Enanta Pharmaceuticals
Great Chemistry Cures

SPRINT Phase 2 Study of EDP-235: Topline Results & Additional Analyses

June 8, 2023

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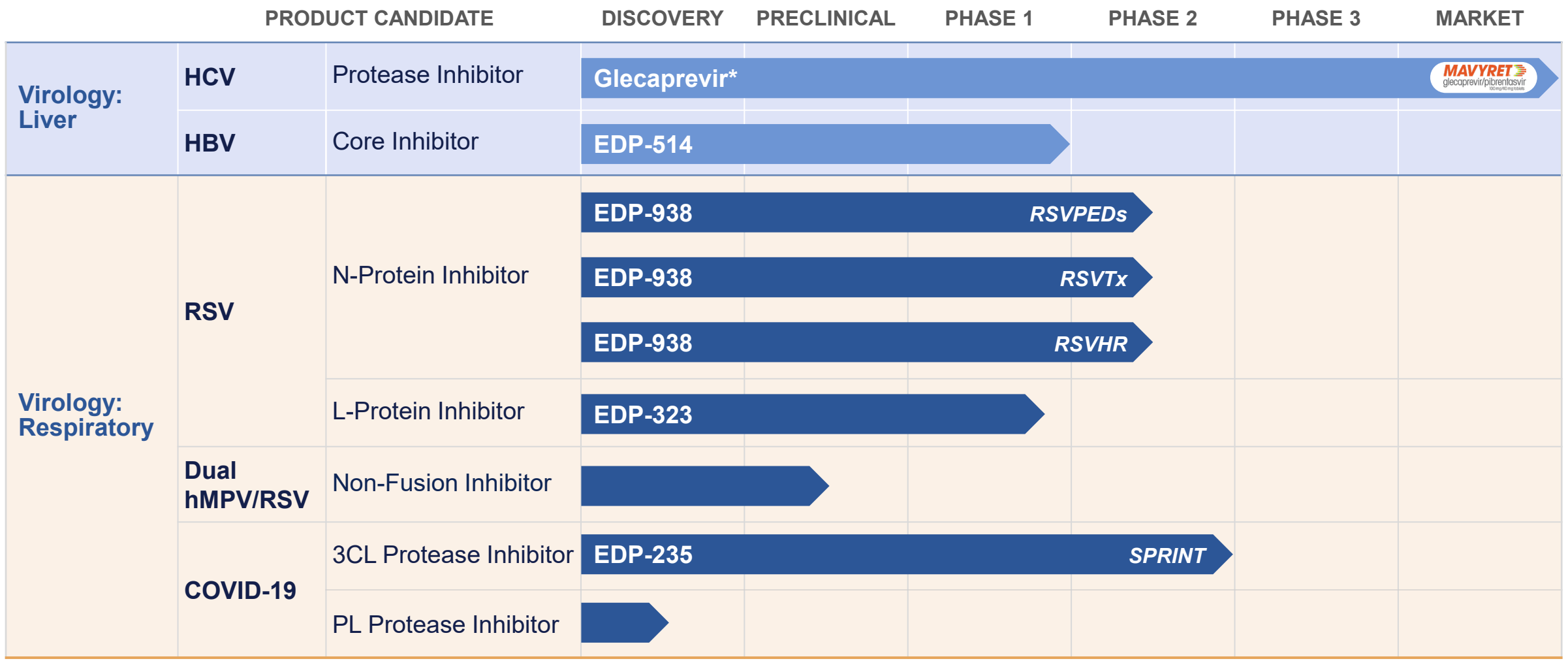
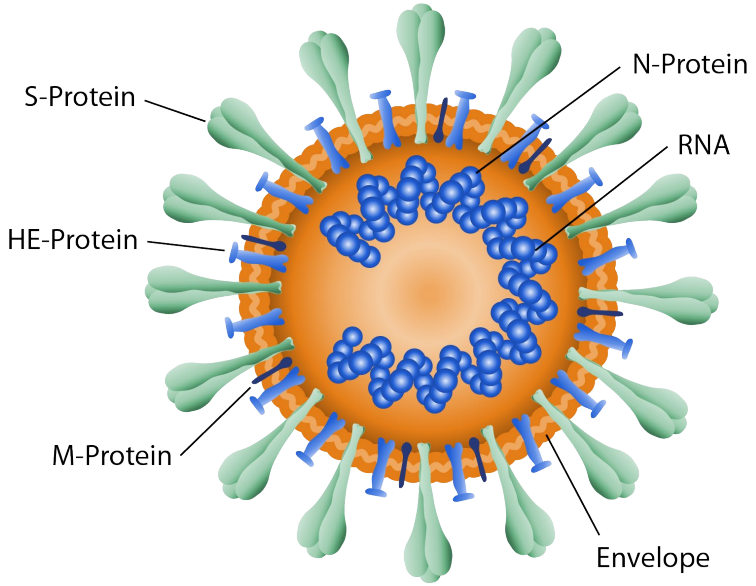
Enanta Pipeline



*Fixed-dose antiviral combination contains glecaprevir and AbbVie's NS5A inhibitor, pibrentasvir. Marketed by AbbVie as MAVYRET® (U.S.) and MAVIRET® (ex-U.S.).

EDP-235: Oral Protease Inhibitor Designed for COVID-19

- Novel, oral, direct-acting antiviral specifically designed to target the SARS-CoV-2 3CL protease
- Granted Fast Track designation by the FDA
- Potent and selective inhibition of SARS-CoV-2 3CLpro enzyme
  - Potent inhibition in multiple cellular models
- Potent against SARS-CoV-2 variants, including Omicron variants
- Preclinically active against other human coronaviruses
- High barrier to resistance preclinically
- Good target tissue distribution (e.g. lung to plasma AUC ratio >4)
- Robust treatment effect and prevention of transmission in ferret model
- Phase 1 supported 200 or 400mg once-daily as safe & efficacious dose
  - Plasma drug levels 7-13x higher than the EC90, without ritonavir boosting
- Phase 2 study (SPRINT) topline data presented in May



EDP-235 Profile Suggests Potential for Best-in-Class Antiviral Treatment for SARS-CoV-2 Infection

Preclinical Properties		EDP-235[1]	Nirmatrelvir[2]	Pomotrelvir[3]	Ensitrelvir[4]	Molnupiravir[5]	Bemnifosbuvir[6]
Mechanism		**Protease**	Protease	Protease	Protease	Polymerase	Polymerase
Potency (nM)*	Enzyme IC_{50}	**5.8**	19	24	13	n/a	n/a
	Vero Cell EC_{50}	**5.1**	75	345	69 (Delta)	1410**	n/a
	Vero Cell EC_{90}	**11**	155	598	n/a	n/a	470*** (In pHAEC)
Oral Bioavailability[7]		**95%**	34 – 50%	n/a	97%	36 – 56%	n/a
Lung Penetration[8]		**4.1**	0.8[9]	~1	0.7[9]	1.8	0.8
Projected Efficacious Dose		**200 or 400mg QD**	300mg/100mg ritonavir BID	700mg BID	375mg (D1)/125 mg (D2-5) QD	800mg Q12h	550mg BID

1. Jiang et al., ISIRV Poster #120, Oct 19, 2021
2. Owen et al., Science November 2021; Owen et al. ACS Spring 2021 meeting; EUA fact sheet for healthcare providers
3. Pardes CHI New Antiviral Conference presentation Oct 19, 2022. Pardes 2022 10K, March 2023
4. Tachibana, et al., ISIRV oral presentation, Oct 20, 2021; Unoh, et al., bioRxiv 2022; Sasaki, et al., bioRxiv 2022; Yotsuyanagi, et al., ECCMID oral presentation, Apr 24, 2022
5. Grobler et al., ID Week 2021, Poster 543; Painter et al., Antiviral Research Nov 2019
6. Good et al., AAC, 2021; Atea 2Q2021 earnings presentation; Atea 1Q2022 earnings presentation; Atea 2Q2022 earnings presentation
7. Oral bioavailability in rats for EDP-235, nirmatrelvir, and ensitrelvir; in mice for molnupiravir
8. AUC lung to plasma ratio in rats (EDP-235, nirmatrelvir, ensitrelvir), mice (molnupiravir); C12 lung to plasma ratio in humans for AT-527
9. Data for nirmatrelvir and ensitrelvir generated by Enanta

*All potency values versus ancestral (A) lineage unless indicated
**Data from N-hydroxycytidine (NHC): molnupiravir is prodrug of NHC
***Data from AT-511 (AT-527 is the hemi-sulfate salt of AT-511)
pHAEC: primary human airway epithelial cells
n/a: not available

