Ensovibep, a SARS-CoV-2 Multi-Variant Neutralizing DARPin Therapeutic

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Antibody Engineering & Therapeutics Europe
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Molecular Partners AG, Switzerland
(SIX: MOLN, NASDAQ: MOLN)

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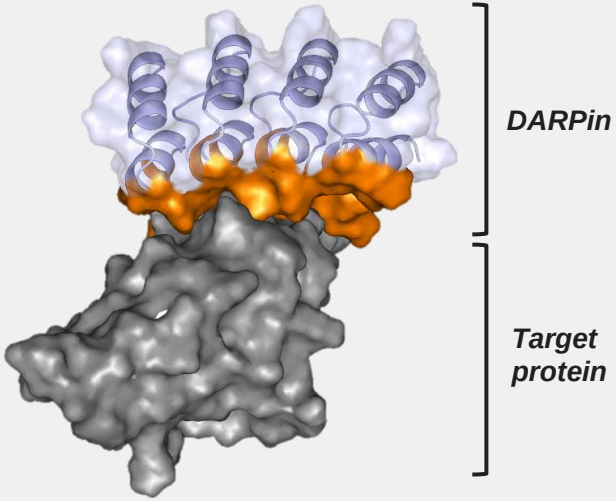
P3 ID 437809

DARPin Modality: The Core of our Drug Engine

DARPins are binding proteins derived from natural ankyrin repeat proteins



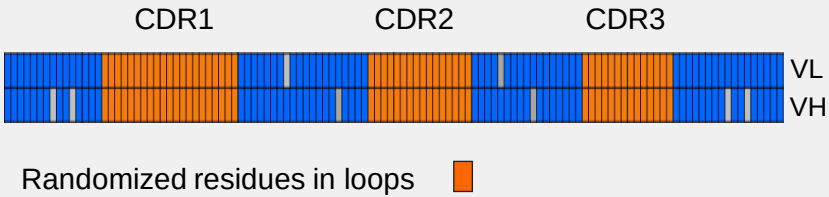
DARPin **KEY PROPERTIES**	DARPin **ADVANTAGE**
Small size (15 kDa)	➢ Deep tissue penetration ➢ High molar concentration
Rigid protein scaffold	➢ Very high affinity & selectivity ➢ Conditional activation
Simple & robust architecture	➢ Turn-key multispecifics ➢ Easy coupling of payloads

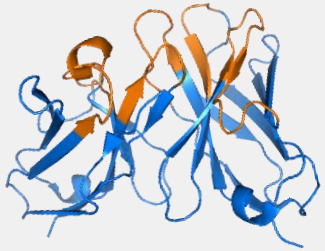
DARPin, designed ankyrin repeat protein; kDa, kilodalton

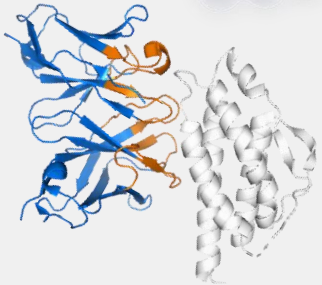
Holt LJ. *Trends Biotechnol.* 2003;21(11):484-490; Walser M. *Biorxiv*. 2021; https://doi.org/10.1101/2020.08.25.256339; Binz HK, et al. *J. Mol. Biol.* 2003;332:489-503;

A Rigid Binding Surface for High Affinity and Specific Targeting

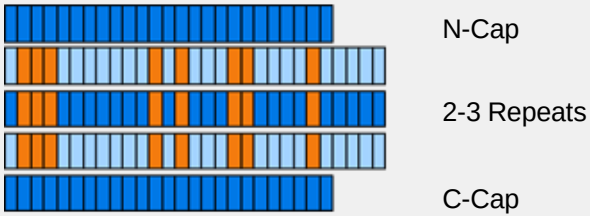
Antibody (Ig-) domain: binding via flexible loops[1]

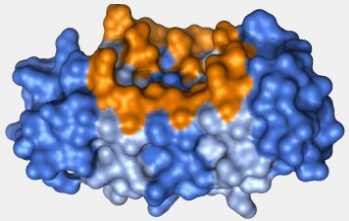


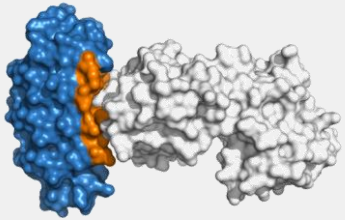




DARPin domain: binding via rigid surface[2,3]





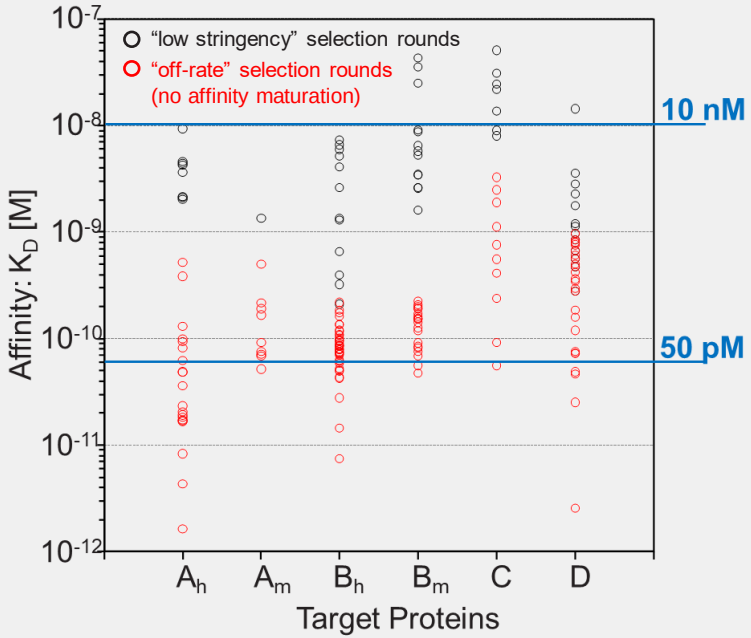


CDR, Complementarity-determining region; DARPin, designed ankyrin repeat protein; Ig, immunoglobulin; VH, variable domain of an antibody heavy chain; VL, variable domain of an antibody light chain.

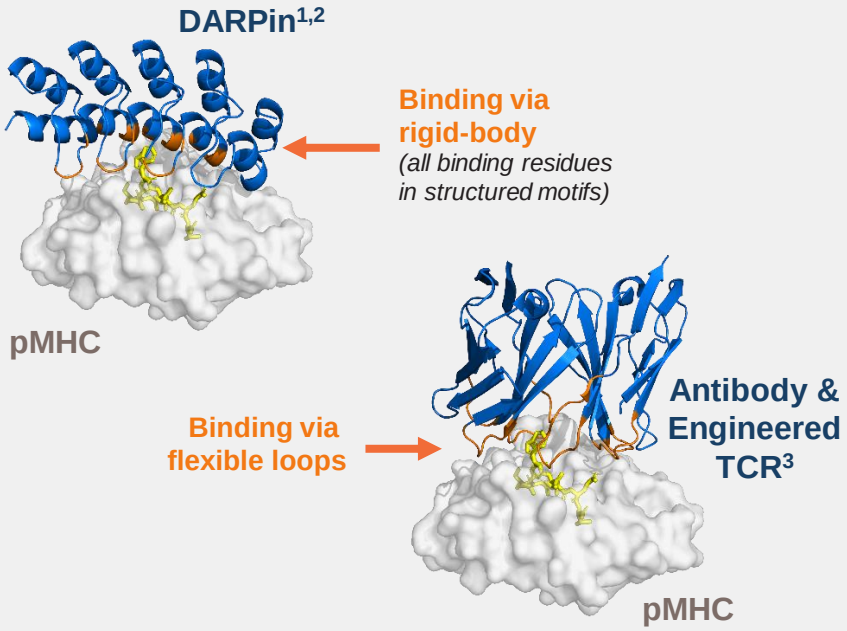
1. Holt LJ. *Trends Biotechnol.* 2003;21(11):484-490; **2.** Walser M. *Biorxiv*. 2021; https://doi.org/10.1101/2020.08.25.256339; **3.** Binz HK, et al. *J. Mol. Biol.* 2003;332:489-503.

