UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER PURSUANT TO RULE 13a-16 OR 15d-16 UNDER THE SECURITIES EXCHANGE ACT OF 1934

For the month of June 2022

Commission File Number: **001-40488**

Molecular Partners AG
(Translation of registrant's name into English)

Wagistrasse 14
8952 Zurich-Schlieren
Switzerland
(Address of principal executive office)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F.
Form 20-F [X] Form 40-F [ ]

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1): ___

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(7): ___

EXHIBIT INDEX

Exhibit No.	Description
99.1	American Society for Microbiology: ASM MICROBE - poster presentation; Title: SARS-CoV-2 Omicron And Multi-variant Neutralization Activity Of Ensovibep: A DARPin Therapeutic Candidate For Treatment Of Covid-19 (a Novartis poster presentation)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Molecular Partners AG
(Registrant)

Date: June 13, 2022

/s/ PATRICK AMSTUTZ
Patrick Amstutz
Chief Executive Officer

5418

12-June-2022

SARS-CoV-2 Omicron And Multi-variant Neutralization Activity Of Ensovibep: A DARPin Therap

Charles G. Knutson, Novartis Institutes for BioMedical Research, Ca

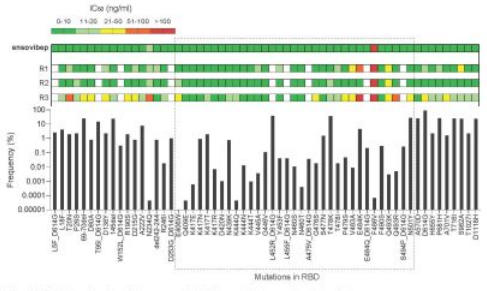
Co-Authors: S. Rothenberger[1], M. Walser[2], F. Malvezzi[2], D. L. Hurdiss[3], J. Mayor[1], H. Moreno[1], S. Ryter[4], N. Liechti[4], A. Bosshart[2], S. Mangold[2], F. Radom

[1]University of Lausanne, Lausanne, Switzerland; [2]Molecular Partners AG, Zurich-Schlieren, Switzerland; [3]Utrecht University, Utrecht, Netherlands; [4]Spiez Lab., Spiez, Switzerland; [5]Novartis Pharma AG, Basel, Switzerland

Background

- The omicron variant of SARS-CoV-2 has altered the COVID-19 pandemic landscape.
- Omicron's increased transmission and ability to evade natural or vaccine-induced immunity developed against earlier variants is a strong reminder of the power of viral evolution.
- Therapies with potential for multi-variant effectiveness are a key component of effective pandemic management.
- **ENSOVIBEP** is a first-in-class anti-SARS-CoV-2 DARPin (Designed Ankyrin Repeat Protein) therapeutic candidate that uses three distinct DARPin domains (R1, R2, R3) with similar paratopes to cooperatively bind to different regions of the receptor binding domain (RBD) of the SARS-CoV-2 spike protein trimer, thereby preventing interaction with the host ACE2 receptor.
- The multi-specific binding of the RBD binding DARPin modules limits the impact of spike protein mutations on antiviral potency (**Figure 1**).

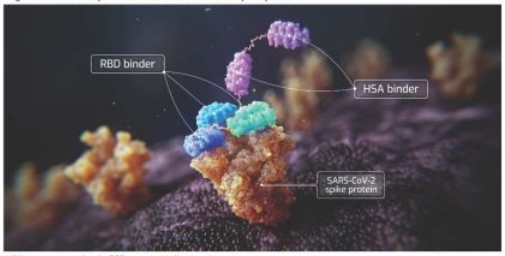
Figure 1. Global frequencies of point mutations in the spike protein of SARS-CoV-2 according to the GISAID database, including a heat map table with IC_{15} values for ensovibep, R1, R2, R3, for all point mutations tested.



Data from VSV/Lentivirus-based pseudovirus assays; dashed box: mutations in 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 (**Figure 2**).
- We present here data supporting the multi-variant potency of ensovibep.

