Safety, Tolerability and Pharmacokinetics of Ensovibep in Patients with Mild-to-Moderate COVID-19

Preliminary report of a phase 2a, open-label, single-dose escalation study

8th ESWI Influenza Conference – virtual edition, 6 Dec 2021
Session: *Antiviral and immune therapy for influenza, RSV disease and COVID-19*

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Disclosures

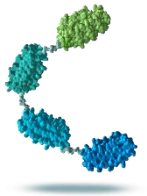
- **J.L. van der Plas, M.F.J.M. Vissers, C.L. Berends, E. Causevic, I.M.C. Kamerling**: are investigators and employees of the Centre of Human Drug Research (CHDR)
- **J.L. van der Plas, I.M.C. Kamerling** have unremunerated affiliations with the Leiden University Medical Center
- **M.L.M. Prins, G.H. Groeneveld** are investigators and are employees of the Leiden University Medical Center
- **G. Tresch, M. Soergel, E. Fernandez, C. Zitt, V. Stavropoulou, M. Zimmermann, R.F. Drake** are employees of Molecular Partners AG, Schlieren, Switzerland
- This study was sponsored by Molecular Partners AG, Schlieren, Switzerland

Introduction

- Therapeutic options for COVID-19 remain* limited

- Conditional approval of antibody therapy (mAb) against COVID-19
  Recommended authorisation for two mAb therapies (11 Nov 2021)

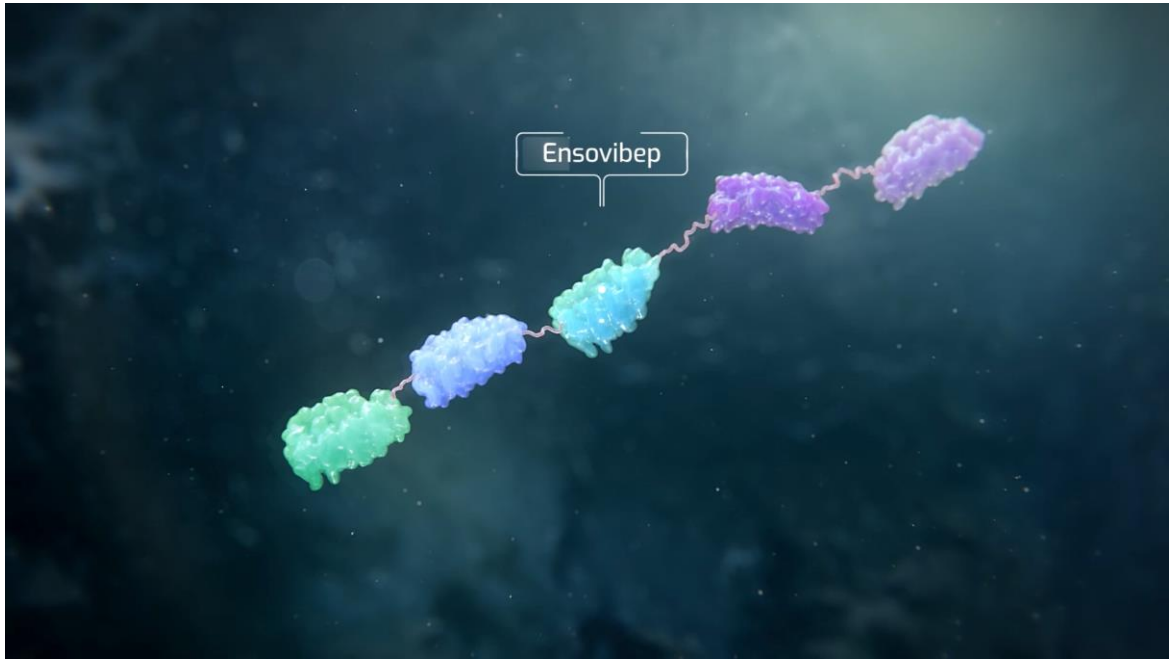
- DARPin therapeutic protein vs mAb for COVID-19



