CLINICAL STUDY PROTOCOL

Protocol Title:	A Double-blind, Randomized Clinical Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity of Single Intravenous Doses of BCD-148 (JSC BIOCAD, Russia) and Soliris® in Healthy Volunteers
Protocol ID:	BCD-148-3, NCT04027803
Protocol Date:	13-Jun-2018
Protocol Amendment:	N/A
Date of Protocol Amendment:	N/A
Protocol Version:	1.0
Study Sponsor:	JSC BIOCAD, Russia Legal address: 34-A, Ul. Svyazi, Strelna, Petrodvortsoviy District, St. Petersburg, Russian Federation, 198515 Mailing address: Petrovo-Dalneye, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 Tel.: +7(495) 992-66-28; Fax: +7 (495) 992-82-98
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ABBREVIATIONS

ABEC	The area between the baseline and effect curves for hemolytic activity of serum complement from 0 to 1392 h.
AE	Adverse event
aHUS	Atypical hemolytic uremic syndrome
AlkPh	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the Concentration *vs*. Time curve
AUMC	Area under the first moment curve
BAbs	Binding antibodies
BCD-148	A monoclonal antibody developed by JSC BIOCAD to target the complement component C5.
BP	Blood pressure
C_{max}	Maximum drug concentration in the serum
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee

Ig	Immunoglobulin
IMU	Instruction for Medical Use
INN:	International non-proprietary name
JSC	Joint Stock Company
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MABEL	Minimal Anticipated Biological Effect Level
MBEDL	Minimal Biological Effect Dose Level
MP	Medicinal product
MTD	Maximum tolerated dose
NAb	Neutralizing antibodies
NBEDL	No Biological Effect Dose Level
NOAEL	The No Observed Adverse Effect Level
PD	Pharmacodynamics
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal hemoglobinuria
RAMS	Russian Academy of Medical Sciences
SAE	Serious adverse event
SD	Standard deviation
SOP	Standard Operating Procedure
$T_{½}$	Elimination half-life
TD	Test drug
Th	T-helper cells
ULN	Upper limit of normal
WHO	World Healthcare Organization
TMA	Thrombotic microangiopathy

TERMS AND DEFINITIONS

Term	Definition
Investigational product	This term includes the test drug, comparator, or placebo. A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use
Study/test product/drug	A pharmaceutical forms the properties of which are investigated in this clinical trial.
Comparator/reference product/drug	An active control being tested as a control in the clinical study to reduce the bias of assessments, keep the study therapy blind, and assess the internal validity of the study and/or comparative effects of the study product.
Case Report Form (CRF)	A printed or electronic document designed to record all the protocol-required information to be reported to the Sponsor on each study subject.
Investigator's Brochure	A compilation of the clinical and non-clinical information on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.
Subject identification code / subject ID |__|__|-|__|__|__|	A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data. Usually, the subject ID is a five-digit code where the first two digits are the site number and the last three digits are assigned sequentially to each participant as he/she enters the study.
Screening ID |__|__|-|__|__|	A unique code assigned to each study subject who have signed the informed consent. The first two digits are the site number, and the last two digits are assigned sequentially to each subject as he/she gets enrolled at this particular study site.
Assessment	The procedure of obtaining the data that have to be gathered in this trial.
Enrollment in the study	A time point when the subject signs the informed consent.
Other therapy used in the study	Any medications other than the investigational product that are used to perform the study procedures. This includes, for example, the drugs used as part of the combination therapy.
Premature withdrawal	The time point when the subject stops participation in the study before the planned investigational treatment is completed and/or assessments

Term	Definition
	are performed. No further assessments are performed beyond this point except for monitoring of the survival and/or disease progression in certain trials. If the subject discontinues the study due to an event planned by the Protocol (for example, a complete response), he/she is considered a dropout anyway.
End-of-study	The time point when the subject attends his/her last study visit.
Study therapy	Any medication or a combination of medications used in any arm as part of study procedures, including concomitant medications and introductory therapy before the active medication.
Concomitant therapy	Therapy with any drugs included in the study therapy, except for the test drug and reference drug. For example, drugs used for combination therapy, pre-medication etc.
Discontinuation of study therapy	The time point when the investigational therapy is terminated regardless of what caused the termination. It does not necessarily coincide with subject's withdrawal from the study.
Variable	An identifier used for the data analysis and derived directly or indirectly from the protocol-specified assessments at pre-determined time points.

DOCUMENT HISTORY

N/A.

Names/positions of investigators responsible for the study conduct. Contacnt information of the study sites

#	Title of the study site (center)	Address	Phone	Full name of the PI	Job Title of the PI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Name, job title, address and telephone number of the qualified physician responsible for taking medical decisions

N/A.

Names and addresses of clinical or other medical and/or technical services and/or organizations involved in the study

#	Institution, role in the study	Address	Phone	Full name of responsible person	Job Title of responsible person
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SYNOPSIS

SYNOPSIS	
Protocol ID:	BCD-148-3
Study Title	A Double-blind, Randomized Clinical Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity of Single Intravenous Doses of BCD-148 (JSC BIOCAD, Russia) and Soliris® in Healthy Volunteers
Study Phase:	Phase I
Study Sponsor:	JSC BIOCAD Mailing address: Petrovo-Dalneye, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 [redacted]
Test Drug:	BCD-148 (INN: eculizumab), concentrate for solution for infusion
Reference Drug:	Soliris® (INN: eculizumab), concentrate for solution for infusion
Study Purpose and Objectives:	**Purpose:** To perform a comparative assessment of the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of a single intravenous infusion of BCD-148 and Soliris® in healthy volunteers. **Study objectives:** 1. To determine and compare the PK parameters of BCD-148 and Soliris®, each given as a single intravenous infusion 2. To determine and compare the PD parameters of BCD-148 and Soliris®, each given as a single intravenous infusion 3. To determine and compare the adverse event profile with a single infusion of BCD-148 and Soliris® 4. To evaluate and compare the proportion subjects positive for binding and neutralizing anti-drug antibodies in the BCD-148 and Soliris® arms after a single drug infusion
Study Population	Healthy male volunteers aged from 18 to 45 years (inclusive)
Planned Sample Size	78 healthy volunteers (39 in each trial arm)

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Study Design	This is a double-blind, randomized clinical study to compare the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of single intravenous doses of BCD-148 (JSC BIOCAD, Russia) and Soliris® in healthy volunteers. The suggested double-blind randomized parallel-group design that utilizes a drug with demonstrated efficacy (reference drug) as an active control is aimed at proving pharmacokinetic equivalence of a biosimilar BCD-148 (test drug) and Solaris® (reference drug) in terms of the key PK parameters. This is a common approach in the development of biosimilars, which complies with the Russian[1] and international[2] regulations. The EMA[3,4] guidelines state that for long half-life products (such as eculizumab) a parallel-group study design is preferred to crossover. **Randomization** It is planned to randomize 78 adult healthy volunteers who then will be assigned at a 1:1 ratio to one of the two treatment arms: 39 subjects in the BCD-148 arm and 39 subjects in the Soliris® arm. During the study, each volunteer will receive a single IV infusion of 900 mg BCD-148 (test drug) or 900 mg Soliris® (reference drug). Before enrollment, all volunteers will be given all the information about this clinical study, its purpose, and the risks associated with study participation. After signing the informed consent form (ICF), each subject will undergo a screening examination (no longer than 20 days), which is to find out whether the subject meets the eligibility criteria. **Study periods** 1. Screening period will include 2 visits and 1 phone call. • *Screening Visit 1/ Days -20 to -18* ICF signing and eligibility assessment (interview, history taking, physical examination, and laboratory and instrumental investigations). • *Visit 2/ Day -17* It has been shown that patients treated with eculizumab may have increased susceptibility to infections caused by encapsulated

[1] A.N. Mironov, V.G. Kukes, V.I. Petrov, A.L. Kuznetsov, D.V. Goryachev, R.R. Niyazov, A.B. Prokofyeva, S.V. Nedogoda, M.Yu.Frolov, A.Shnayder. Bioequivalence evaluation for generic medicinal products // Guidance on evaluation of medicinal products Vol. I – M.: Grif and K, 2013.
[2]Rules for investigation of biologics (Eurasian Economic Commission)
https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78
[3]Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010, 2012.
[4]Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)

