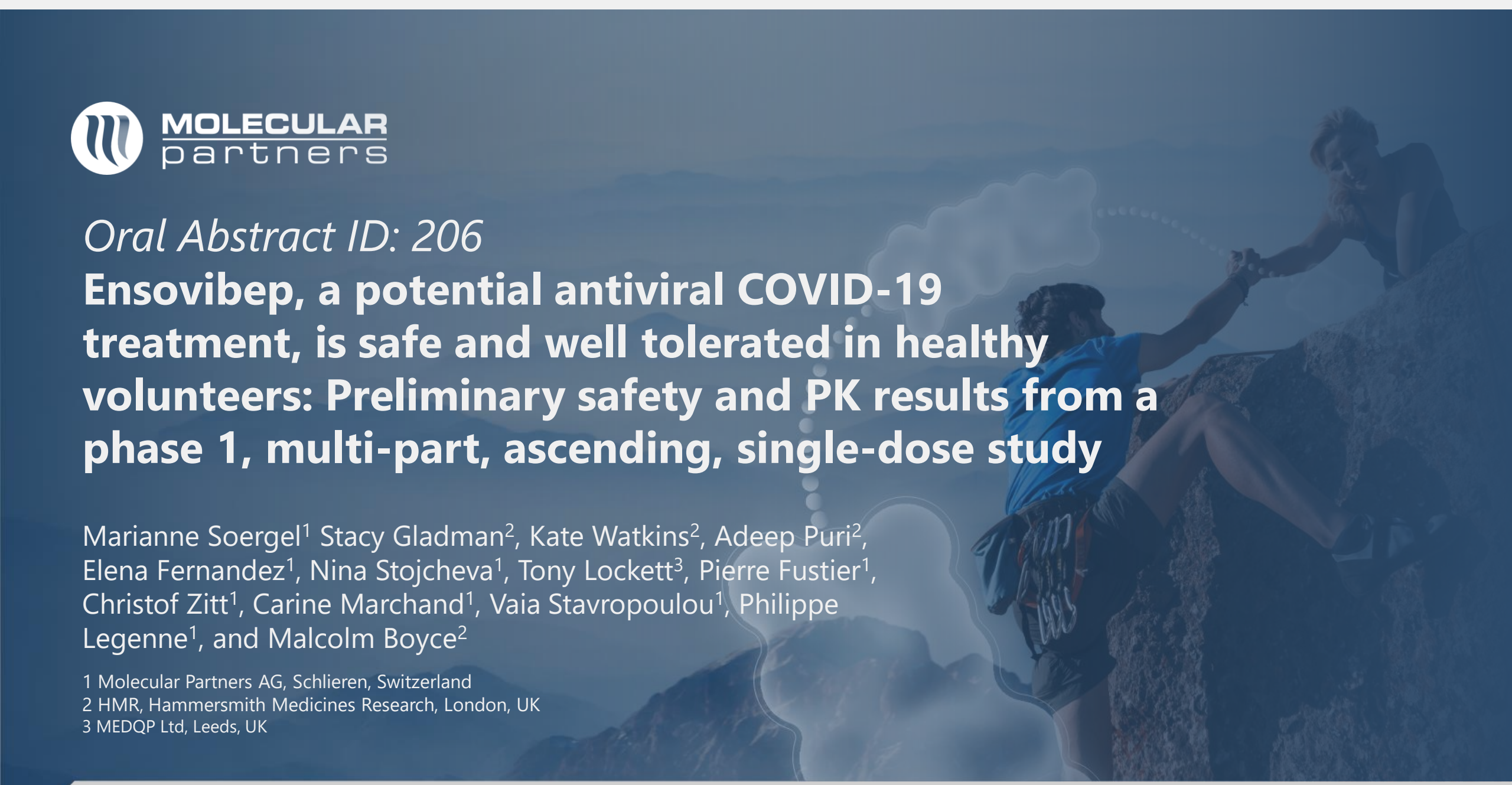


Oral Abstract ID: 206

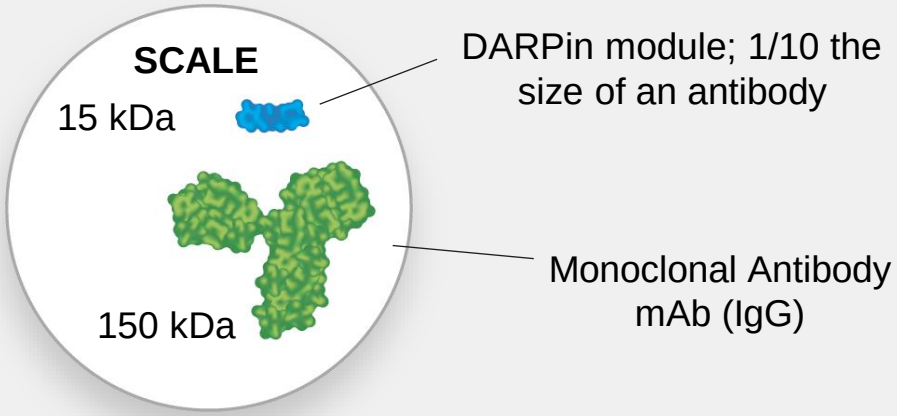
Ensovibep, a potential antiviral COVID-19 treatment, is safe and well tolerated in healthy volunteers: Preliminary safety and PK results from a phase 1, multi-part, ascending, single-dose study

