study drug will be considered treatment emergent.

A treatment-emergent AE (TEAE) is defined as any adverse event not present prior to exposure to study medication (i.e., an event that occurs after starting on study drug) or any condition already present as part of the patient's medical history that worsens in either intensity or frequency following exposure to test medication.

A protocol-related AE is an AE occurring during a clinical study that is not related to the Investigational Drug, but is considered by the Investigator or the Medical Monitor (or designee) to be related to the research conditions, i.e., related to the fact that the patient is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Adverse Event of Special Interest (AESI):

- Injection site reactions (including pruritus, erythema, swelling)

ISRs are to be reported regardless whether they are due to hypersensitivity to the study drug or related to the administration procedure. However, the relationship to either the study drug or the administration procedure needs to be identified and recorded in the CRF.

Table 3: *Site Reactions to Injections and Infusions*

Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness *Report only one > 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Erythema or Redness Report only one *≤ 15 years of age*	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one > 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection	Itching beyond the injection site	Generalized itching causing	NA

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
	site that is relieved spontaneously or in < 48 hours of treatment	that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	inability to perform usual social & functional activities	

Skin signs and symptoms of grades 3 and 4 will result in transient or permanent treatment discontinuation.

17.3 Definition of a Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe
- Requires in patient hospitalization or prolongation of existing hospitalization. Note: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline; hospitalization or surgery related to cancer treatment; hospitalization scheduled to facilitate the treatment or study procedures are not considered to be an AE
- Results in persistent or significant disability/incapacity. Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption or
- Is a congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

17.4 Other Reportable Information.

Other Reportable Information includes certain information that, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes the following:

Pregnancy exposure to an Investigational Drug. If a pregnancy is confirmed, use of the Investigational Drug must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male patient, the necessary information must be collected from the patient, while respecting the confidentiality of the partner.

Lactation exposure to an Investigational Drug with or without an AE.

Overdose of an Investigational Drug as specified in this protocol with or without an AE. Baby formula overdoses without any AEs are excluded.

Inadvertent or accidental exposure to an Investigational Drug with or without an AE.

17.5 Medication Errors

Medication errors are the result of administration or consumption of the wrong product by the wrong patient, at the wrong time, and/or by the wrong administration route, due to human error.

Medication errors include, but are not limited to, the following:

- The administration of the Investigational Drug that has not been assigned to the patient
- The administration of the expired Investigational Drug when it is associated with an AE
- Errors involving rate of administration, reconstitution and dilution, including use of appropriate diluent and the time frame in which Investigational Drug should be used after reconstitution and/or dilution
- Errors related to storage or refrigeration requirements

All AEs and SAEs must be handled as specified in this protocol whether or not they are associate with a medication error. A medication error associated with an SAE (including overdose, inadvertent exposure, and /or accidental exposure) will be reported with the SAE, on the SAE form. All other medication errors will be captured in the database as deviations to the protocol and reported to AB2 Bio as soon as possible.

17.6 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal clinical laboratory findings that are judged by the Investigator as clinically significant must be recorded as AEs or SAEs if they meet the definition of an AE or an SAE, as defined in 16.2 and Section 16.3 respectively. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at Baseline and significantly worsen following the start of the study may be reported as AEs or SAEs.

The Investigator will exercise medical judgment in deciding whether abnormal laboratory values are clinically significant.

The grading of severity of AEs should take into account the reference values according to the ages of the subjects in the study.

