Ensovibep antiviral activity in ambulatory patients with COVID-19 is independent of baseline anti-SARS-CoV-2 antibodies and exhibits minimal selective pressure – Results from the placebo-controlled EMPATHY trial

Poster # 1130

Presenting author: Luis Abrishamian[1], Co-authors: Marc Bonten[2], Richa Chandra[3], Damodaran Solai Elango[4], Pierre Fustier[5], Kinfemichael Gedif[6], Jeff Kingsley[7], Susana Goncalves[8], Awawu Igbinadolor[9], Charles G. Knutson[10], Petra Kukkaro[8], Nagalingeswaran Kumarasamy[11], Philippe Legenne[5], Martha Mekebeb-Reuter[12], Krishnan Ramanathan[8], Evgeniya Reshetnyak[3], Michael Robinson[13], Jennifer Rosa[14], Marianne Soergel[5], Vaia Stavropoulou[5], Nina Stojcheva[5], Michael T. Stumpp[5], Andreas Tietz[8], Xiaojun Zhao[10], Zhaojie Zhang[10]

[1]South Bay Clinical Research Institute, Redondo Beach, CA, USA; [2]UMC, Utrecht, The Netherlands; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [4]Novartis Healthcare Pvt Ltd, Hyderabad, India; [5]Molecular Partners AG, Zurich-Schlieren, Switzerland; [6]Novartis Pharmaceuticals Corporation, Fort Worth, TX, USA; [7]Centricity Research, Columbus, GA, USA; [8]Novartis Pharma AG, Basel, Switzerland; [9]Monroe Biomedical Research, Monroe, NC, USA; [10]Novartis Institutes for BioMedical Research, Cambridge, MA, USA; [11]VHS Infectious Diseases Medical Centre, Chennai Antiviral Research and Treatment Clinical Research Site, Chennai, India; [12]Excellentis Clinical Trial Consultants, George, South Africa; [13]Novartis Institute for Tropical Disease (NITD), Emeryville, CA, USA; [14]Clinresco Centres, Gauteng, South Africa

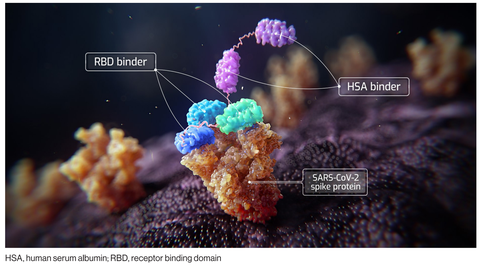
Introduction

- DARPins (Designed Ankyrin Repeat Proteins) are based on naturally-occurring scaffolding proteins that can be synthetically modified to bind different targets[1]

Ensovibep

- Is a DARPin molecule that binds to the spike protein receptor binding domain (RBD) of SARS-CoV-2, preventing its interaction with the host ACE2 receptor thereby inhibiting target cell entry[1] (**Figure 1**)
- Contains five DARPin domains: three bind to the spike protein RBD, two bind to human serum albumin (HSA) for half-life extension[1]
- Has demonstrated in vitro multi-variant neutralization activity against variants of concern, including Omicron BA.1, BA.2, BA.3 and BA.2.12.1[2–4]
  - was not observed to be active against Omicron BA.4 and BA.5 subvariants[5]

Figure 1. Ensovibep bound to the SARS-CoV-2 spike protein



HSA, human serum albumin; RBD, receptor binding domain

Depiction based on structural data showing ensovibep RBD binding DARPin domains (green, blue, cyan) binding to the RBD of the SARS-CoV-2 spike protein trimer. The two additional DARPin domains (purple) bind to human serum albumin (HSA, not shown for clarity) to provide half-life extension

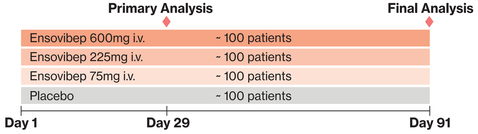
Methods

EMPATHY* study objectives

- To demonstrate superiority of ensovibep, compared to placebo, in reducing SARS-CoV-2 viral load through Day 8
- To identify the optimal dose
- To demonstrate superiority of ensovibep, compared to placebo, in reducing the occurrence of hospitalizations (≥ 24 hours of acute care) and/or emergency room visits related to COVID-19 or death from any cause up to Day 29