DARPins with Very High Affinity and Specificity from *in-vitro* Selections

Diverse low pM DARPin binders from initial selections



Example for high specificity: Binding of pMHC complexes

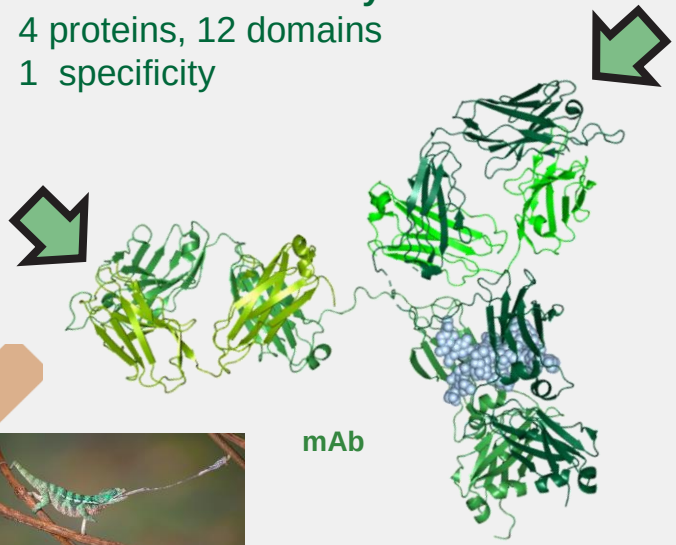


DARPin, designed ankyrin repeat protein;
1. Venetz N et al; Cancer Res (2021) 81 (13_Supplement): 1349. https://doi.org/10.1158/1538-7445.AM2021-1349; **2.** Venetz N. manuscript in preparation; **3.** Chen J. *J Exp Med;* 2005;201(8):1243-55

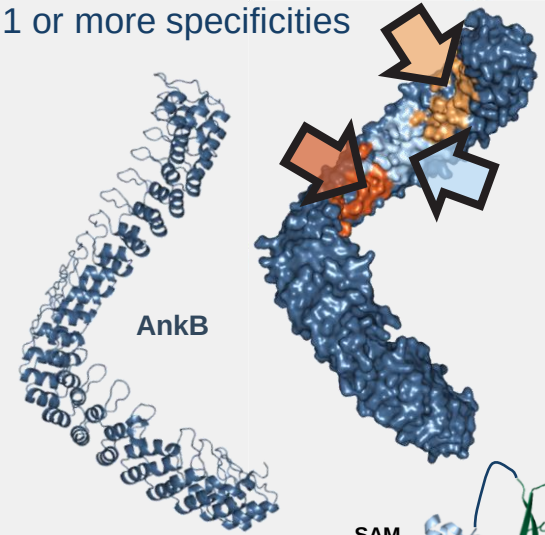
Nature Evolves Highly Specific Solutions

Repeat Proteins: Evolved for Multi-Specific Binding

Monoclonal Antibody:
4 proteins, 12 domains
1 specificity



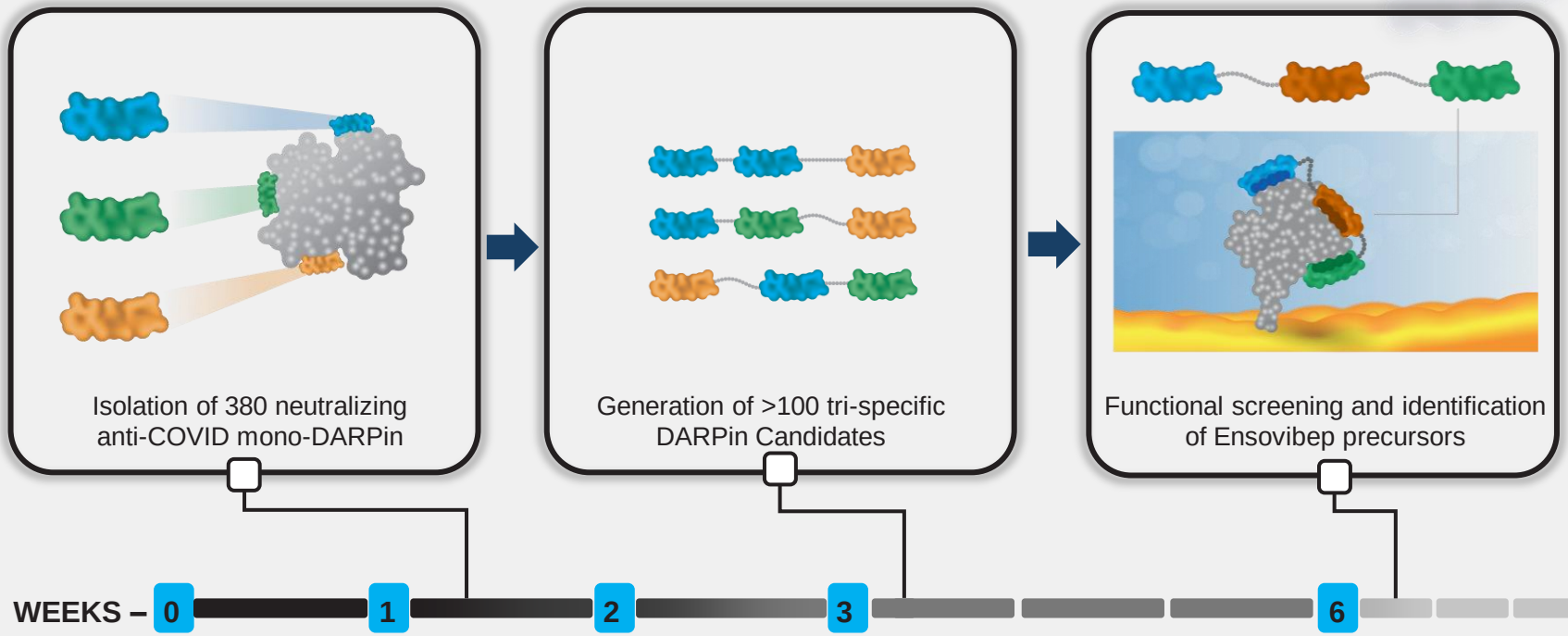
Ankyrin Repeat Protein:
1 protein, 1 domain
1 or more specificities



Ensovibep:

An opportunity to target multiple variants of SARS-CoV-2

Our Platform in Action: Creating Ensovibep

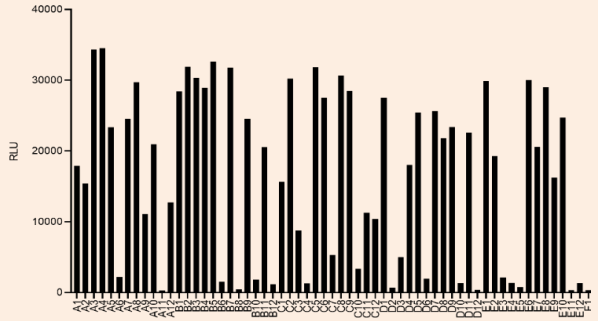


DARPin, designed ankyrin repeat protein;
Walser M. *Biorxiv*. 2021; https://doi.org/10.1101/2020.08.25.256339;

Identification of Highly Potent Tri-DARPin Inhibitors

Pseudotype virus neutralization at 10nM

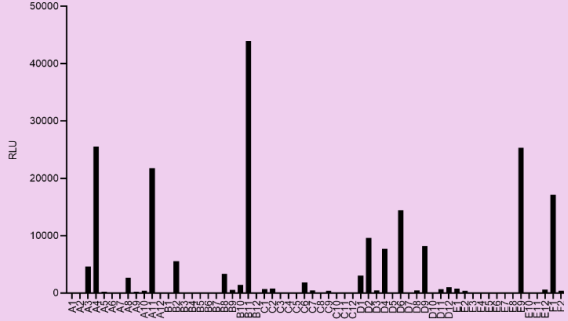
Mono-DARPins



- **Broad epitope coverage**

Random assembly of tri-DARPins

Tri-DARPins

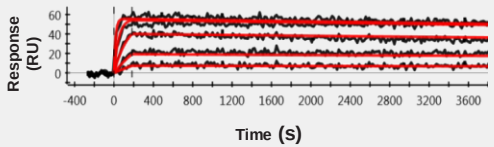


- **Information for rational design**

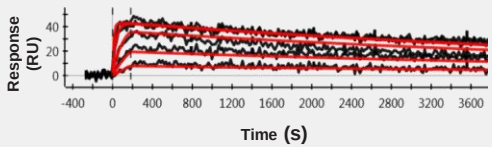
DARPin, designed ankyrin repeat protein;
Walser M. *Biorxiv*. 2021. https://doi.org/10.1101/2020.08.25.256339
Rothenberger S et al, *Biorxiv*. 2021 doi.org/10.1101/2021.02.03.429164

Tri-Specific Target Engagement Leads to Strong Avidity

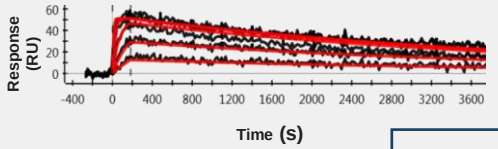
DARPin #1; K_D: 30 pM
1 hour off-rate

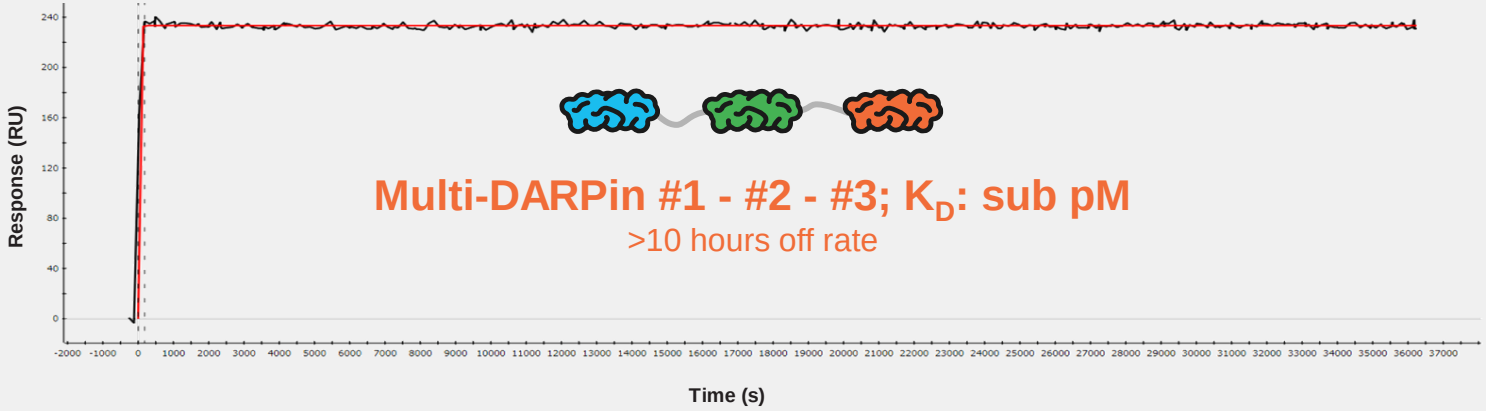


DARPin #2; K_D: 80 pM
1 hour off-rate



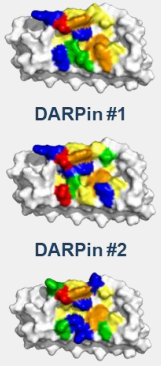
DARPin #3; K_D: 90 pM
1 hour off-rate





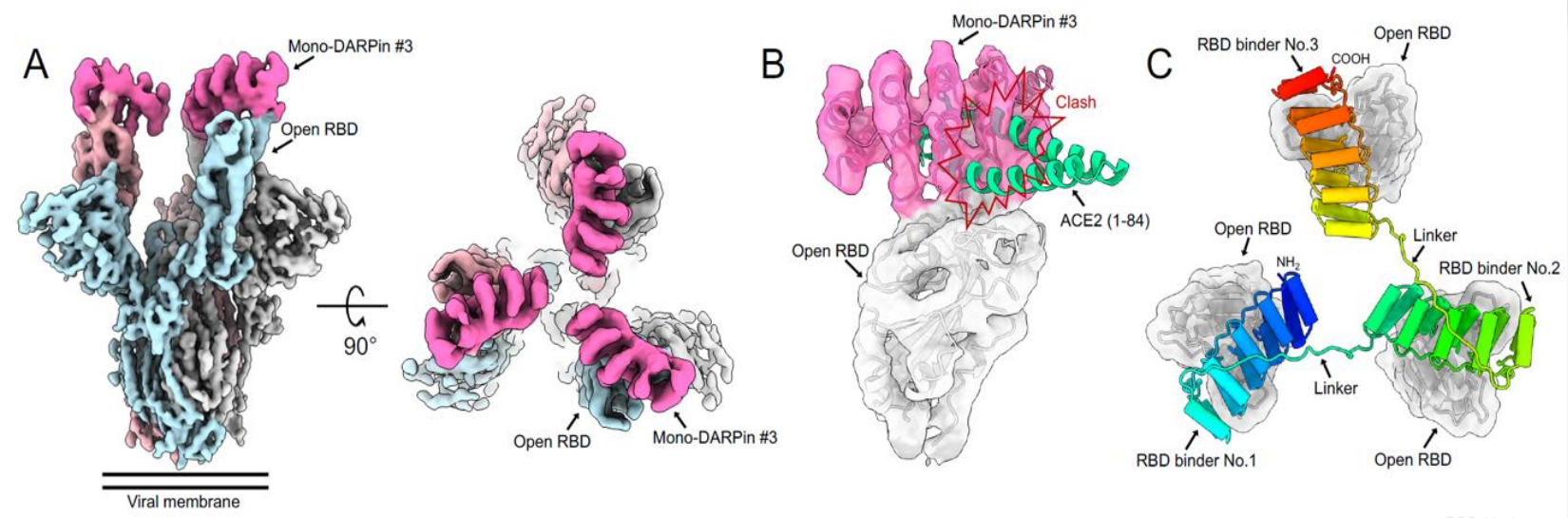
Multi-DARPin #1 - #2 - #3; K_D: sub pM
>10 hours off rate