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	bacteria, especially to meningococcal infection. Therefore, all subjects who are considered eligible for the study will be preventively vaccinated against *Neisseria meningitidis* to ensure their safety. • *Screening phone call / Day -15* The study team member interviews the subject by phone to monitor for any post-vaccination complications. • *Screening Visit 3/ Days -3 to -1* This visit occurs at least 14 days post-vaccination. This time is enough for a subject to develop post-vaccination immunity. During this visit, each subject will be re-evaluated for eligibility based on their clinical and laboratory results. Hematology and chemistry tests will be performed, and the subjects will be assessed for any post-vaccination complications that may interfere with further participation in the study. 2. Main study period The duration of the main study period is 59 days, including the day of the BCD-148/Soliris® infusion. During this period, multiple blood collections will be performed for assessment of PK/PD, safety, and immunogenicity of eculizumab. Because of multiple blood collections and the necessity of monitoring the safety and tolerability of eculizumab, each subject will stay in a hospital for the first 48 h post-infusion. Blood samples will be collected from study subjects for the PK study (assessment of eculizumab concentration in the serum) and PD study (hemolytic complement activity CH50). The immunogenicity assessment is a mandatory part of the drug safety monitoring and will be performed prior to the infusion of eculizumab, 29 days post-infusion, and upon completion of the main study period (Day 59). The study results will be used to test the hypothesis of pharmacokinetic equivalence (in terms of the primary endpoint $AUC_{(0-\infty)}$ of eculizumab following a single IV infusion) of the biosimilar BCD-148 and the reference drug Soliris® and to assess the PD, safety, and immunogenicity of the test drug versus the reference drug.
Test Drug/ Reference Drug and Dosing Regimen	In this clinical study, each healthy volunteer will get one infusion of either the test drug BCD-148 or the reference drug Soliris®, depending on the study arm to which the subject is randomized. Both eculizumab products (BCD-148/Soliris®) will be administered as a single 900 mg drip infusion given over 25-45 min. The drug will be infused at the study site.
Main Inclusion	1. Signed ICF for participation in the study 2. Men from 18 to 45 years old (inclusive) at the time of signing

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Criteria:	the ICF 3. BMI within the normal limits (18.0 to 30.0 kg/m^2) 4. The subject is able to follow the Protocol procedures (in the investigator's opinion) 5. The subject is verified as "Healthy" according to the results of standard clinical, laboratory, and instrumental tests
Main Exclusion Criteria:	1. Psychiatric disorders or other conditions that can affect the ability of the subject to follow the study protocol 2. Acute infections within 4 weeks before signing the ICF 3. Results of laboratory and/or instrumental tests are outside the site's normal range.
PK Endpoints:	**The primary endpoint for PK assessment after a single infusion of BCD-148/Soliris®:** • $AUC_{0-\infty}$ of eculizumab (the area under the *Concentration vs. Time* curve from 0 to infinity). **The secondary endpoints for PK assessment after a single infusion of BCD-148/Soliris®:** • C_{max} of eculizumab (maximum drug concentration in the serum). • T_{max} of eculizumab (time to C_{max}) • AUC_{0-1392} of eculizumab (area under the *Concentration vs. Time* curve from 0 to 1392 h post-infusion) • $T_{1/2}$ of eculizumab (half-life) • Vd of eculizumab (steady-state volume of distribution) • K_{el} of eculizumab (elimination constant) • Cl of eculizumab (clearance)
PD Endpoints:	**The secondary endpoints for PD assessment after a single infusion of BCD-148/Soliris®:** • $ABEC_{(0-1392)}$ CH50 (the area between the baseline and effect curves for hemolytic activity of serum complement from 0 to 1392 h). • $AUEC_{(0-1392)}$ CH50 ((area under the *Time vs. Effect* curve from 0 to 1392 h) • E_{min} CH50 (minimum hemolytic complement activity from 0 to 1392 h) • T_{min} CH50 (time to minimum hemolytic complement activity within the period from 0 to 1392 h).
Safety Endpoints:	• The proportion of subjects who develop AEs/SAEs that, in the Investigator's opinion, are related to eculizumab

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	• The proportion of subjects who develop CTCAE v. 4.03 grade 3/4 AEs that, in the Investigator's opinion, are related to eculizumab, by study arms.
Immunogenicity Endpoints	• The proportion of BAb- and NAb-positive subjects

1. STUDY RATIONALE

1.1. Introduction

1.1.1. Complement system

The complement system is a system of serum proteins consisting of nine main and three inhibitory proteins. The complement system is a part of the innate immune system and activates through an enzyme cascade pathway, where the product from the previous reaction is a catalyst in the subsequent reaction.

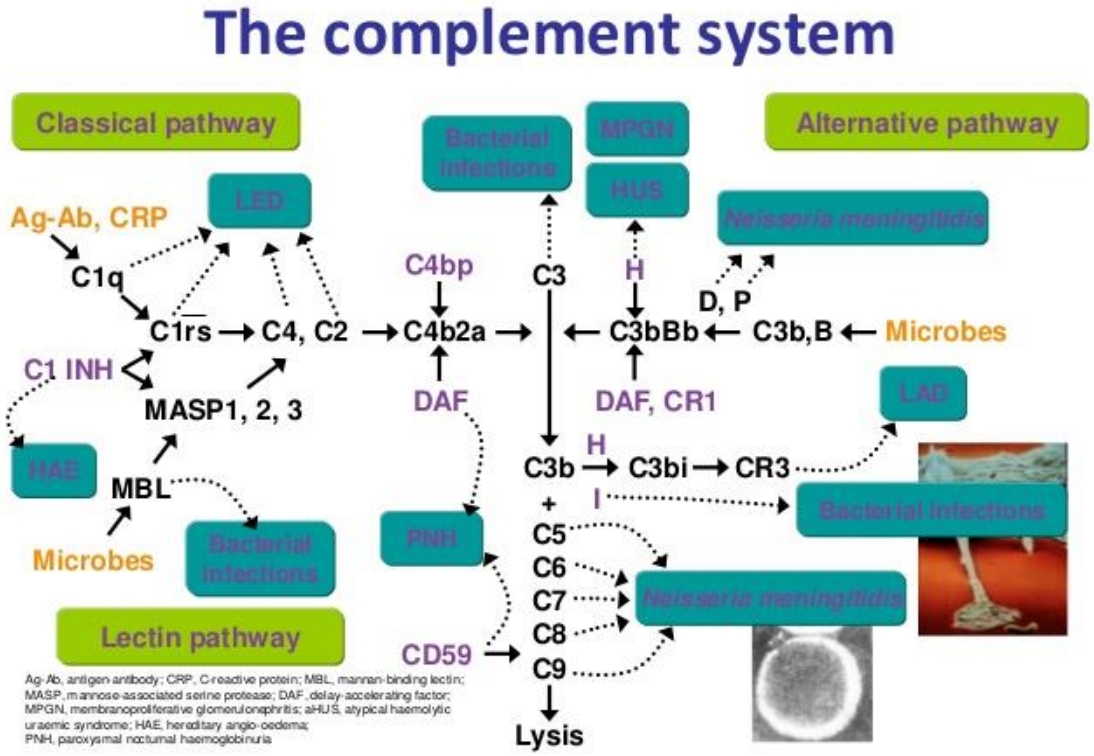
Complement triggers the following immune functions: promotes phagocytosis by releasing certain substances that cover pathogens or immune complexes; promotes inflammation by regulating the expression of biologically active substances by basophils; promotes cytotoxicity through the formation of the membrane attack complex (MAC) from terminal complement components [1].

There are three pathways through which complement can be activated: the classical, lectin, and alternative pathways. The classical and lectin pathways are triggered when antibodies (classical pathway) or pattern-recognition molecules (pentraxins and C1q in the classical pathway and lectins and ficolins in the lectin pathway) recognize pathogens or damage on the cell surface. Both classical and lectin pathways lead to the cleavage of C4 resulting in the formation of the C4bC2a C3 convertase complex on the target surface. The C4bC2a is an enzymatic complex that cleaves C3 into the anaphylatoxin C3a and C3b. The alternative pathway is activated as a result of the spontaneous generation of fluid-phase C3b (C3 tick-over). C3b accumulates on the surface of pathogens or self-cells and, together with the activated factors D and B, forms the C3-convertase enzyme complex of the alternative pathway (C3b/Bb), which triggers additional C3 cleavage, thus creating a positive feedback loop. It is important that, after C3b is generated, the alternative C3-convertase further promotes complement activation by triggering other activation pathways. C3b accumulates on the surface of a pathogen and binds to specific receptors on white blood cells, which induces phagocytosis of cells labeled by complement enzymes. Attachment of C3b to C3-convertase converts this enzyme into C 5-convertase, an enzyme that cleaves C5 into C5a and C5b. C5a is a pro-inflammatory and pro-thrombotic protein, while C5b initiates the terminal complement pathway with the formation of the terminal complement complex C6-C9. Finally, the C5b-9 complex (MAC) is formed on the surface of the target cells. The MAC causes hemolysis, stimulates the production of pro-coagulant micro particles, and activates platelets [1].

The complement activation is regulated by certain complement control molecules - membrane receptors (MCP (membrane cofactor protein), CD55 (DAF), CD59 (MIRL), and THBD (thrombomodulin)) and soluble molecules (e.g., CFH (complement factor H)). These control molecules may cause C3b cleavage into inactive forms and dissociation of C3- and C5-convertases or may prevent MAC assembly.

The complement system imbalance resulting from certain genetic disorders is one of the key components in the mechanism of the atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH).