SPRINT Phase 2 Study of EDP-235: Topline Results & Additional Analyses

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Effects of EDP-235 in Non-hospitalized Adults with Mild or Moderate COVID-19

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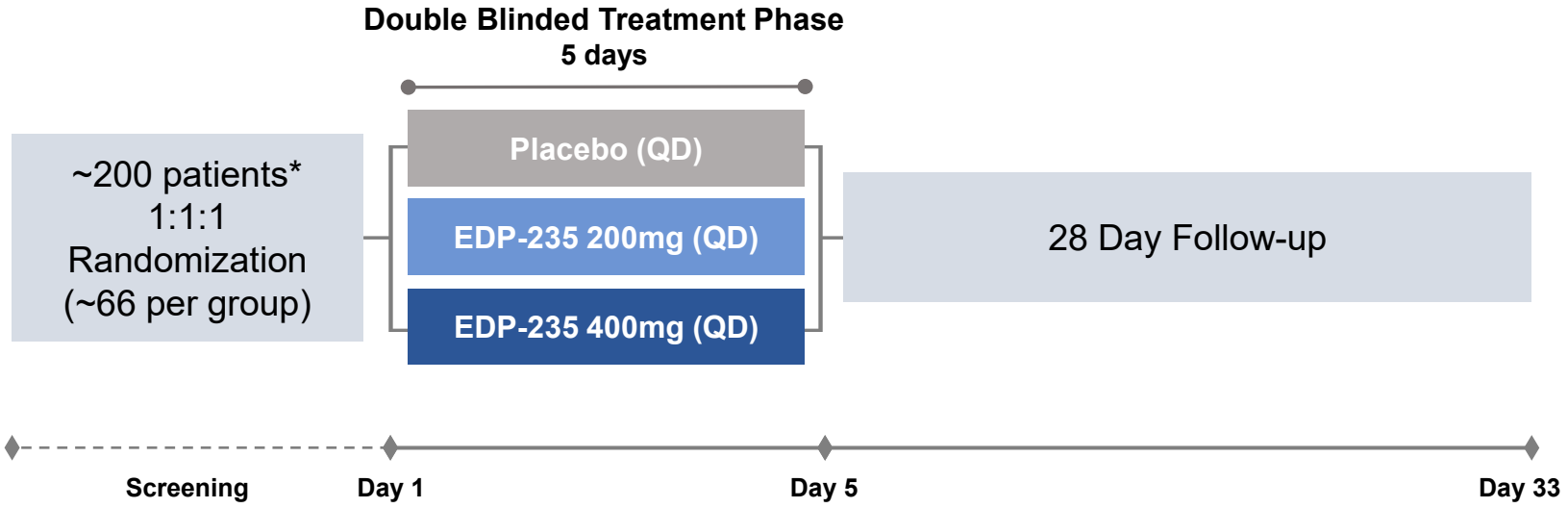
SPRINT: SARS-CoV-2 PRotease INhibitor Treatment
Phase 2 Study for EDP-235 in Non-hospitalized Standard Risk Patients

SPRINT



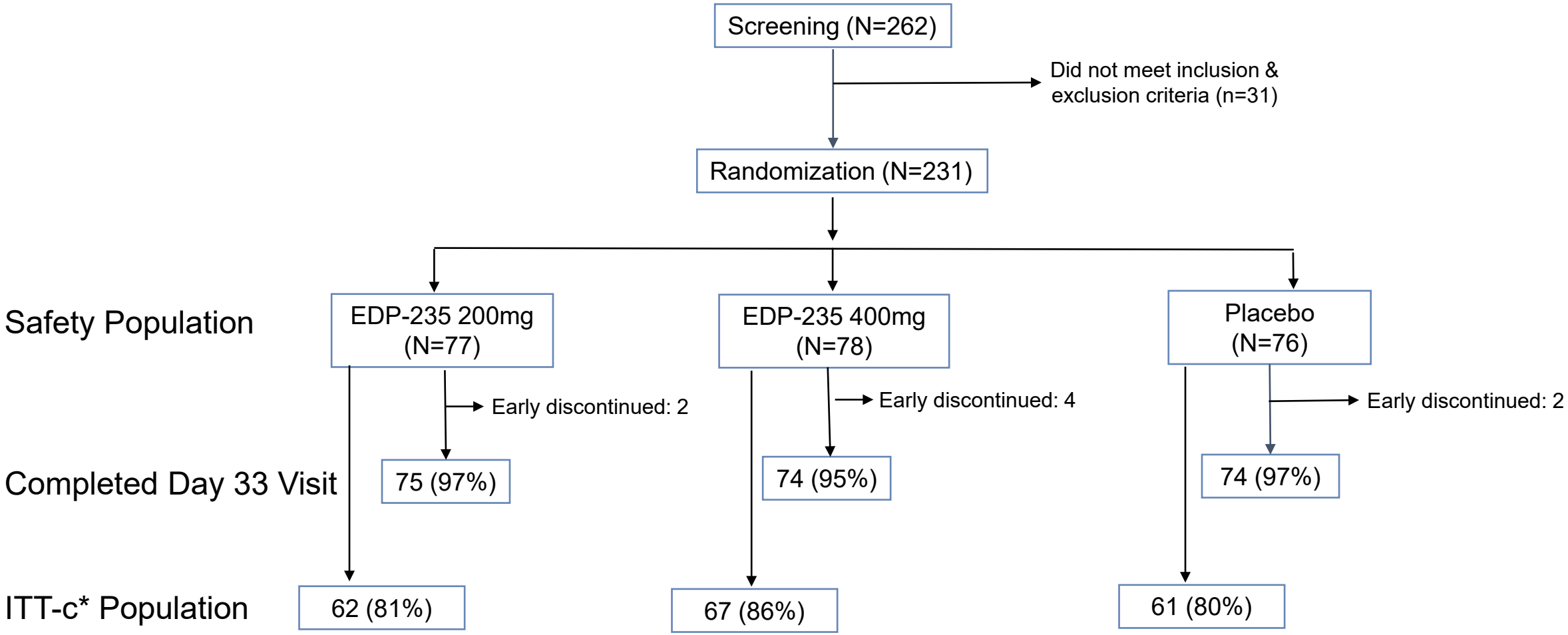
- **Primary Objective:** Evaluation of safety and tolerability
- **Secondary Objectives:** Evaluation of virologic endpoints, clinical symptoms and outcomes, and pharmacokinetics

Eligibility Criteria:

- Non-hospitalized adults who are not at increased risk for developing severe disease
- Initial onset of symptoms within 5 days of randomization
- At least 2 COVID-19 symptoms with one of at least moderate severity
- Have not been vaccinated or infected with SARS-CoV-2 less than 90 days of enrollment

*Patients were stratified by age (≤50 years or 51 to 64 years) and duration of COVID-19 symptoms (≤ 3 days or >3 days and ≤5 days) prior to randomization

SPRINT: Patient Disposition



*ITT-c Population includes all treated subjects with their SARS-CoV-2 status confirmed by central RT-PCR viral load at baseline ≥ lower limit of quantification (LLOQ).

SPRINT: Demographics and Baseline Characteristics

Safety Population

- Demographics and baseline characteristics were well balanced between the arms.
- Majority were White, Hispanic, young, enrolled within 3 days of symptom onset, and seropositive

Parameter	EDP-235 200mg (N=77)	EDP-235 400mg (N=78)	Placebo (N=76)
Age – years Median (Range)	43.0 (19, 64)	46.0 (19, 64)	45.5 (19, 62)
18 to 50 years old – n (%)	50 (64.9)	51 (65.4)	51 (67.1)
Gender: Female – n (%)	50 (64.9)	47 (60.3)	42 (55.3)
Race: White – n (%)	73 (94.8)	75 (96.2)	70 (92.1)
Ethnicity: Hispanic/Latino – n (%)	74 (96.1)	73 (93.6)	71 (93.4)
BMI – kg/m^2 Median (Range)	24.9 (17.0, 33.9)	24.9 (20.4, 38.5)	24.8 (18.8, 32.9)
Smoking History: Never – n (%)	76 (98.7)	75 (96.2)	74 (97.4)
COVID-19 Symptoms ≤ 3 Days – n (%)	57 (74.0)	56 (71.8)	56 (73.7)
COVID-19 Vaccination Status – n (%)			
Vaccinated	56 (72.7)	60 (76.9)	50 (65.8)
Serostatus: Seropositive – n (%)	74 (96.1)	75 (96.2)	73 (96.1)
Baseline Viral Load – log10 copies/mL, Mean	5.0	5.1	5.1

