# Off-label use of Nanogam with anti-COVID19 antibodies – Response to question CBG case 858779

This letter regards a response to the request for clarification from CBG on 01 February 2021.

We would like to make a separation between Nanogam with anti-COVID19 antibodies, the product that was manufactured upon request of the Ministry of Health (product 1) and a hyperimmune product, to be manufactured and potentially registered in cooperation with the Plasma Alliance (product 2).

**Product (1): Nanogam with anti-COVID19 antibodies**

At the start of the pandemic it was realized that the spreading of SARS-CoV-2 virus could be shown by determining the presence and level of antibodies against the virus, further called anti-COVID19 antibodies, in human donor plasma. From March 2020 onwards, Sanquin Research performed regular random testing of donor plasma samples on the presence of anti-COVID19 antibodies. It became clear that many people, including plasma donors, had anti-COVID19 antibodies in their plasma but were not aware that they had been infected. The outcome was that in April 2020 anti-COVID19 antibodies were found in ~3% of the donor population (RIVM Technical briefing Tweede Kamer 5.1.2e, 16-Apr-2020).

The donations from the normal donors of this random testing by Sanquin Research in which anti-COVID19 antibodies were detected, were used for the manufacturing of the Nanogam with anti-COVID19 antibody batches.

As it became clear that donors could have anti-COVID19 antibodies in their plasma without knowing it, Sanquin Blood Bank implemented a test on anti-COVID19 antibodies to be performed on every donation. Furthermore, people who were tested by the GGD for the SARS-CoV-2 virus and tested positive, were requested by the GGD to become a donor at Sanquin Blood foundation after full recovery. Using the results of the anti-COVID19 antibody test on all donations collected by Sanquin Blood Bank, the donations were selected for the manufacturing of Nanogam with anti-COVID19 antibodies. So the donors were not selected; instead, the antibody content in the donation was determined and the donation was selected.

As indicated in the briefing documents that were shared with CBG, SPP manufactured batches of Nanogam containing these donations on behalf of the Dutch Ministry of VWS (Health, Welfare and Sports). The ownership of these batches is at the Ministry of VWS. SPP emphasizes that the batches are manufactured, labelled and released as Nanogam 10%, completely according to the Nanogam dossier. The batches can also be administered as on-label Nanogam for the indications presented in the Nanogam SPC, as besides anti-COVID19 antibodies, the product contains the normal spectrum of antibodies which are normally present in Nanogam.

The efficacy of Nanogam with anti-COVID19-antibodies for post exposure prophylaxis in vulnerable subjects is unknown and not registered, which is why it is regarded as off-label use. The minimal required antibody titer for prophylaxis is unknown, as this hasn't been studied yet in a clinical trial. This is similar to (many) cases in which Nanogam is prescribed off-label, with the assumption that it contains antibodies against specific infectious diseases or infection-related disorders intended to treat life-threatening conditions that affect the human immune system. In most cases there is limited proof of efficacy for these specific indications.

The safety profile of Nanogam is known and is not different for these batches. Safety will be monitored according to the normal PV practice. It is possible that specific monitoring reports regarding the use of Nanogam with anti-COVID19 antibodies are regularly sent to the CBG.

The Ministry of VWS is of the opinion that in times of unmet medical needs, it should provide potential solutions to mitigate the unmet medical need. Given the unmet medical need in this situation, SPP is of the opinion that it is justified to use the Nanogam batches described above for off-label use.

<u>The CBG is kindly requested to support this.</u>

**Product 2: Hyperimmune product**

The regulatory considerations that SPP shared with you in the briefing document of 13 January 2021 regard the option to submit a marketing authorization application for this product, which is a separate issue. This would concern an application for a new marketing authorization of a new hyperimmune product, which would have to include supportive clinical documentation regarding the efficacy of the product for the intended indications, e.g. the study report of the clinical trial of the Alliance. Please note that this study regards a different indication: i.e. treatment of hospitalized patients with confirmed COVID19, than the proposed off-label use of the Nanogam with anti COVID19 antibodies.