DARPin paratopes:



DARPin, designed ankyrin repeat protein;
Rothenberger S et al, *Biorxiv*. 2021 doi.org/10.1101/2021.02.03.429164

Binding Mode of Action to the SARS-CoV-2 Spike Protein RBD based on Cryo-EM Data



Cryo-EM analysis of a monovalent DARPin building block R2 of ensovibep molecule

A) Cryo-EM density for the SARS-CoV-2 spike ectodomain in complex with the RBD targeting monovalent DARPin module

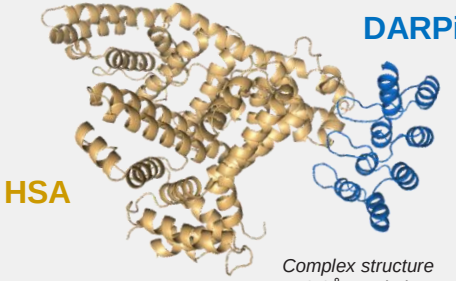
B) Zoomed in view of a single DARPin module bound to the RBD clashing with the binding of the RBD to the human ACE2 receptor

C) Model of 3 covalently linked R2 RBD-targeting DAPRin modules on a spike protein trimer

ACE2, angiotensin converting enzyme 2; CRYO-EM, Single-particle cryo-electron microscopy; DARPin, designed ankyrin repeat protein; RBD, receptor binding domain; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

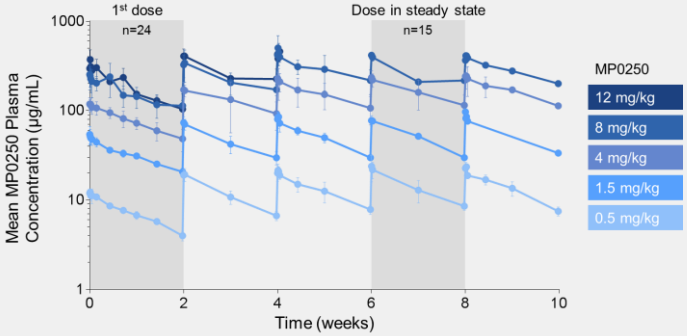
Walser M. *Biorxiv*. 2021. https://doi.org/10.1101/2020.08.25.256339

Fusion to Serum Albumin DARPins for PK Engineering



Complex structure at 2.6Å resolution

MP0250 Phase I clinical[2] (αSA- αVEGF- αHGF- αSA)



- 2x serum albumin DARPins for long systemic half-life

- Serum albumin DARPin platform for systemic PK tuning[1]
  - DARPin technology established to hitch-hike on serum albumin
  - High format flexibility (tested in > 1000 multi-DARPin constructs)
  - Broad species cross reactivity: human, cyno, mouse, rat, dog…
  - Good allometric scaling (e.g. mouse-cyno-human)
  - DARPin variants covering broad affinity range
- Clinically validated with >130 patients (spring 2020)*
  - Clinical candidates: MP0250, MP0274, MP0310
  - 2-3 weeks in humans

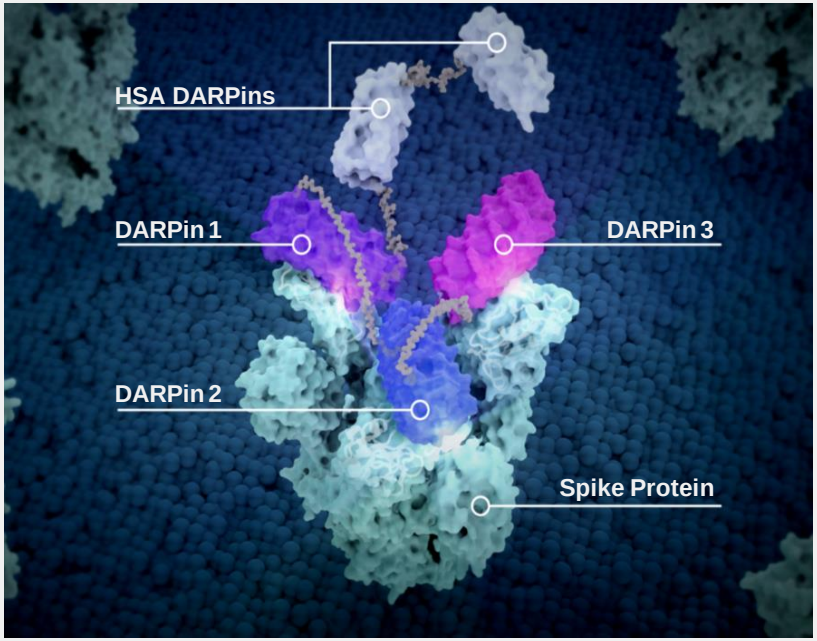
* >700 patients (spring 2022)

DARPin, designed ankyrin repeat protein; αSA, DARPin binding serum albumin; αVEGF, DARPin binding vascular endothelial growth factor

1. Steiner D. *Protein Eng Des Sel;* 2017;30(9):583-591
2. Baird R.D. *Journal of Clinical Oncology;* 2021;39(2):145-154

Ensovibep Design Rationale for Effective SARS-CoV-2 Neutralization

3D model of a DARPin molecule



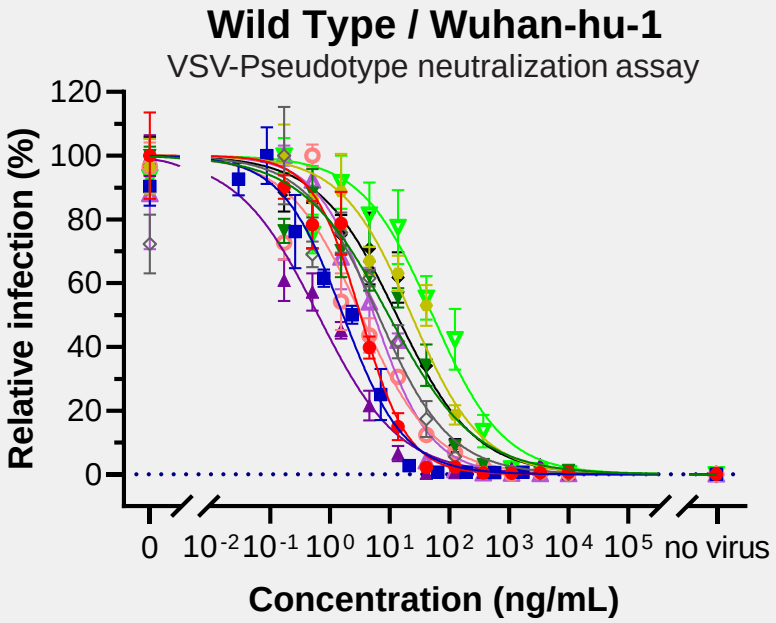
Design Rationale

- 3 high affinity RBD DARPin binders
  - Optimized linker design
    - Molecular modelling supports binding of ensovibep to one trimeric spike protein
  - Avidity leading to sub-pM apparent affinity
    - Potential for high anti-viral potency
    - Enabling low doses
  - Distinct paratopes of DARPins & avidity
    - Low potential for resistance to new variants
    - Potential protection against viral escape
- 2× Serum Albumin DARPin binders
  - Long systemic half-life

DARPin, designed ankyrin repeat protein; RBD, receptor binding domain; HSA, human serum albumin; SARS-Cov-2, Severe acute respiratory syndrome coronavirus 2.