The kidney function will be assessed by the calculation of the glomerular filtration rate using the Schwartz formula:

GFR =KL/Pcr and it is expressed in ml/min per 1.73m2 body surface area. L represents body length in centimeter, Pcr represent plasma creatinine concentration in mg per dl and K is a constant that varies as a function of age and sex, being 0.33 in preterm infants, 0.45 in full-term infants, 0.55 in children and adolescent girls and 0.70 in adolescent boys

Table 4: *Grading of adverse events due to low levels of Creatinine Clearance or eGFR*

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Creatinine Clearance[1] or eGFR, Low *Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10% to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR ≥ 30% to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from baseline or dialysis needed

[1] Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m2)

Low levels of Creatinine Clearance or eGFR reaching grades 3 and 4 will result in transient or permanent treatment discontinuation (see reference values in the Reference Study Manual)

Table 5: *Grading of adverse events due to low levels of hemoglobin*

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Hemoglobin, Low (g/dL; *mmol/L*)[1]				
≥ 18 years of age *(both genders)*	10.0 to <LLN *6.2 to <LLN*	8.0 to <10.0 *4.9 to <6.2*	7.0 to <8.0 *4.34 to <4.9*	< 7.0 *< 4.34*
≥ 13 to <18 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 to <18 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*

[1] The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory; LLN = lower limit of normal according to local or central laboratory

Low levels of haemoglobin reaching grades 3 and 4 may result in transient or permanent treatment discontinuation (see reference values in the Laboratory Specifications).

Table 6: *Grading of adverse events due to low levels of white blood cells*

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Decrease in white blood cell counts of grades 3 and 4 may result in transient or permanent treatment discontinuation. (see reference values in the Laboratory Specifications).

Table 7: *Grading of adverse events due to low levels of neutrophils*

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*

Decrease in neutrophil counts of grades 3 and 4 may result in transient or permanent treatment discontinuation (see reference values in the Laboratory Specifications)

17.7 Recording of Adverse Events and Serious Adverse Events

The Investigator should review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports) relative to the event being reported. The Investigator will then record all relevant information regarding an AE/SAE on the appropriate eCRF page. It is not acceptable for the Investigator to send photocopies of the patients' medical records in lieu of completion of the appropriate AE/SAE pages. However, there may be instances when copies of medical records will assist in the evaluation and reporting of an AE/SAE. In this instance, all patient identifiers should be blinded on the copies of the medical records prior to submission.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs and symptoms.

Information to be reported includes the nature, the dates of onset and resolution of the AE/SAE, severity, duration, causality, and outcome of the event. Even if the AE is assessed by the Investigator as not reasonably attributable to study product, its occurrence must be recorded in the source documents and reported on the CRF.

Investigators obtain, assess, and record the following information about AEs/SAEs:

- Patient
- Date of onset
- Date resolved
- Description of event
- Duration
- Frequency
- Intensity (Severity)
- Seriousness
- Action taken
- Outcome of the event and any sequelae
- Relationship to test product

17.7.1 Severity of Adverse Event

Severity refers to the extent to which an AE affects the patient's daily activities. Severity will be categorized according to the following criteria:

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

For AEs included in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Severity Grading Scale (v4.03, Appendix 11), http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf, including laboratory abnormalities reported as AEs, the Investigator should base severity assessments on the severity grading scale.

For events not listed in the CTCAE, the Investigator will use medical judgment for assignment of severity.

17.7.2 Causality of Adverse Event (AE)

The Investigator must make a causality assessment for all AEs and must decide whether there is a reasonable possibility that the AE may have been caused by the IMP. If there is any valid reason for suspecting that there is a causal relationship between the AE and the IMP, the AE should be judged "possibly related" to study medication. Unless an AE can be excluded from causality, it must be judged "possibly related" (possible) to study medication rather than not related (none) to study medication. See below for further explanation.

The Investigator will assess the possibility of a link between the study product and an AE on the basis of the following criteria:

- Existence of a temporal link between the event and administration of the study medication.
- Partial or complete disappearance of the AE when the drug is fully stopped or decreased in dose (positive dechallenge)
- Recurrence of the adverse event upon reintroduction of the study product (positive rechallenge). For a positive rechallenge to occur, the AE had to have previously disappeared after dechallenge in order for it to restart.
- Similar results after previous treatment with the study product
- Event is not explained by any other condition, measure or environmental factor (no alternative etiology for the event is present).