* As of 15 November 2021

Ensovibep: A Recombinant Multi-unit DARPin Molecule

- DARPin: **D**esigned **A**nkyrin **R**epeat **P**rote**in**s
  - Engineered; based on natural ankyrin scaffold
    - Natural ankyrins are modulators of many biological processes
  - Protein-protein binding with affinities in pM range
- Ensovibep has 5 DARPin units linked in series:
  - 3 DARPin units (3 distinct paratopes) that bind to the RBD of SARS-CoV-2 spike protein trimer
  - 2 identical human serum albumin (HSA) binding units
- Ensovibep characteristics compared with antibodies
  - Smaller size
  - No Fc region (no potential for ADE)
  - Cooperative trivalent binding to target
  - Simple *E. coli* expression system
    - Potential for more rapid production with high yield



Visualisation of ensovibep binding to the SARS-CoV-2 spike protein trimer

Pre-clinical and Early Phase Clinical Data supportive of ongoing registrational work

- Preclinical studies: high potency neutralizing activity against multiple variants and no development of escape mutants[1]

- First-in-Human administration (NCT04870164): favorable safety and pharmacokinetic profile[2]

- Here we present preliminary data of the **First-in-Patient** administration from the:

  Phase 2a Open Label, Non-comparative, Single Dose Escalation Study to Evaluate the Dynamics of Viral Clearance, Pharmacokinetics and Tolerability of Ensovibep in Patients With Symptomatic COVID-19 Disease (NCT04834856).

1. F. Malvezzi et al., Oral Abstract Session 2, ISIRV-WHO Virtual Congress on Covid-19, Influenza and RDV, October 2021
2. M. Soergel et al., Oral Abstract #206, ESWI 2021

Phase IIa open label, non-comparative, single dose escalation study

Study design

- Ambulatory, mild-to-moderate COVID-19 patients
- Single IV administration (flat dose; 225 mg or 600 mg)
- Dose escalation design
- No control group, open label dosing

Primary objectives

- Characterize dynamics of viral clearance (culture and qPCR)
- Evaluate pharmacokinetics in COVID-19 patients

Secondary objectives

- Ensovibep safety and tolerability
- Evolution of clinical symptoms follow administration

Exploratory objectives

- Immunogenicity of single dose of ensovibep (ADA formation)
- Occurrence of endogenous virus neutralising antibodies
- Symptoms of Long-COVID-syndrome

