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Dossier GMO: B/BE/21/BVW3 (2019-003159-12): A Phase 1/2 Ascending Dose Study to Evaluate the Safety and Effects on Progranulin Levels of PR006A in Patients with Fronto-Temporal Dementia with Progranulin Mutations (FTD-GRN) (PROCLAIM)

Geachte mevrouw ,

Wij informeren u dat uw vergunningsaanvraag werd goedgekeurd.

De vergunning is conform het koninklijk besluit van 21 februari 2005 tot reglementering van de doelbewuste introductie in het leefmilieu evenals van het in de handel brengen van genetisch gemodificeerde organismen of van producten die er bevatten.
(http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&cn=2005022131&table_name=wet)

Uw vergunning wordt verleend op basis van het gunstig advies van de Adviesraad voor Bioveiligheid van 12 november 2021, onder de voorwaarden die in de conclusie van bovengenoemd advies zijn vermeld, namelijk:

"Based on the scientific assessment of the notification made by the Belgian expert, the Biosafety Advisory Council concludes that it is unlikely that PR006A developed as a gene therapy approach for the treatment of Fronto-Temporal Dementia with Progranulin mutations will have adverse effects on human health or on the environment in the context of the intended clinical trial provided that all the foreseen safety measures are followed as described in the following new or updated documents:

• IMP Handling Instructions for Study Staff Personnel – taking into account the additional text adaptations provided by the BAC
• Protocol Amendment Version 5.2 (Belgium), dated 07 October 2021
• Main ICF Belgium, v4.3.0 dated 28 September 2021 (ENG, DUT, FRE), taking into account the text adaptation provided by the BAC for Main ICF – French1
• Participating Partner ICF Belgium, v4.3.0 dated 28 September 2021 (ENG, DUT, FRE)

Therefore, the Biosafety Advisory Council issues a **positive advice with the following conditions**:

- The notifier and the investigators must strictly apply the clinical trial protocol version 5.2 (Belgium), and all the safety instructions as described in the dossier and the updated and new documents listed here above.

- Any protocol amendment has to be previously approved by the Competent Authority.

- The 'IMP Handling Instructions for study staff personal' technical sheets are improved by adding information related to the procedure for the management of accidental spills as mentioned in paragraph 5 of this advice. Furthermore, eye protection should be worn as a standard PPE while performing

manipulations that may create aerosols with highly concentrated rAAV and not solely in case of spills. Therefore, "(in case of spills)" reported near "Eye protection" in Personal protective equipment (PPE) section should be deleted. Finally, since eyes and wounds will not be washed with soap, in section "Management of inadvertent exposure to a gene therapy product", it is recommended to adapt the following sentence "the affected area should be washed with soap and water" as follows: "the affected area should be washed with soap and/or water for at least 15 min".

- The SNIF is improved by adding the additional timepoint at Day 7 for vector shedding monitoring.

- The notifier is responsible to verify that the study centre has qualified personnel experienced in handling infectious material and that the investigator has the required authorizations to perform the clinical trial activities inside the hospital (laboratory, pharmacy, hospital room, consultation room...) according to the Regional Decrees transposing Directive 2009/41/EC on Contained use of genetically modified micro-organisms.

- At the latest 15 days after the start of the trial, the notifier should provide, along with the delivery of the control sample, a detailed protocol for the method of conservation and analysis of the control sample.

- The Biosafety Advisory Council should be informed within two weeks when the first patient starts the treatment and the last patient receives the last treatment.

- At the latest six months after the last visit of the last patient included in the trial, the notifier must send to the competent authority at the attention of the Biosafety Advisory Council a report with details concerning the biosafety aspects of the project. This report shall at least contain:
  - The total number of patients included in the trial and the number of patients included in Belgium;
  - A report of the shedding data obtained from the clinical trial (monitoring of viral vector excretion/secretion in stool, urine and saliva at day 7, 14, month 1, 2, 3 and 6 compared to baseline)
  - A summary of all adverse events marked by the investigators as probably or definitely related to the study medication;
  - A report on the accidental releases, if any, of PR006A."

Hoogachtend,

Frank Vandenbroucke
Vice-eersteminister en
minister van Volksgezondheid
en Sociale Zaken

Zakia Khattabi
Minister van Klimaat,
Leefmilieu, Duurzame
Ontwikkeling en Green Deal