25 March 2022
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Executive Director

Letter of support for the Global Platform Study of Novel Medicines in Paediatric and Adolescent Relapsed and Refractory B-cell Non-Hodgkin Lymphoma (Glo-BNHL platform)

On 20 July 2021 the Applicant, University Of Birmingham, requested qualification advice for their product Glo-BNHL platform trial pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

Advice was requested on the statistical and clinical design aspects of a master protocol and platform trial in children, adolescents, and young people with relapsed and refractory mature B-cell Non-Hodgkin Lymphoma (B-NHL).

During its meeting held on 25 – 28 October 2021, the SAWP agreed on the advice to be given to the Applicant. During its meeting held on 08 – 11 November 2021, the CHMP adopted the advice to be given to the Applicant.

Background and rationale for the platform trial development

Mature B-cell malignancies in children and adolescents account for 58% of all lymphomas and comprise the majority type of non-Hodgkin lymphoma (1, 2). Mature paediatric B-NHL are predominantly CD20+ and 98% are classified as aggressive. The most commonly seen subtype is Burkitt Lymphoma (BL) (>80%) with a much smaller proportion of Diffuse Large B-cell Lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) (2, 3).

The outcome for children with paediatric mature B-cell malignancies has improved significantly with 5-year event free survival (EFS) now exceeding 90-94% across all major international frontline protocols (4-9). The recent introduction of the monoclonal antibody rituximab, alongside chemotherapy has provided a new standard of care for treatment of high-risk patients, conferring an additional 10% survival advantage (EFS increased from 82.3 to 93.9%) compared to chemotherapy alone in patients with the highest risk disease (6). However a ceiling of tolerable therapy has clearly been reached, with

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intensive frontline regimes now resulting in an equal number of treatment-related and disease-related deaths for high-risk patients (6). The lack of an established, effective regimen for children failing first line therapy means, though, that de-escalation trials cannot be prioritised until relapse/refractory disease can be substantially cured (10).

Relapsed and refractory B-NHL disease remains a significant challenge in this population. As the prognosis for upfront treatment has improved, the likelihood for successful salvage in relapsed disease has decreased. Despite the use of highly intensive re-induction chemotherapy regimens followed by Haematopoietic Stem Cell Transplantation (HSCT), long-term survival rates are less than 30% historically (11-15) and are likely to be much lower following the introduction of rituximab to frontline therapy for high-risk disease. For patients who relapse after more than one line of prior therapy, the outcome is dismal with only very rare survivors reported. The persistently poor outcome for children with relapsed and refractory B-NHL necessitates urgent attention and prioritisation.

Drug development need

Currently there are no open trials for children with relapsed or refractory B-NHL. A single industry-sponsored randomised trial of the Bruton's tyrosine kinase inhibitor, ibrutinib, combined with chemoimmunotherapy in relapsed and refractory B-NHL (SPARKLE NCT02703272) has recently closed to recruitment due to futility (16) and full results are awaited. In addition, the BIANCA trial (NCT03610724) of CAR T-cells (tisagenlecleucel) in relapsed and refractory paediatric B-NHL has now closed to recruitment and results are awaited. Substantial biological differences between mature B-cell malignancies in adults and children (1, 5, 17-20) make the extrapolation approach not suitable and therefore extrapolation of results from adult studies to children is not appropriate in the majority of cases. This, combined with the need for paediatric pharmacovigilance, necessitates paediatric-specific clinical studies to be conducted.

Overview of the key trial design features

Glo-BNHL is a prospective international academic-led multicentre clinical platform trial designed to evaluate the safety and efficacy of priority novel medicines, alone or in combination with existing therapies, for the treatment of children, adolescents and young adults with relapsed or refractory B-NHL. The platform has been developed as a direct output from the second ACCELERATE multi-stakeholder Paediatric Strategy Forum which included input from the EMA and U.S Food and Drug Administration (FDA) (10).

The Glo-BNHL platform trial will seek to overcome the critical challenge of the imbalance between the number of paediatric patients eligible for clinical evaluation and the many potential medicines in development for the treatment of mature B-cell malignancies. A robust prioritisation process is utilised to ensure that only those medicines showing the greatest promise will be taken forward for evaluation and an adaptive Bayesian statistical design will be employed. The platform currently consists of three parallel single arm trials, each one investigating a different class of novel medicines in defined cohorts of patients. The platform allows a pipeline of novel medicines to be tested in each treatment arm with evaluations of safety and efficacy built into the design at regular intervals in recruitment. Such evaluations will allow each treatment arm to be closed promptly and medicines replaced if dictated by the responses observed. Promising medicines can also move seamlessly from the initial recruitment cohort into an expansion cohort.

