ANNEX I

CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION AND PATIENTS TARGETED AND CONDITIONS FOR SAFETY MONITORING ADRESSED TO MEMBER STATES

FOR

UNAUTHORISED PRODUCT Regkirona (regdanvimab)

AVAILABLE FOR USE

1. MEDICINAL PRODUCT FOR USE

- **Name of the medicinal product for Use: Regkirona**
- **Active substance(s): Regdanvimab**
- **Pharmaceutical form: Concentrate for solution for infusion**
- **Route of administration: Intravenous infusion**
- **Strength: 60 mg/ml**

2. NAME AND CONTACT DETAILS OF THE COMPANY

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3. TARGET POPULATION

Regdanvimab is indicated for the treatment of confirmed COVID-19 in adult patients that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19.

Risk factors may include but are not limited to:
• Advanced age
• Obesity
• Cardiovascular disease, including hypertension
• Chronic lung disease, including asthma
• Type 1 or type 2 diabetes mellitus
• Chronic kidney disease, including those on dialysis
• Chronic liver disease
• Immunosuppressed, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassaemia, and prolonged use of immune-weakening medications.

4. CONDITIONS FOR DISTRIBUTION

Medicinal product subject to medical prescription.

5. CONDITIONS OF USE

Regdanvimab may only be administered in settings in which health care providers have immediate access to medicinal products to treat a severe infusion reaction, such as anaphylaxis.

- **Limitation in Patients with Severe COVID-19**

Monoclonal antibodies, such as regdanvimab may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

5.1 Posology

- **Dosing recommendations**

The recommended dosage of regdanvimab is a single intravenous (IV) infusion of 40 mg/kg. Treatment should be initiated as soon as possible after diagnosis, and not later than 7 days after the onset of symptoms.

- **Treatment duration and monitoring**

Administered as an IV infusion via pump over 90 minutes.

Patients are clinically monitored during administration and observed for at least 1 hour after infusion is complete.

- **Specific populations**

Paediatric Use

The safety and efficacy of regdanvimab in paediatric patients have not yet been established. No data are available.

Geriatric use

No dose adjustment of regdanvimab is required in elderly patients.

Renal impairment

Regdanvimab has not been studied in patients with renal impairment. Elimination of regdanvimab is likely to occur through normal degradation pathways for immunoglobulins and the clearance is not expected to be affected by renal impairment. No dose adjustments are considered necessary.

Hepatic impairment

Regdanvimab has not been studied in patients with hepatic impairment. Elimination of regdanvimab is likely to occur through normal degradation pathways for immunoglobulins and the clearance is not expected to be affected by hepatic impairment. No dose adjustments are considered necessary.

- **Method of administration**

For intravenous use only.

Regdanvimab should be diluted and administered intravenously over 90 minutes.

Preparation

Regdanvimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Remove regdanvimab vial(s) from refrigerated storage and allow to equilibrate to room temperature (not exceeding 30°C) for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vial(s).**
- Regdanvimab is a clear to opalescent, colourless to pale yellow solution for infusion. Inspect regdanvimab vial(s) visually for particulate matter and discolouration prior to dilution. Should either be observed, the vial(s) must be discarded, and new vial(s) should be used for preparation.
- Calculate total volume of regdanvimab to be administered. The volume of regdanvimab is calculated as follows.

Calculation to determine the total volume of regdanvimab to be administered:

$$\frac{\text{Patient's body weight (kg) x regdanvimab dose (40 mg/kg)}}{\text{Vial concentration (60 mg/ml)}} = \text{Volume of regdanvimab (ml)}$$

Calculation to determine the total number of regdanvimab vials needed:

$$\frac{\text{Total regdanvimab volume (ml) to be administered}}{\text{Total volume per vial (16 ml/vial)}} = \text{Number of regdanvimab vials needed}$$

Table 1: Sample calculations for patients receiving the recommended dose of 40 mg/kg of regdanvimab for weight ranging from 40 kg to 120 kg

Body weight (kg)	Total dose (mg)	Volume (ml)	Vials (n)
40	1,600	26.7	1.7
60	2,400	40	2.5
80	3,200	53.3	3.3
100	4,000	66.7	4.2
120	4,800	80	5

Note: If patient's weight is more than 200 kg, the dose calculation should use 200 kg. The maximal recommended dose is 8,000 mg.