17.7.3 Adverse Event Outcomes

If the same AE occurs several times in the same subject, the AE in question must be documented and assessed as a new one at each time unless the event is considered to be a continuation of the previously reported event rather than reoccurrence of the event.

Outcome of the AE will be recorded as follows:

- **Not recovered/not resolved/ongoing -** the event has not improved or subject has not recuperated. No AE stop date should be recorded.
- **Recovered/Resolved -** the event has improved or subject has recuperated. The subject recovered from the AE. Record the AE stop date.
- **Recovering/resolving -** the event is continuing and the subject is in the process of recovery.
- **Resolved with sequelae -** the subject recuperated, but retained pathological conditions resulting from the prior disease or injury and a complete recovery is not expected. A sequelae is a consequence of a previous disease or injury. Record the AE stop date. The AE stop date will represent the date the AE stabilized with no change in event outcome anticipated.
- **Unknown/Lost to follow-up** – refers to the inability to access the subject or the subject's records to determine the outcome (i.e., subject withdraws consent or is lost to follow-up). No AE stop date should be recorded.
- **Fatal -** The AE directly caused death. Record the date of death as the AE stop date. Please note that death is an outcome and not an event and should be recorded as such.

17.7.4 Action Taken with the Study Drug

The following actions taken as a result of an AE should be recorded:

- **Dose not changed**
- **Dose increased**
- **Dose reduced**
- **Drug interrupted**
- **Drug withdrawn**
- **Unknown**
- **Not applicable**

17.7.5 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient and provide further information on the patient's condition. All AEs and SAEs documented at a previous visit/contact that are designated as on-going until resolved and should be reviewed at subsequent visits/contacts.

AEs and SAEs will be followed until resolution, until the condition stabilizes, or until the patient is lost to follow-up. Once resolved, the appropriate AE/SAE eCRF page(s) will be updated. If a patient dies during participation in the study, the Investigator will provide a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE eCRF.

17.7.6 Post-study Adverse Events or Serious Adverse Events

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, the Investigator should promptly notify the Sponsor, or designee, if the Investigator learns of any SAE or death of a study patient within 30 days after a patient has been discontinued from the study, and such event(s) is (are) reasonably related to study participation; these should be reported within 24 hours.

Investigators should promptly notify the Sponsor, or designee, if they become aware of a former study participant who is one of the parents of a subsequently conceived child with a congenital anomaly (see Section 17.4 on Pregnancy Information).

17.8 Reporting Requirements for SAEs

17.8.1 Reporting of All SAEs and AEs Resulting in Withdrawal from the Study

The Investigator will promptly report all SAEs to the Sponsor or Agility Clinical (designee) within the timeframes specified below.

The Investigator will comply with the applicable local regulatory requirements related to reporting of SAEs to his or her Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

All AEs that meet any seriousness criteria, regardless of expectedness or causality, must be reported within 24 hours of the Investigator or any other site personnel's knowledge of the event (see Section 17.9).

The completion of the SAE eCRF is the primary method for reporting SAEs to the designee. If the EDC is unavailable, a paper SAE Report Form is provided as back-up and should be completed and emailed or faxed to Safety at Agility Clinical within 24 hours of the Investigator or any site personnel's knowledge of an SAE. The SAE must be entered into the EDC when accessible. The eSAE should be updated within 24 hours of receipt of new information regarding the event.

In addition, any AE resulting in permanent withdrawal from the study for a patient, even if not serious, should be reported promptly (within 24 hours) to the Sponsor or Agility Clinical.

Do not delay reporting SAEs. Investigators should not wait to receive additional information to fully document the event before notifying Safety at Agility Clinical of the SAE via completion of the eSAE page in the EDC (or sending an SAE Report Form). The SAE report should provide the known information at the time of awareness that an SAE has occurred. A follow-up report should be completed when additional details are known by updating the SAE eCRF.

