EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 January 2024
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Executive Director

Letter of support for UISS-TB-DR

On 26 September 2022 the applicant Mimesis S.r.l. requested a qualification advice pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 25 – 28 September 2023, the SAWP agreed on the advice to be given to the applicant. During its meeting held on 09 – 12 October 2023, the CHMP adopted the advice to be given to the applicant.

The current Letter of Support is issued on the basis of the qualification advice.

Mimesis Srl, on behalf of In Silico World (ISW) Consortium (https://insilico.world), requested a Qualification Advice for the use of UISS-TB-DR as a simulation platform to predict how the circulating interferon gamma (IFN-γ) changes over time as a function of the treatment dose in a cohort of virtual patients, to select the doses to be tested in escalating dose phase IIa trials of new therapeutic whole cell / fragmented based vaccines designed for latent pulmonary TB in adult, HIV negative, drug sensitive patients initially treated with isoniazid antibiotics pre-vaccination. According to the applicant, the focus is proposed to be made on selection of the middle dose in Phase 2a studies to also include the minimum effective dose (MED) and the maximum tolerated dose (MTD).

The Agency supports the application of model-informed drug development (MIDD) approaches, and in particular the use of mechanistic agent-based model such as UISS TB DR for dose regimen selection in the field of tuberculosis given the current need for effective therapies, vaccines, the challenge related to multidrug resistance and need for combination therapies.

However, the current context of use statement assumes that circulating interferon gamma (IFN-γ) changes over time can be considered as informative for clinical dose selection in TB. The value of IFN-γ (i.e. its prognostic and predictive value) as a biomarker for therapeutic vaccines/immune therapies in TB first needs to be established. IFN-γ is (currently) not an established surrogate for clinical endpoints in this clinical setting.

The implementation of the risk-based analysis and the credibility assessment by the Applicant are appreciated, and the overall approach proposed for technical model development, verification, validation and uncertainty quantification is in principle supported. However, the clinical data that the Applicant used to validate their platform (only including results obtained with RUTI vaccine PhIIa study), are considered limited for platform qualification in the claimed context of use. The applicant is

currently narrowing the context of use to whole cell/fragmented based vaccines that are designed for latent pulmonary TB in adult subjects, who are HIV negative and drug sensitive after 1month treatment with INH. Although the rationale for limiting the scope of qualification is understood, the Agency encourages the applicant in the future to expand their approach to the other types of therapeutic vaccines, to widen the range of doses to be optimized and to assess the impact of concomitant antibacterial therapies.

The objective of this letter of support is to foster clinical data sharing initiatives to advance exploratory development of latent TB therapeutic vaccines. It emphasizes the importance of collecting additional data, which are crucial for two primary purposes: firstly, to ascertain the value of IFN-γ as a reliable biomarker for dose regimen selection in therapeutic TB vaccines, and secondly, to address the current limitations in clinical validation of the platform. The Agency recognizes the potential of innovative approaches related to model-informed drug development (MIDD) in tuberculosis, an area that faces significant challenges such as multidrug resistance and the need for effective combination therapies. By encouraging the expansion of the platform's exploratory application to various types of therapeutic vaccines and a broader range of doses, once the limitations are addressed, the Agency underscores its support for advanced, comprehensive solutions in TB therapeutic vaccine development.

Sincerely,

Emer Cooke
Executive Director