BIOCAD
Biotechnology Company

Attn.: CEO "SMA Europe"
Nicole Gusset Im Moos, 4
Freiburg im Breisgau, 79112
Germany

Dear SMA Community,

In response to your request to the developer of the investigational gene therapy product ANB-004 (investigational product, test drug ANB-004) for the treatment of spinal muscular atrophy (SMA), we would like to inform you of the following.

How does the investigational product work?

In patients with SMA, mutations in the Survival of Motor Neuron 1 (*SMN1*) gene lead to impaired gene expression and either the absence or significantly reduced amount of the functional SMN protein. The SMN protein is found in almost all cells of the human body, with the motor neurons being most sensitive to its low or absent expression. As a result of an insufficient amount of the SMN protein, gene expression errors rapidly accumulate in the motor neurons, which results in quick death of these cells. Dead neurons are incapable of sending signals to the muscle tissues, which leads to their progressive degradation[1].

The mechanism of action of the investigational product ANB-004 consists in restoration of the *SMN1* expression in different body tissues (including motor neurons) since the key abnormalities are related to death of this cell type. Thus, motor neurons are the target cells for this replacement gene therapy. The investigational product ANB-004 is a vector carrying the functional *SMN1* gene. The SMN protein encoded by this gene is expected to produce a direct therapeutic effect in the patient's body by restoring the insufficient endogenous SMN protein and protecting the motor neurons from death. The investigational product ANB-004 under development is expected to maintain long-term or even lifelong effect by completely restoring the gene function.

Why is the recombinant adeno-associated virus (rAAV) used?

The recombinant adeno-associated viral vector (rAAV) is used as a delivery tool for the *SMN1* gene in investigational product ANB-004. Adeno-associated virus-based (AAV-based) vectors are small virus-like particles consisting of a protein capsid that can efficiently deliver a single-stranded DNA molecule, which has special structural elements to ensure long-term expression of viral genes inside the cell, to the patient's cells. Therapeutic rAAV-based vectors differ from natural viruses in that their genome completely lacks the genes responsible for the viral life cycle. The rAAV-based vectors are capable of delivering the target transgene into cells, but they cannot replicate or cause a disease.

[1] *Jablonka, S., Hennlein, L. & Sendtner, M. Therapy development for spinal muscular atrophy: perspectives for muscular dystrophies and neurodegenerative disorders. Neurol. Res. Pract. 4, 2 (2022). https://doi.org/10.1186/s42466-021-00162-9*

biocad.ru

JSC BIOCAD
Intracity Municipality the Settlement of Strelna,
the Settlement of Strelna, ul. Svyazi, d. 38,
str. 1, pomeshch. 89

biocad@biocad.ru
Tel.: +7 812 380 49 33
Fax: +7 812 380 49 34

Moreover, the viral genome does not integrate into the patient's cell genome and stays in the nucleus as extrachromosomal DNA called an episome[2].

What are the method of administration and dosage form of the drug?

The drug is administered by an intravenous infusion.

This is pathogenesis-based therapy. A single dose of ANB-004 is expected to be sufficient. Gene therapy products are intended for single-dose administration, therefore, the investigational product will not be administered repeatedly. In addition, it will not be used in patients who have received Zolgensma®.

What are potential side effects?

The overall safety profile of ANB-004 is expected to be good; however, its use may be accompanied by some adverse events that are typical of AAV9-based gene therapy products (including those used for the treatment of SMA). The patients included in the clinical study will be followed up for 60 months after a single infusion of ANB-004.

What is special about the drug under development?

The investigational product ANB-004 is optimized so as to ensure the best efficacy and safety ratio. A potent universal promoter is used in ANB-004. Provided that the *SMN1* gene is successfully delivered to the cell, its expression is expected to be high and long-term. The *SMN1* gene sequence has been modified to enhance its expression and to increase the effectiveness of viral particle assembly. This approach is called codon optimization and is based on the efficient selection of triplets in the DNA sequence responsible for encoding the same amino acid. This approach allows changing the DNA sequence significantly without changing the amino acid sequence of the encoded protein.

The delivery tool for the therapeutic nucleotide sequence of the *SMN1* gene has also been improved compared to naturally occurring adeno-associated virus serotype 9 (AAV9). The recombinant vector was obtained by modifying the AAV9 capsid with a series of unique mutations. The altered serotype has a potentially improved biodistribution profile, that is, better ability to deliver genetic information to the cells of different body tissues. It is expected to reach the brain and spinal cord tissues as effectively as the naturally occurring AAV9. However, the modified vector should potentially be less active in the tissues of non-target organs: heart, lung, liver, and others, thereby reducing the risk of side effects.