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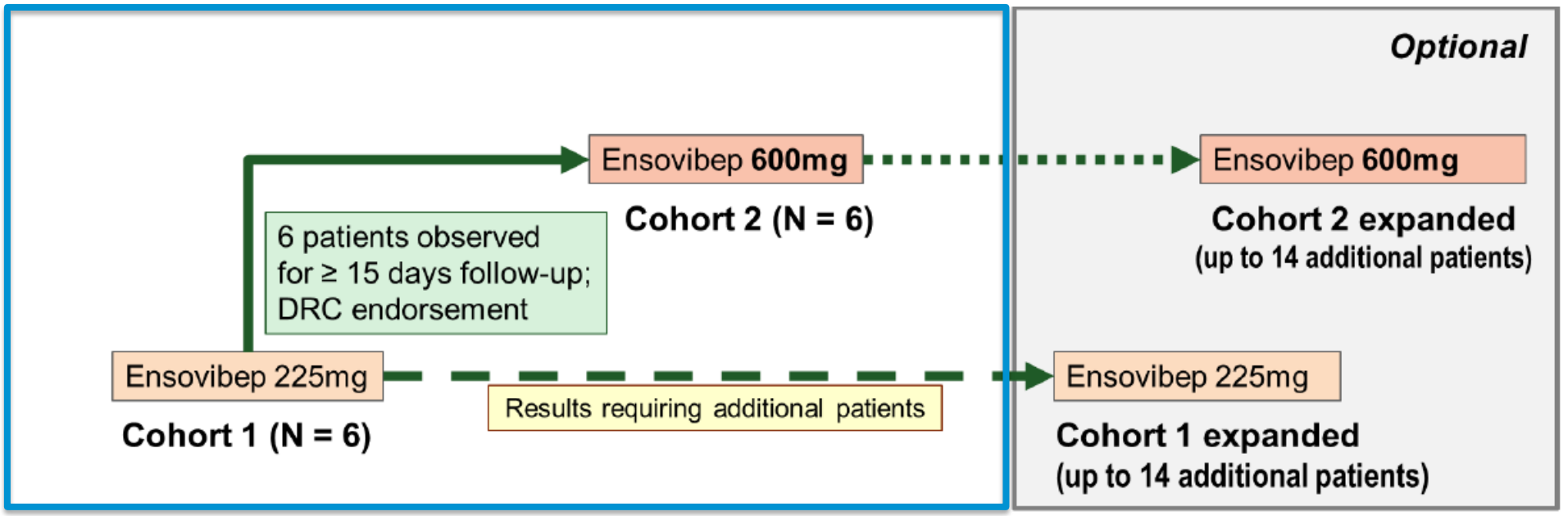
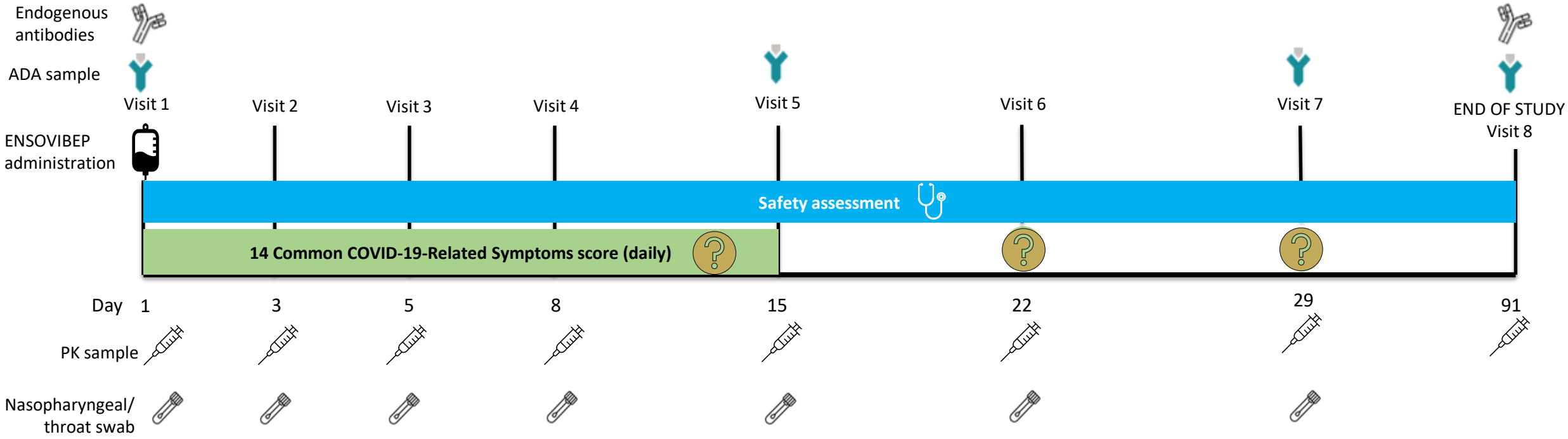
Dose Escalation Design with Options for Cohort Expansion



Schedule of Assessments*



*Simplified version

Patient Population

Recruited via Municipal Health Care Service:

If PCR-confirmed SARS-CoV-2 infection and expressed interest in study participation

Target study population:
Ambulatory symptomatic patients with mild-to-moderate COVID-19

Inclusion:

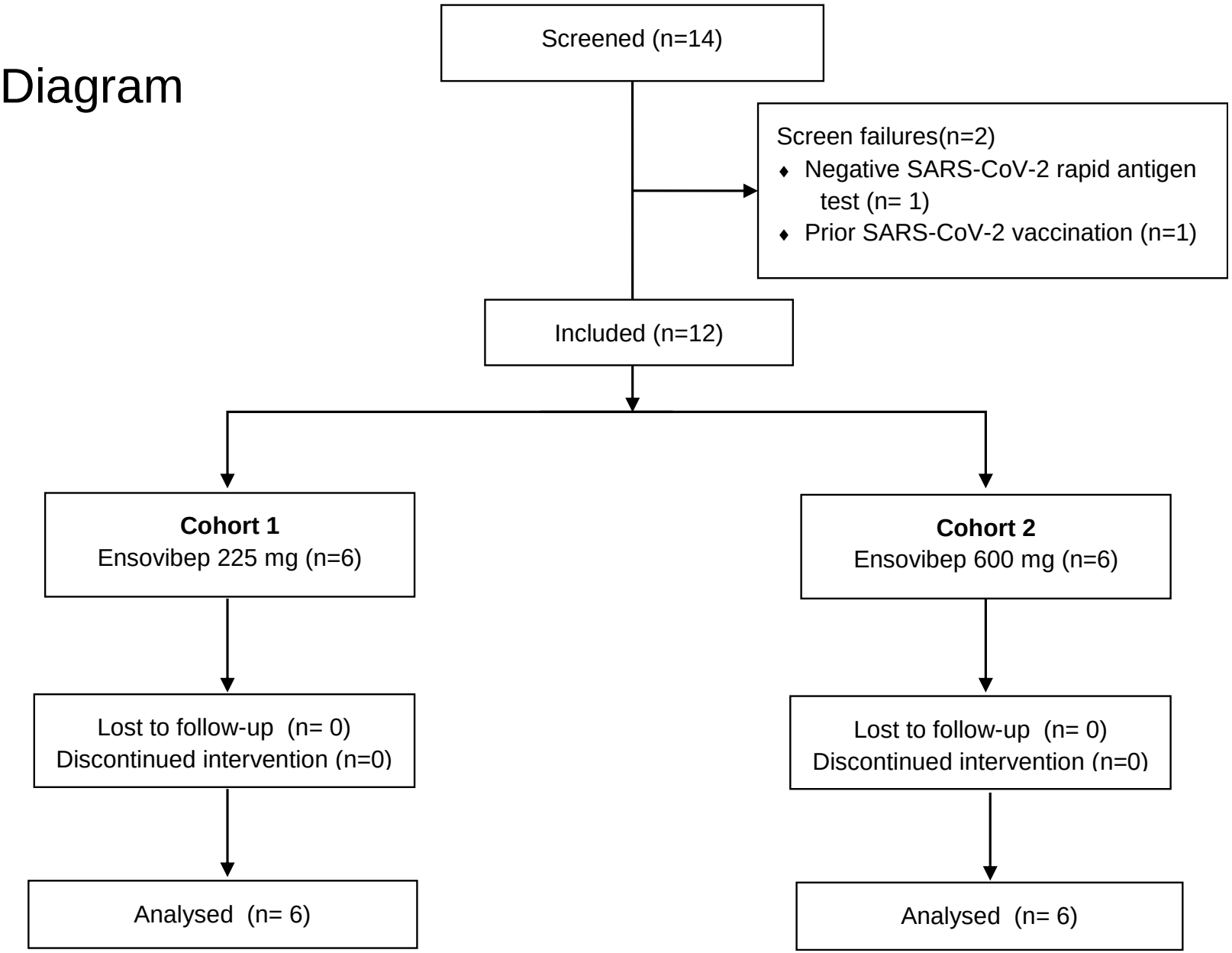
- Males and females
- 18 – 70 years
- 1 or more mild-to-moderate COVID-19 symptoms
- Positive SARS-CoV-2 nose throat swab on dosing day (rapid antigen test – confirmed by PCR at baseline)

Exclusion:

- High risk of COVID-19 related complications or mortality
- Required hospitalization
- Prior or concurrent medication against SARS-CoV-2 (incl Abs and convalescent serum)
- Immunocompromised status

Subjects were not vaccinated prior to inclusion

Consort Diagram



Patient Baseline Demographics

	Cohort 1, 225mg (n=6)	Cohort 2, 600mg (n=6)
Sex, n female (%)	2 (33)	2 (33)
Age	23 (21-26)	24 (22-44)
BMI	26 (24-30)	25 (22-30)
Days between symptom onset and dosing	5 (2-8)	5 (3-5)
Positive qPCR result, n (%)	6 (100)	6 (100)

