# Enanta Pharmaceuticals to Present New Data for EDP-235, its 3CL Protease Inhibitor, in Development as an Oral, Once-Daily Treatment for COVID-19, at the 36th International Conference on Antiviral Research

March 14, 2023

- *Phase 1 Data Demonstrate Favorable Safety, Tolerability and Pharmacokinetics Supportive of Once-Daily Dosing Without Ritonavir*
- *Preclinical Animal Data Indicate the Potential for EDP-235 to Reduce Household Transmission and to Minimize SARS-CoV-2 Rebound*
- *High Throughput Screen Identifies Non-Nucleoside Small Molecule Inhibitors of the SARS-CoV-2 RNA-Dependent RNA Polymerase*

WATERTOWN, Mass.--(BUSINESS WIRE)--Enanta Pharmaceuticals, Inc. (NASDAQ: ENTA), a clinical-stage biotechnology company dedicated to creating small molecule drugs for viral infections, today announced new data supporting the potential of EDP-235 for the treatment of COVID-19, which are being presented at the 36$^{th}$ International Conference on Antiviral Research (ICAR) being held March 13-17, 2023 at the Centre de Congrès de Lyon (Lyon Convention Center) in Lyon, France. The company will have one oral presentation and three poster presentations, showcasing the potential of EDP-235 and Enanta's leadership in the development of small molecules for the treatment of viral respiratory infections.

Phase 1 data presented continue to highlight EDP-235's promising overall safety, tolerability and pharmacokinetic (PK) profile, and preclinical data demonstrate EDP-235's ability to suppress viral replication and transmission in an animal model. Additional preclinical data show EDP-235's targeted tissue penetration and potential to mitigate rebound in COVID-19 patients. A fourth presentation focuses on a high-throughput screen to identify non-nucleoside inhibitors of the RNA-dependent RNA polymerase. EDP-235 is currently being evaluated in SPRINT (**S**ARS-Cov-2 **PR**otease **IN**hibitor **T**reatment), a Phase 2 study of non-hospitalized, symptomatic adults with mild or moderate COVID-19, and has a data readout targeted for May 2023.

"We are excited to present new clinical and preclinical data which continue to add to the robust findings supporting the potential of EDP-235 as a differentiated, once-daily, oral treatment for patients with COVID-19, as well as to demonstrate our broad capabilities in developing small molecules against this virus," said Jay R. Luly, Ph.D., President and Chief Executive Officer of Enanta Pharmaceuticals. "Findings from our Phase 1 study continue to show EDP-235's favorable safety, tolerability and pharmacokinetics with strong exposure multiples over the $EC_{90}$, without ritonavir boosting, while preclinical animal studies support the potential for EDP-235 to reduce household transmission. Additional preclinical data demonstrate that EDP-235's optimized tissue targeting may help to minimize viral rebound. Given the totality of these data, we are encouraged about EDP-235's ability to make a significant impact in the lives of COVID-19 patients and look forward to a Phase 2 data readout in May."

**Abstract ID: #021, Oral Presentation, Wednesday, March 15 from 10:15 – 11:30 am Central European Time (CET)**

***"EDP-235, an Oral 3CL Protease Inhibitor for the Treatment of COVID-19, Suppresses Viral Replication and Spread in SARS-CoV-2-Infected Ferrets"*** Michael Rhodin, Ph.D.

EDP-235's antiviral activity was evaluated in a ferret model of acute SARS-CoV-2 infection and transmission. Therapeutic treatment of infected animals with EDP-235 (either 200 mg/kg once daily or twice daily) beginning 12 hours post-infection with SARS-CoV-2 resulted in a rapid and sustained reduction in both live virus titer and viral RNA in nasal lavage samples. Only vehicle-treated animals had detectable live virus in nasal turbinates four days post-infection, demonstrating complete inhibition of viral replication by both EDP-235 dosing regimens. Further, EDP-235 exposures in ferrets were comparable to previously announced Phase 1 clinical EDP-235 plasma exposures, representing strong multiples over $EC_{90}$. To evaluate the impact of EDP-235 treatment on SARS-CoV-2 transmission, infected source animals were co-housed with uninfected contact animals 60 hours post-infection. Live virus was recoverable from the nasal lavages of contact animals housed with vehicle-treated source animals from 12 hours onwards after co-housing. In contrast, viral RNA and live virus were undetectable in nasal lavage and terminal nasal turbinate samples from contact ferrets co-housed with EDP-235-treated infected animals. Collectively, these data support the potential for EDP-235 to reduce household transmission.