SPRINT: Summary of Treatment Emergent Adverse Events (TEAEs)

Safety Population

- Low frequency of treatment emergent adverse events; most were mild in severity
- No serious adverse events or discontinuations due to adverse events

	EDP-235 200mg (N=77) n (%)	EDP-235 400mg (N=78) n (%)	Placebo (N=76) n (%)
Total Number of Treatment-Emergent Adverse Events (TEAEs)	1	6	3
Number of Subjects With Any TEAEs	1 (1.3)	5 (6.4)	2 (2.6)
Number Of Subjects With Any Study Drug-Related TEAEs*	1 (1.3)	2 (2.6)	1 (1.3)
Number of Subjects With Any TEAEs of Grade 3 or Higher	0	1 (1.3)	0
Number of Subjects with Any TEAEs by Maximum Severity			
Mild (Grade 1)	1 (1.3)	4 (5.1)	1 (1.3)
Moderate (Grade 2)	0	0	1 (1.3)
Severe (Grade 3)	0	1 (1.3)	0
Life-threatening (Grade 4)	0	0	0
Death (Grade 5)	0	0	0
Number Of Subjects With Any TEAEs Leading to Study Drug Discontinuation	0	0	0
Number of Subjects With Any TEAE Leading to Study Discontinuation	0	0	0
Number Of Subjects With Any TEAEs Leading to Death	0	0	0
Number Of Subjects With Any Serious TEAEs	0	0	0
Number Of Subjects With Any Study Drug-Related Serious TEAEs*	0	0	0

*Study Drug-Related TEAEs are considered 'Related' if they are reported as either 'Possible' or 'Related.' If the relationship of an AE is missing, the AE is considered 'Related'.

SPRINT: Treatment-Emergent Adverse Events
Safety Population

- No specific pattern of treatment-emergent adverse events was identified

	EDP-235 200mg (N=77) n (%)	EDP-235 400mg (N=78) n (%)	Placebo (N=76) n (%)
Total Number of Treatment-Emergent Adverse Events	1	6	3
Number of Subjects With At Least One Treatment-Emergent Adverse Event	1 (1.3)	5 (6.4)	2 (2.6)
Preferred Term			
Hepatotoxicity	1 (1.3)	1 (1.3)	0
Periorbital oedema	0	1 (1.3)	0
Face oedema	0	1 (1.3)	0
Gastroenteritis	0	1 (1.3)	0
Fall	0	1 (1.3)	0
Hyperglycaemia	0	0	1 (1.3)
Hypertriglyceridaemia	0	0	1 (1.3)
Arthralgia	0	1 (1.3)	0
Dysgeusia	0	0	1 (1.3)

SPRINT: Laboratory Values

- Laboratory values were generally unremarkable
  - One subject receiving EDP-235 400mg who had concomitant use of alcohol and acetaminophen, experienced asymptomatic, transient elevation of ALT (grade 4), AST (grade 3) and GGT with normal bilirubin and alkaline phosphatase
  - Transient, dose dependent elevations in total cholesterol and triglycerides were seen with EDP-235 treatment, trending toward baseline after completion of treatment

SPRINT: Safety Summary

- EDP-235 was generally safe and well tolerated
- Low frequency of adverse events; most were mild in severity
  - 1.3% in EDP-235 200mg
  - 6.4% in EDP-235 400mg
  - 2.6% in Placebo
- No serious adverse events or discontinuations due to adverse events
- Laboratory values were generally unremarkable
  - One subject receiving EDP-235 400mg who had concomitant use of alcohol and acetaminophen, experienced asymptomatic, transient elevation of ALT (grade 4), AST (grade 3) and GGT with normal bilirubin and alkaline phosphatase
  - Transient, dose dependent elevations in total cholesterol and triglycerides were seen with EDP-235 treatment, trending toward baseline after completion of treatment

SPRINT: Pharmacokinetics Summary

- EDP-235 target exposures were achieved and consistent with Phase 1
- Plasma drug levels were 7x and 12x higher than the protein-adjusted EC_{90} of Omicron for 200mg and 400mg, respectively

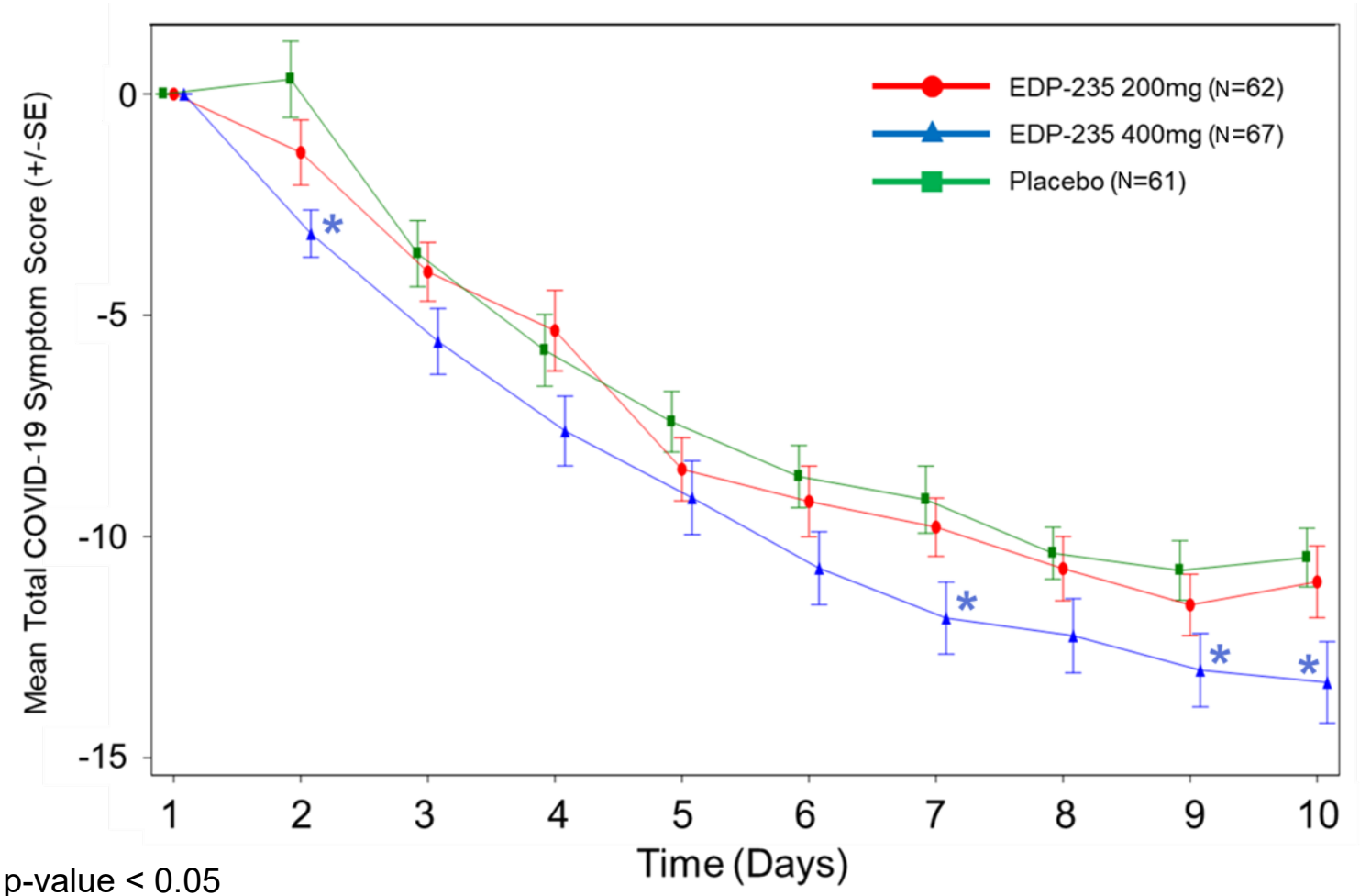
EDP-235 Predose Concentration on Day 5 (ng/mL)

Dose	n	Mean	Median	% CV
200mg	66	1290	1080	78.5
400mg	73	2180	2230	69.1

Total Symptom Score (TSS): Change from Baseline

(ITT-c population within 5 days of symptom onset; all 14 FDA defined symptoms[1])

- Dose-dependent improvement in TSS for all 14 symptoms, with statistical significance achieved at multiple timepoints for EDP-235 400mg compared to placebo