Figure 1. The complement system



1.1.2. Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired, clonal disease of the blood. The disease is characterized by chronic intravascular hemolysis, impaired bone marrow function, high risk of blood clots, kidney disease, and pulmonary hypertension. A somatic mutation in the X-linked gene encoding phosphatidylinositol glycan A (PIG-A) leads to the deficiency of glycosyl phosphatidylinositols (GPI) anchors that attach a number of proteins to blood cell membranes (e.g. certain complement system control molecules such as CD55/DAF, HRF, and CD59). Normally,

these proteins interact with complement components, particularly with C3b and C4b, thus inducing dissociation of the convertase complexes and slowing down the accelerating activation of the complement. The lack of these proteins on the cell membrane in subjects with PNH results in cells (primarily erythrocytes) becoming hypersensitive to complement-induced lysis, intravascular hemolysis, and anemia. Released free hemoglobin partially binds to haptoglobin in the serum, but the concentration of plasma hemoglobin in PNH exceeds the capacity of haptoglobin. Thus, hemoglobin binds irreversibly to nitric oxide, which is a physiological vasodilator. Depletion of nitric oxide induces vasospasm, pulmonary hypertension, impaired renal blood flow, and GI smooth muscle spasm. Excretion of free hemoglobin into urine results in tubular necrosis and renal impairment. Moreover, PNH is frequently associated with thrombotic complications, which may be due to the higher platelet aggregation caused by the deficiency of the membrane CD59 and due to elevated plasma pro-coagulant activity. Typically, the clinical onset of PNH occurs in people from 20 to 40 years old; the median survival based on historical data is about 10 years. [2].

The worldwide prevalence of PNH is approximately 13 cases per 1 000 000 people [3] with the incidence of about 1 case per 1 000 000 people per year. Large-scaled epidemiological studies have shown that 35% of PNH patients lose their lives within 5 years from the date of diagnosis and their 10 years mortality reaches approximately 50% despite supporting therapy. Thrombotic events are responsible for 40-67% of deaths [2, 3, 4, 5, 6, 7, 8]. Other causes of morbidity and mortality can be listed as renal failure, pulmonary hypertension, erectile dysfunction and dysphagia [9].

Allogeneic bone marrow transplantation is the only potentially curative treatment for PNH, however, it is associated with high mortality. In one of the PNH studies, the 10-year survival rate was 42%. Regardless of the indication, the frequency of complications with allogenic bone marrow transplantation remains very high. The average incidence of graft versus host disease has been observed as 42-54%.

Patients with complement-mediated hemolysis may be candidates for eculizumab therapy. According to literature, eculizumab therapy in PNH patients significantly reduces hemolysis, decreases the frequency of thrombosis and transfusion dependence, and alleviates the severity of symptoms such as dyspnea, fatigue, and pulmonary hypertension. Eculizumab also improves the renal function and quality of life. Long-term use of eculizumab increases survival up to the level of general population in the same age group. Eculizumab is not a curative treatment but long-term eculizumab treatment has a good safety profile and reduces complications and the risk of death

significantly. Eculizumab should be prescribed based on clinical and laboratory signs. For patients diagnosed with PNH, Eculizumab treatment indications are available in the following cases:

– Presence of thrombotic event

– Presence of organ damage due to chronic hemolysis

– Transfusion dependence

– If PNH patient is pregnant.

For patients who had thrombotic complications in the past, eculizumab is indicated to prevent further thrombosis. For patients with high LDH activity (>1.5 of the normal limit), PNH complications including life-threatening cases increased significantly. For this reason, eculizumab should be used in the treatment of patients having LDH activity > 1.5 of the normal, which is associated with chronic hemolysis – for example, thrombosis, anemia, acute and chronic renal failure, pulmonary hypertension, smooth muscle dystonia (e.g., abdominal pain, dysphagia, erectile dysfunction etc.). Eculizumab treatment is also indicated to transfusion-dependent patients with chronic hemolysis. Eculizumab blocks hemolysis and significantly decreases the number of transfusions [2]

1.1.3. Atypical hemolytic uremic syndrome

Atypical hemolytic uremic syndrome (aHUS) is a chronic systemic genetic disease caused by uncontrolled activation of the alternative pathway in the complement system. The disease is characterized by generalized thrombotic microangiopathy (complement-mediated TMA). This is an orphan disease with the prevalence of 2 to 7 subjects per 1 000 000 people.

The atypical hemolytic uremic syndrome can manifest at any age; however, children and young adults are affected more often than other categories. Approximately 60% of aHUS cases are diagnosed in children versus 40% in adults. The disease affects males and females in equal numbers. In adulthood, females are affected more often than males.

Atypical HUS is caused by genetic defects in the regulation of the alternative pathway of the complement system, which results in its uncontrolled activation. It is believed that aHUS patients have mutations in the genes encoding certain regulatory proteins (CFH, CFI, MCP, THBD). By causing the deficiency or, more often, dysfunction of these proteins, such mutations deteriorate the defense mechanism against complement-induced endothelial cell activation. This results in increased liberation of MAC at the endothelial surface, causing additional endothelial cell damage with exposure of the subendothelial matrix, conversion of athrombotic phenotype into prothrombotic, and subsequent thrombus formation. The complement activation on the platelet

surface, which triggers the platelet functional activity, is an additional factor contributing to the thrombus formation in aHUS patients with factor H mutations.

Besides improving survival in aHUS patients, aHUS therapy aims at inhibiting the uncontrolled complement activation, alleviating clinical and laboratory signs/symptoms of TMA, preserving and improving damaged organ functions (e.g. preventing terminal renal failure, taking patients off from dialysis, preventing damage of visceral organs other than kidneys) and providing better quality of life.

The aHUS therapy includes fresh frozen plasma infusions, plasma exchange, and heparin therapy if indicated. According to the national guidelines, eculizumab therapy is indicated to adult aHUS patients who do not respond to plasma therapy, have adverse events, have recurrent disease, or have a family history of aHUS.

1.1.4 Current treatment options for aHUS and PNH

Treatment options for aHUS and PNH include eculizumab (Soliris®), a humanized monoclonal antibody binding to the complement protein C5. This inhibits C5 cleavage to C5a and C5b and thereby prevents the generation of pro-inflammatory cytokines (via C5a) and MAC (via C5b).

Clinical studies and further clinical practice have shown that eculizumab therapy in PNH patients significantly reduces hemolysis, decreases the frequency of thrombosis and transfusion dependence, and alleviates the severity of symptoms such as dyspnea, fatigue, and pulmonary hypertension. Eculizumab also improves the renal function and quality of life. Long-term use of eculizumab increases survival up to the level of general population in the same age group. Thus, eculizumab therapy significantly reduces the mortality and incidence of complications, although it is not a curative treatment [2].

In aHUS patients, eculizumab reverses the TMA effect and/or prevents further kidney damage. Although eculizumab suppresses the terminal complement system, the proximal complement system, responsible for opsonization of microorganisms and clearance of immune complexes, remains intact [10].

1.1.5. Brief overview of the study product and its advantages

JSC BIOCAD (Russia) develops BCD-148 as a biosimilar to Soliris®. [redacted]

[redacted]

1.2. Name and description of the investigational product

1.2.1. Test drug

Invented name: Not applicable

Internal code: BCD-148

International non-proprietary name: eculizumab

Dosage form: [redacted]

Composition: [redacted]

Manufacturer: JSC BIOCAD, Russia.

Shelf life: [redacted]

Storage and transportation conditions: [redacted]

Packaging: [redacted]

1.2.2. Reference drug:

Invented name: Soliris®

International non-proprietary name: eculizumab

Dosage form: Concentrate for solution for infusion

Marketing Authorization Holder: Alexion Pharma GmbH[5]

Composition:

[redacted]

[5] If the product is not available or difficult to purchase in the Russian Federation, it will be purchased in other countries.

Shelf life: [redacted].

Storage and transportation conditions: [redacted]

Packaging: [redacted].

1.2.3. Labeling of the study and reference products in this study

This study is blind, so the investigational products will be labeled identically.

Labeling: [redacted]

1.2.4. Posology and route of administration

In this clinical study, each healthy volunteer will get one infusion of either the test drug BCD-148 or the reference drug Soliris®, depending on the study arm to which the subject is randomized. Both eculizumab products (BCD-148/Soliris®) will be administered as a single 900 mg drip infusion given over 25-45 min. The infusion will be given at the study site.

The subject should be warned not to smoke for 1 h before the infusion of BCD-148/Soliris® and for 3 h following the infusion.

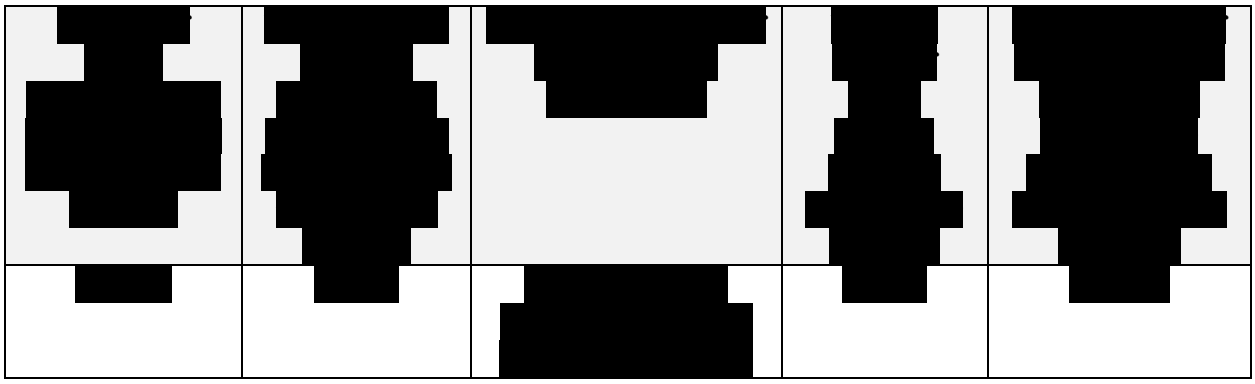
Route of administration:

The infusion of BCED-148/Soliris® will be given at the study site. Subjects will stay at the study site for monitoring for 48 h post-infusion. The study site where the infusion is given and the following monitoring is performed must have all the necessary equipment for emergency care.