17.8.2 Unexpected or Expected SAE

An unexpected AE is an event, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure (IB) if available) or the assessment of the medical safety officer.

The Sponsor or designee will notify the Competent Health Authority (FDA, Health Canada, BfArM) by telephone or fax transmission of any unexpected, fatal, or life-threatening experience (expedited report) associated with the use of the IP as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within 15 calendar days. For serious unexpected SUSARs, the Sponsor or designee will notify the Competent Health Authority in the participating countries, as soon as possible, but no later than 15 days, following the initial receipt of information.

Contact information for Safety at Agility Clinical for notification of SAEs is provided in Section 17.9.

Note to emergency unblinding:

In the event of a medical emergency which may warrant unblinding of a subject's treatment assignment, the PI will contact the Medical Monitor at AB2Bio and the CRO to discuss the request. The Medical Monitor will review the request and determine the decision for unblinding. If approval has been granted, a subject's treatment assignment information may be obtained by emailing a completed Individual Subject Unblinding Authorization Form (located in the Investigator Site File binder) to: [redacted]. The Medical Monitor will discuss the unblinding with the Lead Statistician and the outcome of the request is completed on the form and returned to the site. In an effort to minimize unblinding of additional site study staff, the completed Subject Unblinding Authorization Form and all other documentation associated with the subject's unblinding must be maintained in a secure location within the Pharmacy Manual, where access to such information is limited.

In addition, measures are in place as in a First-in-Human setup, in case of emergencies. (See Section 17.10)

17.9 Reporting and Documentation

Serious adverse event

Safety at Agility Clinical must be notified of all serious or unexpected AEs within 24 hours by entering all known data and saving the SAE section of the eCRF in the EDC. In the event the EDC is not available, a paper back-up SAE Report Form should be completed and emailed or faxed. Once the EDC is accessible, the SAE must be entered into the system.

Notification does not depend on whether there is a relationship to study product or not.

All SAEs must also be documented on the appropriate pages of the eCRF (AE).

The SAE Report Form can be emailed or faxed to:

[redacted]

SAE Fax Number: [redacted]

Non-serious adverse event

All AEs must be documented on the appropriate pages of the eCRF (AE).

17.10 Patient Emergency Contact Card

The Patient Emergency Contact Card (see example in Appendix 5) will be completed by the Investigator for each patient receiving tadekinig alfa study therapy prior to the start of study treatment. The Patient Emergency Contact Card will be given to each patient receiving tadekinig alfa study treatment and/or to the patient's authorized representative. The patient and/or the authorized representative must read the Patient Emergency Contact Card prior to starting tadekinig alfa study treatment.

17.11 Notification

The Sponsor is responsible for the ongoing safety evaluation of the IMP.

The Sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of patients, impact the conduct of the study, or alter the IRB/IEC's approval/favorable opinion to continue the study.

17.12 Safety Reporting

The sponsor should expedite the reporting to all concerned investigator(s)/institution(s), to the IRB(S)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected (see Section 17.8.2). Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

18 LEGAL AND ETHICAL PREREQUISITES

18.1 Legal Requirements

This study will be conducted in accordance with ICH guideline on Good Clinical Practice (GCP), the GCP's applicable to any region where the study is conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki.

18.2 Ethical Aspects

18.2.1 Protection of the Patient's Confidentiality

Identification of patients in CRFs shall be by initials, screening numbers, or randomization numbers only. If required by local agencies, initials will be coded per local regulations (e.g., AAA, BBB). Additionally, if required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

18.2.2 Informed Consent

Child assent and/or informed consent will be obtained from the potential patient prior to any study related activities and in accordance with all applicable regulatory requirements.

The Investigator and/or his/her designee will inform the patient in addition to the written informed consent about all aspects of the patient's study participation. The written Informed Consent must be approved by the Institutional Review Board (IRB) or Independent Ethics committee (IEC) and/or by the *Competent Health Authority (as applicable)*. Any amendments to these documents must be approved by the IRB/IEC and/or *Competent Health Authority (as applicable)*.