**Abstract ID: #524, Poster Presentation, Tuesday, March 14 from 6 – 7 pm and Wednesday, March 15 from 12:15 – 1:15 pm CET**

***"EDP-235, an Oral, Once Daily, Ritonavir-Free, 3CL Protease Inhibitor for the Treatment of COVID-19: Results from Phase 1 Study in Healthy Subjects"*** Guy De La Rosa, M.D.

EDP-235 was evaluated in a Phase 1, randomized, double-blind, placebo (PBO)-controlled study to assess its safety and PK profile during single

ascending dose (SAD), multiple ascending dose (MAD) and food effect cohorts in healthy subjects. A total of 72 subjects were randomized. Forty subjects were enrolled into five SAD cohorts and thirty-two subjects were enrolled into four MAD cohorts dosed for seven days.

EDP-235 was generally safe and well-tolerated in healthy subjects. Three MAD dosing discontinuations resulted from one moderate headache in the 400 mg fasted cohort, one severe headache in the 800 mg fed cohort, and one grade 3 ALT/grade 2 AST elevation in the 800 mg fed cohort. There were no serious treatment emergent adverse events. Linear PK supported once daily dosing, with strong multiples over the $EC_{90}$ without the need for ritonavir boosting. In the SAD phase, EDP-235 exposure increased in an approximately dose-proportional manner, up to 800 mg. Plasma PK from the 200 mg fed cohort indicated a 4-fold food effect. Geometric mean $t_{1/2}$ was 13-18 hours across dose range, supporting once daily dosing. In the MAD phase, EDP-235 exposure increased with ascending multiple doses in an approximately dose-proportional manner, up to 400 mg. Steady state was reached 48 hours after the first dose and geometric mean $t_{1/2}$ ranging from 13-22 hours. EDP-235 administered once daily for seven days resulted in steady state $C_{24}$ concentrations up to 13-fold over the protein adjusted $EC_{90}$ determined in Vero E6 cells infected with the Omicron lineage. These data support the further evaluation of EDP-235 which is currently being studied in a Phase 2 clinical trial in non-hospitalized adults with mild or moderate COVID-19.

**Abstract ID#: 523, Poster Presentation, Tuesday, March 14 from 5 – 6 pm and Wednesday, March 15 from 2:15 – 3:15 pm CET**

***"EDP-235, a Potent, Once-daily, Oral Antiviral, Demonstrates Excellent Penetration Into SARS-CoV-2 Target Tissues, with the Potential for Mitigation of Viral Rebound in COVID-19 Patients"*** Indy Zang, Ph.D.

EDP-235's penetration into target tissues was compared to nirmatrelvir in human cells and preclinical species infected with SARS-CoV-2. Intracellular uptake of EDP-235 was tested side-by-side with nirmatrelvir in human cells. The ratios of intracellular to extracellular concentrations of EDP-235 were 8.7 in human lungs, 9.9 in cardiac myocytes, 11.3 in salivary glands, 18.0 in kidneys, and 33.6 in adipocytes. In contrast, nirmatrelvir had ratios of 0.6 to 1.2 in these human cells.

To determine the *in vivo* drug distribution into SARS-CoV-2 target tissues, rats were dosed orally with 10 mg/kg of EDP-235 or nirmatrelvir. EDP-235 showed favorable rat plasma exposure of 19.0 µg-hr/mL, whereas nirmatrelvir had a significantly lower rat plasma exposure of 4.9 µg-hr/mL. Consistent with *in vitro* observations, EDP-235 displayed excellent target tissue exposure in rats with tissue to plasma ratios of 4.1 in lungs, 4.7 in heart, 6.5 in salivary glands, 6.3 in kidneys, and 23.0 in adipose tissues, whereas nirmatrelvir had corresponding ratios of 0.8, 0.9, 0.8, 1.2 and 0.6 in those tissues.

These data demonstrate a more targeted tissue distribution and penetration, enabling EDP-235 to reach sites of potential viral reservoirs, which may help minimize viral rebound in COVID-19 patients.