Instructions for reconstitution of the test/reference drug solution

[redacted]

[redacted]



[redacted]

1.3. Relevant non-clinical and clinical aspects

1.3.1. Non-clinical studies

[redacted]

[6]Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2)

1.4. Summary of the known and potential risks and benefits to human subjects, if any (risk/benefit balance)

Given the mechanism of action, eculizumab is considered safe with regard to the health and wellbeing of the study participants.

The risks for study subjects will be minimized through the protocol-specified inclusion/exclusion criteria and procedures. A single dose of BCD-148/Soliris® is not expected to cause any severe adverse events. The study participants will be monitored for 59 days, which covers five Soliris® half-life periods (the mean half-life of Soliris® is 11.3 days, hence 11.3 x 5 $T_{1/2}$ = 56.5 days).

No medical benefit is expected for the study participants other than a comprehensive medical examination and immunization (development of bactericidal antibodies) against meningococcus serotypes A, C, W_{135}, and Y.

Thus, the benefit-risk ratio is expected to be suitable.

1.5. Description and justification of route of administration, doses, and dosing regimen

1.5.1 Description and justification of the study design

The BCD-148-3 trial is a double-blind, randomized clinical study to compare the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of single intravenous doses of BCD-148 (JSC BIOCAD, Russia) and Soliris® in healthy subjects. The study is planned to involve two parallel arms: the BCD-148 arm and the Soliris® arm.

The suggested double-blind randomized parallel-group design that utilizes a drug with demonstrated efficacy (reference drug) as an active control is aimed at proving pharmacokinetic equivalence of a biosimilar BCD-148 (test drug) and Soliris® (reference drug) in terms of the key PK parameters. This is a common approach in the development of biosimilars, which complies with the Russian [7] and international[8] regulations.

[7] A.N. Mironov, V.G. Kukes, V.I. Petrov, A.L. Kuznetsov, D.V. Goryachev, R.R. Niyazov, A.B. Prokofyeva, S.V. Nedogoda, M.Yu.Frolov, A.Shnayder. Bioequvalence evaluation for generic medicinal products // Guidance on evaluation of medicinal products Vol. I – M.: Grif and K, 2013.
[8]Rulesfor investigation of biologics (Eurasian Economic Comission)
https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78

The EMA[9,10] The EMA, guidelines state that for long half-life products (such as eculizumab) a parallel-group study design is preferred to crossover *("A parallel group design may be necessary due to the long half-life of MAbs and the potential influence of immunogenicity").*

The study population was selected according to recommendations laid out in the EMA's *Guideline on Similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*[11] in the Eurasian Economic Unit's guidelines[12] *("… if feasible, a single dose study in healthy volunteers is recommended, which could provide important information on biosimilarity.").*

Blood sampling points for PK assessment were chosen based on the available information on eculizumab PK. According to the international guidelines, blood sampling in single-dose studies should cover a long-term period including the late-phase elimination. With the knowledge of the Soliris® half-life ($T_{½}$ 11.3±3 days or 272±82 h), this study with multiple blood collections for PK, PD, and safety assessment was planned to last for 59 days. This period is approximately 5 half-lives of eculizumab (56.5 days 1360 h). The sampling time should ensure several collections for each fragment of the PK curve - at least 3 samples in the initial increase phase and at least 5 samples in the decrease phase. With this consideration in mind and with the available data on eculizumab PK, the following blood collection timepoints were chosen for the study of BCD-148/Soliris®: immediately before dosing, then 5 min, 4 h, 8 h, 12 h, 24 h, 48 h, 72 h, 120 h, 192 h, 264 h, 360 h, 528 h, 696 h, 864 h, 1032 h, 1200 h and 1392 h post-dose.

The primary endpoint to test the hypothesis ($AUC_{(0-\infty)}$ - the area under the *Time vs. Concentration* curve from 0 h to infinity) and secondary PK parameters were chosen as suggested in the EMA's guideline on biosimilar monoclonal antibodies[13] *("In a single dose study, the primary parameter should be the $AUC_{(0-inf)}$. Secondary parameters such as C_{max}, T_{max}, volume of distribution, and half-life, should also be estimated").*

This study also includes a thorough assessment and comparison of eculizumab PD marker - hemolytic complement activity. This is to provide the most valid and comprehensive data on the comparability of BCD-148 and the reference drug Soliris® (*"Pharmacokinetic studies should be*

[9]Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010, 2012.
[10]Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)
[11] Guideline on Similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May, 2012.
[12]Rules for investigation of biologics (Eurasian Economic Commission) https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78
[13] Guideline on Similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May, 2012.

combined with pharmacodynamic (PD) endpoints, where available. This could add valuable information for the overall comparability exercise. PD markers are especially valuable if they are sensitive enough in order to detect small differences, and if they can be measured with sufficient precision) [14].

1.5.2. Description and justification of the route of administration, doses, and dosage regimen

In this clinical study, healthy subjects will receive a single infusion of 900 mg BCD-148 or 900 mg Soliris® each.

The test drug BCD-148 is a biosimilar to Soliris®, a drug used to treat PNH and aHUS. Therefore, the dose and route of administration (900 mg given as an IV drip infusion) proposed in this study match the standard single therapeutic dose used in the maintenance treatment phase in PNH patients as described in the approved Soliris® Instruction for Medical Use[15].

A single dose of the test drug puts the subjects at a minimal risk of any health damage. A single dose administration with a subsequent follow-up period allows investigating, as full as possible, the PK and PD of the drug. This regimen avoids any carry-over (cumulative) effects, which are possible upon repeated dose administration of a monoclonal drug with unknown pharmacokinetics. Therefore, such regimen brings to a minimum the risk of data contamination. Since there are certain health risks associated with immunosuppression caused by complement C5 inhibition, assessment of the clinical effects of the repeated-dose regimen in patients is preferred in Phase II clinical studies.

A single drip infusion of eculizumab with subsequent follow-up is to demonstrate whether BCD-148 and Soliris® have equivalent PK as well as to investigate and compare their PD and safety.

Eculizumab is used to treat PNH and aHUS. In both diseases, it is used at a 900 mg dose (maintenance phase in PNH and initial phase in aHUS. Thus, this dose is the most sensitive one to detect the differences (if any) in the PK between BCD-148 and Soliris®. This approach is consistent with the international requirements stated in the above listed guidelines *("In principle, it is not required to test all therapeutic dosage regimens; the most sensitive dose should be selected to detect potential differences in PK between the biosimilar and the reference products").*

Conclusions

[14]Rules for investigation of biologics (Eurasian Economic Commission) https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78
[15]https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=775bf971-249e-427e-9b82-1c5c2a9c2c51&t=

The study design, route of administration, dosing regimen, and follow up methodology are feasible, ethically and scientifically justified, and do not bring any excessive risk to study subjects.

1.6. Clinical study compliance with regulatory requirements

The clinical trial will be conducted according to this Protocol developed in full compliance with the current law of the Russian Federation, Federal Law No. 61-FZ of April 12, 2012: *On the Circulation of Medicines*; National Standard of the Russian Federation GOST R 52379-2005 *Good Clinical Practice*; the rules of Good Clinical Practice of the Eurasian Economic Union; the Constitution of the Russian Federation; Federal Law No. 323-FZ of November 21, 2011: *On Public Health Protection in the Russian Federation*; the WMA Declaration of Helsinki (Fortaleza 2013), Order No. 200n of April 01, 2016 *On Approval of the Good Clinical Practice*; the GCP principles, and the current law and regulations of the participating countries.

1.7. Study population

Healthy male subjects aged from 18 to 45 years (inclusive) and meeting the eligibility criteria set by the Protocol.

1.8. References

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12. Extension of indication variation assessment report EMA/CHMP/204109/2015.

2. STUDY PURPOSE AND OBJECTIVES

2.1 Study purpose

To perform a comparative assessment of the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of a single intravenous infusion of BCD-148 and Soliris® in healthy subjects.

2.2 Study objectives

1. To determine and compare the PK parameters of BCD-148 and Soliris®, each given as a single intravenous infusion
2. To determine and compare the PD parameters of BCD-148 and Soliris®, each given as a single intravenous infusion
3. To determine and compare the adverse event profile with a single infusion of BCD-148 and Soliris®
4. To evaluate and compare the proportion of BAb- and NAb-positive subjects in the BCD-148 and Soliris® arms after a single drug infusion.

3. STUDY HYPOTHESIS

The study is to test the hypothesis that the test drug BCD-148 and the reference drug Soliris® have equivalent pharmacokinetics. The equivalence hypothesis will be tested for the primary PK endpoint – $AUC_{(0-\infty)}$ of eculizumab after a single IV infusion of BCD-148/Soliris®. BCD-148 will be proved equivalent to Soliris® if the limits of the two-sided 95% CI for the ratio of the geometric means of eculizumab $AUC_{(0-\infty)}$ values after a single IV infusion of BCD-148 and Soliris® fall within 80.00-125.00%.