- Dilute regdanvimab in a 250 ml bag containing sodium chloride 9 mg/ml (0.9%) solution for intravenous infusion.
  - Withdraw and discard the required volume (which is identical to the calculated volume of regdanvimab) of sodium chloride 9 mg/ml (0.9%) from the infusion bag.
  - Withdraw the calculated volume of regdanvimab from the vial(s) using a sterile syringe.
  - Transfer regdanvimab to the infusion bag.
- Gently invert IV bag by hand approximately 10 times to mix. **Do not shake.**
- This product is preservative-free and therefore, the diluted solution for infusion should be administered immediately. After aseptic dilution in sodium chloride 9 mg/ml (0.9%) solution, the prepared infusion solution of regdanvimab in sodium chloride 9 mg/ml (0.9%) solution is physically and chemically stable for 72 hours at 2°C - 8°C or 4 hours at ≤30°C.
- From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, allow the solution for infusion to equilibrate to room temperature (not exceeding 30°C) for approximately 20 minutes prior to administration.

Administration

Regdanvimab solution for infusion should be administered by a qualified healthcare professional.

- Gather the recommended materials for infusion: Infusion set with in-line filter (PES (Polyethersulfone) filter with pore size of 1.2 µm or less would be recommended).
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer as an IV infusion via pump over 90 minutes.
- The prepared solution for infusion should not be administered simultaneously with any other medicinal product. The compatibility of regdanvimab with IV solutions and medicinal products other than sodium chloride 9 mg/ml (0.9%) is not known.
- After infusion is complete, flush the infusion line with sodium chloride 9 mg/ml (0.9%).
- Do not reuse or save unused regdanvimab solution or diluted solution.

5.2 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients (L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, L-arginine monohydrochloride, water for injections).

5.3 Special warnings and precautions for use

- **Traceability**

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis have been observed rarely with other IgG1 monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medicinal products and/or supportive therapy.

- **Infusion-related reactions**

Infusion-related reactions have been observed with administration of regdanvimab.

Signs and symptoms of infusion related reactions may include fever, dyspnoea, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.

If an infusion-related reaction occurs, consider slowing or stopping the infusion should be considered and appropriate medicinal products and/or supportive care should be administered.

- **Immune Response Attenuation**

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

5.4 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with regdanvimab.

Regdanvimab is a monoclonal antibody which is not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medicinal products that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are considered unlikely.

- **Immune Response**

Concomitant administration of regdanvimab with COVID-19 vaccines has not been studied.

5.5 Pregnancy and lactation

- **Pregnancy**

Reproductive and developmental studies have not been performed with regdanvimab.

Nonclinical reproductive toxicity studies have not been conducted with regdanvimab. In tissue cross-reactivity (TCR) studies with regdanvimab using human foetal and neonatal tissues, no binding of clinical concern was detected in the foetal tissues. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, regdanvimab has the potential to be transferred from the mother to the developing foetus. It is unknown whether the potential transfer of regdanvimab provides any treatment benefit or risk to the developing foetus.

As experience is limited, the use of regdanvimab in pregnancy should only be considered if the possible benefit to the patient is thought to outweigh any possible risk to the foetus.

- **Breast-feeding**

It is not known whether regdanvimab is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production.

- **Fertility**

Fertility studies have not been performed.

5.6 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 5.1.

5.7 Overdose

There is no human experience of acute overdosage with regdanvimab. Single doses up to 8,000 mg have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with regdanvimab.

5.8 Shelf life

- Unopened vials

One year

- Diluted solution for infusion

After aseptic dilution in sodium chloride solution, the prepared infusion solution of regdanvimab in sodium chloride 9 mg/ml (0.9%) solution is physically and chemically stable for 72 hours at 2°C - 8°C or 4 hours at ≤30°C.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

5.9 Storage conditions

Store in a refrigerator (2°C – 8°C).

Do not freeze. Keep the medicinal product in its outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 5.8.

5.10 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6. OTHER INFORMATION

- **Undesirable effects**

Summary of the safety profile

The safety of regdanvimab is based on interim data from a Phase 2/3 trial of 325 non-hospitalised patients with COVID-19 (Study CT-P59 3.2 Part 1).

The most commonly reported adverse reaction associated with regdanvimab in mild to moderate COVID-19 patients was hypertriglyceridaemia (2.8%).