Marianne Soergel[1] Stacy Gladman[2], Kate Watkins[2], Adeep Puri[2], Elena Fernandez[1], Nina Stojcheva[1], Tony Lockett[3], Pierre Fustier[1], Christof Zitt[1], Carine Marchand[1], Vaia Stavropoulou[1], Philippe Legenne[1], and Malcolm Boyce[2]

1 Molecular Partners AG, Schlieren, Switzerland
2 HMR, Hammersmith Medicines Research, London, UK
3 MEDQP Ltd, Leeds, UK

8th ESWI Influenza Conference – virtual edition, 4 – 7 Dec 2021
SCS11: Human influenza, RSV disease and COVID-19 challenge studies

DARPin* Platform

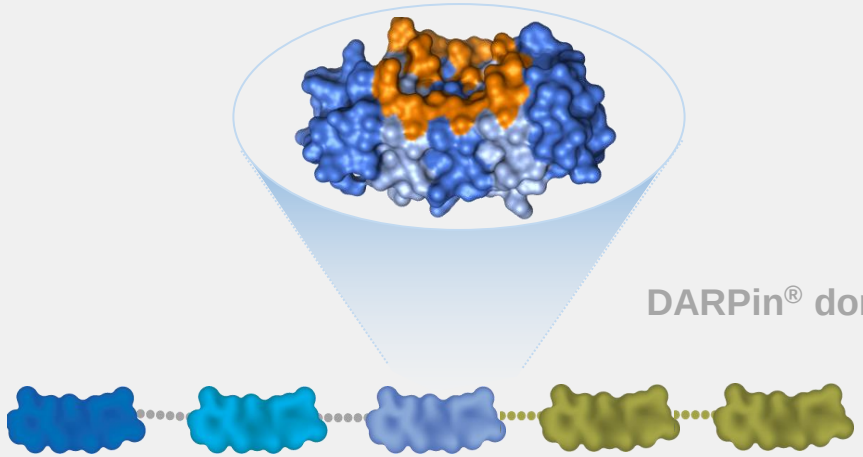


DARPin drug candidates are best-in-class multi-specific binders

- Fast generation of multi-DARPin candidates (within weeks)
- High potency (<5-100 pM) - active at very low concentration
- High solubility (> 100 mg/ml) – ideal drug properties
- Long half-life (HSA DARPin) – 2+ weeks in humans
- No DARPin backbone toxicity reported in 3 clinical programs for systemic administration
- Production in *E. coli* (not in cell cultures), i.e., fast with high yield, and not competing for mAb production facilities

DARPin Designs

Rigid-body target binding



- DARPin module – Small size – 15 kDa
- **Multi-DARPin drug candidates** are assembled from mono-DARPin modules
- Multiple targeting in one drug candidate

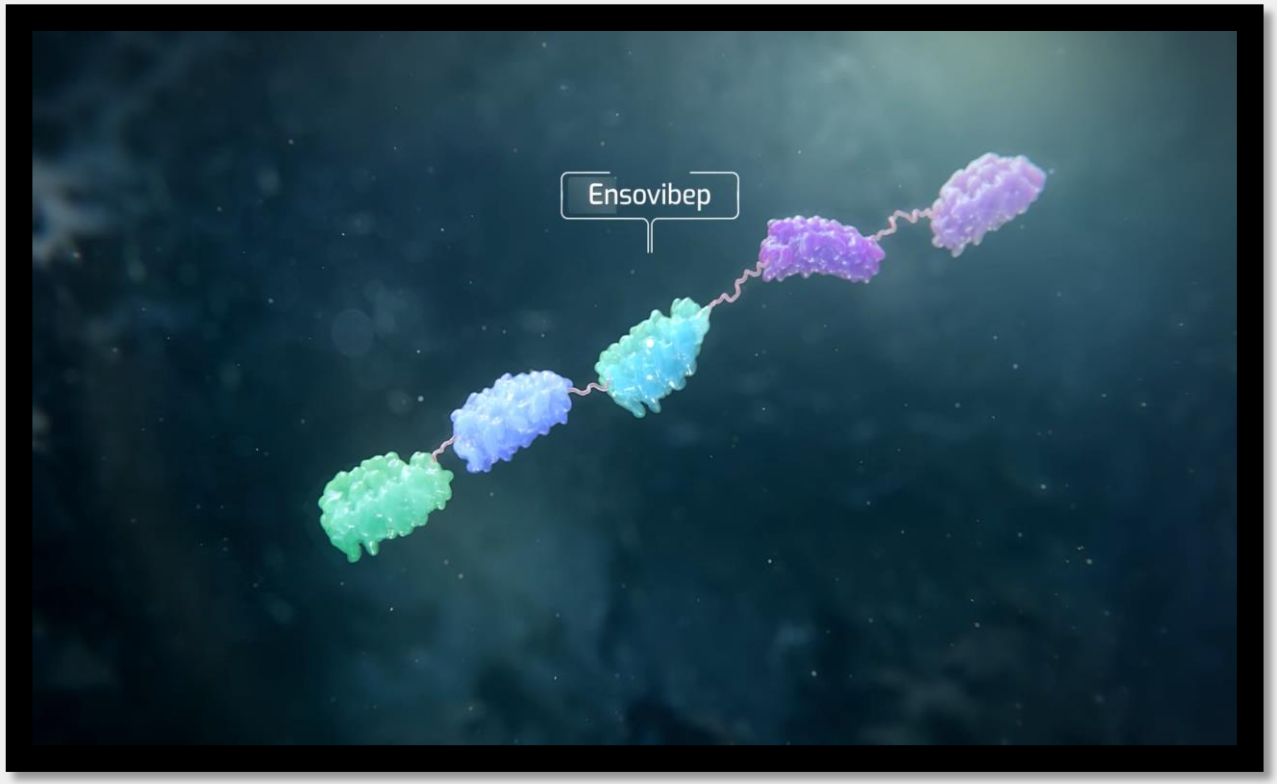
* DARPin: designed ankyrin repeat protein

Ensovibep – A DARPin that Binds 3 RBD of the Spike Protein Trimer

The COVID-19 pandemic has highlighted the need for not only effective vaccines but also effective antivirals.

