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Votre lettre du	Vos références	Nos références	Annexe(s)	Date
		AFMPS/DGPRE/R&D/[redacted]		28/06/2022

Dossier OGM : B/BE/21/BVW7 (2020-003902-30): Phase I open-label, dose escalation trial of BI 1831169 monotherapy and in combination with ezabenlimab in patients with advanced or metastatic solid tumors

[redacted]

Par la présente, nous vous informons que votre demande d'autorisation a été approuvée.

L'autorisation est conforme à l'arrêté royal du 21 février 2005 réglementant la dissémination volontaire dans l'environnement ainsi que la mise sur le marché d'organismes génétiquement modifiés ou de produits en contenant.
(http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=2005022131&table_name=loi)

Votre autorisation est accordée sur base de l'avis favorable du Conseil de Biosécurité daté du 3 juin 2022, aux conditions reprises dans la conclusion de cet avis, à savoir:

"Based on the scientific assessment of the notification made by the Belgian expert, the Biosafety Advisory Council concludes that it is unlikely that BI 1831169 developed as an oncolytic virotherapy 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 (and for some still to be adapted in accordance with the conditions stipulated below):

- *Part 1A_VSV-GP-CAF - to be updated in accordance with condition 1 here below*
- *Part 1B_Confidential_Annex_CAF (version 1.2, 17 May 2022)*
- *Technical Sheet for Site Staff (version 1.0, 07 Dec 2021)*
- *1456-0001 Study Participant Summary Sheet (version 12, May 2022)*
- *ICF-Main-M_03_BEL01 (version 03, 16 Nov 2021) and Protocol (version 2.0, 09 Nov 2021) – to be updated in accordance with condition 2 here below*

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

1- According to the Belgian classification and the Canadian Pathogen Safety Data Sheet, the Indiana Vesicular Stomatitis virus corresponds to a risk group 2 for human pathogens. It is therefore not correct to claim that "VSV is not considered a human pathogen". The notifier is requested to correct this sentence by clearly indicating that Indiana VSV is classified as Risk Group 2 human pathogens in the following documents:

- *o ICF_EN (page 7/59),*
- *o ICF_FR (page 7/65),*
- *o ICF_NL (page 7/69),*
- *o SNIF (pages 2/19 and 5/19)*
- *o CAF (pages 7/41, 9/41 and 37/41)*

2- The protocol and the Informed Consent Form will be updated and submitted to the Biosafety Advisory Council prior to initiating the study in Belgium with the following changes:

- *o Rodents must be added in the list of animals to avoid from C1D1 to the end of treatment visit (Part 1 patients) or C5D1 (Part 2 patients)*
- *o An exclusion criteria for restriction on blood/cells/tissues/organs donation for 6 weeks following last injection of BI 1831169 must be added in the list of criteria*
- *o The recommendation to abstain from sexual intercourse for the 10 days following treatment due to the possibility of shedding must be added in the list of instructions for the patient*
- *o It should also be clearly indicated in the protocol that Indiana VSV is classified as Risk Group 2 human pathogen*

3- The notifier and the investigators must strictly apply the clinical trial protocol and all the safety instructions as described in the dossier and the updated and new documents listed here above.

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

5- 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.

6- 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.

7- 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.

8- 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:

- *o The total number of patients included in the trial in Belgium;*
- *o A report of the shedding data obtained from the clinical trial (monitoring of viral vector excretion/secretion in buccal swabs, nasal swabs, i.v./i.t. administration site swabs and urine samples after each injections at C1D1, C1D2, C1D4, C1D5, C1D8, C1D15, C2D1, C2D2, C2D8, C3D1, C3D8, C4D1, C4D8, EOT)*
- *o A summary of all adverse events marked by the investigators as probably or definitely related to the study medication;*
- *o A report on the accidental releases, if any, of BI 1831169."*

Sincères salutations,

Frank Vandenbroucke
Vice-Premier Ministre et
Ministre de la Santé publique et
des Affaires sociales

Zakia Khattabi
Ministre du Climat, de
l'Environnement, du
Développement durable et du
Green Deal