4. STUDY DESIGN

4.1. Primary and secondary outcome measures to be assessed in the study

4.1.1 PK endpoints

Pharmacokinetic assessment will be based on the concentration of eculizumab (monoclonal antibodies to complement C5) measured in the serum of healthy volunteers.

The primary endpoint for PK assessment after a single infusion of BCD-148/Soliris®:

- $AUC_{0-\infty}$ of eculizumab (the area under the *Concentration vs. Time* curve from 0 to infinity).

The secondary endpoints for PK assessment after a single infusion of BCD-148/Soliris®:

- C_{max} of eculizumab (maximum concentration of eculizumab in the serum)
- T_{max} of eculizumab (time to C_{max})
- AUC_{0-1392} of eculizumab (the area under the *Concentration vs. Time* curve from 0 to 1392 h post-infusion)
- $T_{1/2}$ of eculizumab (half-life)
- Vd of eculizumab (steady-state volume of distribution)
- K_{el} of eculizumab (elimination constant)
- Cl of eculizumab (clearance).

[redacted]

4.1.2 PD endpoints

Pharmacodynamics will be investigated by measuring the hemolytic complement activity in the serum (CH50), where one unit of hemolytic activity is the reciprocal of the serum dilution which causes a 50% hemolysis.

The secondary endpoints for PK assessment after a single infusion of BCD-148/Soliris®:

- $ABEC_{(0-1392)}$ CH50 (the area between the baseline and effect curves for hemolytic activity of serum complement from 0 to 1392 h)
- $AUEC_{(0-1392)}$ CH50 ((area under the *Time vs. Effect* curve from 0 to 1392 h)
- E_{min} CH50 (minimum hemolytic complement activity from 0 to 1392 h)
- T_{min} CH50 (time to minimum hemolytic complement activity within the period from 0 to 1392 h).

[redacted]

[redacted]

The PD endpoints will be analyzed when all the subjects complete the main study period.

4.1.3. Safety endpoints:

- The proportion of subjects who develop AEs/SAEs that, in the investigator's opinion, are related to eculizumab
- The proportion of subjects who develop CTCAE v. 4.03 grade 3/4 AEs that, in the investigator's opinion, are related to eculizumab, by study arms.

The safety endpoints will be analyzed when all the subjects complete the main study period.

4.1.4. Immunogenicity endpoints

- The proportion of BAb- and NAb-positive subjects

[redacted]

The immunogenicity endpoints will be analyzed when all the subjects complete the main study period.

4.2. Study Design

This is a double-blind, randomized clinical study to compare the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of single intravenous doses of BCD-148 (JSC BIOCAD, Russia) and Soliris® in healthy volunteers

The suggested double-blind randomized parallel-group design that utilizes a drug with demonstrated efficacy (reference drug) as an active control is aimed at proving pharmacokinetic equivalence of a biosimilar BCD-148 (test drug) and Soliris® (reference drug) in terms of the key PK parameters. This is a common approach in the development of biosimilars, which complies with the Russian [16] and international[17] regulations.

The EMA[18,19] guidelines state that for long half-life products (like eculizumab) a parallel-group study design is preferred to crossover.

[16] A.N. Mironov, V.G. Kukes, V.I. Petrov, A.L. Kuznetsov, D.V. Goryachev, R.R. Niyazov, A.B. Prokofyeva, S.V. Nedogoda, M.Yu.Frolov, A.Shnayder. Bioequvalence evaluation for generic medicinal products // Guidance on evaluation of medicinal products Vol. I – M.: Grif and K, 2013.
[17]Rulesfor investigation of biologics (Eurasian Economic Comission)
https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78
[18]Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010, 2012.
[19]Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)

It is planned to randomized 78 adult healthy volunteers who then will be assigned at a 1:1 ratio to one of two treatment arms: 39 subjects in the BCD-148 arm and 39 subjects in the Soliris® arm.

During the study, each volunteer will receive a single IV infusion of 900 mg BCD-148 (test drug) or 900 mg Soliris® (reference drug).

Before enrollment, all volunteers will be given all the information about this clinical study, its purpose and the risks associated with study participation. After signing the informed consent form (ICF), each subject will undergo a screening examination (no longer than 20 days), which is to find out whether the subject meets the eligibility criteria.

4.3. Measures to minimize/eliminate bias

4.3.1. Inclusion of subjects in the study and assigning the screening and study IDs

Subjects will be randomized and assigned study IDs according to internal JSC BIOCAD procedures.

[redacted]

4.3.2. Stratification procedure

As this study involves only healthy male subjects all from the same age group, no stratification will be performed.

4.3.3. Randomization procedure

Randomization in the study will be centralized. The subjects will be randomized in 1:1 ratio to the BCD-148 and Soliris® arms.

[redacted]

4.3.4. Blinding

Neither subjects nor investigators will be aware of what drug was administered to which subject during Visit 1 / Day 1. The study/reference drug will be delivered to the study site in identical secondary packaging (cartons) differing only by lot numbers and expiry dates. The lot numbers will be subject-specific.

4.4. Description of the study treatment, dose and dosing regimen for the investigational product(s). Pharmaceutical form, packaging, and labeling of investigational products

4.1.4. Description of the study treatment, dose, and dosing regimen for the investigational product(s)

In this clinical study, each healthy volunteer will get one infusion of either the test drug BCD-148 or the reference drug Soliris®, depending on the study arm to which the subject is randomized. Both eculizumab products (BCD-148/Soliris®) will be administered as a single 900 mg drip infusion given over 25-45 min. The infusion will be given at the study site.

[redacted]

4.4.2. Pharmaceutical form, packaging, and labeling of investigational products

4.4.2.1. Test drug

See Section 1.2.1. *Test Drug* and 1.2.3. *Labeling of the Study and Reference Products in this Study*.

4.4.2.2. Reference drug

See section 1.2.2. *Reference Drug* and 1.2.3. *Labeling of the Study and Reference Products in This Study.*

4.4.2.3. Meningococcal vaccine

Invented name: Menactra® (meningococcal (serotypes A, C, Y and W-135 polysaccharide diphtheria toxoid conjugate vaccine).

[redacted]

[20] If the product is not available or difficult to purchase in the Russian Federation, it will be purchased in other countries.

[redacted]

4.5. Expected duration of the study and subjects' participation in the study

[redacted]

4.6. Study periods

4.6.1 Study visits and procedures

The visit schedule and procedures are the same for both study arms. The study includes the screening period and 12 visits in the main study period.

[redacted]

Table 6. Schedule of study visits and assessments

Visit	**Screening - Visit 1**	**Screening - Visit 2**	**Screening Phone Call**	**Screening - Visit 3**	**1**			**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit	**-20 – -18**	**-17**	**-15**	**-3 – -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 6**	**Day 9**	**Day 12**	**Day 16**	**Day 23**	**Day 30**	**Day 37**	**Day 44**	**Day 51**	**Day 59**
Signing the ICF	+																	
Life and disease history	+																	
Information about concomitant therapies	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vital signs[21]	+	+		+	+[22]				+			+		+				+
Physical examination	+	+		+	+				+			+		+				+
Chest x-ray and fluorography[23]	+																	
ECG	+													+				+
Venous catheter inserted into the vein					+													
Venous catheter removed						+												
Hematology	+			+		+			+	+		+	+	+		+		+
Chemistry	+			+					+			+		+				+
Coagulation pattern	+								+			+		+				+
Urinalysis	+								+			+		+				+
Blood for PK/PD assessment[24]					+[25]	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood for immunogenicity testing					+[26]									+				+

[21]BP, wrist pulse, body temperature, body weight, and height (body weight and height are measured on Screening Visit 1).
[22]BP, wrist pulse, and body temperature are checked on Day 1 before the infusion, immediately after the infusion, and 1 h, 4 h, 8 h, and 12 h post-infusion.
[23] Results obtained within 2 months before signing the ICF can be used at screening.
[24] Details of timepoints for blood sampling are described in Table 9.
[25]Blood samples for PK/PD study on Day 1 are collected 5 min before the infusion and then 5 min, 4 h (±5 min), 8 h (±10 min), and 12 h (±15 min) post-infusion.
[26]Blood is collected before the infusion of BCD-148/Soliris.

Visit	Screening - Visit 1	Screening - Visit 2	Screening Phone Call	Screening - Visit 3	1			2	3	4	5	6	7	8	9	10	11	12
Visit	**-20 – -18**	**-17**	**-15**	**-3 – -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 6**	**Day 9**	**Day 12**	**Day 16**	**Day 23**	**Day 30**	**Day 37**	**Day 44**	**Day 51**	**Day 59**
Blood tests for HIV, hepatitis and syphilis[27].[28]	+																	
Alcohol test	+				+[29]													
Urine test for psychotropic and recreational drugs, psychoactive medications	+				+[30]													
Vaccination		+[31]																
Infusion of BCD-148/Soliris®					+													
Documenting SAEs/AEs	+	+[32]	+	+	+[33]	+	+	+	+	+	+	+	+	+	+	+	+	+
Assess conformance to inclusion/exclusion criteria	+			+[34]														
Phone interview			+															

[27] [redacted]

5. ELIGIBILITY AND EXCLUSION OF STUDY SUBJECTS

5.1. Inclusion criteria

1. Signed ICF for participation in the study
2. Men from 18 to 45 years old (inclusive) at the time of signing the ICF
3. BMI within the normal limits (18.0 to 30 kg/m^2)
4. The subject is able to follow the Protocol procedures (in the investigator's opinion)
5. The subject is verified as "Healthy" according to results of standard clinical, laboratory and instrumental tests
6. Normal hemodynamic parameters: systolic BP from 90 mmHg to 130 mmHg; diastolic BP from 60 mmHg to 90 mmHg; HR from 60 bpm to 90 bpm
7. The subject and his sex partner of childbearing potential consent to implement reliable contraceptive methods from the moment the subject signs the ICF and until the subject completes the study. This requirement does not apply to those subjects who had undergone surgical sterilization. Reliable contraception methods mean one barrier method in combination with one of the following: spermicides, intrauterine device and/or oral contraceptives used by the subject's partner.
8. The subject agrees not to drink alcohol for 24 h prior to the infusion of the test/reference drug and for the entire period while the subject is in the study.