Ensovibep is the first in a new class of antivirals that utilizes three-concatenated DARPin domains to cooperatively bind all three RBD units of the SARS-CoV-2 spike protein trimer. This effectively stops the spike protein interaction with the ACE2 receptor, neutralizing the virus particle.

Ensovibep has been shown to maintain potency against all currently known variants of concern in *in vitro* pre-clinical studies[1], shown encouraging *in vivo* activity in animal models[2], and has two additional Human Serum Albumin (HSA) binding DARPin domains to increase half-life.

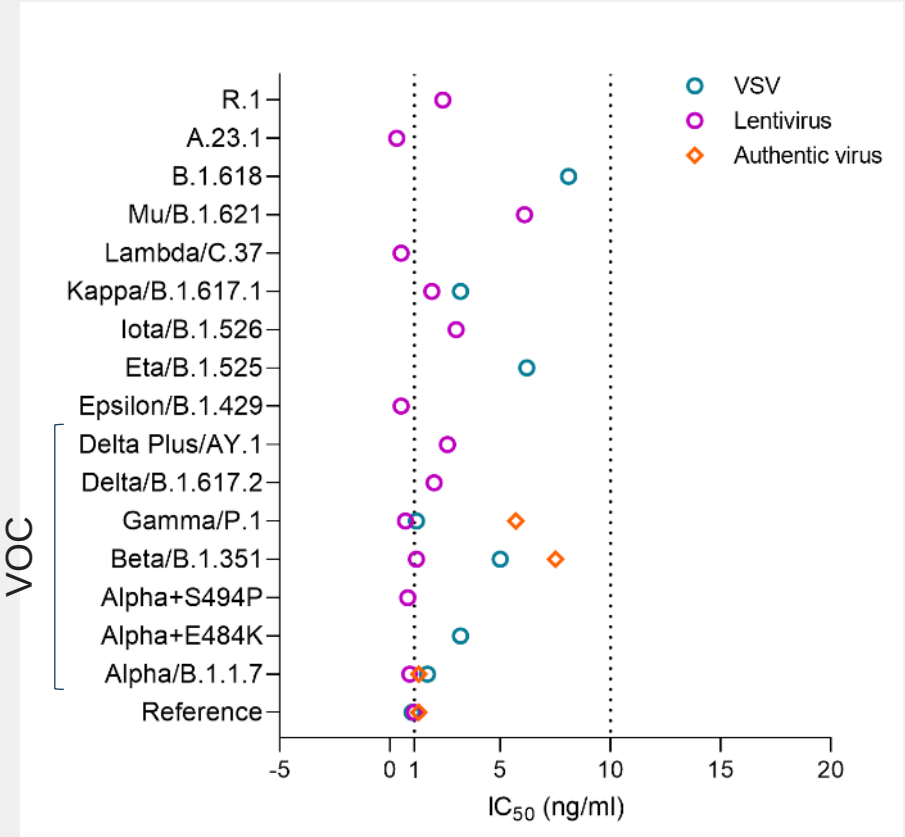


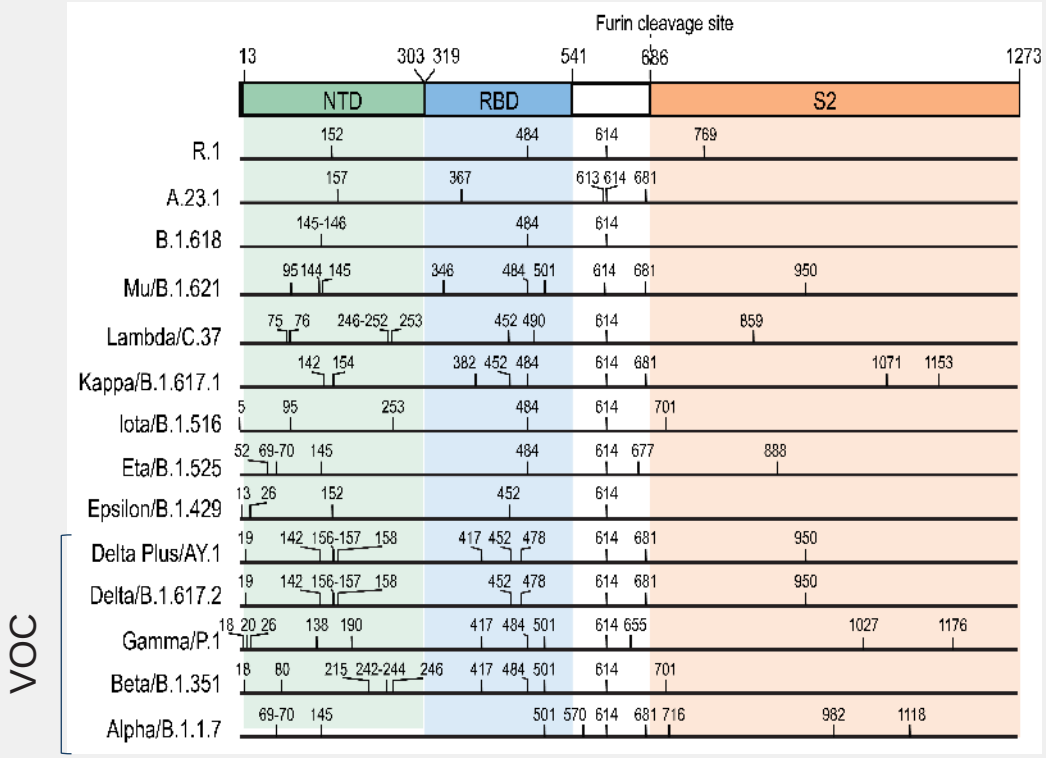
Visualisation of ensovibep binding to the SARS-CoV-2 spike protein trimer