The Investigator and/or his/her designee and the patient and/or the patient's legal authorized representative (guardian, next of kin, other authorized individual) must sign and date the Written Informed Consent prior to any study related activities are performed. The patient or the authorized representative must complete the printed name and enter the date of signature themselves. If an authorized representative signs the ICF, all efforts should be made to obtain an additional signature from the patient himself/herself.

In case of the conduct of telemedicine visits due to the COVID-19 pandemic or long distance from the patient`s home to the study site, patients and/or parents (or legal representative, if applicable) will sign a respective assent/informed consent prior to the conduct of such visit.

The ICF will be signed in double and the patient and/or the authorized representative obtain one original of the signed written ICF. The second original is filed with the study documents at the investigational site.

The decision to participate in the study is entirely voluntary by the patient and/or by the authorized representative. The Investigator and/or his/her designee must emphasize to the patient and/or the authorized representative that the consent to participate can be withdrawn at any time without penalty or loss of benefits to which the patient is otherwise entitled.

18.2.3 Institutional Review Board/Ethics Committee Approval

The study protocol will be submitted to the IRB/IEC by the Investigator for examination and written approval. The Sponsor will ensure that this protocol and all appropriate documentation according to the applicable regulations will be reviewed and approved by the IRB/IEC responsible for each site. Commencement of the clinical study is not permitted without written approval of the IRB/IEC and the competent Health Authorities (FDA, Health Canada, BfArM).

The IRB/IEC must be notified of all subsequent additions or changes in the study protocol. Notification of the IRB/IEC is also required in the event of a SAE during the clinical study.

18.2.4 Declaration of Helsinki

This study will be conducted according to the principles and rules laid down in the Declaration of Helsinki (Appendix 4) and its subsequent amendments.

19 QUALITY CONTROL AND QUALITY ASSURANCE

19.1 Monitoring

Regular monitoring visits by representatives of the sponsor will be made during the study.

Monitoring will begin with an initiation visit prior to study commencement to clarify all aspects of the protocol and documentation. The purpose of later visits during the implementation period will be to evaluate study progress and adherence to protocol. The monitor will check the eCRF for completeness, clarity and consistency with the information in the patient's file (source data checking). During the COVID-19 pandemic, when access to the study site locations may be restricted, telephone/remote monitoring may be implemented ensuring data quality and integrity in compliance with ICH / GCP guidelines. Details are specified in a clinical monitoring plan, with respect to data protection regulations per site/country, as well as the individual site policies regarding remote monitoring.

At the end of the study, the monitor will attend a study closure visit at each site to ensure that all documentation is complete. In all cases, it is the responsibility of the CPM / monitor to maintain patient confidentiality.

19.2 Source Documents

A 100% SDV will be performed.

19.3 Quality Control

19.3.1 Quality Control of Essential Documents

Quality control of essential documents will be ensured by the CPM.

19.3.2 Co-monitoring

Co-monitoring visits will be performed by the CPM or designee with the monitor as deemed necessary.

19.4 Audits and Inspections

In addition to the routine monitoring procedures, AB2 Bio may proceed to a special audit. Periodically during the study, a representative of AB2 Bio may conduct audits of clinical research activities to evaluate compliance with GCP guidelines and regulations.

The Investigator(s) is required to permit direct access to the facilities where the study took place, source documents, CRF and applicable supporting records of patient participation for audits and inspection by IRB/IEC, regulatory authorities and company authorized representatives. The Investigator(s) should make every effort to be available for the audit and/ or inspections. If the Investigator(s) is contacted by any regulatory authority regarding an inspection, he/she should contact AB2 Bio immediately.