Tabulated summary of adverse reactions

Adverse reactions reported with regdanvimab based on experience from clinical trials in healthy subjects and mild to moderate COVID-19 patients are listed in Table 2 by system organ class and frequency. Frequencies are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: Tabulated list of adverse reactions

System organ class **Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	
Common	Neutropenia
Metabolism and nutrition disorders	
Common	Hypertriglyceridaemia
Uncommon	Hyperkalaemia, dyslipidaemia
Nervous system disorders	

Uncommon	Headache
Hepatobiliary disorders	
Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	Rash
Renal and urinary disorders	
Uncommon	Proteinuria
General disorders and administration site conditions	
Uncommon	Fever
Investigations	
Uncommon	Blood triglycerides increased, gamma-glutamyltransferase increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, C-reactive protein increased
Injury, poisoning and procedural complications	
Uncommon	Infusion-related reaction (e.g. fever and dyspnoea)

Description of selected adverse reactions

Infusion-related reactions

Immediate non-serious infusion-related reactions were noted for 0.5% of regdanvimab-treated patients in Study CT-P59 3.2 Part 1. Reported events of dyspnoea was mild and fever was moderate in severity. One patient in the 40 mg/kg treatment group recovered from the event after taking paracetamol and oxygen therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

- **Summary of relevant pharmacological properties**

Mechanism of action

Regdanvimab is a recombinant human IgG1 monoclonal antibody. The mechanism of action for regdanvimab in treating patients with SARS-CoV-2 infection is the binding of regdanvimab to the receptor binding domain (RBD) of the spike(s) protein of SARS-CoV-2 with dissociation constant K_D = 0.065 nM, thus, inhibiting the interaction between the SARS-CoV-2 RBD and the cellular receptor, namely the angiotensin-converting enzyme 2 (ACE2), and consequently blocking cellular entry and SARS-CoV-2 infection.

Antiviral activity

The *in vitro* neutralisation activity of regdanvimab against SARS-CoV-2 was assessed by plaque reduction neutralisation test (PRNT) using VeroE6 cells. Regdanvimab neutralised SARS-CoV-2 with an IC_{50} value of 9.70 ng/ml.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to regdanvimab.

The escape study by serially passaging authentic SARS-CoV-2 viruses in VeroE6 cells in the presence of regdanvimab identified a S494P amino acid substitution with amino acid 494 located in the RBD of the spike protein. The variant showed reduced susceptibility to regdanvimab in the plaque reduction neutralisation assay.

It is possible that regdanvimab resistance-associated variants could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. The clinical impact is not known.

Impact of viral variants on activity

The IC_{50} value for the virus isolated as UK variant (B.1.1.7 or 20I/501Y.V1) was 3.77 ng/mL, whereas that for the South Africa variant (B.1.351 or 20H/501Y.V2) could not be estimated. Thus, activity against the latter is abrogated.

- **Summary of relevant Clinical properties**

Clinical efficacy and safety

The efficacy of regdanvimab was assessed in Study CT-P59 3.2 Part 1 which is a randomised, double-blind, placebo-controlled clinical trial studying regdanvimab for the treatment of adult patients with mild to moderate COVID-19 (patients with symptoms of COVID-19 who are not hospitalised). This study enrolled adult patients who were not hospitalised and had at least 1 or more symptoms of COVID-19.

Treatment was initiated after obtaining a positive SARS- CoV-2 viral infection determination. Patients were randomised in a 1:1:1 manner to receive a single infusion of regdanvimab at doses of 40 mg/kg (N=105), 80 mg/kg (N=111), or placebo (N=111). For all efficacy endpoints for Part 1, analyses were conducted in the intent to-treat infected (ITTI) set defined as all randomly assigned patients who had a positive RT-qPCR test at Day 1 or Day 2 and received a complete or partial dose of study drug (regdanvimab 40 mg/kg [N=101], regdanvimab 80 mg/kg [N=103], or placebo [N=103]).

At baseline, median age was 51 years (with 16.5% of patients aged 65 or older); 50.8% of patients were male, 87.5% were White, and 12.5% were Asian (8.3% were Hispanic or Latino) in the intent-to-treat (ITT) set. Patients had mild (40.4%) to moderate (59.3%) COVID-19; 70.7% of patients were considered high risk (as defined in section 3); the median time from the initial symptom onset was 3 days; mean viral load was 6.2 $\log_{10}$ copies/ml (6.3 $\log_{10}$ copies/ml in the combined regdanvimab treatment group and 6.0 $\log_{10}$ copies/ml in placebo group) at baseline in the ITTI set. The baseline demographics and disease characteristics were well balanced across regdanvimab and placebo groups.