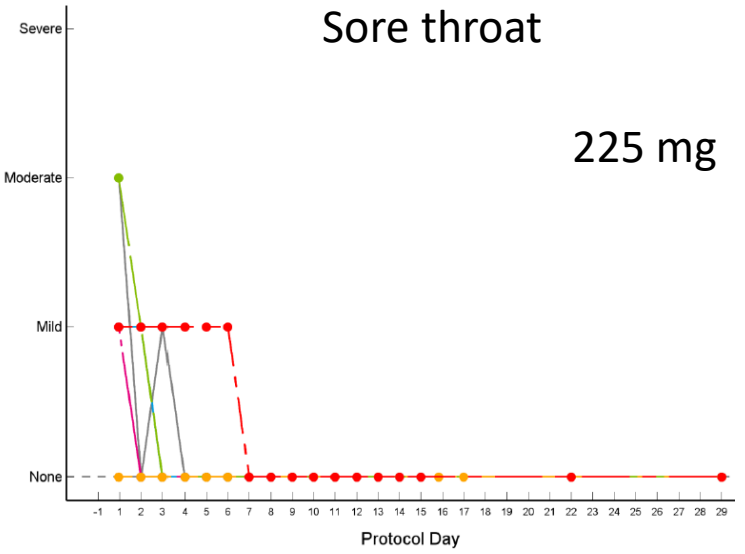
Data are presented as median (range) unless indicated otherwise. BMI, body mass index; qPCR, quantitative polymerase chain reaction.

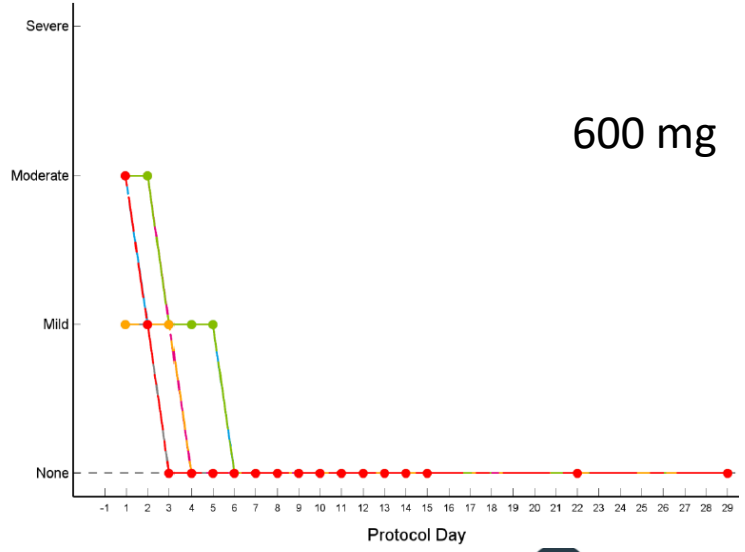
Favorable safety and tolerability profile

- Treatment emergent adverse events (TEAE) were of mild-to-moderate severity and transient
- Reporting rate of IMP-related TEAEs was higher (4) in low dose 225 mg group compared with high dose 600 mg group (0)
- No infusion related reactions, hypersensitivity, or worsening of COVID-19 severity following ensovibep administration in patients
- No findings of clinical concern in vital signs, safety blood chemistry
- No discontinuations, hospitalizations or deaths → No serious adverse events (SAE)

Reduction of COVID-19 Symptoms

- Time course of symptoms and severity was explored using the 14-common COVID-19-related symptoms questionnaire*
- Symptom severity decreased over time with no recurrence during the surveillance period
- Symptoms such as sore throat, shortness of breath, myalgia, chills, feeling feverish, nausea, vomiting, diarrhea resolved within a week in both dose groups.
- Runny nose (2 weeks) and headache (4 weeks) took more time to resolve in individual subjects
- Cough, fatigue, smell and taste loss persisted longer, in line with literature[3,4]
- Time course and severity of symptoms was overall similar for the 225 mg and 600 mg dose levels