The novel medicine classes prioritised for allocation at the initiation of the Glo-BNHL platform trial are:

- Treatment arm I: Bispecific Antibodies (BsAb)
- Treatment arm II: Antibody-Drug Conjugates (ADC) combined with standard chemotherapy
- Treatment arm III: Chimeric Antigen Receptors (CAR) T-cells

Following regulatory assessment, the overall approach taken by the Applicant for the Glo-BNHL platform trial was supported by the Committee for Medicinal Products for Human Use (CHMP) and Paediatric Committee (PDCO) (EMA/SA/0000066921). The CHMP/PDCO believe that the merits of a master protocol in order to sensibly allocate patients to experimental treatments in this rare disease setting are obvious and the effort to globally enrol patients across the breadth of the paediatric B-NHL population is fully supported. Additionally, the CHMP/PDCO acknowledges that there is a transparent and equitable prioritisation process before the clinical trial is initiated for new medicines wishing to be included in the Glo-BNHL trial and they would consider it unfortunate, should companies worldwide choose not to engage with the Glo-BNHL platform trial because of this prioritisation process, since recruitment competition between trials is likely to result in trial failure for all and this should be avoided. However, prioritisation should not necessarily mean that only one drug per cohort can be investigated. Prioritisation must be balanced against the risk that patients are treated outside the platform if there is substantial disagreement about which drug should be prioritised whilst inclusion of all patients into the platform is of paramount importance.

One key aim of the Glo-BNHL platform trial is to produce data for marketing authorisation applications (MAA) and therefore the absence of randomisation makes these applications more challenging, particularly from the perspective that a recent randomised trial has failed to demonstrate efficacy. Whilst the CHMP/PDCO accept that randomisation may not be feasible for two cohorts within the platform, they welcome consideration of randomisation in the expansion phase of cohort II, dependent on the results of the initial cohort of 15 patients. Furthermore, where randomisation is not feasible, in the long run consideration may be given to utilising available data in the same cohort as a historical control arm.

Overview of the key statistical design features

The CHMP/PDCO consider it to be reasonable that decisions on one experimental drug in one cohort are made independent to the others in the platform, a type-1 error is assigned to each of them, and the arms are powered separately. The CHMP/PDCO acknowledge that, although the one-sided 5% level is twice as large as the usual acceptable level, it may be considered acceptable in this rare disease setting.

Whilst the CHMP/PDCO would prefer a frequentist design, it is acknowledged that the proposed design of group sequential testing in a Bayesian framework may provide similarly interpretable point- and interval effect estimates. The clinically relevant critical values defining the success criteria should be justified and specified in advance, and the statistical design will include a justification for a Bayesian design with appropriate comparison to a frequentist approach. It is acknowledged that the chosen values are in line with expectations based on adult studies taking into account the toxicity of the drugs under investigation.

No objection exists to implementing non-binding futility analyses with Bayesian decision support at regular intervals in patient recruitment.

The CHMP/PDCO also recommend separating out the learning and confirming stages in the trial such that the data from the first 15 patients would form the learning experience and the potential expansion arm would form the confirmatory evidence. The Applicant is encouraged to seek further regulatory interaction once Glo-BHNL's success criteria are met for a specific medicine. This could be as part of Paediatric Investigation Plan (PIP) submissions of medicines evaluated within the platform, as the objective of a PIP is to generate data sufficient for a MAA.

Conclusion

The CHMP/PDCO support the approach by the Applicant to set up the Glo-BNHL platform trial (master protocol) in paediatric and adolescent with relapsed and refractory B-NHL. The platform offers an opportunity to ensure that the most promising medicines are prioritised for development in this rare population with a high clinical need. Competition for recruitment of these rare patients to competing trials is highly undesirable. The CHMP/PDCO believe that the merits of a master protocol in order to sensibly allocate patients to experimental treatments in this rare disease setting (an estimated n=30 patients per year are expected to be realistically recruited globally) are obvious and the effort to globally enrol patients across the breadth of the paediatric B-NHL population is fully supported. Joint efforts are a mandatory pre-requisite to generate scientifically meaningful results and considerations regarding commercial confidence should not get in the way of this important aim.

The letter of support is issued on the basis of this qualification advice.

Yours sincerely,

Emer Cooke
Executive Director

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