Walser M. *Biorxiv*. 2021. https://doi.org/10.1101/2020.08.25.256339

Ensovibep Shows *In Vitro* Potency in the Low pM Range



Compound	IC_{50} (ng/mL)
Ensovibep	**1.6**
REGN10933	3.2
REGN10987	3.3
AZD8895	0.6
AZD1061	5.5
LY-CoV555	13
LY-CoV016	6.4
Brii-196	9.5
Brii-198	52
S309	23

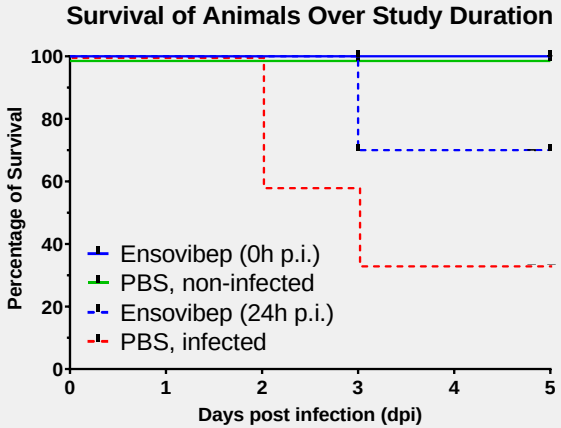
Publicly available sequences of variable domains from monoclonal antibodies were used to generate a panel of antibodies used in this assay

High Potency Inhibition Translates to *In Vivo* Therapeutic Properties

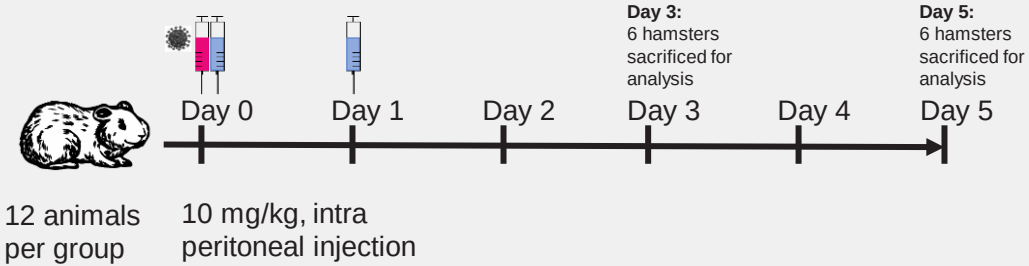
Shake flask production of 2 Lead Candidates for animal studies

PK assessment in hamsters

***In vivo* Proof of Concept**



- Expression of 2 constructs in 10L shake flask *E.coli* cultures and IMAC/SEC purification (>100 mg per construct in 1 week)
- Pharmacokinetic parameters for ensovibep in Roborovski dwarf hamsters $t_{1/2}$ of 52 h → allometric scaling to human based on serum half-life translates to $t_{1/2}$ >2 weeks in human.
- Ensovibep protects Roborovski dwarf hamsters from fulminant symptoms

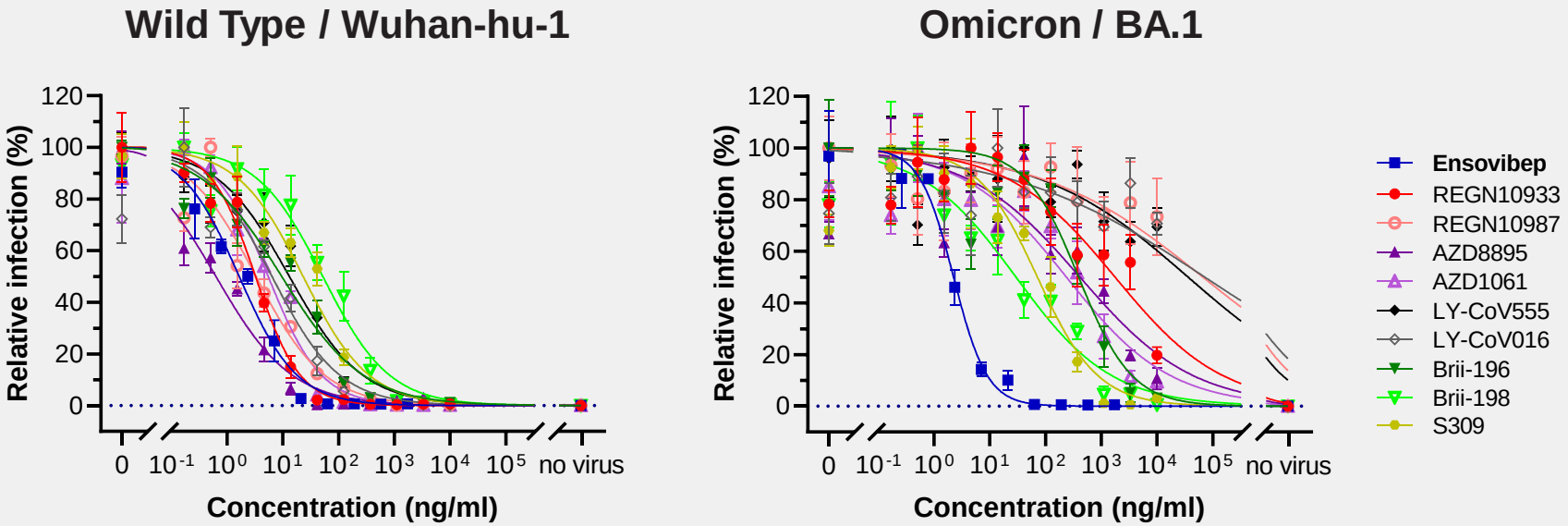


12 animals per group

10 mg/kg, intra peritoneal injection

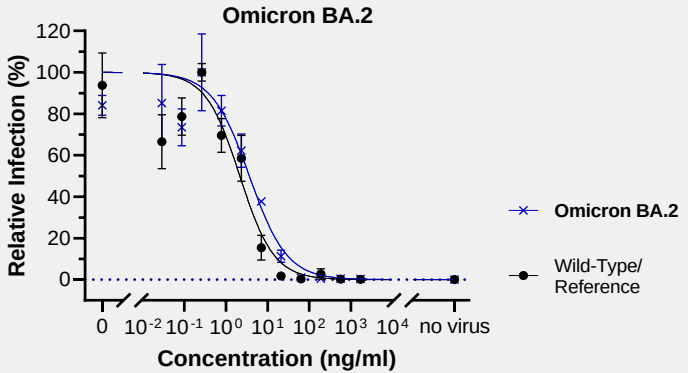
Walser M. *Biorxiv*. 2021. https://doi.org/10.1101/2020.08.25.256339
Rothenberger S. et al, *Biorxiv*. 2021 doi.org/10.1101/2021.02.03.429164