[1]COVID-19 Symptoms:

Respiratory: Cough, Shortness of Breath, Sore Throat, Stuffy or Runny Nose

Systemic: Chills or Shivering, Feeling Hot or Feverish, Headache, Low Energy or Tiredness, Muscle or Body Aches

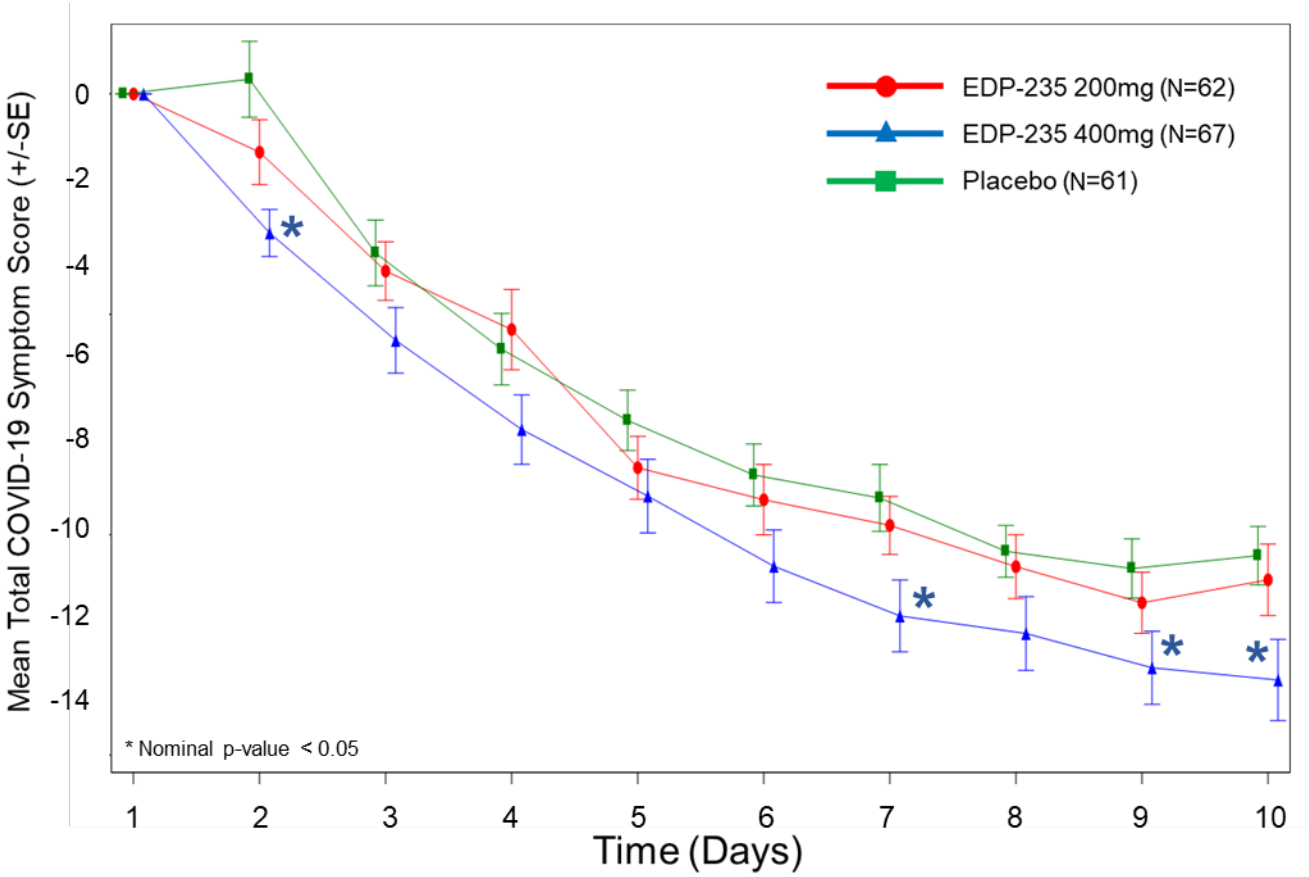
Digestive: Nausea, Vomiting, Diarrhea

Other: Sense of Smell, Sense of Taste

* Nominal p-value < 0.05

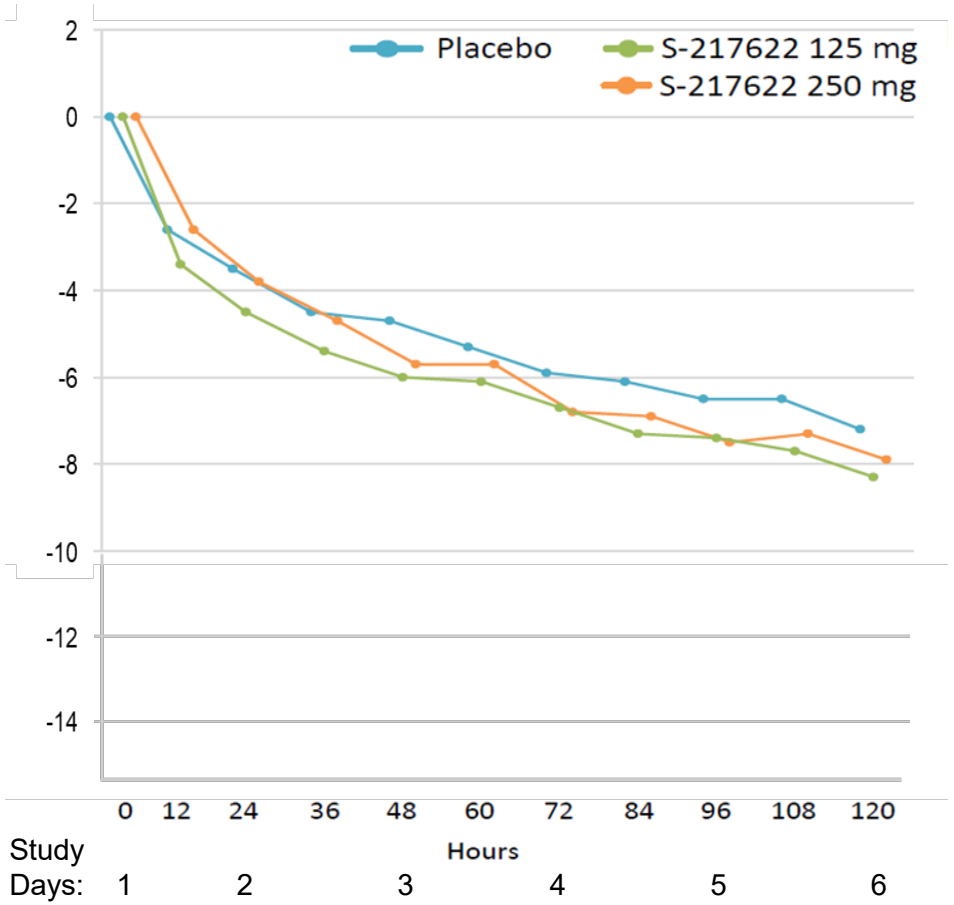
Total Symptom Score (TSS): Change from Baseline
(Population within 5 days of symptom onset)

SPRINT Phase 2 EDP-235
N=190, 14 symptoms



Symptoms:
Respiratory: Cough, Shortness of Breath, Sore Throat, Stuffy or Runny Nose
Systemic: Chills or Shivering, Feeling Hot or Feverish, Headache, Low Energy or Tiredness, Muscle or Body Aches
Digestive: Nausea, Vomiting, Diarrhea ;
Other: Sense of Taste, Sense of Smell (Enanta only)