*clinicaltrials.gov NCT04828161

Figure 2. EMPATHY study design



Eligible patients

- Ambulatory, SpO2 >93%, presence of ≥ 2 symptoms of COVID-19, positive SARS-CoV-2 rapid antigen test on the dosing day, no exclusion for co-morbidities (e.g., renal impairment, hepatic impairment, HIV) or co-medications, except other antivirals, included vaccinated patients
- Patients were randomised (1:1:1:1) to receive a single, intravenous infusion of ensovibep 75, 225, or 600 mg or placebo over 60 minutes
- Patients were enrolled between May and October 2021

Clinical question of interest

- What is the treatment effect of ensovibep compared with placebo on log_{10} SARS-CoV-2 viral load through Day 8 in ambulatory adult patients with newly symptomatic COVID-19?

Primary endpoint

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

Secondary endpoints

- Proportion of patients with hospitalizations and/or ER visits related to COVID-19, or all-cause death up to Day 29
- Time-to-sustained clinical recovery based on resolution or improvement of clinical systems** with no worsening up 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

- **Sub-group analysis was performed to assess the effect of baseline anti-SARS-CoV-2 antibodies**
- **The exploratory endpoint to evaluate the effect of ensovibep on mutation emergence was assessed**

Analyses

- In patients, the baseline serostatus was determined on Day 1, prior to commencing treatment, using chemiluminescent immunoassays for antibody detection (anti-SARS-CoV-2 S1/S2 IgG and anti-SARS-CoV-2 IgM)
- A pre-specified subgroup analysis was performed based on baseline anti-SARS-CoV-2 antibody status
- To track SARS-CoV-2 genetic variants and monitor for possible viral resistance, whole viral genome sequencing was performed on viral nucleic acids isolated from nasopharyngeal swabs
- Analysis of changes in viral genome from baseline to Day 8, Day 15, Day 29 and Day 91 (i.e. all visits from Day 8 onwards at time points with a positive RT-PCR and sufficient viral load) was performed to evaluate treatment-emergent mutations

Results

Baseline demographics and disease characteristics

- 600 patients were screened, 407 of whom were randomized in a 1:1:1:1 ratio into four treatment arms, with 100, 102, 103, and 102 patients to ensovibep 600 mg, 225 mg, 75 mg, and placebo arms, respectively; in total 400 patients received treatment
- Baseline demographics and disease characteristics were similar across treatment groups
- **Anti-SARS-CoV-2 antibodies were present in 48.5% of patients in total (194/400) prior to treatment**
- The predominant variant in trial participants was delta (B.1.617.2; 322/400; 80.5%), with similar distribution across ensovibep and placebo arms[6] (**Table 1**)