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



HSA, human serum albumin; RBD, receptor binding domain

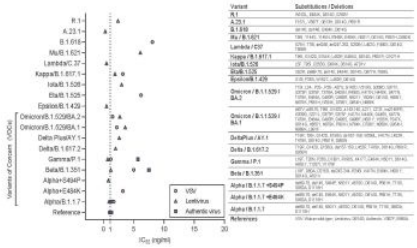
Methods

- The VSV pseudotype viral system (CHUV) was based on the recombinant VSV*DELG-Luc vector in which the glycoprotein gene (G) was deleted and replaced with genes encoding green fluorescent protein and luciferase. Wild-type spike was based on the Wuhan-Hu-1 sequence. Pseudoviruses were mixed with serial dilutions of ensovibep and pre-incubated for 90 min at 37°C before adding to pre-seeded VeroE6 cells. After 90 min incubation, the inoculum was removed, fresh medium was added, and cells were further incubated for 16 h. Cells were lysed according to the ONE-Glo™ luciferase assay system. Relative light units were measured and IC_{50} values were calculated using non-linear regression. Additional details can be found in Rothenberger et al 2022.
- Lentivirus pseudoviruses (ACTIV/FDA) bearing the spike proteins and carrying a firefly luciferase reporter gene were produced in 293T cells by co-transfection of pCMVDELR8.2, pHR'CMVLuc and pCDNA3.1(+)-spike variants. Wild-type spike was based on the Wuhan-Hu-1 sequence. Pseudoviruses were pre-incubated with serially diluted ensovibep for 2 h at 37°C before adding to pre-seeded 293T-ACE2.TMPRSS2s cells. Pseudovirus infection was scored 48 h later by measuring luciferase activity, and IC_{50}s were calculated using non-linear regression. Additional details can be found in Neerukonda et al 2021.
- Live authentic virus assay (Spiez Laboratory): Wild-type virus was a French isolate with the following changes compared with Wuhan-Hu-1: V367F, E990A. Serial dilutions of ensovibep were pre-incubated with 100 $TCID_{50}$ SARS-CoV-2 variants for 1 h at 37°C before adding to pre-seeded VeroE6-TMPRSS2 cells. After 3 day incubation, cell viability was measured using CellTiter-Glo. Luminescence was measured and IC_{50} values were calculated using non-linear regression. Additional details can be found in Rothenberger et al 2022.
- Live spike chimeric reporter viruses (UTMB) were constructed on the genetic background of an infectious cDNA clone derived from clinical strain WA1 (2019-nCoV/USA_WA1/2020) containing a mNeoGreen (mNG) reporter gene, and spike mutations were engineered using a PCR-based mutagenesis protocol. The full-length genomic cDNAs were in vitro ligated, transcribed, and electroporated into VeroE6 cells, and mutant viruses were recovered 3 days after electroporation. Mutant viruses were pre-incubated with serial dilutions of ensovibep for 1 h at 37°C before adding to pre-seeded Vero E6-TMPRSS2 cells. After 1 h infection, the inoculum was removed and replaced with overlay medium (DMEM with 0.8% methylcellulose, 2% FBS, and 1% P/S). After 16 h, raw images of mNG fluorescent foci were acquired, foci were counted, and IC_{50}s were determined using non-linear regression. Additional details can be found in Zou et al 2022.

Results

- Notably, ensovibep potency (IC_{50}) against all tested variants remains in the range of 1-10 ng/mL; less than an order of magnitude difference from the reference/Wuhan WT virus (**Figure 3**) (Rothenberger et al 2022).

Figure 3. Ensovibep activity measured in neutralization assays performed with lentivirus, VSV-based pseudoviruses or authentic viruses for the SARS-CoV-2 variants of concern and variants of interest.