5.2 Exclusion criteria

1. Psychiatric disorders or other conditions that can affect the ability of the subject to follow the study protocol
2. Acute infections within 4 weeks before signing the ICF
3. Results of laboratory and/or instrumental tests are outside the site's normal range
4. Any surgery done within 30 days before the screening or planned within 30 days after the subject completes the study
5. Impossibility to insert an intravenous catheter for blood collection (e.g., because of a skin condition at the venipuncture site)
6. A history of allergies
7. Known hypersensitivity to any component of BCD-148 or Soliris®, murine proteins or other drug components; hypersensitivity to any component of the meningococcal vaccine
8. The subject had used any medications that significantly affect hemodynamics, liver

function, etc. (barbiturates, omeprazole, cimetidine, etc.) within 30 days before signing the ICF and/or the subject needs any medications (other than the study drugs) to be taken during the entire study period

9. The subject had previously used eculizumab and/or other therapeutic monoclonal antibodies against complement C5
10. Regular use (oral or parenteral) of any drugs, including OTC products, vitamins or biologically active supplements within 14 calendar days before signing the ICF
11. A history of recurrent/chronic hemorrhages or any hemorrhage within 30 days prior to signing the ICF
12. Acute or chronic infections or other diseases that, in the investigator's opinion, may affect the PK, PD or safety of the study products
13. HIV, HCV, HBV infection, syphilis.
14. Meningococcal infection in the past (documented or mentioned verbally by the subject)
15. Vaccination within 4 weeks before the planned infusion date, except for vaccination against *Neisseria meningitidis* given to all subjects in the screening period
16. The subject refuses to get a vaccination against *Neisseria meningitidis* during the screening period[35].
17. The subject smokes more than 10 cigarettes per day
18. The subject consumes more than 10 units of alcohol per week (1 unit equals to 0.5 L of beer, 200 mL of wine or 50 mL of a strong alcohol beverage) or has a history of alcohol, recreational drug or medication abuse, or tests positive for alcohol and/or psychoactive substances during the screening examination
19. Donation of ≥ 450 mL of blood or plasma within 60 calendar days before signing the ICF.
20. Participation in any drug clinical studies within 30 calendar days prior to signing the informed consent form and through the entire period of study participation.

5.3. Withdrawal criteria

Refer to section 4.7. *Stop rules and criteria for premature withdrawal for study subjects, study periods, and study as a whole*.

The investigator must inform JSC BIOCAD about the subject's premature withdrawal within 24 h and specify the reason.

[35] Except for cases when the subject has a documented evidence that he received a tetravalent meningococcal vaccine (serogroups A, C, Y, and W-135) within 2 years before signing the informed consent form If the previous vaccination was performed with a vaccine other that MCV4, the subject has to be re-vaccinated.

5.3.1. Replacing drop-outs

Those subjects who dropped out after randomization will not be replaced. The sample size was calculated with an account for potential dropouts.

5.4 Follow-up of subjects withdrawn from the study or subjects who discontinued the study treatment but remain in the study for follow-up

5.4.1. Follow-up of subjects who received at least one dose of BCD-148/Soliris®

If the subject discontinues the study after receiving the test/reference drug, an Early Withdrawal Visit is performed and the Early Withdrawal Form is filled out.

[redacted]

6. ADMINISTRATION OF THE INVESTIGATIONAL PRODUCT

6.1 Route of administration used in the study

In this clinical study, each subject will get one infusion of either the test drug BCD-148 or the reference drug Soliris®, depending on the study arm to which the subject is randomized. Both eculizumab products (BCD-148/Soliris®) will be administered as a single 900 mg drip infusion given over 25-45 min. The infusion will be given at the study site.

See section 1.2.4. *Posology and route of administration*.

6.2. Dose modification for the study drug

Not applicable.

6.3. Overdose

Any dose higher than the dose specified by the Protocol is considered an overdose. Repeated administration of the study drug is also considered an overdose, regardless of the dose and time of infusion.

In the case of an overdose, the subject should be monitored for any toxicity signs. If any toxicity signs are observed, standard symptomatic therapy should be given.

In the case of an overdose, either associated or not with an adverse event (serious or non-serious), the investigator must fill out the Overdose Report Form. An Overdose Report has to be **immediately (within 24 h)** submitted to the Sponsor at safety@biocad.ru (please put "ATTN Responsible Pharmacovigilance Officer" in the subject field).

6.4. Concomitant therapy, medications allowed and prohibited by the Protocol

The Protocol does not include any medications other than the test/reference drug.

[redacted]

6.5. Compliance with study procedures

[redacted]

7. PK AND PD ASSESSMENT

7.1. List of pharmacokinetic parameters

Pharmacokinetic assessment will be based on the concentration of eculizumab (monoclonal antibodies to complement C5) in the serum of healthy subjects.

The primary PK endpoint for PK after a single infusion of BCD-148/Soliris®:

- AUC0-∞ of eculizumab (the area under the *Concentration vs. Time* curve from 0 to infinity).

The secondary PK endpoints after a single infusion of BCD-148/Soliris®:

- C_{max} of eculizumab (maximum drug concentration in the serum).
- T_{max} of eculizumab (time to C_{max})
- AUC_{0-1392} of eculizumab (area under the *Concentration vs. Time* curve from 0 to 1392 h post-infusion)
- $T_{1/2}$ of eculizumab (half-life).
- Vd of eculizumab (steady-state volume of distribution)

[36]If the study visit is performed on the scheduled date but outside the acceptable time window, all the visit procedures should be performed including blood collections for immunogenicity testing, but no blood should be collected for PK and PD assessment.
If the visit is performed not on a scheduled date (deviation in the visit date), the procedures scheduled for this visits are not performed. This visit is considered a missed visit. The subject should attend the next scheduled visit. All other situations should be discussed with the Sponsor.
[37]If the subject did not attend Visit 1/ Day 1 due to force majeure, this visit can be re-scheduled but has to be performed within 5 days from the original visit date. In this case, dates of all subsequent visits will be counted from the actual date of Visit 1.

- K_{el} of eculizumab (elimination constant)
- Cl of eculizumab (clearance).

The PK endpoints will be analyzed when all the subjects complete the main study period.

7.2. List of pharmacodynamics parameters

Pharmacodynamics will be investigated by measuring the hemolytic complement activity in the serum (CH50), where one unit of hemolytic activity is the reciprocal of the serum dilution which causes a 50% hemolysis.

The secondary endpoints for PD assessment after a single infusion of BCD-148/Soliris®:

- $ABEC_{(0\text{-}1392)}$ CH50 (the area between the baseline and effect curves for hemolytic activity of serum complement from 0 to 1392 h).
- $AUEC_{(0\text{-}1392)}$ CH50 ((area under the *Time vs. Effect* curve from 0 to 1392 h)
- E_{min} CH50 (minimum hemolytic complement activity from 0 to 1392 h)
- T_{min} CH50 (time to minimum hemolytic complement activity within the period from 0 to 1392 h).

The PD endpoints will be analyzed when all the subjects complete the main study period.

8. SAFETY ASSESSMENT

8.1 List of safety endpoints

- The proportion of subjects who develop AEs/SAEs that, in the investigator's opinion, are related to eculizumab
- The proportion of subjects who develop CTCAE v. 4.03 grade 3/4 AEs that, in the investigator's opinion, are related to eculizumab, by study arms.

Immunogenicity assessment:

- The proportion of BAb- and NAb-positive subjects

9. STATISTICAL METHODOLOGY

9.1 Calculation of PK and PD parameters

9.1.1. PK parameters

Eculizumab (anti-C5 MAb) concentrations in the serum of each study subject will be measured at timepoints specified by the Protocol, and the following PK parameters will be calculated:

$AUC_{0-\infty}$ of eculizumab (the area under the *Concentration vs. Time* curve from 0 to infinity).

$$AUC_{0-\infty} = AUC_{0-1392} + \frac{C_{1392}}{k_{el}}, \text{ where}$$

C_{1392} refers to eculizumab concentration in the serum over 1392 h post-infusion, where k_{el} is the elimination constant.

AUC_{0-1392} (the area under the *Concentration vs. Time* curve from 0 to 392 h). AUC_{0-1392} will be determined with the trapezoidal rule and the formula where Cp is the concentration of eculizumab in the serum at t_p (h:)

$$AUC_{(0-1392)} = \sum_{p=2}^{18} \frac{(C_p + C_{p-1}) * (t_p - t_{p-1})}{2}$$

t_p

$\in \{0; 0{,}083; 4; 8; 12; 24; 48; 72; 120; 192; 264; 360; 528; 696; 864; 1032; 1200; 1392\}_{p=1,\ldots,18}$

C_{max} is the maximum eculizumab serum concentration achieved during the observation period.