At what stage of development is the product currently?

The research of the investigational product ANB-004 started at the beginning of 2018, and the first animal experiments to evaluate the efficacy of the product started in 2019. By the middle of 2019, the first prototype of the product was obtained, which was later improved.

[2] *Wang, D., Tai, P.W.L. & Gao, G. Adeno-associated virus vector as a platform for gene therapy delivery Nat Rev Drug Discov 18, 358–378 (2019). https://doi.org/10.1038/s41573-019-0012-9*

JSC BIOCAD
Intracity Municipality the Settlement of Strelna,
the Settlement of Strelna, ul. Svyazi, d. 38,
str. 1, pomeshch. 89

biocad@biocad.ru
Tel.: +7 812 380 49 33
Fax: +7 812 380 49 34

BIOCAD
Biotechnology Company

By now, the preclinical development phase is completed, and the development has transitioned to clinical trials in SMA patients. Currently, this clinical study is actively recruiting patients, and there is first experience with the product administration.

What are the results of animal studies?

The non-clinical studies evaluated the specific activity, biodistribution and safety of the product. The specific activity Cliassessment was conducted in SMN knock-out mice, which simulated SMA type 1. The results demonstrated a significant increase in the survival of animals treated with the investigational product ANB-004 compared to placebo-treated animals. The biodistribution studies showed the presence of the human SMN1 protein in the target organs (nervous system cells) of the experimental animals following the administration of ANB-004. The safety assessment was conducted in non-human primates (cynomolgus monkeys) under one year of age. The results of potency, safety and biodistribution studies were used to determine the first-in-human dose.

What is the overall study design?

On August 11, 2022, a clinical trial authorization was issued for the clinical study ANB-004-1/BLUEBELL "An Open-Label, Non-Comparative Clinical Study of the Safety and Efficacy of an Adeno-Associated Viral Vector Carrying the SMN Gene (ANB-004 (JSC BIOCAD, Russia)) After a Single Intravenous Administration of Escalating Doses in Children With Spinal Muscular Atrophy" (CS, clinical study) by the Ministry of Health of the Russian Federation (clinical trial authorization (https://grls.rosminzdrav.ru/CIPermissionMini.aspx?CIStatementGUID=4c084663-f537-432e-99e6-5b0d29b9f7b6&CIPermGUID=42D3B096-775A-41DB-868B-980219737B67). This clinical trial is currently recruiting patients. This clinical study is carried out in accordance with all local regulatory requirements and international standards and is designed to evaluate the safety, immunogenicity and efficacy of ANB-004 in pediatric patients with SMA type 1.

Clinical study is taking a part in in study centers in Moscow, St. Petersburg and Yekaterinburg (the full list of healthcare institutions is provided below). The study doctor will explain in detail to the legal representative of the child participating in this clinical study in which cases such trips may be required and the procedure for ordering transportation and accommodation services. When transportation and/or accommodation services are ordered, the Sponsor will not receive data or information that can identify the child participating in this clinical study.

The duration of the study for a patient will be 5 years.

The study will include pediatric patients with SMA who meet the eligibility criteria (the full list of criteria is provided below).

What will be considered a positive outcome?

The pathogenesis-based therapy aimed at increasing the level of the SMN protein can potentially change the course of the disease and prevent the death of pediatric patients with SMA type 1 in their early childhood.

ANB-004 is an adeno-associated virus vector-based gene therapy product designed to deliver a copy of the gene encoding the human SMN protein. It is assumed that a single dose of the investigational product ANB-004 will result in the cell transduction of the SMN gene and its expression followed by restoring the deficiency of this protein in pediatric patients with SMA type 1 and, therefore, changing the disease phenotype by increasing the survival and quality of life of these patients.

BIOCAD
Biotechnology Company

How will the safety and efficacy of the product be evaluated?

The efficacy of ANB-004 will be assessed in the clinical study using motor development and neurological development scales.

The safety of ANB-004 will be assessed based on the analysis of reported adverse events. Throughout the clinical study, the clinical condition of the study participants will be monitored, and laboratory tests and investigations will be performed.

What are the inclusion and exclusion criteria for the study?

Pediatric patients from the Russian Federation and other countries who meet the eligibility criteria are participating in this clinical trial.