19.5 Responsibilities of Investigator

The Investigators are responsible for the following:

- Obtaining the written and dated approval of the local ethics committee (and other local regulatory agency, if any) prior to the beginning of the study.
- Selection of participants in accordance with the inclusion and exclusion criteria; obtaining the written informed consent of the patient or legal guardian.
- Maintain confidentiality of patients and potential patients in accordance with the Declaration of Helsinki.

- Adherence to the study protocol and the spirit of Good Clinical Practice. If modification becomes necessary, the rationale will be provided in a protocol amendment signed by the Investigator and Sponsor for submission to the ethics committee.
- Accurate, complete and timeliness data reported to the Sponsor (eCRF).
- During the course of the study, provide patients with any newly available information which may be relevant to them.
- Identification of AEs with notification to Sponsor, ethics committee and health authorities, as applicable.
- Co-operation with monitoring visits, audits and regulatory inspections. Providing direct access to source data and documents.
- Investigator may select a second contact at their study center to assist in implementation of the study. However, in all cases the main responsibility with respect to all aspects of this implementation rest with the principal and co-Investigators.
- Archiving of the Investigator's file (including the original signed informed consent forms of all patients) for at least 15 years after the end or the termination of the study.

20 STUDY END PROCEDURES

20.1 Premature Termination of Study

Patient withdrawal/Physician discontinuation:

The physicians and the patients (or legal representative) will have the option to discontinue the treatment if they feel that pursuing the treatment is not appropriate. The physician can decide anytime to start rescue immunosuppression and therefore discontinue the patient from the study*.

* All key safety and efficacy outcomes will be followed up. Patients will continue to come to the scheduled visits for safety and efficacy assessments.

Note: A patient experiencing a partial or full disease reactivation during the 16 weeks RW phase and thus proceeding to the End of Study Visit will not be considered as having early terminated the study.

Study discontinuation:

Stopping of the study will be strictly determined for safety concerns.

At any time, the DSMB may recommend to the Sponsor the early termination of the study after reviewing study safety data including AEs, SAEs, and SUSARs.

At any time, the Sponsor may recommend terminating the study.

NOTE: Temporary Stop of Treatment

Temporary treatment interruptions will be allowed in case the patient shows fever or any sign of undergoing an infection process unrelated to the treated condition. For the injections done by the home care nurse (HCN) every 2 days, the HCN should contact the Investigator for advice on treatment continuation or stopping. In case of any doubt, the treatment must be discontinued temporarily.

In case of treatment interruptions ≥ 3 weeks the effect of the investigational drug is lost and the case will be considered a dropout.

20.2 Termination of Study

After the completion or termination of the study, the Investigator will inform the IRB or IEC of the end of the study. A certificate of study closure will be established. Every serious or unexpected AE that might affect the patient's safety must be brought to the IRB's/IEC's attention, if required by his/her IRB/IEC regulations. In addition, every report concerning an AE that the Sponsor sends to the Investigator must be sent by the latter to his/her IRB/IEC.

All biological samples will be destroyed, as well as the study product. Certificates of destruction will be issued and filed in the Trial Master File.

20.3 End of Trial

The end of the entire trial will be defined as the date of the final clinical database lock. This provides for a single and conservative definition across all trial sites.

21 PUBLICATIONS

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by AB2Bio, in advance of submission. The Sponsor has proprietary rights to all information generated from this study and reserves the right to use it in any manner it deems appropriate, including but not limited to regulatory submissions, annual reports, and other scientific or business affairs of the company. The review is aimed at protecting AB2 Bio's proprietary information existing either at the date of the commencement of the study or generated during the study.

22 CONFIDENTIALITY

Data collected during this study may be used to support the development, registration, or marketing of the IMP and documentation will remain confidential. Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. After patients have consented to take part in the study, their medical records and the data collected during the study will be reviewed by AB2 Bio and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of AB2 Bio; third parties with whom AB2 Bio may develop, register or market AB2 Bio's product; and the Competent Health Authority in the participating country and the IRBs/IECs that gave their approval for this study to proceed.