Table 1. Baseline demographics by ensovibep dose and in the overall population

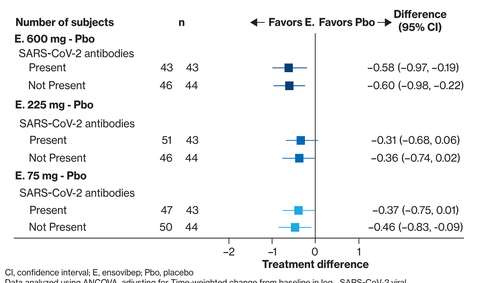
Characteristic Statistic/category	Ensovibep 600 mg N=100	Ensovibep 225 mg N=100	Ensovibep 75 mg N=101	Ensovibep total N=301	Placebo N=99	All N=400
Age - Median (IQR) – yr	41.0 (18–71)	39.0 (19–66)	41.0 (19–70)	40.0 (18–71)	41.0 (18–81)	41.0 (18–81)
Age group – no. (%)						
< 25 years	7 (7.0)	11 (11.0)	8 (7.9)	26 (8.6)	10 (10.1)	36 (9.0)
25 – < 45 years	56 (56.0)	51 (51.0)	52 (51.5)	159 (52.8)	49 (49.5)	208 (52.0)
45 – < 65 years	35 (35.0)	37 (37.0)	37 (36.6)	109 (36.2)	35 (35.4)	144 (36.0)
≥65 years	2 (2.0)	1 (1.0)	4 (4.0)	7 (2.3)	5 (5.1)	12 (3.0)
Male sex - no. (%)	53 (53.0)	46 (46.0)	41 (40.6)	140 (46.5)	42 (42.4)	182 (45.5)
Weight - Median (IQR) - kg	76.45 (46.3–183.3)	80.05 (53.6–130.0)	75.00 (40.8–131.7)	76.40 (40.8–183.3)	75.40 (42.2–132.0)	76.40 (40.8–183.3)
BMI* - Median (IQR) - kg/m²	26.75 (17.9–59.2)	28.15 (18.8–45.6)	26.70 (16.7–52.1)	26.90 (16.7–59.2)	26.60 (17.8–46.2)	26.90 (16.7–59.2)
BMI group - no. (%)						
< 18.5 kg/m²	1 (1.0)	0	2 (2.0)	3 (1.0)	1 (1.0)	4 (1.0)
18.5 – <25 kg/m²	33 (33.0)	26 (26.0)	32 (31.7)	91 (30.2)	34 (34.3)	125 (31.3)
25 – <35 kg/m²	59 (59.0)	67 (67.0)	61 (60.4)	187 (62.1)	62 (62.6)	249 (62.3)
≥ 35 kg/m²	7 (7.0)	7 (7.0)	6 (5.9)	20 (6.6)	2 (2.0)	22 (5.5)
Risk for COVID-19 disease progression – no. (%)						
High risk (Protocol definition)	15 (15.0)	16 (16.0)	22 (21.8)	53 (17.6)	13 (13.1)	66 (16.5)
High risk (Updated FDA definition)	73 (73.0)	78 (78.0)	75 (74.3)	226 (75.1)	72 (72.7)	298 (74.5)
Log_{10} baseline SARS-CoV-2 viral load						
no.	86	90	84	260	87	347
Median (min-max)	6.68 (2.7–8.7)	6.85 (2.9–8.7)	6.67 (3.3–8.5)	6.73 (2.7–8.7)	6.36 (2.7–8.6)	6.65 (2.7–8.7)
≥ 6 – no. (%)	61 (61.0)	62 (62.0)	63 (62.4)	186 (61.8)	52 (52.5)	238 (59.5)
Anti-SARS-CoV-2 antibodies at baseline						
Present -no. (%) (seropositive)	47 (47.0)	52 (52.0)	50 (49.5)	149 (49.5)	45 (45.5)	194 (48.5)
SARS-CoV-2 variant - no. (%)						
Delta / B.1.617.2	82 (82.0)	82 (82.0)	78 (77.2)	242 (80.4)	80 (80.8)	322 (80.5)
Other (incl. WT, α, β, γ)	6 (6.0)	5 (5.0)	10 (9.9)	21 (6.97)	5 (5.1)	26 (6.5)
Missing	12 (12.0)	13 (13.0)	13 (12.9)	38 (12.6)	14 (14.1)	52 (13.0)
Baseline COVID–19 disease severity - n (%)						
Mild	61 (61.0)	61 (61.0)	67 (66.3)	189 (62.8)	70 (70.7)	259 (64.8)
Moderate	38 (38.0)	39 (39.0)	33 (32.7)	110 (36.5)	29 (29.3)	139 (34.8)
Severe	1 (1.0)	0	1 (1.0)	2 (0.7)	0	2 (0.5)

*BMI between 25 and 35 was also considered high risk

BMI, body mass index; FDA, Food and Drug Administration; IQR, interquartile range; WT, wild type

- SARS-CoV-2 viral load reduction showed in favor of ensovibep compared with placebo up to Day 8 regardless of presence of anti-SARS-CoV-2 antibodies prior to treatment (**Figure 3**)

Figure 3. Forest plot of estimated treatment differences and associated 95% confidence intervals in time-weighted change from baseline in log_{10} SARS-CoV-2 viral load through Day 8 by subgroups for presence of anti-SARS-CoV-2 antibodies



CI, confidence interval; E, ensovibep; Pbo, placebo

Data analyzed using ANCOVA, adjusting for Time-weighted change from baseline in log_{10} SARS-CoV-2 viral load = treatment + baseline log_{10} SARS-CoV-2 viral load + baseline risk for COVID-19 disease progression + presence of anti-SARS-CoV-2 antibodies at baseline + geographical region + presence of anti-SARS-CoV-2 antibodies at baseline.

