June 27 2024

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Regarding Reports on "AKUUGO Suspension for Intracranial Implantation"

SanBio Co., Ltd. hereby provides on this matter as per the attached document.

June 27, 2024
SanBio Co., Ltd.

Regarding Reports on "AKUUGO® Suspension for Intracranial Implantation"

Following the June 19, 2024, yesterday, meeting of the Pharmaceutical Affairs and Food Sanitation Council's Subcommittee on Regenerative Medicine Products and Biologically Derived Technology, various reports have been published regarding the conditional and time-limited manufacturing and marketing approval for "AKUUGO® suspension for intracranial implantation." Below, we outline our views on this matter.

The approval conditions stipulated in the press release materials (see attached) distributed by the Ministry of Health, Labour and Welfare to the media last night are as follows.

1. Considering the limited manufacturing record for the Product, the Company shall promptly collect information on the Product's quality based on a pre-determined plan, and evaluate and report on the equivalence/homogeneity, in terms of quality, of the investigational product (clinical trials product) and the Product intended for commercial distribution. Based on the evaluation results, the Company shall apply for a partial change of approved matters. It shall not ship the Product until the partial change application has been approved.
2. The Company must ensure that the Product is used in medical facilities fully equipped to handle emergencies, by physicians who possess sufficient knowledge and experience in the diagnosis and treatment of traumatic brain injury and stereotactic brain surgery techniques. The physicians must also have sufficient knowledge of the clinical trial results and adverse events of the Product.
3. Until the Company re-applies for marketing approval for the Product prior to the expiration of the conditional and time-limited approval, the Company must conduct post-marketing evaluation of all cases where the Product is used.
4. Until the Company re-applies for marketing approval for the Product prior to the expiration of the conditional and time-limited approval, the Company must collect information on the biological characteristics reflecting the mechanisms of action of the Product and take necessary measures, such as improving its quality control strategy.

There are four conditions to the approval, the first of which relates to shipment. The remaining three are conditions for obtaining full approval after shipment. Below is an explanation of our plans in each respect.

In order to meet the condition for shipment, the Company will promptly run two or so rounds of commercial production to accumulate inventories in preparation for launch, gauging the product's equivalence and homogeneity during this process. The Company expects that this condition will be met, and shipments will become possible, in the first quarter of the following fiscal year (first quarter of the fiscal year ending January 31, 2026).
In order to obtain full approval, we plan to conduct post-marketing surveillance trials during

the seven-year manufacturing and marketing approval period.
Note that the Company has no plans to conduct a clinical trial to meet the condition for shipment, as some reports have stated.

For more information, contact:
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Press release materials*

* Issued by the Ministry of Health, Labour and Welfare on June 19, 2024

Press release material: Overview of planned product

Generic name	Vandefitemcel
Trade name	AKUUGO suspension for intracranial implantation
Applicant name	SanBio Co., Ltd.
Product overview	The product is a combination product. The main component is a human (allogeneic) cell agent (SB623) for intracranial transplantation. It is produced by transiently transfecting a plasmid vector encoding the human Notch-1 intracellular domain gene into mesenchymal stem cells isolated and expanded by culturing bone marrow fluid collected from a donor (healthy adult). The secondary components are a dedicated preparation solution used to prepare the cell suspension for transplantation, and a dedicated administration device set. The cytokines secreted from the product are expected to have a restorative effect on damaged nerve cells by inducing proliferation and differentiation of endogenous neural stem cells and promoting angiogenesis and immune regulation.
Efficacy, effects, and performance	Improving chronic motor deficit resulting from traumatic brain injury
Dosage and administration	Typically, for adults, a cell preparation containing 5 x 10^6 live cells (300 µL) of human (allogeneic) bone marrow-derived mesenchymal stem cells is transplanted into the periphery of the damaged tissue by stereotactic neurosurgery using the dedicated administration device. Three transplantation routes are formed through one small hole in the skull to the periphery of the injury, and 100 µL of cell suspension is injected per transplantation route into five sites at 5-6 mm intervals from the deepest part, in the amount of 20 µL per site. The injection rate is approximately 10 µL/min. The following steps must be taken at the time of transplantation. - Before the surgery begins, the guide & stop and stylet inserts of the dedicated administration device must be attached to the stereotactic neurosurgery head frame. - The cell agent for intracranial transplantation must be thawed and washed with a special solution, then suspended in a buffer to achieve a transplantation concentration of 1.67 x 10^6 cells/100 µL. Another special solution is used to clean the dedicated administration device's micro syringe attached with injector cannula, which is then loaded with the cell suspension.
Eligibility for conditional and time-limited approval	Eligible
Overview of efficacy assessment	Global Phase II clinical trial (TBI-01 study: the U.S., Japan, Ukraine). Multicenter, sham-operated, randomized, double-blind, and controlled study, in which subjects were randomized to SB623 cell treatment or sham surgery in a 3:1 ratio, with the SB623 treatment group further randomized in a 1:1:1 ratio to receive 2.5 × 10^6, 5.0 × 10^6, or 10.0 × 10^6 SB623 cells. Study results: <Efficacy> Change from baseline in Fugl-Meyer Motor Scale (FMMS) score at 24 weeks, the primary endpoint, was 8.3 ± 10.6 in the SB623 pooled group, and 2.3 ± 4.7 in the sham surgery group, demonstrating a statistically significant difference (mean ± standard deviation, p = 0.0401)
Overview of plan for post-marketing	The following post-marketing surveillance trial will be conducted on all patients receiving this product to evaluate the conditions for approval. ・Post-marketing surveillance trial: Verification of the product's efficacy in patients with

evaluation	chronic motor deficit due to TBI. A control group will be set up in which the device is not implanted and only rehabilitation is performed, and results will be compared with those of the device implantation group. ・Treatment outcome study: Verification of the product's safety and effectiveness in actual medical practice. Approval: Seven years

Reference	[Approval conditions] 1. Considering the limited manufacturing record for the Product, the Company shall promptly collect information on the Product's quality based on a pre-determined plan, and evaluate and report on the equivalence/homogeneity, in terms of quality, of the investigational product (clinical trials product) and the Product intended for commercial distribution. Based on the evaluation results, the Company shall apply for a partial change of approved matters. It shall not ship the Product until the partial change application has been approved. 2. The Company must ensure that the Product is used in medical facilities fully equipped to handle emergencies, by physicians who possess sufficient knowledge and experience in the diagnosis and treatment of traumatic brain injury and stereotactic brain surgery techniques. The physicians must also have sufficient knowledge of the clinical trial results and adverse events of the Product. 3. Until the Company re-applies for marketing approval for the Product prior to the expiration of the conditional and time-limited approval, the Company must conduct post-marketing evaluation of all cases where the Product is used. 4. Until the Company re-applies for marketing approval for the Product prior to the expiration of the conditional and time-limited approval, the Company must collect information on the biological characteristics reflecting the mechanisms of action of the Product and take necessary measures, such as improving its quality control strategy. [Designation-related details] Received Sakigake designation as a regenerative medicine product on April 8, 2019 (Sakigake H30;2) Received orphan regenerative medicine products designation on June 23, 2020 (R2;19) [Overseas approval status] Not approved overseas. [Matters to be addressed prior to product shipment] Evaluation of equivalence/homogeneity between this product and the investigational product (used in the TBI-01 study) [Attachment] Attached document (draft)