Shionogi Phase 2b Ensitrelvir*
N=341, 12 symptoms

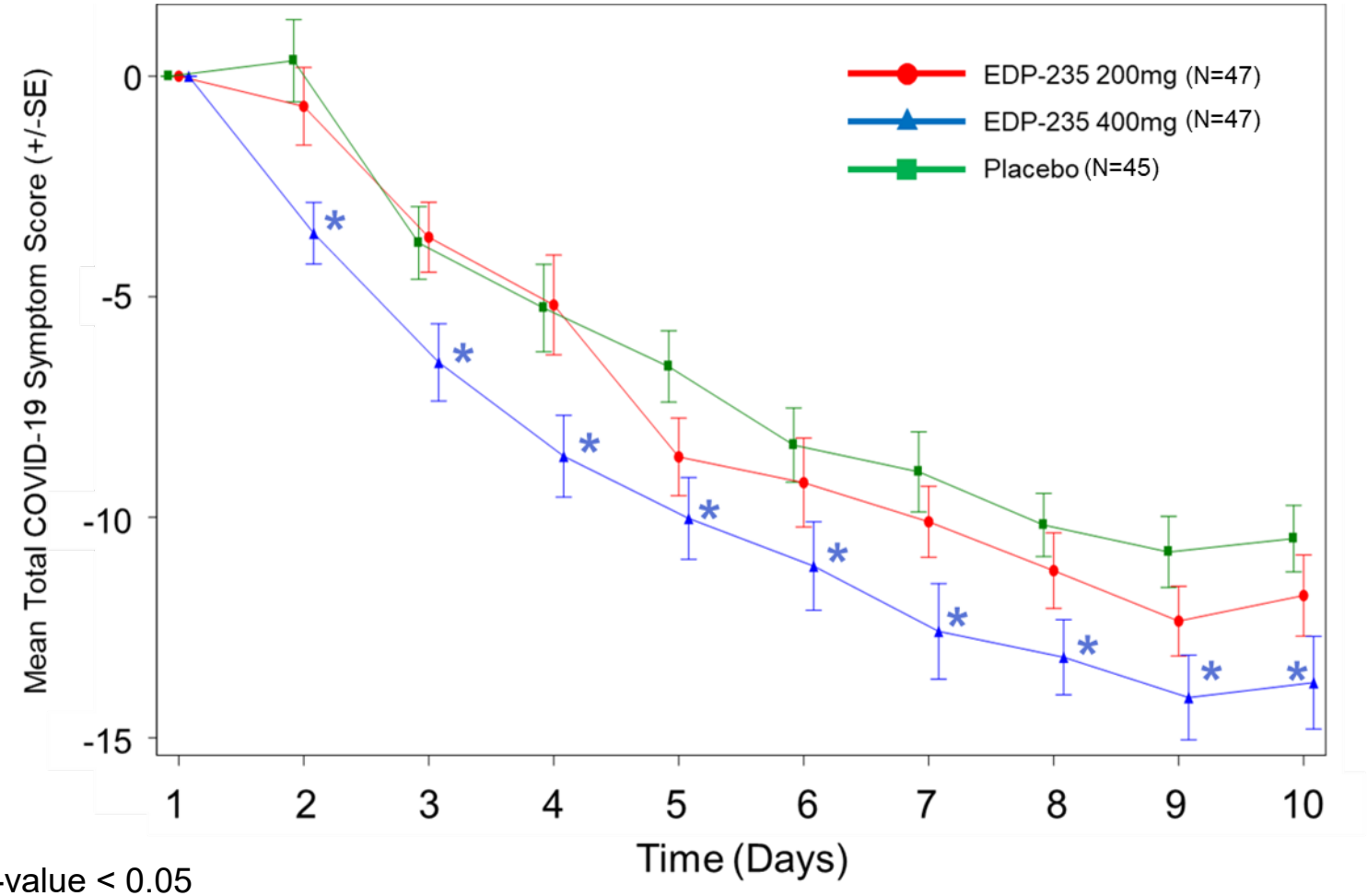


* ECCMID April 2022, Lisbon; Ohmagari et al, Phase 2b

Total Symptom Score (TSS): Change from Baseline

(ITT-c population within 3 days of symptom onset; all 14 FDA defined symptoms[1])

- Prespecified population enrolled within 3 days of symptom onset showed a statistically significant improvement in TSS for all 14 symptoms for EDP-235 400mg compared to placebo at all time points



[1]COVID-19 Symptoms:

Respiratory: Cough, Shortness of Breath, Sore Throat, Stuffy or Runny Nose

Systemic: Chills or Shivering, Feeling Hot or Feverish, Headache, Low Energy or Tiredness, Muscle or Body Aches

Digestive: Nausea, Vomiting, Diarrhea

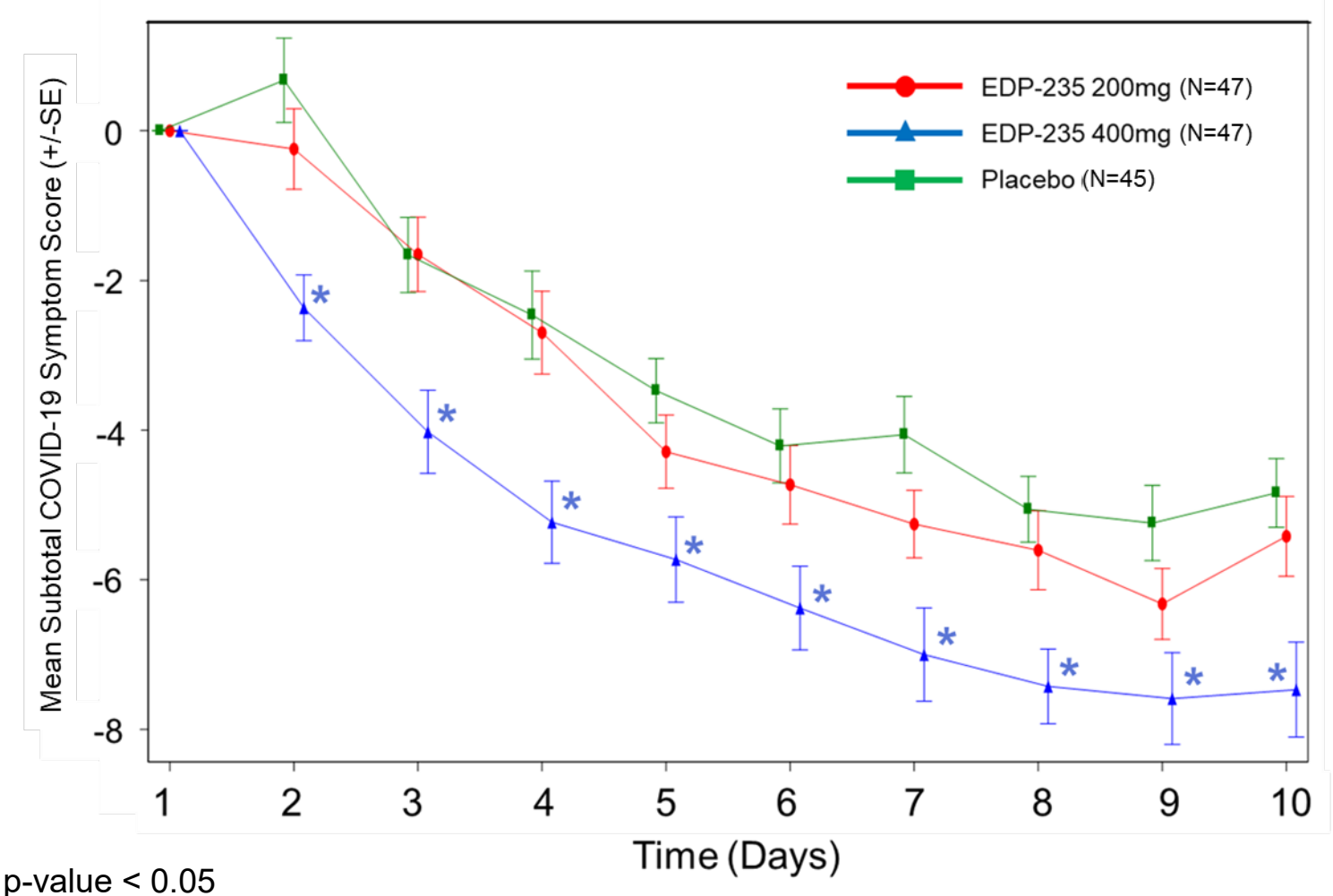
Other: Sense of Smell, Sense of Taste

* Nominal p-value < 0.05

Subtotal Symptom Score: Change from Baseline

(ITT-c population within 3 days of symptom onset; 6 selected symptoms[1])

- Prespecified population enrolled within 3 days of symptom onset showed a statistically significant improvement in a subset of 6 symptoms for EDP-235 400mg compared to placebo at all time points



[1]COVID-19 Selected Symptoms:

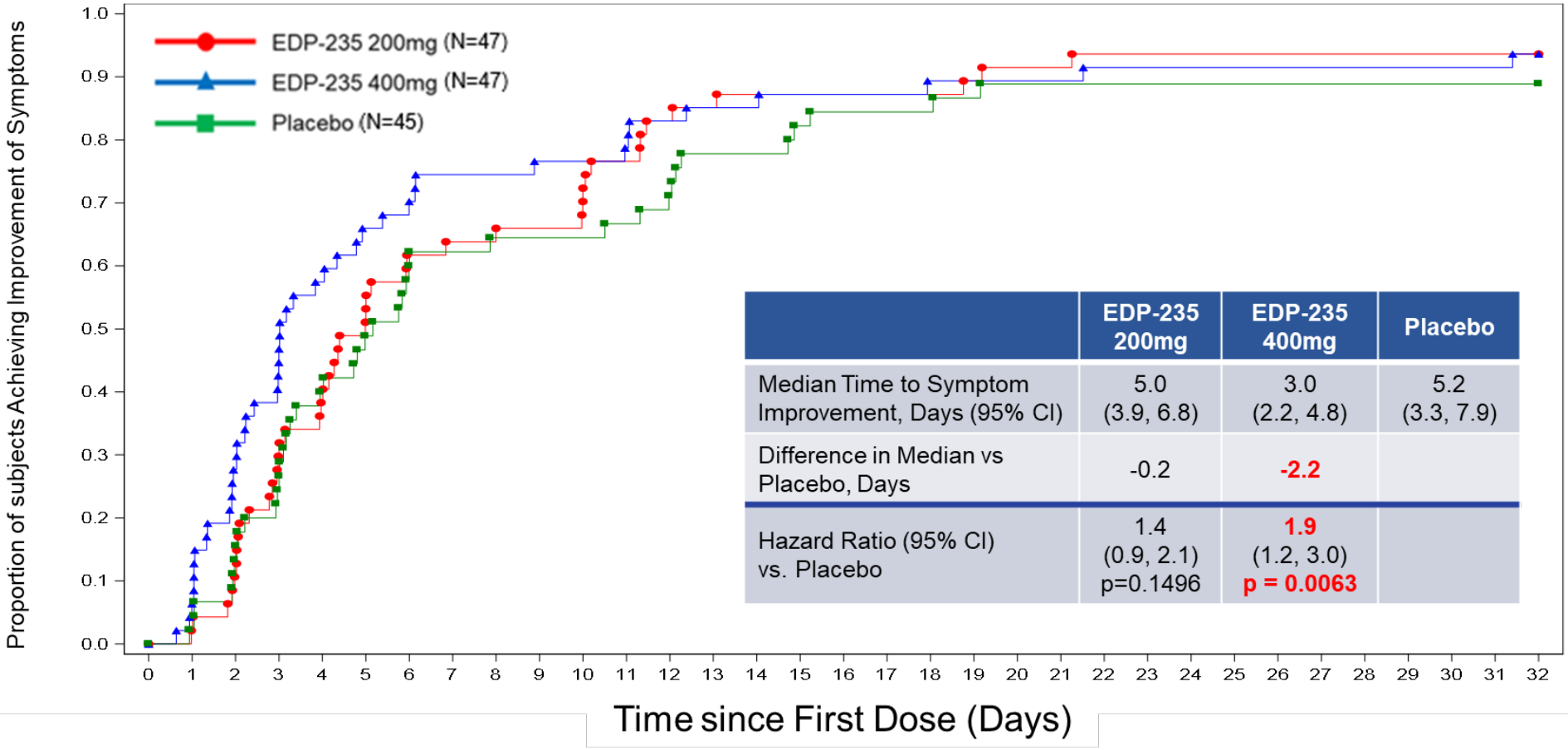
Respiratory: Shortness of Breath, Sore Throat, Stuffy or Runny Nose

Systemic: Chills or Shivering, Feeling Hot or Feverish, Headache

* Nominal p-value < 0.05

Time to Symptom Improvement
(ITT-c population within 3 days of symptom onset; 6 selected symptoms[1])

- EDP-235 400mg significantly reduced duration of 6 symptom subset by 2-days compared to placebo in patients enrolled within 3 days of symptom onset



	EDP-235 200mg	EDP-235 400mg	Placebo
Median Time to Symptom Improvement, Days (95% CI)	5.0 (3.9, 6.8)	3.0 (2.2, 4.8)	5.2 (3.3, 7.9)
Difference in Median vs Placebo, Days	-0.2	**-2.2**	
Hazard Ratio (95% CI) vs. Placebo	1.4 (0.9, 2.1) p=0.1496	**1.9** (1.2, 3.0) **p = 0.0063**	

[1]COVID-19 Selected Symptoms:

Respiratory: Shortness of Breath, Sore Throat, Stuffy or Runny Nose

Systemic: Chills or Shivering, Feeling Hot or Feverish, Headache

No difference in time to 14 symptom improvement was observed for EDP-235 compared with placebo

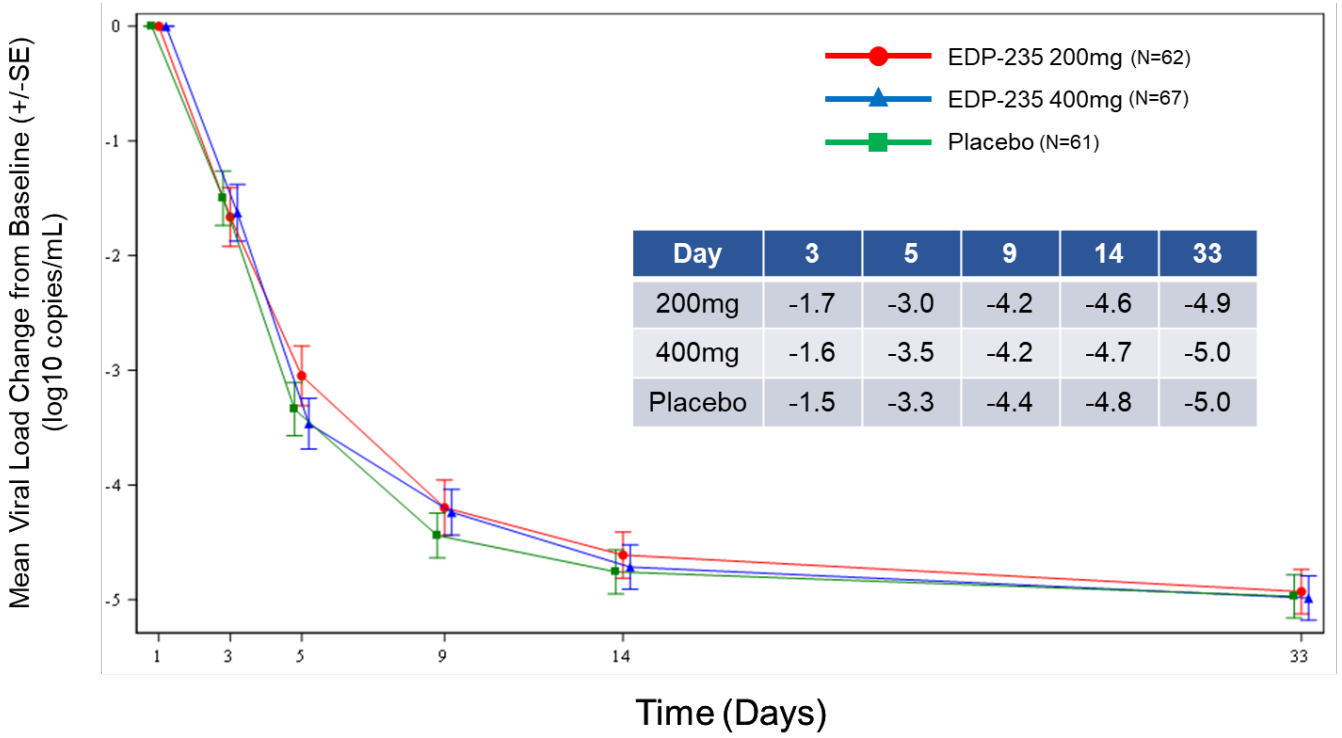
SPRINT: Symptom Summary

- Improvement in 14 symptom TSS for 400mg EDP-235 compared to placebo:
  - Statistical significance achieved at multiple timepoints in full ITT-c population
  - Statistical significance at all time points in a prespecified population enrolled within 3 days of symptom onset
  - Effect enhanced in prespecified population enrolled within 3 days of symptom onset in a subset of 6 symptoms
- Statistically significant reduction in median time to symptom improvement by with EDP-235 400mg compared to placebo for the subset of 6 symptoms
  - 1-day improvement in full ITT-c population
  - 2-day improvement in patients enrolled within 3 days of symptom onset

SPRINT: Viral RNA Change from Baseline

Intent-to-Treat-c Population

- No difference between treatment arms and placebo for viral RNA decline (ITTc)