Identification of patients in CRFs shall be by initials, screening numbers, or randomization numbers only. If required by local agencies, initials will be coded per local regulations (e.g., AAA, BBB). Additionally, if required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

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APPENDIX 1: MODIFIED AUTO-INFLAMMATORY DISEASE ACTIVITY INDEX

Fever > 100.4	Abdominal Pain/Colic	Nausea/ vomiting	Diarrhea	Transaminitis	Organomegaly	Rash	Uveitis 3+/4+	Uveitis 1+/2+	Arthralgia	Arthritis	Radiologic CNS involvement	CNS symptoms	Cytopenia (HgB < 9.0, PLT <100, WBC < 3.0)
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/2	0/1	0/1	0/1	0/1	0/1	0/1

mAIDAI component	Identified subjective component	Included in objective evaluation of response to therapy and disease reactivation
Fever >100.4 F/38C		x
Abdominal Pain/ Colic	x	-
Nausea/Vomiting	x	-
Diarrhea		x
Transaminitis		x
Organomegaly		x (separated into hepatic and lymphatic system)
Rash		x
Uveitis 3+/4+		x (all grades grouped together to create an unweighted scale)
Uveitis 1+/2+		
Arthralgia	x	-
Arthritis		x
Radiologic CNS involvement		x
CNS symptoms	x	-
Cytopenia (HgB <9.0, PLT <100, WBC <3.0)		x

APPENDIX 2: LOCAL TOLERABILITY INDEX

Pain

Description
NONE
MILD
MODERATE
SEVERE

The subjects will be asked to assess the degree of pain they are experiencing from each injection.

Redness

Description	
NONE	No visible redness
MILD	0 to 2 cm redness
MODERATE	2.1 to 5 cm redness
SEVERE	Greater than or equal to 5.1 cm redness

The subjects will be asked to assess the amount of redness they are experiencing from each injection as per the above guidance.

Swelling

Description	
NONE	No swelling detected
MILD	Palpable "firmness" only
MODERATE	< 4 cm swelling
SEVERE	≥ 4 cm swelling

The subjects will be asked to assess the amount of swelling they are experiencing from each injection as per the above guidance.

Bruising

Description	
NONE	No visible bruising
MILD	0 to 2cm bruising
MODERATE	2.1 to 5cm bruising
SEVERE	Greater than or equal to 5.1 cm bruising

The subjects will be asked to assess any bruising that they experience with each injection as per above the guidance.

Tenderness

Description
NONE
MILD
MODERATE
SEVERE

The subjects will be asked to note the degree of tenderness they are experiencing from each injection

Itching

Description
NONE
MILD
MODERATE
SEVERE

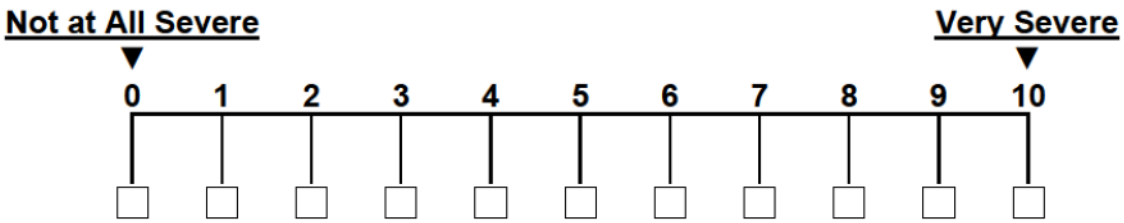
The subjects will be asked to note the degree of itching they are experiencing from each injection.

APPENDIX 3: PHYSICIAN GLOBAL ASSESSMENT OF DISEASE-RELATED (AUTOINFLAMMATORY) SYMPTOMS - QUESTIONS FOR INVESTIGATORS

INSTRUCTIONS: Complete the following questions for each patient at each clinic visit to assess the patient's level of disease-related symptoms.