Ensovibep Retains Full Activity Against Omicron BA.1



Ensovibep Retains Full Activity Against Omicron BA.1 and BA.2 – Table

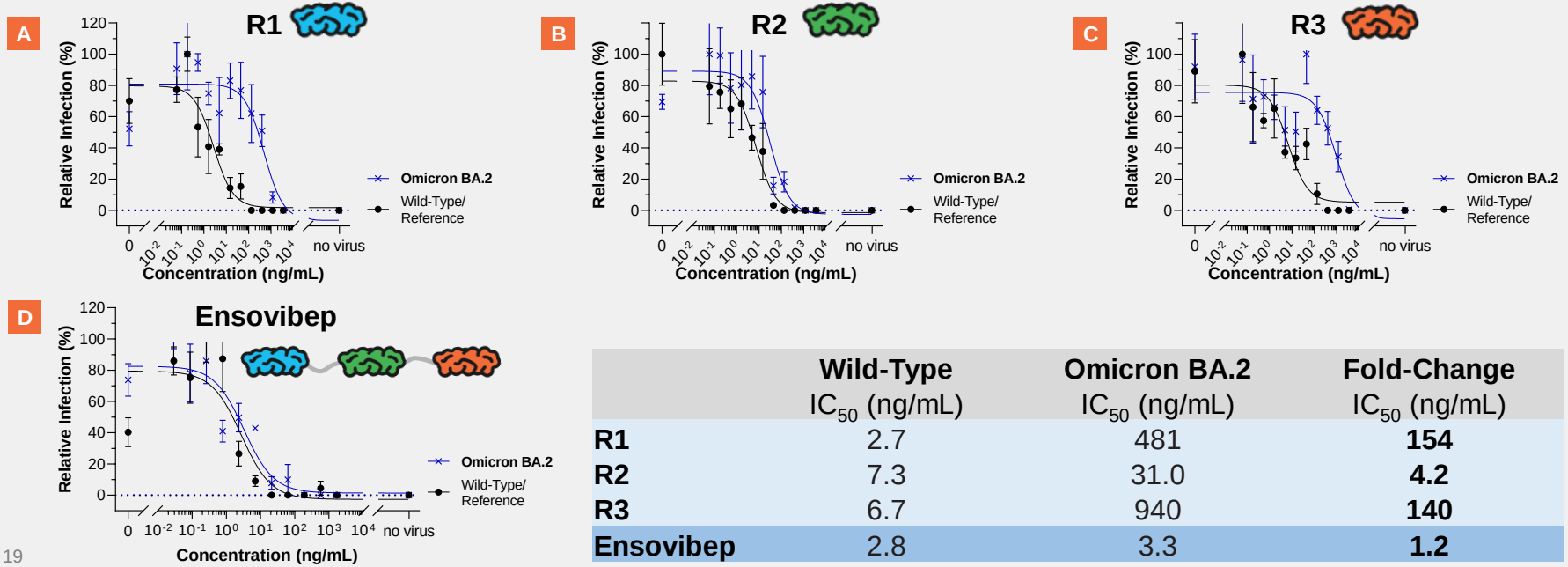
	Wild Type	Omicron BA.1		Wild Type	Omicron BA.2	
Compound	IC_{50} (ng/mL)	IC_{50} (ng/mL)	fold change to wt	IC_{50} (ng/mL)	IC_{50} (ng/mL)	fold change to wt
Ensovibep	**1.6**	**2.2**	**1.4**	**2.2**	**3.6**	**1.6**
REGN10933	3.2	>1000	>100			
REGN10987	3.3	>1000	>100			
LY-CoV555	13	>1000	>100			
LY-CoV016	6.4	>1000	>100			
S309	23	72	3.1			
AZD8895	0.6	415	>100			
AZD1061	5.5	237	43			
Brii-196	9.5	392	41			
Brii-198	52	30	0.6			



Publicly available sequences of variable domains from monoclonal antibodies were used to generate a panel of antibodies used in this assay

Maintained Neutralization of Ensovibep Against Omicron BA.2

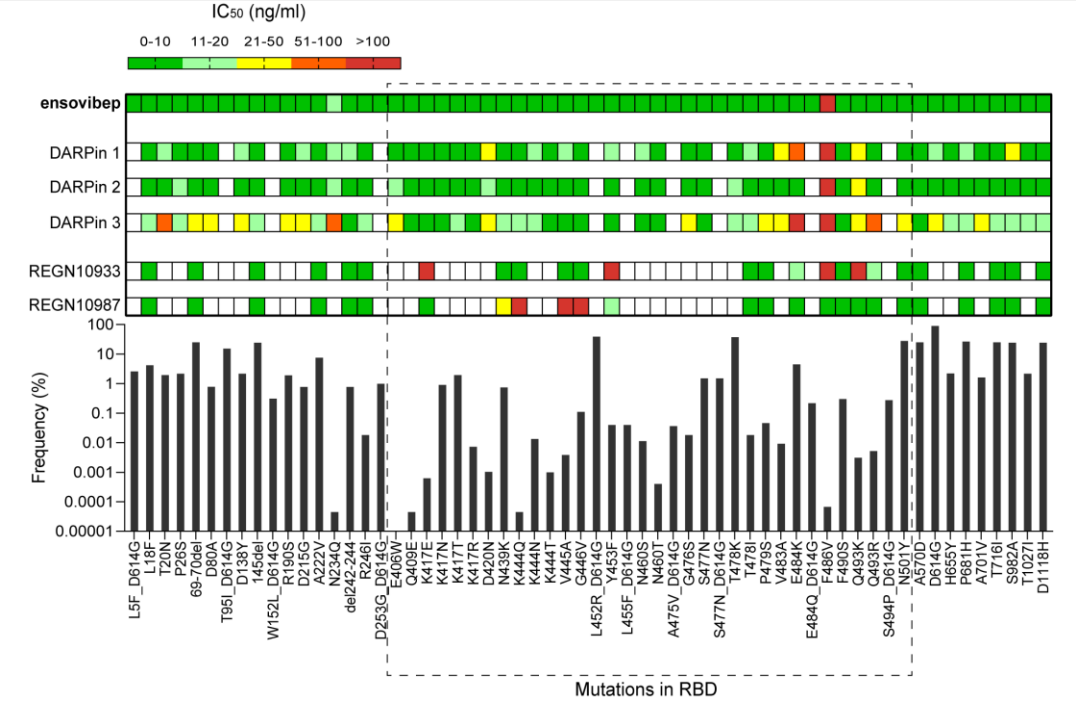
- In a VSV-pseudotype assays, reduction in neutralization on the omicron BA.2 variant may be observed for the individual RBD-binding DARPins (R1, R2, R3) but not for the trispecific ensovibep

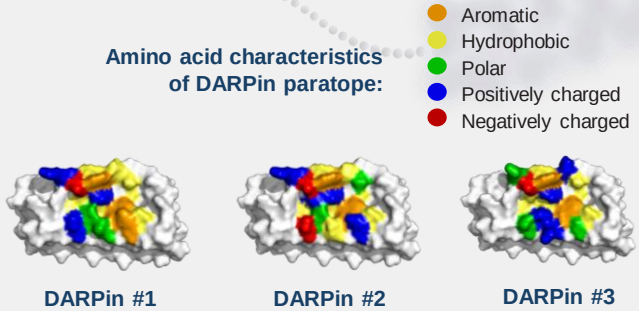


	Wild-Type IC_{50} (ng/mL)	Omicron BA.2 IC_{50} (ng/mL)	Fold-Change IC_{50} (ng/mL)
R1	2.7	481	**154**
R2	7.3	31.0	**4.2**
R3	6.7	940	**140**
Ensovibep	2.8	3.3	**1.2**