1. F. Malvezzi et al., Oral Abstract Session 2, ISIRV-WHO Virtual Congress on Covid-19, Influenza and RDV, October 2021
2. Walser et al., bioRxiv 2020.08.25.256339; doi 10.1101/2020.08.25.256339

Ensovibep; High potency on known* frequent variants of concern

- Neutralization assays on Lentivirus or VSV-based pseudoviruses, as well as on authentic SARS-CoV-2 virus, demonstrate high potency (IC_{50}: ~1-8 ng/ml) against all frequent variants to date (October 2021)

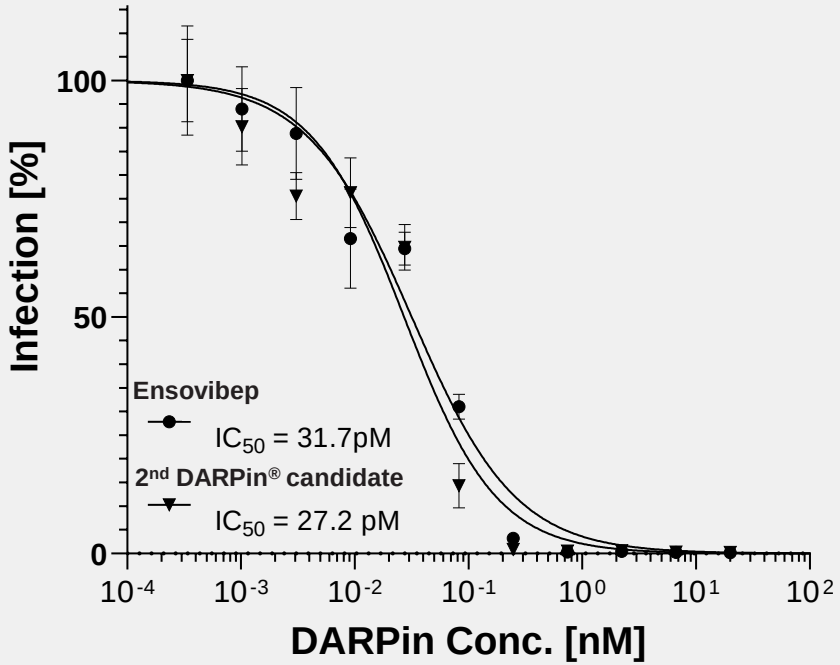




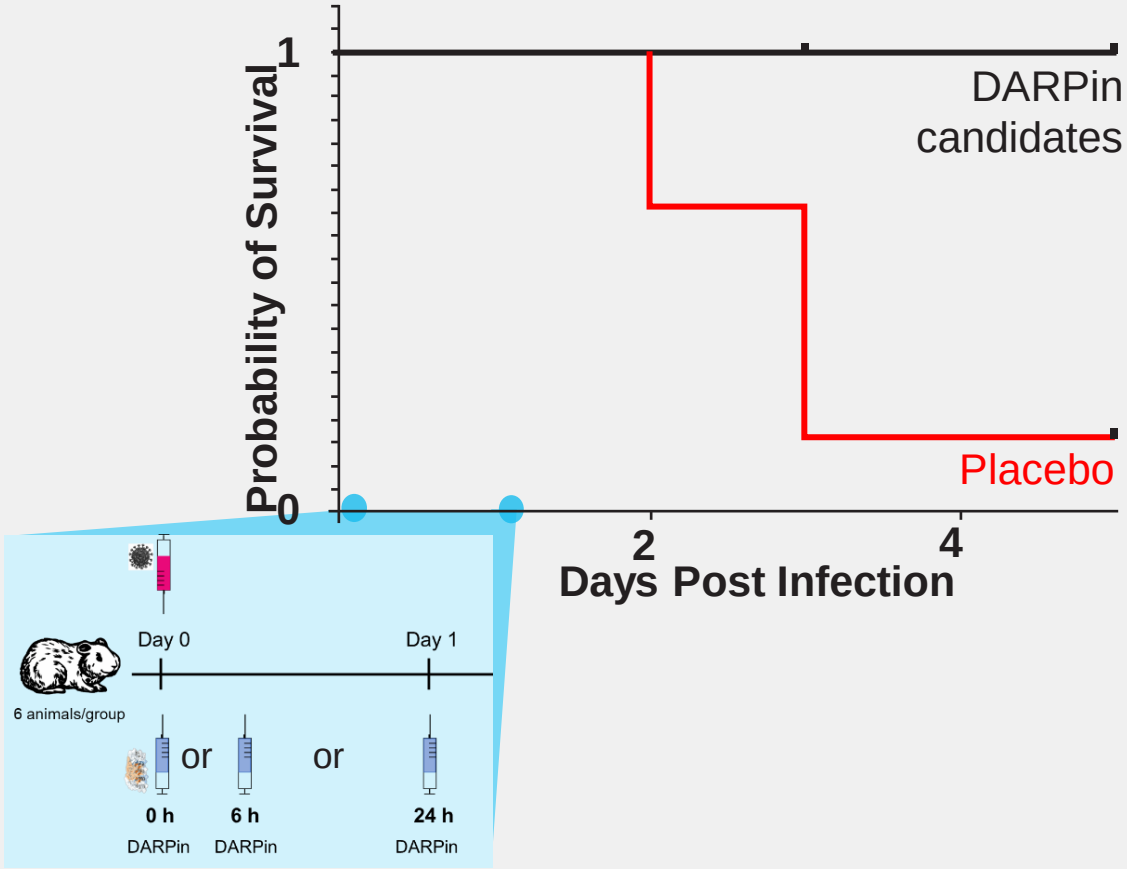
Neutralization assays performed in collaboration with CHUV, Lausanne, CH; Spiez Laboratory, CH; ACTIV consortium/FDA

