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Your letter from	Your reference	Our reference	Annex	Date
		FAGG/R&D/MKN	1	

Onderwerp
Titre de l'objet
Subject

Goedkeuring van een klinische proef op 15/10/2018
Approbation d'un essai clinique le 15/10/2018
Authorisation of a clinical trial dated 15/10/2018

A prospective, multi-center, Phase 1b/2a study to assess the safety and tolerability of different doses of AG019 administered alone or in association with teplizumab in subjects with clinical recent-onset Type 1 Diabetes Mellitus (T1D)

EudraCT: 2017-002871-24

Chère Madame,

Conformément à l'article 12 de la Loi du 7 mai 2004 relative aux expérimentations sur la personne humaine, j'ai décidé d'autoriser l'essai clinique ci-dessus mentionné.

Cependant, un suivi doit être apporté aux points mentionnés en annexe.

Salutations sincères,

Pour la Ministre des Affaires sociales et de la Santé publique

Geachte Mevrouw,

In overeenstemming met artikel 12 van de wet van 7 mei 2004 inzake experimenten op de menselijke persoon, heb ik besloten de hierboven vermelde proef goed te keuren.

Niettemin moet er gevolg gegeven worden aan de opmerkingen vermeld in bijlage.

Met de meeste hoogachting,

Voor de Minister van Sociale Zaken en Volksgezondheid

Dr. Greet Musch

In accordance with article 12 of the Law of 7 May 2004 concerning experiments on the human person, I have decided to authorise the above mentioned clinical trial. However, the points as mentioned in annex are to be followed up.

Annex

Safety

Recommendations

Additionally, the sponsor is recommended to take into consideration the following recommendations during further development of the product. They may be readdressed at the time of assessment of future applications related to this investigational medicinal product.

*R1. In view of the update of the CTFG - Q&A document on RSI, published on: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf, the sponsor should fully comply with the Q&A during the **IB updates for teplizumab** that follow this publication.*

R2. The teplizumab information provided in the IB for AG019 should be removed

Quality

Recommendations

Additionally, the sponsor is recommended to take into consideration the following recommendations during further development of the product. They may be readdressed at the time of assessment of future applications related to this investigational medicinal product.

R1. The applicant states that L. lactis control strain (sAGX0347) did not produce either hPINS or hIL-10. This is not supported by data presented in table 2.1.S-15 where expression analysis of hPINS has not been determined. Furthermore, while for hIL-10 no difference has been observed between the positive control sAGX0299 and sAGX0407, the applicant is requested to explain the hPINS different level observed between the positive control pAGX0053 and sAGX0407.

R2. The applicant is requested to explain why different negative controls has been used during Elisa and western blotting analysis of hPINS and hIL-10 protein expression (e.g. L. lactis control strain (sAGX0347) for ELISA and L. Lactis MG1363 (pT1NX) for western blotting.

R3. The applicant should bear in mind that non-viable L. lactis shall be considered as impurities as they are not considered as part of the active pharmaceutical ingredient due to their non-contribution to the product strength. Therefore, we do think that setting up limits is not necessary because of their general safety.

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Votre lettre du	Vos références	Nos références	Annexe(s)	Date
		AFMPS/DGPRE/R&D/MKN		

Dossier OGM : B/BE/18/BVW5 (2017-002871-24): A prospective, multi-center, Phase 1b/2a study to assess the safety and tolerability of different doses of AG019 administered alone or in association with teplizumab in subjects with clinical recent-onset Type 1 Diabetes Mellitus (T1D)

Chère Madame Genin,

Par la présente, nous vous informons que l'autorisation imposée en vertu de l'arrêté royal du 21 février 2005 règlementant la dissémination volontaire dans l'environnement ainsi que la mise sur le marché d'organismes génétiquement modifiés ou de produits en contenant vous est accordée sur base de l'avis favorable du Conseil de Biosécurité daté du 13 septembre 2018, et ce, aux conditions reprises dans la conclusion de l'avis précité, c'est-à-dire :

"The notifier and the investigators must strictly apply the clinical trial protocol, and all the safety instructions as described in the dossier. In addition, the patient instruction leaflet should clearly mention that the IMP should be stored in a lockable container at the patient's private home.

- *Any protocol amendment has to be previously approved by the Competent Authority.*
- *The notifier is responsible to verify that each study center has qualified personnel experienced in handling infectious material and that the investigator has the required authorisations 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.*
- *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 will at least contain:*
    - *the total number of patients included in the trial and the number of patients included in Belgium;*
    - *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 AG019."*

Salutations sincères,

Maggie De Block
Ministre des Affaires Sociales
et de la Santé publique

Marie Christine Marghem
Ministre de l'Energie, de l'Environnement et du Développement durable