Development of CoVIg-19, an anti-COVID-19 immunoglobulin product – Briefing document for CBG

Agreement with Ministry of Health, Welfare and Sport (HWS/VWS)

The Dutch Ministry of VWS (Health, Welfare and Sports) sponsors the collection and testing of 50,000 plasma donations of donors who recovered from COVID-19 (convalescent plasma) by Sanquin Blood Supply Foundation. The collection will be performed by Sanquin Blood Bank; Sanquin Diagnostics will perform the testing. Sanquin Diagnostics has been involved in the nationwide study to the seroprevalence of SARS-CoV-2 antibodies sponsored by the RIVM, and has several test methods available and validated.
The plasma will be used by Sanquin Plasma Products BV (SPP) for the manufacturing of at least 1 batch of hyperimmune 5.1.2f 10%. This batch will be made available to RIVM for use at the discretion of the RIVM (e.g. prophylaxis for vulnerable patients, or treatment of COVID-19). Projected timeline for release of this batch is October 2020, in order to have the batch available for use in autumn 2020, when an eventual second wave of large numbers of patients with COVID-19 can be expected. It is not anticipated that the product is registered for these indications at the time of release and first potential use. Depending on demand, SPP may manufacture more batches of hyperimmune 5.1.2f .

CoVIg-19 Plasma Alliance

Sanquin Plasma Products BV is participating as a contributor in the CoVIg-19 Plasma Alliance. This is a partnership of world-leading plasma companies formed in response to the challenge of COVID-19. The Alliance is led by Takeda and CSL Behring; other participants are a.o. BPL, Biotest, LFB and Octapharma.

The Alliance plans to develop an unbranded hyperimmune immunoglobulin (H-Ig), an IVIg product for treatment of patients with COVID-19. A global clinical trial is planned . The Alliance has confirmed it will work with the U.S. National Institute of Allergy and Infectious Diseases (NIAID) at the NIH to test the safety, tolerability and efficacy of the hyperimmune therapy in adult patients with COVID-19. This global study (in US and EU countries) is currently anticipated to start in summer and will form the foundation for the potential regulatory approval of the hyperimmune therapy.

According to the current planning, the clinical trial will start in August. When the products prove to have effect, the concept is that all Alliance companies manufacture COVID-19 H-Ig according to their own registered IVIG manufacturing process and can register their IVIG product for COVID-19 treatment, based on the clinical trial results of the Alliance. In such case the comparability of products may need to be demonstrated. The Alliance has requested (accelerated) scientific advice to EMA and FDA to discuss the clinical, non-clinical, quality and regulatory aspects of this project.

SPP supplies plasma containing SARS-CoV-2 antibodies to the Alliance for the manufacturing of the clinical batches. In return, SPP will receive the clinical data for regulatory requirements regarding marketing authorization of their own H-Ig product. It is included in the scientific advice briefing document that MA application of all Alliance companies in the EU will be performed via the Centralized Procedure.

Regulatory considerations

It is foreseen that during a certain period the 5.1.2f hyper immune product may already be required to be used in Dutch patients without a Marketing Authorisation for this indication. RIVM is in the lead of the use and supply of the product to a specific population. However, CBG will presumably be involved in assessment of the risks and benefits to use this product.

The manufacturing process (including filling size) will be identical to the 5.1.2f manufacturing process, with additional control of the specific antibody titre for SARS- Cov-2 antibodies in the final product. All characteristics of the product that differ from 5.1.2f are listed in the table below with in the comments field some considerations are provided.

Parameter	Proposal	Considerations
Clinical study data (Alliance)	Provide clinical study report if available. Anticipated timeline: *<not known yet>*	• Clinical trial report will probably not be available in Q3 2020, when the (start of the 2nd waive is expected.
Control of SARS-CoV-2 antibody titer ipc and on finished product.	Method and validation report will be provided to CBG. A specification for finished product including its rationale will be shared with CBG.	• It has not been decided yet which method will be used for this purpose. Options are: - Same method as used for the clinical trial batches of the Alliance. - Commercially available method, validated for the matrix and performed by Sanquin Diagnostics. - In-house method, developed by Sanquin Research and validated and performed by Sanquin Diagnostics. A reference standard will be made available by the Alliance, which may be used for validation of the test.
Comparability	Overview of the critical quality attributes of the IVIG product for the clinical study and of 5.1.2f with analyis of the impact on efficacy of the product for treatment of COVID-19. If considered comparable with regard to efficacy, it will be justified why the differences will not impact the efficacy. Please note that safety is not in the scope of this comparability exercise, as the safety of 5.1.2f is already proven and monitored for the regular use of the product. Safety of patients treated with H-IVIG will be monitored according to routine pharmacovigilance processes.	• Alliance companies manufacturing COVID-19 H-Ig may register their IVIG product for COVID-19 treatment, based on the clinical studies of the Alliance, if comparability of product is demonstrated. • Is it agreed by CBG-MEB that comparability of PK data can be demonstrated by literature data?
Labelling (label, SPC, PIL)	Label options: • Use current 5.1.2f label (immediate and outer packaging) and include annotation (e.g. sticker?) to indicate the anti-COV19 antibody titre → preferred option for off-label use (first batch) • Create unique label with non-proprietary name (i.e. SARS-CoV-2 IVIG)	• Additional labelling of the pack and vial to be discussed with RIVM and CBG. • Additional information (SPC and PIL) to be discussed with RIVM and CBG • Distribution of additional information for (at least) first batch in cooperation with RIVM.

	SPC and PIL: use the 5.1.2f SPC and PIL. Optionally: Prepare an additional document for treatment of COVID-19 (both for HCP and patients) to be included with the distribution of the product to the HCP and which is handed over to the patient at administration.	
Stability data	Initiation of stability study for first batch of hyperimmune 5.1.2f to control the antibody titre over the shelf life, preferably the whole shelf life of 5.1.2f. Indications that the antibody titre decreases to below the specification during the shelf life will be reported.	At this moment no information is available on the stability of the aCOV antibody titer. However, there is also no indication that the antibody stability differs from normal stability of IgG antibodies.