High-Potency in vitro Inhibition Translates to Pre-clinical in vivo Prophylactic and Therapeutic Properties

In vitro activity: Pseudotype neutralization assay[1,2]



In vivo activity: Kaplan-Meier plot - Hamster model (6 animals/group)[2]



High potency

Trispecific binding leads to potency in the low pM range

DARPin, designed ankyrin repeat proteins; nM, nanomolar; pM, picomolar.

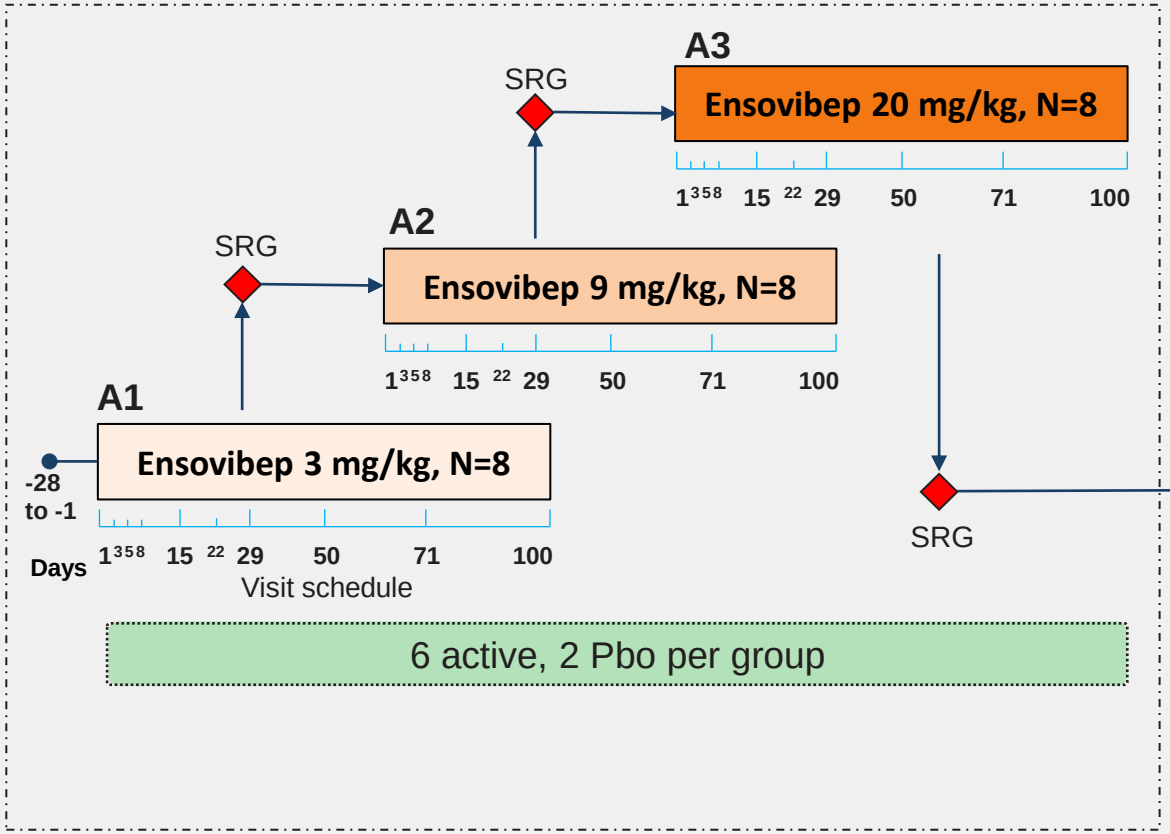
1. Walser M. *Biorxiv*. 2021. https://doi.org/10.1101/2020.08.25.256339;
2. Walser M. *Top Antivir Med.* 2021;29(1):483 (session: Spotlight-H1)