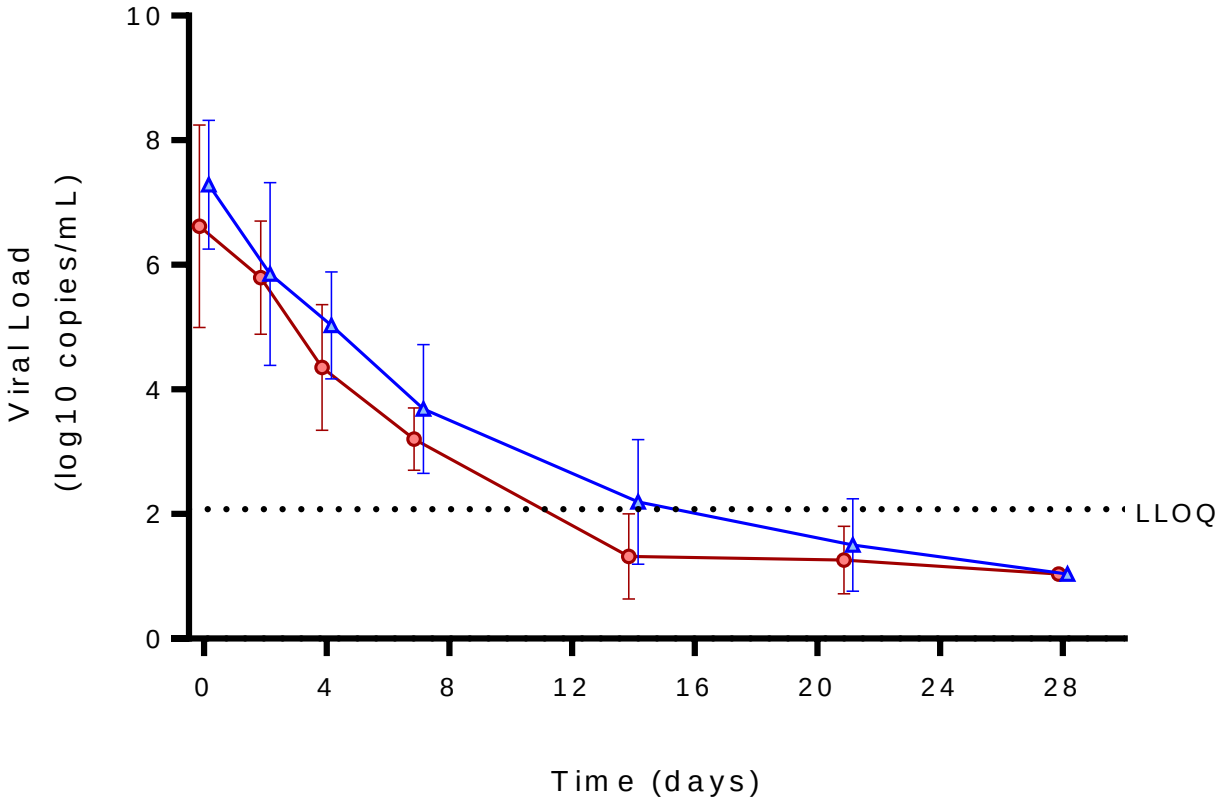


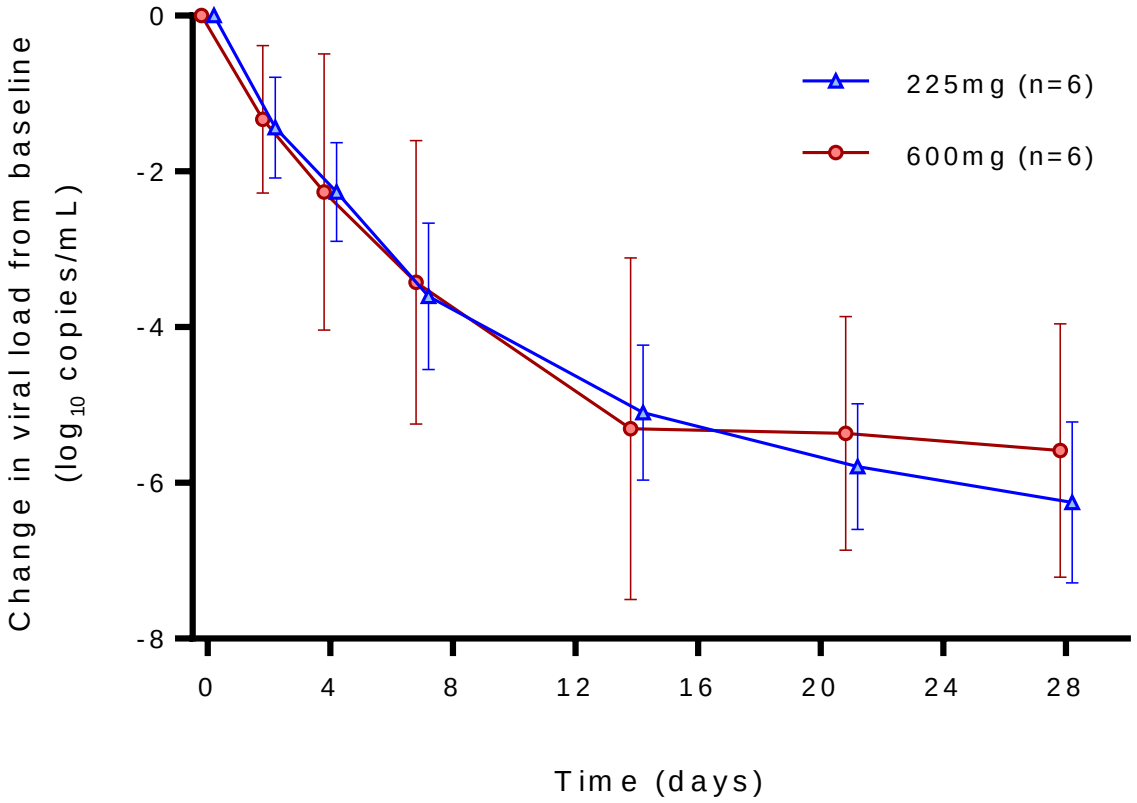
*FDA. Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment- Guidance for industry. September 2020.

[3]Lechien JR et al., 2020, Clinical and Epidemiological Characteristics of 1,420 European Patients with Mild-to-Moderate Coronavirus Disease 2019, J Intern Med, 2020 Sep;288(3):335-344. doi: 10.1111/joim.13089.

[4]Boscolo-Rizzo P,, et al., 2020, Evolution of Altered Sense of Smell or Taste in Patients With Mildly Symptomatic COVID-19, JAMA Otolaryngol Head Neck Surg, 146(8):729–732.