Rothenberger S et al, *Biorxiv*. 2021 doi.org/10.1101/2021.02.03.429164

Multi-Specific Therapeutic Design Matters



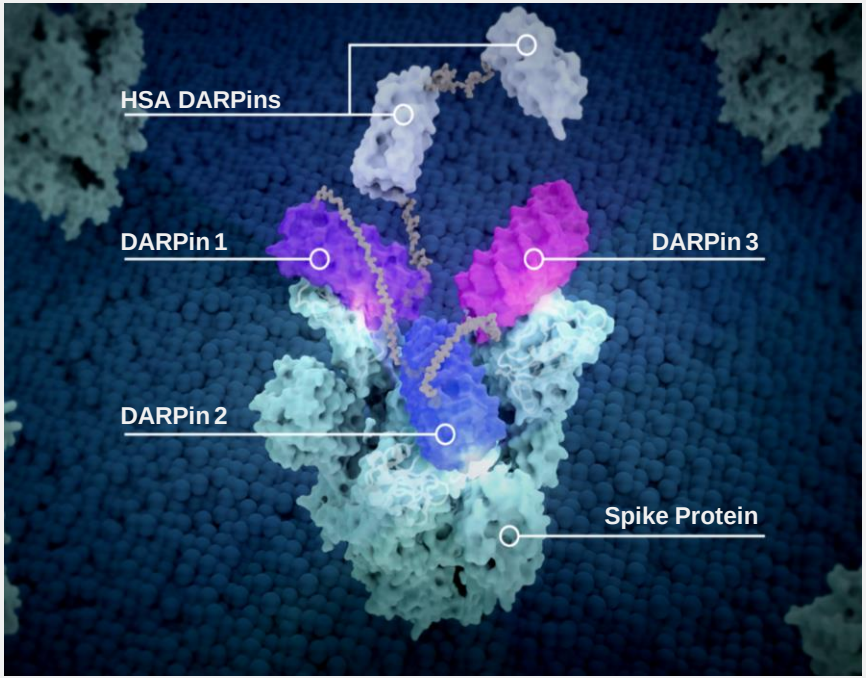


- Ensovibep is potent even on mutations where the single mono-DARPins show reduced activity (ex. E484K and Q493K), thanks to the avidity effect and complementarity of the mono-DARPins
- Exception is F486V, where all mono-domains and ensovibep lose potency. F486 is also a key residue for the virus to interact with ACE2.

PsV neutralization assays performed in collaboration with CHUV, Lausanne, CH; ACTIV consortium/FDA

Structure and Features of Ensovibep Neutralizing the SARS-CoV-2 Spike Protein

3D model of a DARPin molecule



Characteristics

- High potency: high binding affinity and avidity leads to one of the highest anti-viral potencies reported to date
- Multi-variant activity: multi-specific binding of three sites allows blocking of prevalent variants of concern
- Simple administration: long half life, high solubility and high potency to allow for single injection

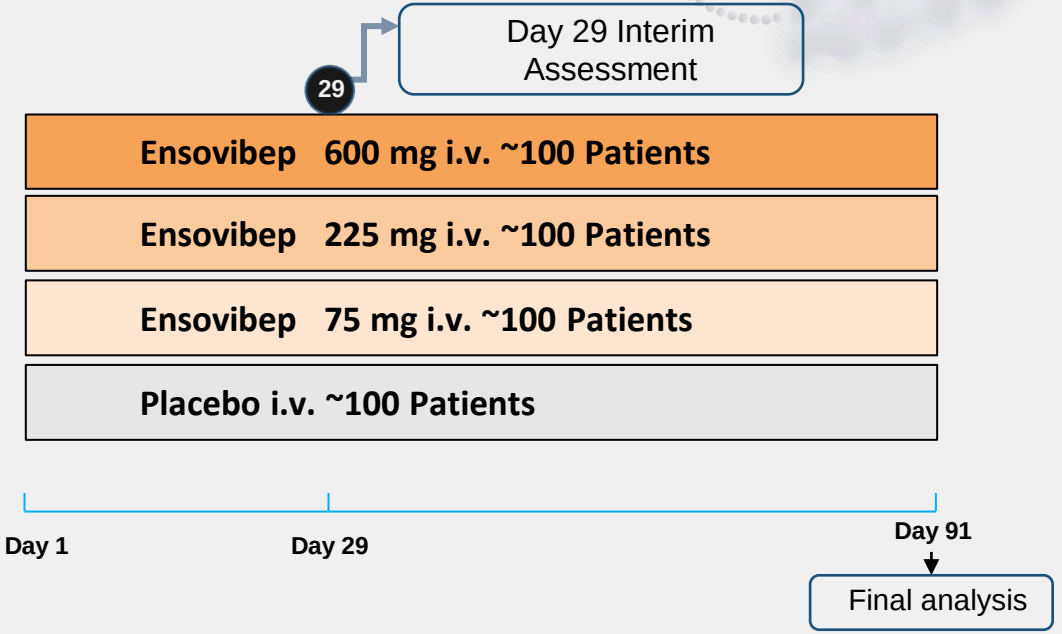
DARPin, designed ankyrin repeat proteins; RBD, receptor binding domain; HSA, human serum albumin; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

Walser M. *Biorxiv*. 2021. https://doi.org/10.1101/2020.08.25.256339

Clinical Development

EMPATHY Phase 2: Randomised, Multicentre, Dose-Finding Placebo-Controlled Trial to Evaluate Safety and Efficacy of Ensovibep

- Eligible patients:
  - Ambulatory, not hypoxic
  - ≥2 COVID-19 symptoms (onset within the past seven days) and
  - Positive SARS-CoV-2 rapid antigen test on the dosing day
- No exclusion of co-morbidities (e.g. renal impairment, hepatic impairment, HIV) or co-medications, except other antivirals
- No exclusion of vaccinated patients
- Enrolled from May – Oct 2021



Patients were randomised (1:1:1:1) to receive a 60-minute single intravenous infusion of ensovibep 75, 225, or 600 mg *or* placebo

EMPATHY Study Endpoints (Virological & Clinical Assessments)

Primary endpoint

- Time-weighted change from baseline in log_{10} SARS-CoV-2 **viral load** in nasopharyngeal swabs through Day 8, versus placebo*