Key inclusion criteria:

- The diagnosis of 5q SMA established clinically and confirmed by molecular genetic testing (a homozygous exon 7 deletion in the SMN1 gene, or a heterozygous exon 7 deletion + confirmed point mutation in the SMN1 gene), presence of two copies of the SMN2 gene and the age of the disease onset (manifestations of the first symptoms of the disease) <180 days (6 months).
- Age <240 days (8 months).

Key exclusion criteria:

- An anti-AAV9 antibody titer (a test for anti-adeno-associated virus serotype 9 antibodies) >1:50 in a potential participant.
- The need for respiratory support ≥16 hours a day or the use of a tracheostomy tube .
- A history of therapy (or planned therapy within 12 months after the investigational product administration) with nusinersen, risdiplam, branaplam, onasemnogene abeparvovec, or other antisense oligonucleotides/selective SMN2 splicing modifiers, or gene therapy products for the SMN1 gene transduction, or other AAV-based (any serotype) gene therapy products.
- The need for use of any medicinal products for the treatment of myopathy or neuropathy, diabetes medications, ongoing immunosuppressive therapy after the start of the study (e.g. glucocorticoids [except for medicines specified by the clinical study protocol], cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab, etc.).
- Other concomitant disorders or conditions that may affect the safety of ANB-004 or make it impossible to carry out all the necessary study procedures.
- Simultaneous participation of the subject in other clinical trials or previous participation in another clinical trial using experimental therapy.

The study doctor tells the child's legal representative about other eligibility criteria and contraindications for participation in this clinical trial.
At the moment, the clinical study protocol does not provide for the inclusion of patients of another age or SMA type and no other clinical trial is planned yet for patients of another age or SMA type.

Please note that the recruitment of patients inclinical trial is carried out in a study center according to the following procedure: a study doctor from an approved study center based on the results of screening tests doctor decides if the patient is eligible for the participation in this study. Clinical study is taking a part in the study centers in Moscow, St. Petersburg, and Yekaterinburg listed below.

biocad.ru

JSC BIOCAD
Intracity Municipality the Settlement of Strelna,
the Settlement of Strelna, ul. Svyazi, d. 38,
str. 1, pomeshch. 89

biocad@biocad.ru
Tel.: +7 812 380 49 33
Fax: +7 812 380 49 34

BIOCAD
Biotechnology Company

Study center	Address
Federal State Autonomous Educational Institution of Higher Education "Pirogov Russian National Research Medical University" of the Ministry of Health of the Russian Federation, a separate division "Veltischev Research and Clinical Institute for Pediatrics", Department of Psychoneurology and Epileptology; 2 Taldomskaya Street, Moscow 125412.	2 Taldomskaya Street, Moscow 125412.
Federal State Autonomous Educational Institution of Higher Education "Pirogov Russian National Research Medical University" of the Ministry of Health of the Russian Federation, a separate division "Russian Children's Clinical Hospital"; 117 Leninsky pr., Moscow 119571	1 Ostrovityanova Street, Moscow 117997
Federal State Budgetary Educational Institution of Higher Education St. Petersburg State Pediatric Medical University, Ministry of Health of the Russian Federation	2, Litovskaya Street, St. Petersburg 194100
Federal State Autonomous Institution "National Medical Research Center for Children's Health" of the Ministry of Health of the Russian Federation	2 Lomonosovsky pr., str. 1, Moscow 119991
State Autonomous Healthcare Institution of Sverdlovsk Region "Regional Pediatric Clinical Hospital"	32, Serafimy Deryabinoy Street, Yekaterinburg, 620149
Federal State Budgetary Institution "Almazov National Medical Research Center" of the Ministry of Health of the Russian Federation	2, Akkuratova Street, St. Petersburg 197341

To obtain the updated information about the clinical study ANB-004-1/BLUEBELL "An Open-Label, Non-Comparative Clinical Study of the Safety and Efficacy of an Adeno-Associated Viral Vector Carrying the SMN Gene (ANB-004 (JSC BIOCAD, Russia)) After a Single Intravenous Administration of Escalating Doses in Children With Spinal Muscular Atrophy", visit the website https://ct.biocad.ru/en/nozology/anb-004-1bluebell or call the hotline 8-800-511-00-37.

Sincerely,
Vice President Clinical Research&Development
Yuliya Nikolaevna Linkova

biocad.ru

JSC BIOCAD
Intracity Municipality the Settlement of Strelna,
the Settlement of Strelna, ul. Svyazi, d. 38,
str. 1, pomeshch. 89

biocad@biocad.ru
Tel.: +7 812 380 49 33
Fax: +7 812 380 49 34