Frequency of emergent mutations between treatment arms

- Patients in ensovibep 75 mg, 600 mg, and placebo groups had a comparable incidence of emergent mutations, nonsynonymous emergent mutations, and nonsynonymous emergent mutations in the S gene
- Patients in the ensovibep 225 mg group had a higher incidence of all described emergent mutations than the other groups. However, the dominant emergent mutations were also found in baseline samples of other treatment groups
- Overall, 77 patients were found to have emergent nonsynonymous mutations in the S gene. Of these patients, two had an SAE with hospitalization not related to COVID-19, both were in the placebo group and did not have mutations in the key epitope residues, and there were no deaths. The viral load of the 77 patients was similar to the overall population (**Table 2**)

Table 2. Summary statistics for emergent mutations

	Ensovibep 600 mg	Ensovibep 225 mg	Ensovibep 75 mg	Placebo
Patients with:				
Baseline viral sequencing data, n	88	85	89	86
Emergent mutations, n	36	48	34	38
Nonsynonymous emergent mutations, n	31	42	31	34
Nonsynonymous emergent mutations in S protein, n	18	24	18	17

- Three substitutions in the S gene were observed in >2 patients: G142D, T95I, and Y489H
- Both G142D and T95I substitutions were found at high percentages in baseline patient samples and are likely part of the normal variation of the SARS-CoV-2 genome
- Five residues are key for ensovibep binding: Y489, F456, Y473, F486, and N487. In total, six patients in ensovibep arms were identified harboring mutations to any of these residues
  - 3 patients (2 in ensovibep 75 mg and 1 in ensovibep 225 mg) had the Y489H mutation, of which two patients successfully cleared virus and showed no viral load at Day 5 and Day 8, respectively. The other patient showed a decreasing trend of viral load until Day 15, after which results for viral load were not available
  - The F486L mutation was seen in 2 patients (1 in ensovibep 75 mg and 1 in ensovibep 225 mg) and 1 patient (ensovibep 600 mg) had the mutation F486S
  - All F486 mutations were detected at single time points (Day 8 and Day 15), and were not detected at later time points, suggesting that this mutation was transient in all 3 patients

Conclusions

- Ensovibep effectively reduces SARS-CoV-2 viral load regardless of the presence of anti-SARS-CoV-2 antibodies (either seropositive or seronegative) prior to treatment
- F486 and Y489 are among the key residues for ensovibep binding. Six patients in ensovibep arms in total were identified harboring mutations to either of these ensovibep binding residues
- Mutations in these residues have been implicated with reduced affinity at SARS-CoV-2 RBD. Due to the limited number of samples displaying emergent mutations Y489H, F486L and F486S, the clinical impact of these substitutions is unclear
- There were no emerging mutations of concern, indicating that a single dose administration of ensovibep is associated with minimal selective pressure

Acknowledgements

The authors wish to acknowledge the trial sites, the investigators and their teams, the participating patients and the Novartis and Molecular Partners clinical trial teams, and Seónadh O'Leary (Novartis) for medical writing support. The authors acknowledge Rasbehari Koner (Novartis) for designing the poster layout.

References

1. Walser M, et al. bioRxiv. 21 July 2021. doi: https://doi.org/10.1101/2020.08.25.256339
2. Rothenberger S, et al. Nat Biotechnol (2022). https://doi.org/10.1038/s41587-022-01382-3
3. Lusvhargu S, et al. Sci Transl Med. 18 May 2022. doi: 10.1126/scitranslmed.abn8543
4. https://opendata.ncats.nih.gov/variant/activity. Accessed 22 Sept 2022
5. Rothenberger S, et al. ASM Microbe. June 2022 Abstract number: 5418
6. Kumarasamy N, et al. ECCMID. 2022 Abstract number: 05017

Poster presented at IDWeek 2022
October 19-23, 2022, Washington D.C., USA

Presenter email address: abrishamian@gmail.com

Scan this QR code