Study Objectives and population

- Primary objective:
  - To determine the safety and tolerability of single ascending doses of ensovibep in healthy subjects.
- Secondary objectives:
  - To determine concentration-time traces and PK parameters of ensovibep after single dose administration via IV infusion or bolus IV injection, SC injection, or IM injection
  - To assess the formation of anti-drug antibodies (ADA) to ensovibep and their impact on safety, pharmacokinetics and pharmacodynamics
- Inclusion criteria:
  - Males and Females aged 18 – 65 y; BMI 18 – 35 kg/m^2; normotensive, non-smokers, otherwise healthy

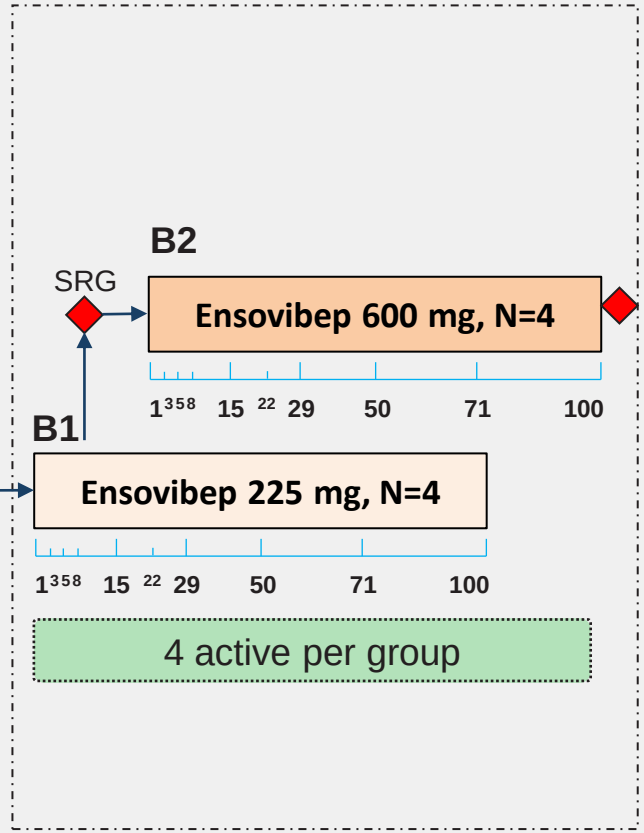
Study Design

Part A: double-blind, randomised, placebo controlled, sentinel ascending dose



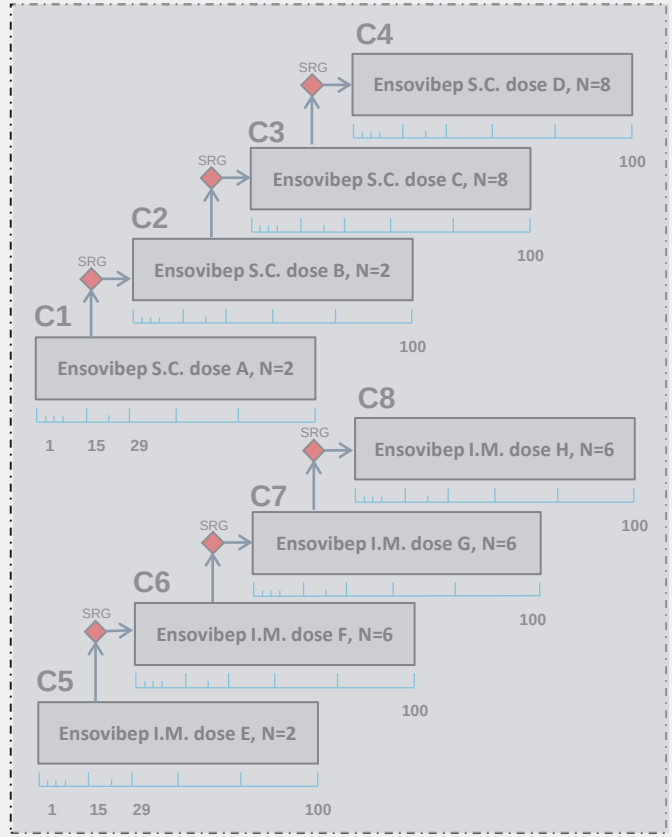
1 hour i.v. infusion

Part B: open-label, single ascending dose



Rapid “bolus” i.v. administration

Part C: open-label, single ascending dose



s.c. and i.m. administration

Subject Demographics and Disposition

	Part A (IV infusion over 60 min)					Part B (bolus injection)	
Variable	**Placebo**	**3 mg/kg**	**9 mg/kg**	**20 mg/kg**	**All**	**225 mg**	**600 mg**
n	6	6	6	5	23	4	4
Age [y], median (range)	40.0 (29-64)	50.5 (28-60)	57.0 (31-64)	39.0 (20-61)	45.0 (20-64)	47.5 (31-61)	44 (22-51)
Sex, F (%)	2 (33.3)	1 (16.7)	0	1 (20.0)	4 (17.4)	0	0
BMI [kg/m^2] median (range)	26.25 (20.8-29.7)	26.05 (21.0-34.1)	25.85 (22.6-29.6)	26.00 (22.3-29.1)	26.10 (20.8-34.1)	28.85 (26.6-33.2)	23.6 (21.2-28.1)
Prior Covid-19 Vaccination	0	1	0	0	1	0	0

