Final minutes and answers from the Scientific Scientific Advisory Group (SAG) on Cardiovascular Issues meeting on TZIELD

Background

Upon request from the CHMP, the Scientific Advisory Group (SAG) on Cardiovascular Issues meeting was convened on 09 September 2025.

Minutes from the SAG meeting

The meeting started at 10.00. .

Declaration of Interest Statement

In accordance with the Agency's policy on handling of declarations of interests of scientific committees' members and experts and based on the topics in the agenda of the meeting, the EMA checked the declarations of interests of the meeting participants. No relevant interests were declared for this meeting.

At the beginning of the meeting, participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. No new interests were declared.

The CHMP Rapporteurs provided the SAG with an overview of the issues to be discussed and summarised the questions addressed to the SAG. The meeting ended at 15.00 with a summary of the discussion and the conclusions for each of the issues for discussion by the SAG. The Applicant was briefed about the conclusions of the SAG.

A presentation was made by the Applicant followed by a session of questions and answers.

FINAL SAG CVS ANSWERS FOR TZIELD

1. **The proposed indication "to delay the onset of stage 3 T1D" is mainly supported by the phase 2 study TN-10.**

a. **Notwithstanding the fact that there are some methodological concerns that complicate the interpretation of the study results, please discuss the clinical**

relevance of the observed delay in the onset of stage 3 T1D in the proposed target population.

The experts confirmed the clinical relevance of delaying the onset of stage 3 T1D in stage 2 patients. Postponing the onset of the disease will also delay the onset of the "honeymoon period" with less treatment requirements.

From a clinical perspective, the delay might change the trajectory of the disease in terms of e.g. less hyperglycemia, hypoglycaemia and could also positively impact the long-term complications of T1D, acknowledging that this has not yet been demonstrated.

Experts highlighted available data from screening programs showing a positive psychological impact of earlier awareness of patients, and although the diagnosis of stage 3 has a psychological impact, the fact that the information is available earlier enables better management of the disease with e.g. fewer ICU admissions...

Experts noted the importance of patients screening, which in some parts of Europe has reduced the incidence of DKA. Availability of teplizumab would enable identification of patients and an earlier diagnosis and treatment to delay the onset of the disease would impact the life expectancy.

Some experts highlighted however that this delay might be more relevant for the pediatric population:

-Difference in the time of onset of the disease between adults and children once autoantibodies are detected were critically discussed by some experts. In addition, there is evidence that childhood-onset T1D involves a more aggressive, multi-autoantibody immune response with strong genetic susceptibility and distinct immune regulatory pathway alterations. Adult-onset T1D generally displays a milder onset.

- Furthermore, in the TN-10 study, the majority of clinical data is derived from the paediatric population or from young adults hence the experts considered the data is the adult setting less convincing.

The experts discussed an age cut-off and a possible restriction of the treatment to the paediatric population. Some experts believed that an age cut-off was justified, however this was not supported by the majority of the experts who felt that despite the limitation of the available data there is still a benefit to have the product available for adults.

It was reminded that in any case a discussion between the prescriber and the patient will need to take place on the appropriateness of the use of the product for each patient, also considering the frequency and severity of adverse drug reactions.

One patient representative who got T1D at a young age highlighted the importance of delaying the onset of the disease which allows to prepare and adapt the lifestyle and would probably have a positive psychological impact when compared to the diagnosis of the T1D and the need to directly initiate insulin treatment.

Another patient representative who was diagnosed as an adult expressed no interest in receiving the information earlier and that the diagnosis of T1D allowed improvement in lifestyle habits. The patient representative also indicated the need to well inform health care professionals about the characteristics of teplizumab.

b. Considering the limited number of patients in the TN-10 study (n=76), please discuss the relevance of the study results for the general population with stage 2 T1D (e.g., considering age, antibody status, hereditary status).

Generalizability of the results is important here in view of the broad indication applied for, and the fact that the majority of clinical data is derived from the paediatric population and young adults and only patients with specific T1D phenotype (double autoantibodies) were included in the trial with no data available about other phenotypes.

Results are consistent across the sub-groups so generalizability could be expected, however the experts noted the sub-analysis relates to small size population and from the statistical perspective, the data from the sub-analysis is the same data from the TN-10 study, which implies interdependencies between the sub-group analyses and hence less strong evidence than would be obtained, for example, from a meta-analysis.

Differences in the mechanism of action/ physiology of T1D between children and adults are currently not well documented. Whilst biological plausibility might be expected with the same effect across the different groups of patients, the experts highlighted there is currently no available robust data to support this.

One expert indicated that some data available show that mechanistic aspects might be different for young patients under 7 years old.

c. Please discuss the feasibility of performing a confirmatory trial in patients with stage 2 T1D, considering the potential difficulties in identifying eligible study subjects. If considered feasible, are there specific patients characteristics that should be taken into account, when defining the most adequate target population (e.g., fast /slow progressors).

The experts indicated that a confirmatory clinical trial would be feasible and valuable, but also challenging, recognizing the difficulties in conducting such a study in particular with regards to identification of relevant patients and timely enrolment.

The proposed global post-MA registry could also be acceptable and be very valuable provided it is well-designed to enable the collection of safety data and additionally data on real world effectiveness. The experts commented that a large population beyond the current proposal from the Applicant should be enrolled.

2. The proposed indication "to delay the progression of stage 3 T1D in adults and children with recently diagnosed stage 3 T1D" is mainly based on the PROTECT study. Please discuss the clinical relevance of the results showing a slowing of the progression of beta-cell decline considering that the results for the secondary endpoints (exogenous insulin use, HbA1c, hypoglycaemia, TIR) failed to confirm a beneficial effect. What would in your view constitute relevant benefits of treatment for the proposed target population?

The positive effect on C-peptide was acknowledged. Higher C-peptide values are a favorable biological indicator but on their own are not a clinical confirmation, and such an increase does not necessarily imply a potential clinical benefit, as it could reflect masked pharmacokinetic effects or even a hidden deleterious effect counteracting possible beneficial ones.

This was the only positive biological finding, and the absence of clinically relevant endpoints reaching statistical significance implies that the evidence is not sufficient for this indication. Demonstrating statistical significance in at least one clinically relevant endpoint would have been necessary, which was not the case in this trial. Missing data on clinically relevant endpoints is considered a major issue by experts; positive impact on e.g insulin use, TIR, glucose variability, HbA1C would have been expected.

Experts reminded that the CHMP Scientific Advice Working Party has also suggested the applicant to include clinically relevant endpoints together with C-peptide.

It could be assumed hypothetically that protecting C-peptide function will have long-term positive impact but there is currently no available data to confirm this. An epidemiological relationship was not considered sufficient evidence.

Patients' representatives also agreed with the importance to have a clinical outcome that impacts positively the patients' disease management.