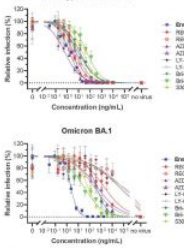
Reference variant is the Wuhan-Hu-1 strain for VSV-based pseudovirus, a D614G variant for the lentivirus-based pseudovirus or a patient isolate from the early pandemic for the authentic virus. VSV, vesicular stomatitis virus

- Ensovibep was tested together with a panel of clinically relevant monoclonal antibodies (**Figure 4**).

Figure 4. Neutralization activities (titration curves and IC_{15}) of ensovibep and monoclonal antibodies.

Compound	Wild Type IC_{50} (ng/mL)	Omicron BA.1 IC_{50} (ng/mL)	Omicron BA.1 Fold change to WT
Ensovibep	1.6	2.2	1.4
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
AZD8896	0.6	415	>100
AZD1061	5.5	237	43
Bri-196	9.5	392	41
Bri-198	52	30	0.6

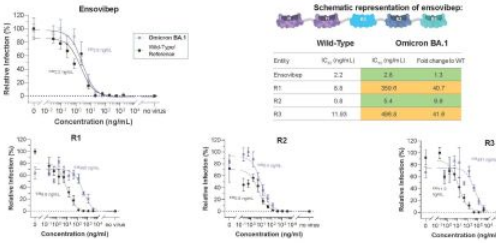
IC_{50}: green: <10 ng/mL; orange: 10-100 ng/mL; dark orange: 100-1000 ng/mL; red >1000 ng/mL Fold change to wt: green <10-fold; orange: 10–100-fold; red: >100-fold



Titration curves (right panels; mean ±SEM) and IC_{50} values (above) for VSV-pseudotype neutralization assays with wild-type and Omicron BA.1 variant spike protein. Ensovibep was tested together with a panel of clinically validated monoclonal antibodies. The table provides the numeric IC_{50} values as well as the fold change with respect to the wild-type. Wild-type virus is Wuhan-Hu-1.

- A 10- to 40-fold increase in IC_{50} was seen for each individual DARPin (R1, R2, R3), however the multi-specific ensovibep containing all three RBD binding domains retained potency against BA.1 (**Figure 5**

Figure 5. Titration curves and IC_{50} values of individual ensovibep DARPin modules against wild-type and variant of SARS-CoV-2 in VSV-pseudotype neutralization assay.

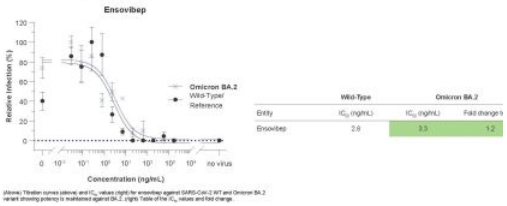


Entity	Wild-Type IC_{50} (ng/mL)	Omicron BA.1 IC_{50} (ng/mL)	Omicron BA.1 Fold change to WT
Ensovibep	2.2	2.8	1.3
R1	8.8	350.6	40.7
R2	0.8	5.4	6.8
R3	11.65	496.8	41.6

The table provides the numeric IC_{50} values as well as the fold change with respect to the wild-type. Wild-type virus is Wuhan-Hu-1.

- Ensovibep maintained its potency against omicron BA.2, as seen from the titration curves and IC_{50} va (**Figure 6**).

Figure 6. Ensovibep activity against SARS-CoV-2 wild-type (Wuhan-Hu-1) and omicron BA.2 variant in V pseudotype neutralization assay.



Entity	Wild-Type IC_{50} (ng/mL)	Omicron BA.2 IC_{50} (ng/mL)	Omicron BA.2 Fold change t
Ensovibep	2.8	3.3	1.2

(Above) Titration curves (above) and IC_{50} values (right) for ensovibep against SARS-CoV-2 WT and Omicron BA.2 variant showing potency is maintained against BA.2. (right) Table of the IC_{50} values and fold change.

The table provides the numeric IC_{50} values as well as the fold change with respect to the wild-type. Wild-type virus is Wuhan-Hu-1.