**Abstract ID#: 528, Poster Presentation, Tuesday, March 14 from 6 – 7 pm and Wednesday, March 15 from 12:15 – 1:15 pm CET**

***"High Throughput Screen to Identify Non-Nucleoside Small Molecule Inhibitors of SARS-CoV-2 RNA-Dependent RNA Polymerase"*** Tessa Cressey, Ph.D.

Approaches for developing small molecule antivirals include targeting non-structural proteins such as the proteases 3CL pro and PLpro, nsp13, nsp14, nsp16, and the RNA-dependent RNA polymerase (RdRp). Remdesivir, a nucleoside analog targeting the SARS-CoV-2 RdRp, has been successfully used for the treatment of hospitalized or high-risk patients with COVID-19, but its utility is limited by the intravenous delivery route. A high throughput screen was conducted to identify non-nucleoside RdRp inhibitors, which could be useful additions to the SARS-CoV-2 treatment arsenal.

A biochemical assay was developed where purified recombinant RdRp consisting of nsp12, nsp7, and nsp8 elongates a primer in an annealed primer/template pair and incorporates a fluorescent UTP analog, releasing the fluorophore. Using this assay, a library of approximately 400,000 small molecules was screened for RdRp inhibition. After counter-screens to remove RNA intercalators, redox cyclers, and compounds with undesirable medicinal chemistry properties, 15 compounds from 11 structural families with half-maximal inhibitory concentrations (IC50s) <10 µM were selected for mechanism of inhibition studies. None of the compounds were RNA or NTP competitive inhibitors. Biochemical assays and analytical size-exclusion chromatography showed 11 compounds disrupted nsp12-nsp8 protein-protein interactions. Nano differential scanning fluorimetry analysis suggested five compounds target nsp12 directly. This high throughput screen identified multiple, structurally diverse, non-nucleoside SARS-CoV-2 RdRp inhibitors as potential starting points for hit optimization.

**About Enanta Pharmaceuticals, Inc.**

Enanta is using its robust, chemistry-driven approach and drug discovery capabilities to become a leader in the discovery and development of small molecule drugs for the treatment of viral infections. Enanta's research and development programs include clinical candidates for the following disease targets: respiratory syncytial virus (RSV), SARS-CoV-2 (COVID-19) and hepatitis B virus (HBV). Enanta is also conducting research on a single agent targeting both RSV and human metapneumovirus (hMPV).

Enanta's research and development activities are funded by royalties from hepatitis C virus (HCV) products developed under its collaboration with AbbVie. Glecaprevir, a protease inhibitor discovered by Enanta, is part of one of the leading treatment regimens for curing chronic HCV infection and is sold by AbbVie in numerous countries under the tradenames MAVYRET® (U.S.) and MAVIRET® (ex-U.S.) (glecaprevir/pibrentasvir). Please visit www.enanta.com for more information.

**Forward Looking Statements**

This press release contains forward-looking statements, including statements with respect to the prospects for advancement of Enanta's clinical programs in COVID-19. Statements that are not historical facts are based on management's current expectations, estimates, forecasts and projections about Enanta's business and the industry in which it operates and management's beliefs and assumptions. The statements contained in this release are not guarantees of future performance and involve certain risks, uncertainties and assumptions, which are difficult to predict. Therefore, actual outcomes and results may differ materially from what is expressed in such forward-looking statements. Important factors and risks that may affect actual results include: the impact of development, regulatory and marketing efforts of others with respect to competitive treatments for COVID-19; the discovery and development risks of Enanta's COVID-19 program; the competitive impact of development, regulatory and marketing efforts of others in this disease area; any continuing impact of the COVID-19 pandemic on business operations and clinical trials; Enanta's lack of clinical development experience; Enanta's need to attract and retain senior management and key research and development personnel; Enanta's need to obtain and

maintain patent protection for its product candidates and avoid potential infringement of the intellectual property rights of others; and other risk factors described or referred to in “Risk Factors” in Enanta’s Form 10-K for the fiscal year ended September 30, 2022, and any other periodic reports filed more recently with the Securities and Exchange Commission. Enanta cautions investors not to place undue reliance on the forward-looking statements contained in this release. These statements speak only as of the date of this release, and Enanta undertakes no obligation to update or revise these statements, except as may be required by law.

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