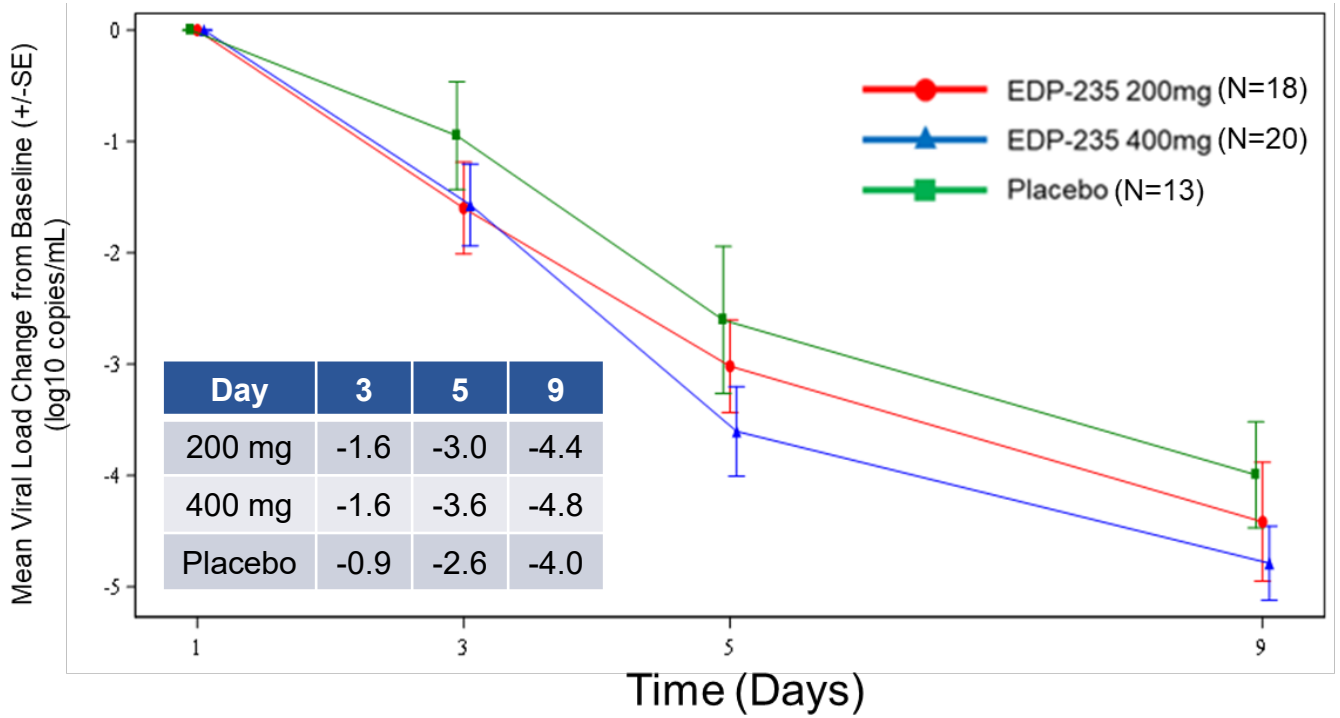
Day	3	5	9	14	33
200mg	-1.7	-3.0	-4.2	-4.6	-4.9
400mg	-1.6	-3.5	-4.2	-4.7	-5.0
Placebo	-1.5	-3.3	-4.4	-4.8	-5.0

- Additional analysis of patients with a baseline viral load greater than 5 log (~50% of patients)
  - Day 3: viral RNA decline of **0.4 log** in both EDP-235 groups vs placebo
  - Day 5: viral RNA decline of 0.4 log (400mg) vs placebo

SPRINT: Viral RNA Change from Baseline

ITT-c population within 3 days of symptom onset and nucleocapsid negative

- Seropositive: presence of antibodies to COVID, generated by prior natural infection and/or vaccination (≥1)
  - Natural infection produces antibodies to both nucleocapsid and spike viral proteins
  - Vaccination produces antibodies only to spike viral protein
  - All antibodies are detected for years after vaccination or natural infection
- Nucleocapsid seropositive indicates prior natural infection, which produces greater sustained mucosal immunity (nasal IgA antibody levels) [1,2]



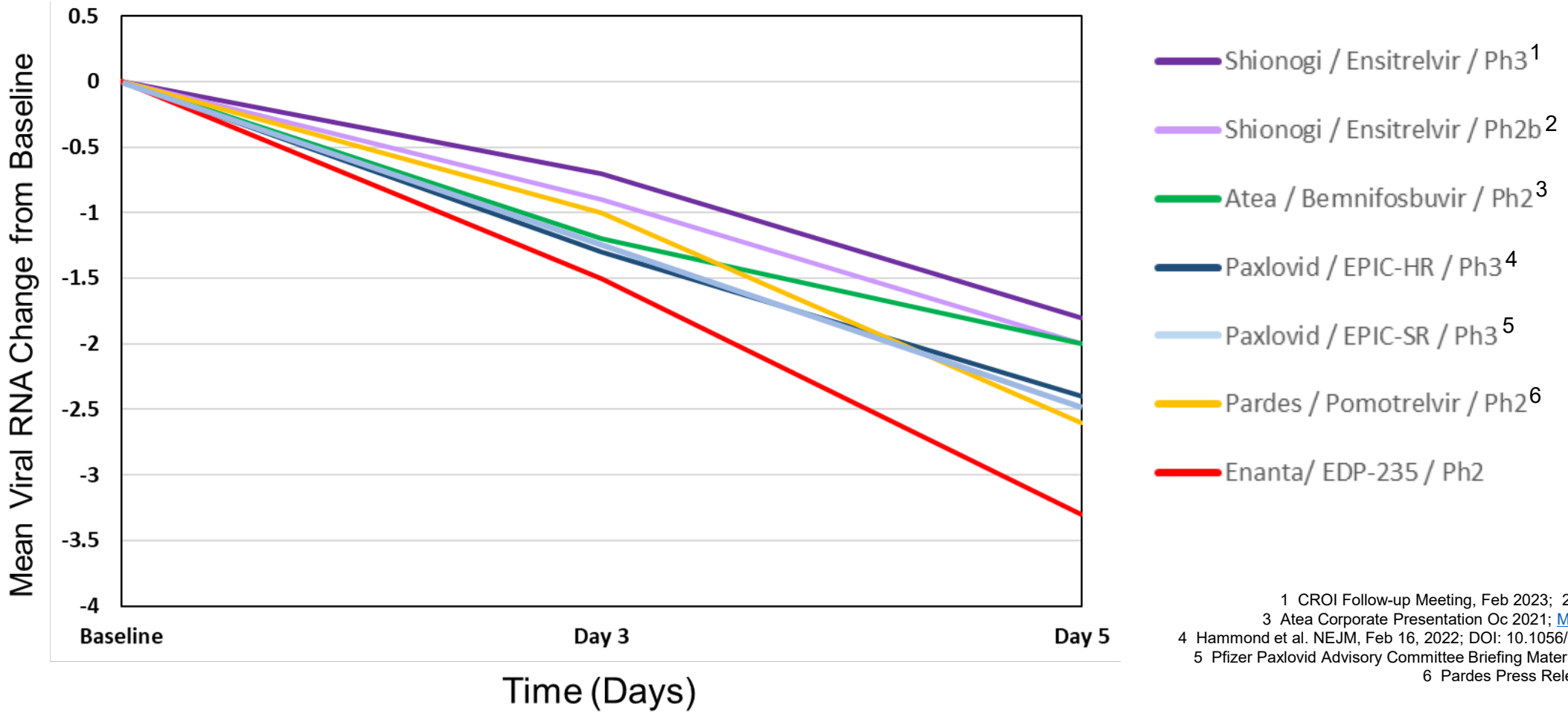
Day	3	5	9
200 mg	-1.6	-3.0	-4.4
400 mg	-1.6	-3.6	-4.8
Placebo	-0.9	-2.6	-4.0

- Viral load decline at Day 5 for the 400mg arm compared to placebo:
  - **0.8 log** in nucleocapsid seronegative patients (~40% of the ITT-c population)
  - **1 log** in nucleocapsid seronegative patients enrolled within 3 days of symptom onset

1 Mucosal IgA against SARS-CoV-2 Omicron Infection, N Engl J Med 2022; 387:e55.
2 Collier, A. Y. et al. Sci. Transl Med. 2022 Apr 20;14(641):eabn6150.