	Subject Disposition at Day 100 (End of Study)					Subject Disposition at Day 100	
Included	6	6	6	5	23	4	4
Completed	6	6	6	5	23	4	4
Withdrawn	0	0	0	0	0	0	0

Ensovibep – Overview of Treatment-emergent AEs

	Part A TEAEs at End Of Study (EOS)					Part B TEAEs up to Day 100		
Number of subjects with	**Placebo (N=6) n**	**3 mg/kg (N=6) n**	**9 mg(kg (N=6) n**	**20 mg/kg (N=5) n**	**All Subjects (N=23) n (%)**	**225 mg (N=4) n**	**600 mg (N=4) n**	**All B Subjects (N=8) n (%)**
Any TEAE	4 [8]	1 [2]	1 [1]	4 [6]	10 (43.5) [17]	1 [2]	3 [7]	4 (50.0) [9]
Any TE SAE	0	0	0	0	0	0	0	0
Any Related TEAE	0	0	1 [1]	2 [3]	3 (13.0) [4]	1 [1]	1 [3]	2 (25.0) [4]
Any TEAE leading to Withdrawal	0	0	0	0	0	0	0	0
Severity of any TEAE:								
Mild	2	0	1	2	5	1 [2]	3 [3]	4 (50.0) [5]
Moderate	2	1	0	2	5	0	2 [4]	2 (25.0) [4]
Severe	0	0	0	0	0	0	0	0

n = number of subjects (subjects with ≥1 TEAE are counted only once per system organ class and preferred term)
[ ] = number of TEAEs

Ensovibep – Overview of AEs Reported as Drug-related

System Organ Class	Preferred Term	Part A drug-related TEAEs at End Of Study					Part B drug-related TEAEs up to Day 100		
		Placebo (N=6) n	3 mg/kg (N=6) n	9 mg(kg (N=6) n	20 mg/kg (N=5) n	All A Subjects (N=23) n (%)	225 mg (N=4) n	600 mg (N=4) n	All B Subjects (N=8) n (%)
N subjects with any drug-related TEAEs		0	0	1 [1]	2 [3]	3 (13.0) [4]	1 [1]	1 [3]	2 (25.0) [4]
General disorders and administration	Infusion site bruising	0	0	0	1 [1]	1 (4.3) [1]	0	0	0
	Infusion site erythema	0	0	1 [1]	0	1 (4.3) [1]	0	0	0
	Infusion site pain	0	0	0	0	0	1 [1]	1 [1]	2 (25.0) [2]
Musculoskeletal and connective tissue disorders	Pain in extremity	0	0	0	1 [1]	1 (4.3) [1]	0	0	0
Skin and subcutaneous tissue disorders	Hypersensitivity vasculitis	0	0	0	1 [1]	1 (4.3) [1]	0	0	0
Gastrointestinal disorders	Nausea	0	0	0	0	0	0	1 [1]	1 (12.5) [1]
	Diarrhoea	0	0	0	0	0	0	1 [1]	1 (12.5) [1]

n = number of subjects (subjects with ≥1 TEAE are counted only once per system organ class and preferred term)
[ ] = number of TEAEs

AEs of Interest

Cutaneous hypersensitivity vasculitis and body aches (non-serious, moderate)

- Dose 20 mg/kg via 1 hour i.v. infusion
- Skin manifestations Day 21 post dose, diagnosed as leucocytoclastic vasculitis by dermatologist, resolved Day 38; body aches Day 24 – 26; no further clinical manifestations
- Labs: CRP and D-dimer transiently elevated;
  Complement C3 normal;
  Pre-treatment RF 16.8 IU (< 14); ANA 1:80, both stable during event; remaining autoimmune panel negative
- Renal: urine free of protein or blood,
  serum creatinine normal
- PK: non-linear decline of exposure after day 15

Symptomatic COVID-19

- Dose 600 mg via rapid i.v. administration (“bolus”)
- Routine COVID test Day 8 positive, thus quarantined for 10 days (no sampling till day 19)
- Symptoms Day 10, resolved by Day 16:
  fever, loss of smell/taste, runny nose, cough
- Mild shortness of breath ~ Day 21,
  resolving after ~ 3 weeks
- PK: non-linear decline of exposure between day 8 and day 19