Viral Load (qPCR) Showed a Consistent Decrease for Both Dose Levels

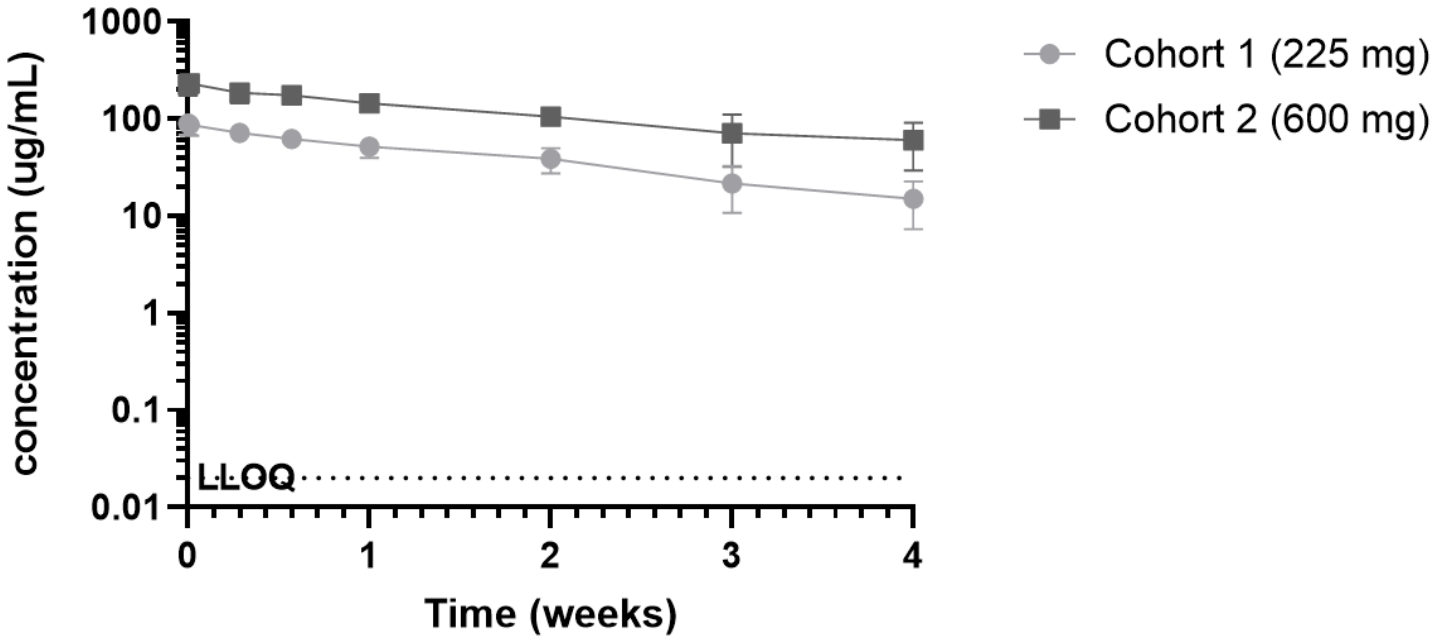




Mean viral load. Error bars depict standard deviations. qPCR results that were less than the lower limit of quantification (LLOQ) were imputed as LLOQ/2 (= 1.04 $\log_{10}$ copies/mL).

Ensovibep Serum Concentrations Followed Mono-exponential Elimination with Long Half-life

- Estimated median half-life for ensovibep in patients across cohorts was approximately 13 days (range: 10-19 days)
- Approximate dose-proportional increase in C_{max} and AUC_{D0-29}
- All patients had expected exposure at 2 weeks - consistent with healthy volunteer study (CP101)
  - 10 patients maintained full exposure at 29 days
  - 2 patients demonstrated an initial decrease of expected exposure after Day 21



Mean (+/- SD) serum concentration time traces of ensovibep in COVID-19 patients. LLOQ: lower limit of quantification of the analytical assay is 0.02 ug/mL.
PK assay: electrochemiluminescence assay measuring ensovibep able to bind RBD (free drug)

Endogenous SARS-COV-2 Virus Neutralizing Activity Detectable at Day 91

- No patients had virus neutralizing activity in serum prior to drug administration
  - MN_{80} assay; measures the titer at which viral cell infection is inhibited by 80%
- Virus neutralizing activity was detected in 50% of the patients at day 91 (Final Follow-up Visit) in both dose groups
- Literature suggests a great heterogeneity in the kinetics of virus neutralizing response waning in patients recovered from COVID-19
- Ensovibep did not prevent the development of endogenous virus neutralizing response

Limitations

- Exploratory study (small sample size, no control group)
- Study population consisted predominantly of young subjects (20-30 yrs)
- Limited literature on FDA COVID-19 symptom questionnaire for comparison with natural disease course (stratified for age)

Conclusions

- Ensovibep first-in-patient data: 225 mg and 600 mg **safe and well tolerated**
  - No disease enhancement, infusion related reactions, dose limiting toxicities observed
- Viral load data (qPCR) showed a **comparable decline for both dose levels**
- **Viral cultures titers of NP swabs became negative** in those with positive titers on baseline (3-5 days)
- **Favorable PK profile:** Confirmation of long half life (~13 days) + prolonged exposure >2 weeks in all dosed patients
- **Complete COVID-19 clinical symptom recovery** in the study population

- Phase II/III study of ensovibep in symptomatic ambulatory patients with COVID-19 (**EMPATHY:** NCT04828161) ongoing

Acknowledgements

Centre for Human Drug Research
Ingrid de Visser – Kamerling
Maurits Vissers
Cecile Berends
Erica Klaassen
Kirsten Bergmann
Erna Causevic

Leiden University Medical Center
Geert Groeneveld
Manon Prins
Research Nurses (Klinische Research unit Interne Geneeskunde)

Molecular Partners
Roxana Drake
Philippe Legenne
Michael Stumpp
Randall Watson
Marcel Walser

Viroclinics
Danny Duijsings