Better Health, Brighter Future

Date: 29-May-2024

EU Trial Number:	2024-511998-30-00
Protocol code:	TAK-861-3002
Protocol title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-861 for the Treatment of Narcolepsy with Cataplexy (Narcolepsy Type 1)
Sponsor:	Takeda Development Center Americas, Inc.
Subject:	Request for Authorization of an Initial Clinical Trial Application under Regulation (EU) No 536/2014

Dear Madam, Dear Sir,

Takeda Development Center Americas, Inc. as sponsor of the above clinical trial, hereby submits a request for Clinical Trial Authorisation.

The documents in this submission have been prepared in accordance with the European Union Regulation No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

Clinical Technology Centre (Ireland) Limited, with its registered office at Building C1, Athlone Business and Technology Park, Garrycastle, Athlone, County Westmeath N37 TE84 Ireland will act as the Sponsor's Legal Representative in the EU.

Study details

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, 12-week, parallel-group study to evaluate the efficacy and safety of TAK-861, an orexin type-2 receptor agonist, in the treatment of Narcolepsy with cataplexy (Narcolepsy Type I).

Narcolepsy Type I has been defined by the International Classification of Sleep Disorders, 3rd Edition (ICSD-3) criteria as having low levels of orexin (OX) in the cerebrospinal fluid (CSF), most likely due to a selective loss of hypothalamic OX-producing neurons. An OX type-2 receptor (OX2R) agonist is the first approach to directly address the loss of OX peptide in the

brain as it may restore OX2R signalling at the postsynaptic receptors and may be more effective than current therapies in treating the entire Narcolepsy Type I pentad, especially Excessive Daytime Sleepiness (EDS) and cataplexy.

This is a Phase 3 clinical trial, aiming to recruit 93 subjects with Narcolepsy with cataplexy (Narcolepsy Type I) and is planned to be conducted in 11 EU/EEA countries Austria, Belgium, Czech Republic, Denmark, Finland, France, Hungary, Italy, Poland, Spain and Sweden, as well as in Australia, China and South Korea.

Target population

The target trial population in EU/EAA countries is male and female subjects aged 18 to 70 years with narcolepsy with cataplexy (Narcolepsy Type I). Female subjects of non-childbearing potential and female subjects of childbearing potential using contraceptives will be eligible to be included in the study.

The target trial population does not include vulnerable subjects (subjects unable to give informed consent and pregnant or breastfeeding women). The trial population does not include minors in EU/EAA countries.

Orphan Status:

The sponsor has obtained an orphan designation for the investigational medicinal product TAK861 for the treatment of narcolepsy (EU/3/23/2851). A description of the indication may be found in the clinical trial protocol section 2.2 Background.

Scientific Advice:

No scientific advice from EMA or regulatory authorities in EU was received to date. EMA scientific advice procedure for TAK-861 clinical development is currently ongoing.

Scientific advice relating to the TAK-861-3001 clinical trial has been given by the Food and Drug Administration (FDA). Due to close similarity of TAK-861-3001 study design, the advice is considered applicable to TAK-861-3002 study. The FDA scientific advice document is included within this application.

Paediatric Investigation Plan:

The clinical trial is not part of a Paediatric Investigation Plan (PIP) per Title II, Chapter 3, of Regulation (EC) No 1901/2006.

The EU PIP was submitted on 14 December 2023 and is undergoing assessment by the PDCO. TAK-861-3002 is not part of the proposed PIP key elements.

Investigational Medicinal Product:

The following Investigational Medicinal Product (IMP) is included in the clinical trial:

Product name	*Regulatory status*	*Reference Safety Information*	*Additional information*
TAK-861	Investigational product – no marketing authorisation	Investigator's Brochure edition 5 dated March 8th, 2024 (section 6.4.1. Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions)	Not applicable

There is no Auxiliary Medicinal Products (AxMP) included in the clinical trial.

The TAK-861 dosage is considered Commercially Confidential Information by the Sponsor for this study. The dosage chosen for this study has not been disclosed publicly. The Sponsor considers this information must be redacted to protect its legitimate economic interest and competitive position.

There is no in vitro diagnostic (IVD) or medical device (MD) being investigated in this clinical trial to achieve the objectives of the clinical trial.

Labels

Labels for IMPs do not include the Sponsor phone number as this is included on the patient card which is given to patients at the first study visit after consent is signed. The patient card will list only the protocol number that applies to the patient. Patient cards will not be submitted as they are not required per Regulation (EU) No 536/2014.

Patient cards are distributed to each participant before the start of the clinical trial and the participants are instructed to keep the patient card in their possession at all times. Each country patient card will contain both a country telephone number and an international back-up number that can also be used in case of emergency, as shown in the table below:

Country	Country Phone Number	International Back Up number
Austria	43 72 088 35 82	44 122 358 15 04
Belgium	02 401 91 82	44 122 545 84 11
Czech Republic	42 022 888 07 50	44 122 358 15 31
Denmark	45 78 79 54 93	44 124 263 90 77
France	33 17 670 10 47	44 124 589 89 29
Finland	35 897 479 03 91	44 203 538 66 34
Hungary	36 18 48 06 87	44 113 209 30 06
Italy	06 88 750 39 84	44 174 964 92 45
Poland	02 23 07 50 26	44 122 358 12 49
Sweden	46 850 61 96 77	44 147 758 69 29
Spain	91 414 66 16	44 268 500 09 56

Patient-Facing material

The patient facing materials are provided in paper format. During the conduct of the trial, electronic format will be used for patient facing materials. The text between the paper and the electronic formats is identical. To ease the review, all patient facing materials were combined in a single file per language.

Additional Local Requirements

For any additional information according to Member State requirements, please see below:

Country	**Local requirement**
Czech Republic	See Cover Letter Czech Republic Appendix
Denmark	See Cover Letter Denmark Appendix
Italy	See Cover Letter Italy Appendix
Spain	See Cover Letter Spain Appendix

We trust that the above information and the submitted documents are sufficient to support the assessment of this clinical trial application. If you require further information, please do not hesitate to contact us.

Sincerely,

Takeda Development Center American Inc.

Takeda Development Center Americas Inc.

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