1. Using the 0 to 10 scale below where 0 is ***Not at All Severe*** and 10 is ***Very Severe***, please mark an "X" in the box (☒) which best describes your medical assessment of the severity of the subject's disease-related (autoinflammatory) symptoms at this visit.

At this visit, how severe are the patient's disease-related (autoinflammatory) symptoms?



2. **Clinical stability:** This question regarding the clinical stability of disease-related (autoinflammatory) symptoms over the past two weeks will be used to determine if the subject's symptoms have been stable, improved or gotten worse.
   Please mark an "X" in the box (☒) which best describes your medical assessment of the stability of the subject's disease-related (autoinflammatory) symptoms over the past two weeks.

☐	Stable
☐	Improved
☐	Worse

KEY TO SYMPTOM SEVERITY FOR QUESTION #1

Score	Rating	Impact on Subject	Severity Key
0	None	No Impact	No Symptoms
1	Mild	Does Not Interfere With Activities	Mild Symptoms Not Associated With Discomfort
2			Mild Symptoms Associated With Discomfort
3	Moderate	Interferes With Activities	Moderate Symptoms With A Limited Impact On Usual Activities
4			Moderate Symptoms With A Moderate Impact On Usual Activities
5			Moderate Symptoms With A Marked Impact On Usual Activities
6	Severe	Interferes With Activities, Requires Lifestyle Change	Severe Symptoms Requiring Some Changes In Lifestyle
7			Severe Symptoms Requiring Major Changes In Life Style
8	Very Severe	Prevents From Engaging With Normal Activities	Very Severe Symptoms Preventing From Engaging In Most Normal Activities
9			Very Severe Symptoms Completely Preventing From Engaging In Normal Activities
10	Extreme	No Normal Activities Possible	Extreme Symptoms

APPENDIX 4: DECLARATION OF HELSINKI

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added) 59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity,

integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders,

no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient- physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after for such research. In such situations the research may be done only after consideration

and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 5: EXAMPLE PATIENT EMERGENCY CONTACT CARD

PATIENT EMERGENCY CONTACT CARD FOR PATIENT OR THEIR LEGAL REPRESENTATIVES PARTICIPATING TO THE NLRC4 MUTATION UND XIAP-DEFICIT CLINICAL STUDY PLEASE SHOW THIS CARD TO ANY MEDICAL DOCTOR WHO EXAMINES YOU. I AM CURRENTLY PARTICIPATING TO A CLINICAL STUDY WITH TADEKINIG ALFA (R-HIL-18BP) WITH NLRC4-MUTATION AND XIAP-DEFICIT. THE STUDY TAKES PLACE AT: HOSPITAL NAME: _____ ADDRESS: _____ **IN CASE OF EMERGENCY OR IF YOU NEED MORE INFORMATION PLEASE CALL US:** **NAME OF THE INVESTIGATOR:** _____ **PHONE:** _____ **PLEASE CARRY THIS CARD AT ALL TIMES WITH YOU!**	**SPONSOR OF THE CLINICAL STUDY:** AB2 BIO LTD. EPFL INNOVATION PARK BUILDING B, 4TH FLOOR CH-1015 LAUSANNE, SWITZERLAND **MEDICAL MONITOR (24/24H 7/7)** **MOBILE: +X XXX XXXXXXX** **CLINICAL RESEARCH ORGANIZATION:** PRECISION FOR MEDICINE, ONCOLOGY AND RARE DISEASE CARLSBAD, CA USA **PROTOCOL NUMBER: NLRC4/XIAP.2016.001** **PATIENT'S INITIALS:** _____ **PATIENT'S NUMBER:** _____ **DOSAGE: R-HIL-18BP DOSED AT 2 MG/KG SUB CUTANEOUS EVERY 2 DAYS (MAXIMAL DOSE: 160 MG)** **VERSION XX. DATED DDMMMYYYY**

Contact details and languages will be adapted to countries where used; locally approved version to be distributed to patients