The study was explorative and did not have a type-1 error controlled primary endpoint. The proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28, was recorded. No deaths were reported in this study.

Proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28

Table 3: Proportion of Patients with Clinical Symptoms Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28 in Study CT-P59 3.2 Part 1: Intent-to-Treat Infected Set

	Regdanvimab 40 mg/kg	Regdanvimab 80 mg/kg	All Regdanvimab Doses	Placebo
All patients	4/101 (4%)	5/103 (4.9%)	9/204 (4.4%)	9/103 (8.7%)
Patients at high risk[a]	3/70 (4.3%)	5/76 (6.6%)	8/146 (5.5%)	9/71 (12.7%)

[a] High risk patients were defined as patients with 1 or more of the following risk factors: Age >50 years; BMI >30 kg/m^2; Cardiovascular disease, including hypertension; Chronic lung disease, including asthma; Type 1 or type 2 diabetes mellitus; Chronic kidney disease, including those on dialysis; Chronic liver disease; and Immunosuppressed, based on investigator's assessment. This data was generated by post-hoc analysis.

Note:Criterion of Hospitalisation is ≥24 hours of acute care. Criteria of oxygen therapy are at least 24 hours of supplemental oxygen care and SpO_2 measure in room air before applying supplemental oxygen showing ≤94%.

Virology

In Study CT-P59 3.2 Part 1, patients randomised to the regdanvimab treatment groups had a greater reduction in viral shedding in nasopharyngeal swab specimens (titers) based on RT-qPCR up to Day 7 compared to patients in the placebo group. The mean (SD) changes from baseline for viral shedding at Day 7 were -3.184 (1.496) and -2.290 (1.709) $\log_{10}$ copies/ml in the combined regdanvimab treatment group (-3.183 [1.579] and -3.184 [1.423] $\log_{10}$ copies/ml in the 40 mg/kg and 80 mg/kg treatment groups, respectively) and placebo group, respectively which was 39%

more reduction at Day 7 in patients treated with regdanvimab in comparison to patients administered with placebo.

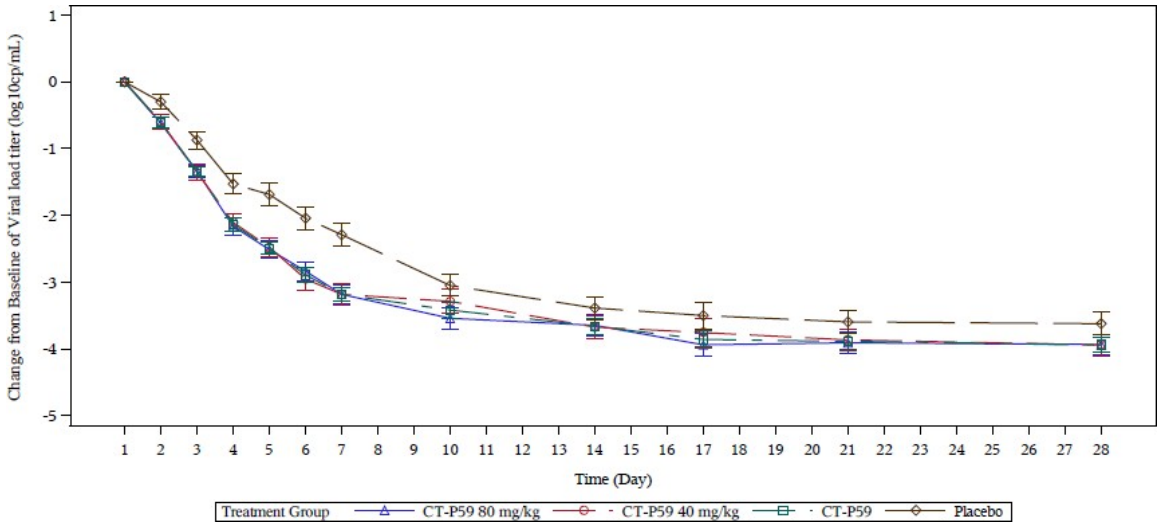

Figure 1: Mean (±SE) Change from Baseline for Viral Titer (in log_{10} cp/ml) from RT-qPCR in Study CT-P59 3.2 Part 1: Intent-to-Treat Infected Set

7. CONDITIONS FOR SAFETY MONITORING

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 6 for how to report adverse reactions.

8. DATE OF CHMP OPINION