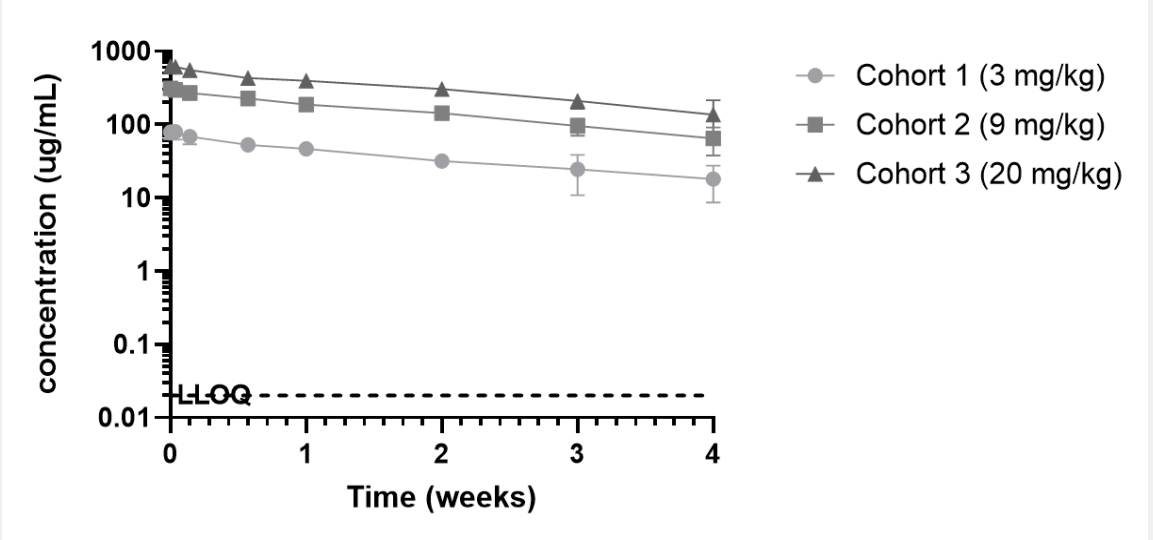
Ensovibep is Safe and Well Tolerated

- Ensovibep showed clinically good tolerability and a favorable safety profile
  - No serious or severe adverse events reported
  - One hypersensitivity event at a supratherapeutic dose; moderate and self-limited

- Triplicate ECGs compared to baseline: No QTc prolongation

Half-life and Exposure in Group A (1-hour infusion)

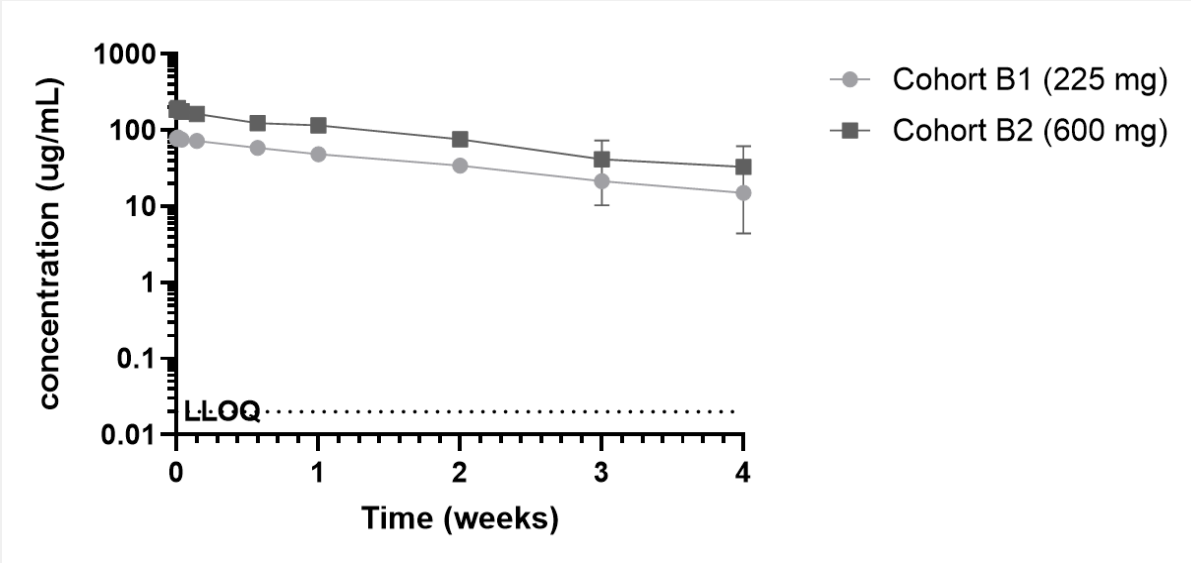
- Estimated median half-life for ensovibep in healthy subjects across Part A cohorts was approximately 15 days (range: 10-24 days);
- Approximately dose-proportional increase in C_{max} and AUC_{D0-29}
- All subjects maintained exposure for at least 2 weeks, with clearance following an expected mono-exponential elimination
  - In 3 subjects (one on each dose level) drug levels diverged from mono-exponential elimination after week 3



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

Half-life and Exposure in Group B (rapid i.v. administration)

- In Bolus cohorts (Part B) estimated median half-life for ensovibep in healthy subjects was approximately 14.0, range: 12.1 – 20.4 days
- Approximately dose-proportional increase in C_{max} and AUC_{D0-29}
- All subjects maintained exposure for at least one week, with clearance following an expected mono-exponential elimination
  - In 2 subjects (on the high dose) drug levels diverged from mono-exponential elimination after week 2



Mean (+/- SD) serum concentration time traces of ensovibep in healthy subjects following rapid intravenous infusion. LLOQ: lower limit of quantification of the analytical assay, 0.02ug/mL. PK assay: electrochemiluminescence assay measuring ensovibep able to bind to RBD (free drug)

Summary and Conclusions

- Ensovibep, at the doses examined and administered intra-venously by 1h infusion or as a rapid i.v. “bolus” administration was well tolerated and safe in healthy volunteers
- Ensovibep’s PK parameters and half-life of 14-15 days are suitable for a single-dose administration for treatment of COVID-19

- Viral clearance is being evaluated in an open label Phase 2a study in ambulatory Covid-19 patients (NCT04834856 see J. v.d. Plas – Oral Abstract 186 ESWI 2021)
- Evaluation of clinical and virologic efficacy is ongoing in randomized controlled Phase 2b/3 trials: EMPATHY and Phase 3 ACTIV3 trials (NCT04828161, NCT04501978) in ambulatory and hospitalised patients, respectively

Thank you! Questions?