COVID Trial Placebo Arms: Change in Viral RNA from Baseline

- Rapid decline in viral RNA from nasal swabs in placebo arm of SPRINT was more robust than in placebo arms from other trials of antivirals published to date, indicating this highly immune population rapidly cleared virus from the nose



1 CROI Follow-up Meeting, Feb 2023; 2 ISIRV Oct 2022
3 Atea Corporate Presentation Oc 2021; Moonsong slide 11
4 Hammond et al. NEJM, Feb 16, 2022; DOI: 10.1056/NEJMoa2118542
5 Pfizer Paxlovid Advisory Committee Briefing Materials, 23-Feb-2023
6 Pardes Press Release, Apr 3, 2023

SPRINT: Virology Summary

- High degree of nucleocapsid positivity and rapid decline in viral RNA from nasal swabs in placebo arm indicate a highly immune population that quickly cleared virus from the nose
- No difference between treatment arms and placebo for viral RNA decline (ITTc)
- Additional analyses demonstrate a virologic effect in multiple subsets of patients, with a placebo-adjusted viral load decline at Day 5 in the 400mg group of:
  - 0.4 log: baseline viral load greater than 5 log
  - 0.8 log: nucleocapsid negative (suggesting no recent natural infection)
  - 1 log: nucleocapsid negative and symptom onset within 3 days

SPRINT Phase 2 Results: Conclusions

Safety

- EDP-235 was generally safe and well-tolerated
- Low frequency of adverse events; most were mild in severity
  - 1.3%, 6.4%, and 2.6% in the EDP-235 200mg, 400mg and placebo arms
- No serious adverse events or discontinuations due to adverse events

Clinical Symptoms

- Statistically significant improvement in total symptom score (TSS) achieved at multiple timepoints for EDP-235 400mg
  - Patients enrolled within 3 days of symptom onset showed a statistically significant improvement in TSS for EDP-235 400mg at all time points
- No difference in time to 14 symptom improvement for EDP-235 compared with placebo
  - EDP-235 400mg significantly reduced duration of 6 symptom subset by 2 days compared to placebo in patients enrolled within 3 days of symptom onset

Virology

- No difference between treatment arms and placebo for viral RNA decline
- Virologic effect observed in multiple patient subsets at 400mg: 0.4 log for baseline viral load >5 log, 0.8 log for nucleocapsid negative (suggesting no recent natural infection), and 1 log for nucleocapsid negative and symptom onset within 3 days
- High degree of nucleocapsid positivity & rapid decline in nasal RNA in all study arms indicates a highly immune population

Reference Slides

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Seroprevalence by Natural Infection

CDC US Nationwide Blood Donor Survey

Background

- Seroprevalence: % of a population who have antibodies to an infectious agent
  - Indicates past infection and/or vaccination
- Natural infection produces antibodies to both Nucleocapsid and Spike viral proteins
- Vaccination produces antibodies only to Spike viral protein
- All antibodies are detected for years after vaccination or natural infection
- CDC nationwide blood donor survey provides estimates seroprevalence every 3 months

Conclusions

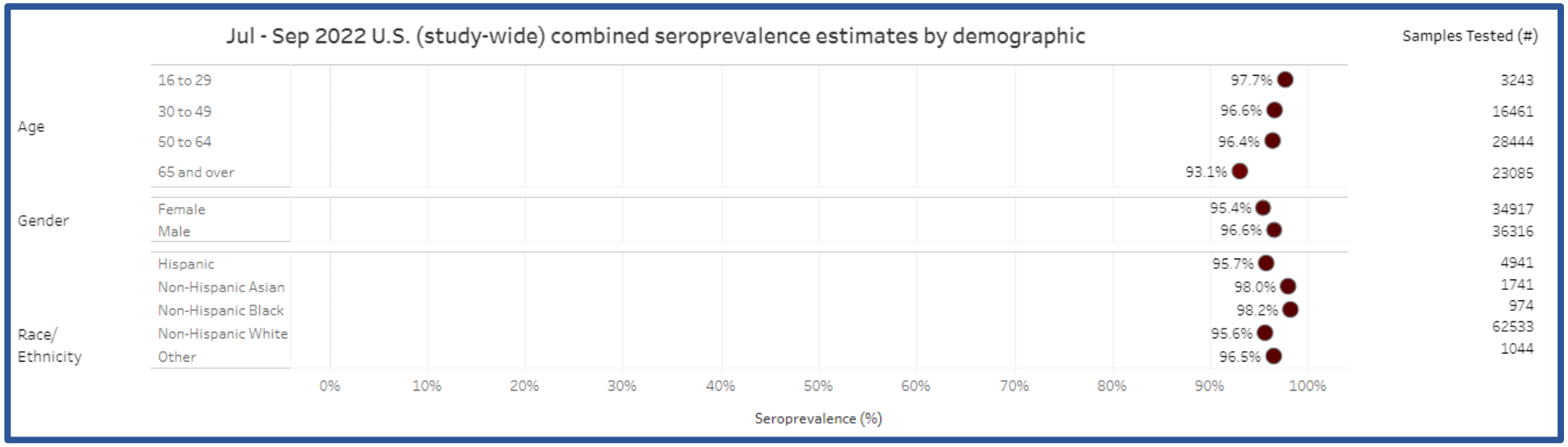
- Most of the people in the US (93-98%) are seropositive for COVID-19 (as of Sept 2022) through either vaccination, natural infection, or both
- Majority (70%) of the US have been naturally infected with COVID-19 (as of Sept 2022)
- The proportion of the US population with hybrid immunity has grown significantly

Beginning in January, 2022, the nationwide blood donor seroprevalence survey was modified to become a longitudinal study of ~143,000 blood donors. For each quarter in 2022, one randomly selected blood donation is selected per donor and tested for anti-spike antibodies using the Ortho VITROS® SARS-CoV-2 quantitative IgG assay and anti-nucleocapsid antibodies using the Ortho VITROS SARS-CoV-2 total antibody assay. Seroprevalence estimates are calculated every 3 months

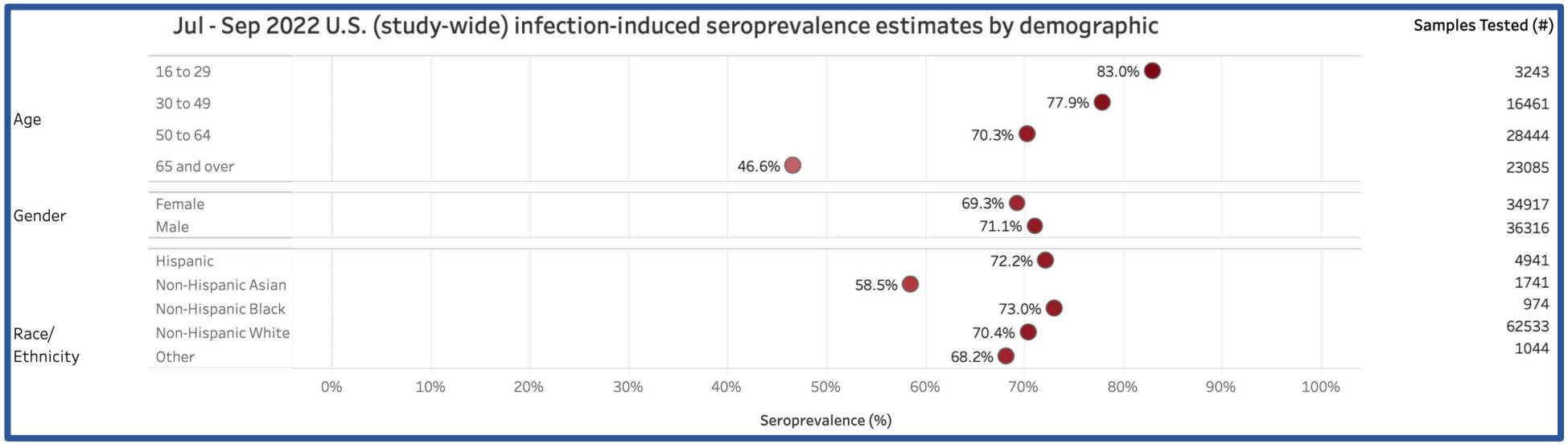
https://covid.cdc.gov/covid-data-tracker/#nationwide-blood-donor-seroprevalence-2022

Seroprevalence by Natural Infection (Jul – Sep 2022)

CDC US Nationwide Blood Donor Survey



Majority of people in the US are seropositive for COVID-19 (as of Sept 2022) through either vaccination, natural infection, or both.



Majority of people in the US have been naturally infected with COVID-19 (as of Sept 2022).

https://covid.cdc.gov/covid-data-tracker/#nationwide-blood-donor-seroprevalence-2022

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