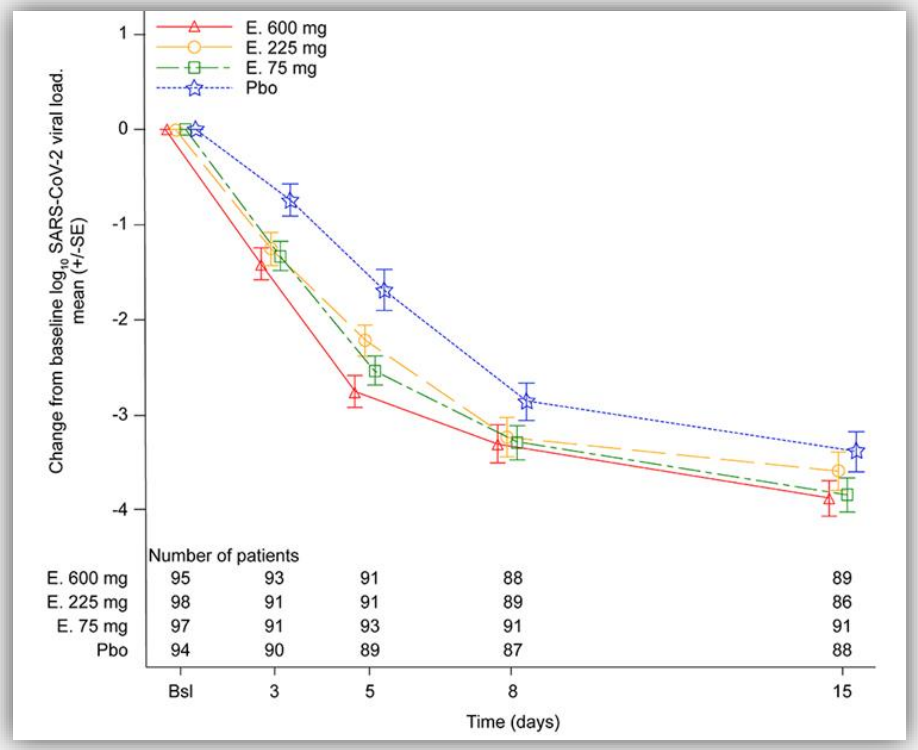
Secondary endpoints

- Proportion of patients with **hospitalisations** and/or **ER visits** related to COVID-19, or any-cause **death** to Day 29
- Time-to-sustained **clinical recovery** based on resolution or improvement of clinical symptoms** with no worsening to Day 29
- **Safety**

Time-weighted change from baseline assessed at Days 3, 5, and 8 in log_{10} SARS-CoV-2 viral load in nasopharyngeal swabs;
**Patient-reported outcome; Kumarasamy et al. Oral Presentation ECCMID 23 April 2022.

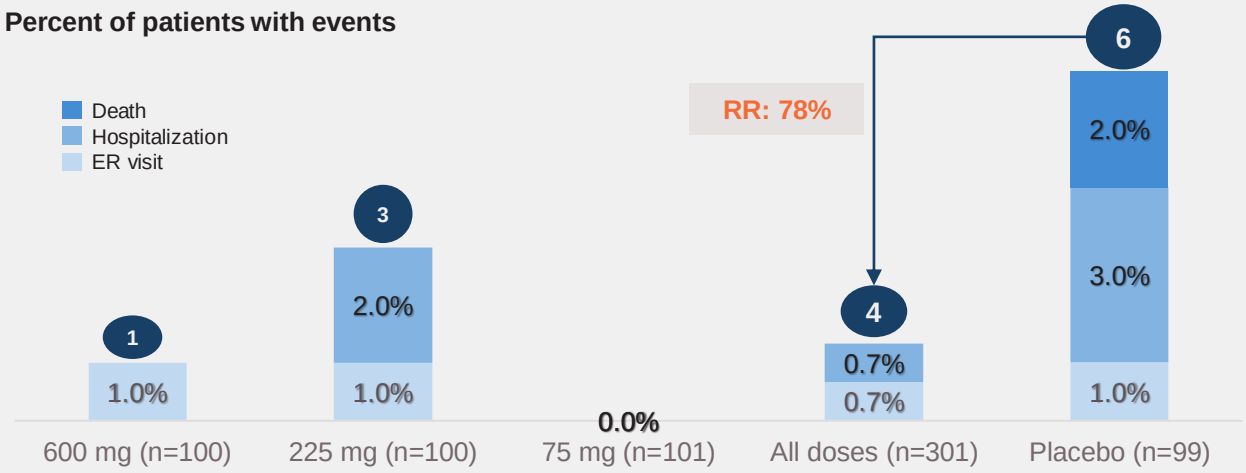
Ensovibep showed significant viral load reduction at all doses

Mean change from baseline in viral load ± SE to Day 15 ensovibep vs placebo



Reductions in Hospitalization and/or ER Visit, or Death

Patients with hospitalization and/or ER visit related to COVID-19 or death



Numbers indicate absolute number of patients

Note:

In the hierarchy of ER-visit/ hospitalization/ death- patients are counted in the highest category

- ER visits exclude those resulting in hospitalization/ death
- Hospitalizations exclude those that resulted in death

Significant Reductions in Viral Load, Risk of Hospitalization and Death, and Faster Time to Recovery (Top Line Results)

- Statistically significant reduction of viral load from baseline, through Day 8 over placebo for all doses (primary endpoint)
- Fewer hospitalization and/or ER visits related to COVID-19 and no deaths for ensovibep treated patients vs. those on placebo (secondary endpoint)
  - **4/301** patients with hospitalizations (2) and/or ER visits (2) related to COVID-19 or death across all treatment arms
  - **6/99** patients with death/hospitalization (2), hospitalization (5), ER (1) in the Placebo arm
- Clinically meaningful benefit for patients treated with ensovibep (secondary endpoint)
  - **Median time to clinical recovery was faster** for ensovibep treated patients vs. placebo
  - **More patients demonstrated clinical recovery** when treated ensovibep vs. placebo (at day 29)
- No unexpected safety findings were observed

Outlook

Applying our DARPin Advantages to Address Disease Biology

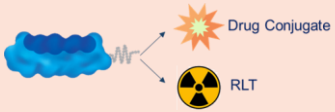
Delivery Vectors "radical simplicity"

Multispecificity enabled possibilities

Conditional activation

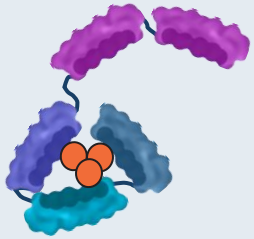
RLT & DDC

Small size – very high affinity for efficient delivery with limited systemic exposure



Ensovibep

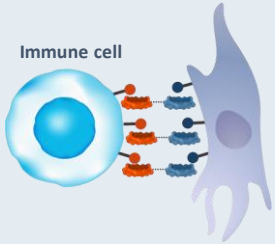
Highly potent SARS-CoV-2 multi-variant neutralization



NOVARTIS

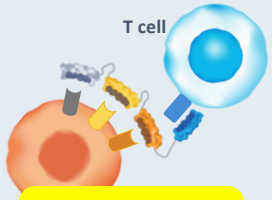
MP0310 & MP0317

Tumor localized clustering to activate effector cells in tumor microenvironment



MP0533

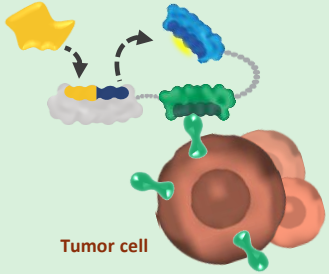
Avidity driven TCE for tumor-specificity and control of tumor heterogeneity



Christian R. 11:10-Track1

SWITCH

Programming highly potent effectors to omit off-tumor activity



NOVARTIS / New

New infectious disease

New oncology

New

DARPin, designed ankyrin repeat protein; RLT, Radio Ligand Therapy; DDC, DARPin Drug Conjugate

Acknowledgments

Spiez Laboratory – Federal Office of Civil Protection (FOCP)
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Group of Berend-Jan Bosch for cryo-EM analysis, target material and pseudotype assays.

Free University of Berlin
Group of Jakob Trimpert for Roborovski dwarf hamster studies

National Institute of Health (NIH)
ACTIV team for conducting neutralization assays, in vivo and clinical studies with many US Government organizations.

Thank you for your interest!

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