$Tmax_{max}$ is the time to maximum concentration (C_{max}).

$AUMC_{0-1392}$ is the total area under the first moment curve from 0 to 1392 h. $AUMC_{0-1392}$ is calculated using the following formula:

$$AUMC_{0-1392} = \sum_{p=2}^{18} \frac{(C_p * t_p + C_{p-1} * t_{p-1}) * (t_p - t_{p-1})}{2},$$

где C_p – концентрация экулизумаба

в сыворотке крови в момент времени t_p

t_p

$\in \{0; 0{,}083; 4; 8; 12; 24; 48; 72; 120; 192; 264; 360; 528; 696; 864; 1032; 1200; 1392\}_{p=1,\ldots,18}$

Total clearance (Cl) is the volume of a test tissue from which a drug is completely removed per unit time. It is calculated as a drug dose (*DOSE*) divided by AUC_{0-1392}:

$$CL = \frac{DOSE}{AUC_{0-1392}}$$

Mean residence time (MRT) is calculated as a $AUMC_{0\text{-}1392}$ to $AUC_{0\text{-}1392}$ ratio:

$$\mathrm{MRT} = \frac{\mathrm{AUMC}_{0-1392}}{\mathrm{AUC}_{0-1392}}$$

Elimination rate constant (k_{el}) will be calculated as follows:

$$k_{el} = \frac{1}{MRT}$$

Elimination half-life ($T_{1/2}$) will be calculated as follows:

$$T_{1/2} = \frac{\ln(2)}{k_{el}} = \ln(2) * MRT$$

Volume of distribution (V_d) is a proportionality factor that relates the drug concentration in a test tissue to the amount of drug in the body. It shows the intensity of drug distribution between a test tissue and other tissues:

$$V_d = CL * MRT$$

9.1.2. PD parameters

The hemolytic complement activity (CH50) (where one unit of hemolytic activity is the reciprocal of the serum dilution which causes a 50% hemolysis) at protocol-specified endpoints will be used to calculate the following PD measures:

$AUEC_{(0\text{-}1392)}$ - the area under the *Time vs. Effect* curve from 0 to 1392 h) The $AUEC_{0\text{-}1392}$ will be calculated using the trapezoidal rule and the following formula:

$$AUEC_{0-1392} = \sum_{p=2}^{18} \frac{(C_p + C_{p-1}) * (t_p - t_{p-1})}{2},$$

Where Cp is the hemolytic complement activity in the serum at t_p (h)
$\in \{0; 0{,}083; 4;\ 8; 12; 24; 48; 72; 120; 192; 264; 360; 528; 696; 864; 1032; 1200;\ 1392\}_{p=1,\ldots,18}$

ABEC - the area between the baseline and effect curves for hemolytic activity of serum complement from 0 to 1392 h. To account for baseline variations, the baseline (pre-infusion) values will be subtracted from all subsequent measurements.

$$ABEC = AUEC_{0-1392} - c_0 * 1392\,,$$

Where c_0 is the pre-infusion hemolytic complement activity.

E_{min} CH50 - the minimum hemolytic complement activity from 0 to 1392 h.

T_{min} CH50 - the time to minimum hemolytic complement activity within the period from 0 to 1392 h.

9.2. Statistical methods

The statistical analysis will be performed using two-tailed hypothesis tests. The statistical significance level is 0.05.

The normally distributed quantitative data will be compared using the following tests: the two-tailed Student's *t*-test, Welch's *t*-test, and ANOVA.

The non-normally distributed quantitative data will be compared by using the Mann-Whitney test, Wilcoxon test, Kruskal-Wallis test, and Friedman's test.

The quantitative data:

- **Safety:**
  - ✓ Hematology results
  - ✓ Chemistry results
  - ✓ Coagulation pattern.
- **Assessment of PK and PD**
- **Demographics**

  Demographic data will be tested for normality using the Shapiro-Wilk test.

Normally-distributed quantitative variables will be described with the following characteristics: Mean values, geometric means (PK/PD), SD, CV, medians, quartiles, Min, and Max. In addition, the 90% CIs for the ratio of the geometric means will be calculated for $AUC_{(0-1392)}$ and C_{max}.

The categorical data:

Safety and tolerability:

- ECG findings
- Urinalysis results
- The proportion of subjects with AEs/SAEs
- The proportion of subjects with a grade 3/4 AE/SAE.

Immunogenicity:

- The proportion of BAb- and NAb-positive subjects

The categorical data will be processed using the frequency tables, exact Fisher's test, χ^2 test, and Cochran-Mantel-Haenszel test. The categorical data will be described using percentages or proportions.

Statistical methods will be chosen based on the type and distribution of raw data. Applicability of certain statistical tests will be evaluated after all the data are collected because it is impossible to predict the distribution pattern, data homogeneity and other data characteristics in advance.

9.3. Justification of sample size, including reasoning or calculations to justify statistical power and clinical justification of the study

The study is to test the hypothesis that the test drug BCD-148 and the reference drug Soliris® have equivalent pharmacokinetics. The equivalence hypothesis will be tested for the primary PK endpoint – $AUC_{(0-\infty)}$ of eculizumab after a single IV infusion of BCD-148/Soliris®. BCD-148 will be proved equivalent to Soliris® if the limits of the two-sided 95% CI for the ratio of the geometric means of eculizumab $AUC_{(0-\infty)}$ values after a single IV infusion of BCD-148 and Soliris® fall within 80.00-125.00%.

The sample size sufficient for testing the equivalence of eculizumab $AUC_{(0-\infty)}$ was calculated. [redacted]

[38]http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000791/WC500054212.pdf
[39]https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125166s0000_ClinPharmR.pdf (table 1, page 10)

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[40] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125166s0000_ClinPharmR.pdf
[41] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125166s0000_ClinPharmR.pdf

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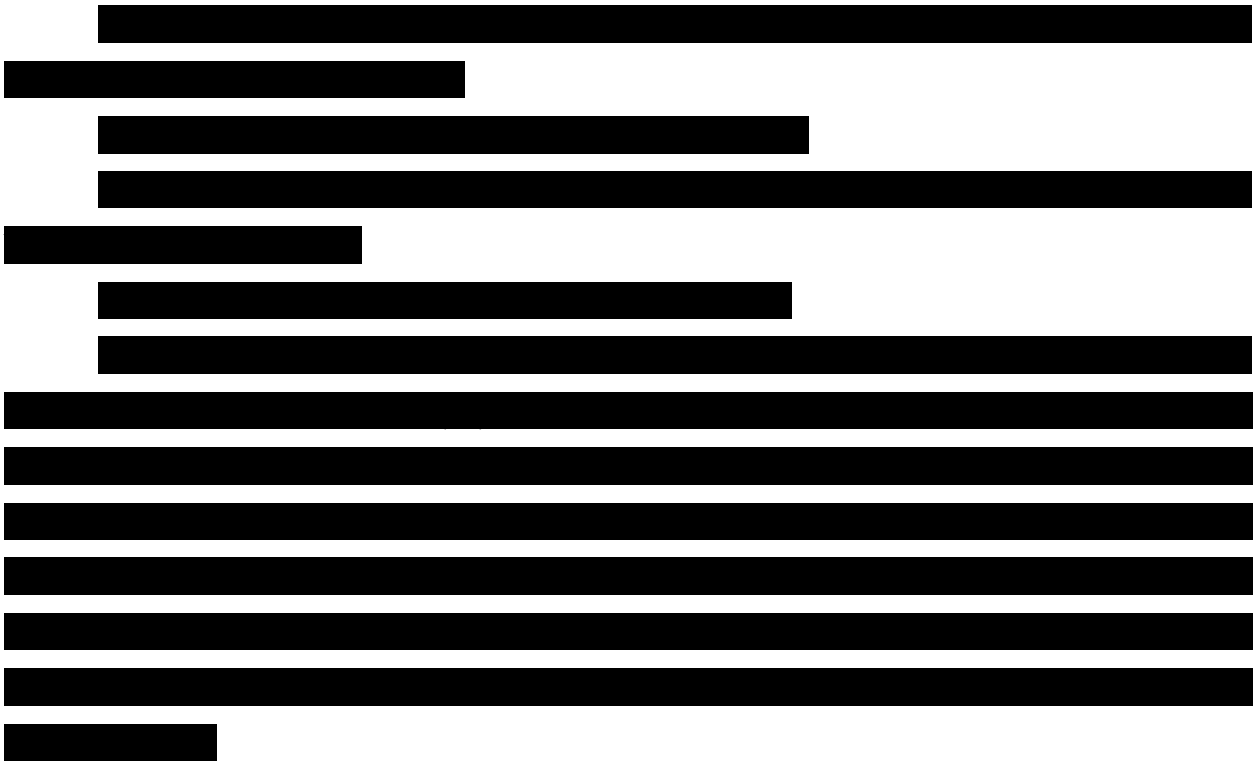

9.4. Statistical analysis steps and timelines for reports

Clinical study results will be analyzed after all protocol-specified data of the last study subject have been received (i.e. after all subjects have completed the trial).

9.5. Study termination criteria

[redacted]

[redacted]

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution involved in the study must ensure direct access to source data/documents by the monitor, the auditor, the LEC/IRB or regulatory authorities.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Data quality assurance

According to the National Standard "Good Clinical Practice", ICH GCP, and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory authorities, or LEC/IRB may perform audits/inspections to assure the quality of the study. Audits/inspections can be performed at any time during the study or after its completion. The investigator must give the auditor/inspector direct access to all study documents (including source documents) and discuss (personally, or designate someone from the study team) the audit/inspection results and other matters with the auditor/inspector.

11.2. Investigator adherence to the Protocol

Before beginning the study, the investigator must read and accept all provisions of this Protocol. The investigator must conduct the study in accordance with this Protocol, the current law of the Russian Federation, Federal Law #61-FZ of April 12, 2012: *On the Circulation of*

Medicines; National Standard of the Russian Federation GOST R 52379-2005 *Good Clinical Practice*; the rules of Good Clinical Practice of the Eurasian Economic Union; the Constitution of the Russian Federation; Federal Law #323-FZ of November 21, 2011: *On Public Health Protection in the Russian Federation*; the WMA Declaration of Helsinki (Fortaleza 2013), Order #200n of April 01, 2016 *On Approval of the Good Clinical Practice*; the GCP principles, and the applicable regulations.

No protocol deviations are allowed during the study without a previous written approval from JSC BIOCAD, the Ministry of Healthcare of the Russian Federation and Local Ethics Committees, except for the cases when the deviation is necessary to protect a subject from an immediate hazard.

The investigator should have enough time to accurately perform and complete the study within the timeframes specified by JSC BIOCAD, enough employees of appropriate qualification, and adequate equipment to conduct the study according to the Protocol.

Each sub-investigator participating in the study must read the Protocol and be aware of his/her responsibilities/functions in the study. If the principal investigator delegates some of his/her functions to sub-investigators, this must be documented in a relevant section of the Investigator's File.

11.3. Investigator responsibility to comply with the Protocol

If the investigator decides to withdraw a subject from the study, he/she must notify the responsible Clinical Trial Manager (CTM) or CRA at JSC BIOCAD via e-mail within 48 h after making this decision. The e-mail should contain the Subject ID, reason and date of withdrawal from the study. The fact of withdrawal must be captured in the eCRF.

If the subject missed the scheduled visit, or if any study drug dose modification was revealed other than those allowed by the Protocol, the investigator must notify the responsible CTM or CRA at JSC BIOCAD via e-mail within 24h of event discovery. The event must be captured in the eCRF.

If the investigator fails to follow these procedures or if multiple Protocol violations occur, JSC BIOCAD may suspend or terminate the study at this particular study site.

11.4. Study monitoring

Before the study start(during the Study Initiation Visit or Investigators' Meeting), a CRA/CTM of JSC BIOCAD or an authorized CRO will explain the Protocol, IB, eCRF, and other

study documentation to the investigators and members of the study teams. The CRA will periodically come to the study site during the study to check that the rights and wellbeing of the study subjects are being protected, the data submitted are valid, complete, and supported by appropriate source documents, and that the study is being conducted according to the current approved Protocol version/amendment, GCP, and regulations. During these visits, key members of the study team should be available to assist the CRA and resolve arising issues (if any).

Study monitoring is performed according to appropriate SOPs of JSC BIOCAD.

For each study subject, the investigator should keep source documents containing the subject data and records made during visits (medical records of the study center), including demographics, medical information, laboratory findings, ECG, and all other tests or examinations. Any information contained in the eCRF should be also recorded in the subject's source documents. The investigator must keep the original ICF. A copy of the signed ICF will be given to the subject.

The investigator has to provide the CRA with all relevant subject source documents to confirm that data in the source documents is consistent with the data in the eCRF. The investigator should ensure the timely completeness of the eCRFs before the CRA's visit.

To confirm the conformance of the study to the Declaration of Helsinki, Russian National Standard *Good Clinical Practice*, ICH GCP, regulatory requirements, and the Study Protocol, as well as the authenticity, accuracy, and completeness of data, the CTM will check the eCRFs and other study-related documents by verifying raw data.

Upon the study completion, a BIOCAD representative (CTM/CRA) should visit the study site to perform the study closeout visit. During this visit, the Sponsor's representative will collect all necessary documentation in accordance with the SOP of JSC BIOCAD.

11.5. Data management and quality control

In the trials that involve eCRFs, JSC BIOCAD employees (or employees of an authorized CRO) will check the data entered by the study team members for accuracy and completeness. If there are any inconsistent or missing data points, queries will be generated with a request for clarification. All queries are sent to the study site. A designated member of the study team must immediately answer the request and make all required changes to the database.

At the end of the study, any protocol deviations will be determined. After all these actions have been taken and the completeness and accuracy of study data have been verified, the database is locked.

11.6. Study termination

JSC BIOCAD can suspend or terminate the study due to safety or ethical issues, Protocol compliance issues, or due to other reasons. If JSC BIOCAD suspends or terminates the study, the study site will be notified in advance. In case of suspension or termination, JSC BIOCAD and the investigator have to inform Ethics Committees and regulatory authorities in due time. If the study is suspended or terminated, all study information must be transferred to and all unused investigational product must be returned to JSC BIOCAD.

12. ETHICS

12.1. Ethical aspects of the study

This clinical study will be conducted in accordance with the ethical principles laid out in the WMA Declaration of Helsinki (Fortaleza 2013); Federal Law #61-FZ of April 12, 2012: *On the Circulation of Medicines*; Order #200n of April 01, 2016 *On Approval of the Good Clinical Practice*; National Standard of the Russian Federation GOST R 52379-2005 *Good Clinical Practice*; the rules of Good Clinical Practice of the Eurasian Economic Union; the Constitution of the Russian Federation; Federal Law #323-FZ of November 21, 2011: *On Public Health Protection in the Russian Federation*; the GCP principles, and the applicable regulations.

The final version of the Protocol, including the Subject Information Sheet with the Informed Consent Form, will be submitted to regulatory authorities and local ethics committees for approval before the study start.

All subsequent protocol amendments (other than administrative amendments) must be approved before implementation.

Informed consent must be obtained from the subject before any study procedures are initiated. The Subject Information Sheet contains all the information that a subject may need to make a conscious and independent decision about whether to participate.

During the study, all cases of SAEs will be reported to JSC BIOCAD within 24 hours. JSC BIOCAD will analyze the reports and may suspend the study if considered necessary. Local Ethics Committees will also be notified of all SAEs that are related, in the investigator's opinion, to the investigational product.

All subject personal information is confidential and can be disclosed only if required by law (including court decisions).

All study subjects will be insured. If a subject gets injured directly due to the investigational product, the Sponsor will cover all reasonably justified treatment expenses.

12.2. Confidentiality of study subjects

The investigator should keep confidentiality concerning subjects' identity, the text of this Protocol, and all other study materials and results.

[redacted]

13. DATA HANDLING AND RECORD KEEPING

13.1. Record keeping at the study site

All study documents must be archived at the study site or at the central archive of the institution. A list of all study subject identifiers should be made.

According to the ICH GCP, essential documents include: signed Protocol and amendments; signed ICFs for all subjects; medical records and other source documents; approvals from LECs and regulatory authorities and all correspondence including approved documents; drug accountability records; study correspondence; and the list of subject names and addresses. These are the essential documents that must be kept in the Investigator's File.

The investigator must keep all the essential documents over a period of time specified by applicable regulations.

By the end of this period, the Sponsor will inform the investigator(s) about the date when the documents may be destroyed.

Study subject documentation will be archived in accordance with the site in-house SOPs.

The investigator must inform the Sponsor about the place where essential documents are stored and request an approval from JSC BIOCAD before destroying any of the essential documents. Appropriate measures must be taken to prevent the accidental or premature destruction of these documents.

13.2. Confidentiality of data

All information about study subjects will be kept confidential. The information will be processed in compliance with all applicable laws and regulations. These regulations require informing study subjects and obtaining their written authorization regarding the following: questions:

- What protected health information will be collected in this study?
- Who will have access to this information and on what grounds?
- Who will use or disclose this information?
- Do study subjects have the right to recall their consent for using their confidential health information?

According to the current regulations, if the subject recalls his/her authorization to collect or use his/her protected health information, the investigator still can use all information obtained before the authorization was withdrawn. If the subject recalls authorization to collect or use his/her protected health information, the investigator should do as much as possible to get subject's permission for collecting at least the safety information (i.e. onset of new or aggravation of existing adverse events) until the scheduled end of the study period.

To prevent unauthorized access to protected subject information, the data management system uses integrated safety elements encrypting all the data when sending them in both directions. The access to the system will be controlled with a sequence of individually assigned identification codes and user passwords. These codes and passwords will be given only to authorized members of the study team who have received a special training.

13.3. Collection of data

[redacted]

14. FINANCE AND INSURANCE

[redacted]

15.0. PUBLICATIONS

After completion of the study, its results will be summarized and prepared for publication. The investigator must not publish any study results, including those obtained at his/her study site, without a permission from JSC BIOCAD. Results from individual study sites must not be published before the publication of the overall study results.