Supplementary Material

Safety, Pharmacokinetics, and Predicted Neutralizing Activity of the SARS-CoV-2 Monoclonal Antibody Sipavibart: Results from Little DIPPER and the SUPERNOVA Substudy

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Eligibility Criteria for the Little DIPPER study

Inclusion Criteria

Provision of signed and dated, written informed consent prior to any study-specific procedures.

Healthy male or female participants aged 18 to 55 years (inclusive).

Participants were required to have suitable veins for cannulation or repeated venipuncture.

Negative SARS-CoV-2 reverse transcription-polymerase chain reaction or SARS-CoV-2 rapid antigen test result at Visit 1.

Body weight ≥ 45 kg and ≤ 110 kg and body mass index ≥ 18 and ≤ 32 kg/m^2 at screening.

Participants had to be able to attend all scheduled visits and to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative, or equivalent representative as locally defined) based on the assessment of the investigator.

Participants had to be able to complete the follow-up period up to day 365 as required by the protocol.

Exclusion Criteria

History of any clinically important disease or disorder which, in the opinion of the investigator, might have either put the participant at risk because of participation in the study, or influenced the results or the participant's ability to participate in the study. This included any clinically significant bleeding disorder (e.g., factor

deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following intramuscular injections or venipuncture.

Receipt of any immunoglobulin, either COVID-19- or non-COVID-19-related, or blood products within 6 months prior to day 1.

Receipt of tixagevimab and/or cilgavimab within last 15 months before day 1.

Receipt of a COVID-19 vaccine within 14 days prior to visit 1.

SARS-CoV-2 infection within 1 month prior to visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

Women who were pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from ≥ 4 weeks prior to study intervention administration and until ≥ 6 months after study intervention administration.

Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 1 month prior to screening.

Any clinically important illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of study intervention. This included any acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness could be dosed if illness resolved within the screening period or could be rescreened once.

History of malignancy other than treated nonmelanoma skin cancers or locally treated cervical cancer in previous 5 years.

Any laboratory values with the following deviations at the screening visit or at visit 1. Abnormal values could be repeated once at the discretion of the investigator: alanine aminotransferase > 1.5 × upper limit of normal (ULN); aspartate aminotransferase > 1.5 × ULN; total bilirubin > 1.5 × ULN (except for Gilbert Syndrome); creatinine > 1.5 ULN.

Any laboratory value in the screening panel that, in the opinion of the investigator, was clinically significant or might have confounded analysis of study results.

Any known human immunodeficiency virus or hepatitis B or C infection at screening.

History of alcohol or substance abuse that in the opinion of the investigator might interfere with the trial conduct or completion.

Known hypersensitivity to sipavibart.

Previous hypersensitivity or severe adverse reaction following administration of a monoclonal antibody (mAb).

Blood drawn in excess of 450 mL (1 unit) for any reason within 30 days prior to visit 1.

Receipt of any investigational medicinal product in the preceding 90 days or expected receipt of an investigational medicinal product during the period of study follow-up, or concurrent participation in another interventional study.

An employee of AstraZeneca, Parexel, or study center, or any other individual involved with the conduct of the study, or close relatives of such individuals.

Participants who could not communicate reliably with the investigator.

Vulnerable participants, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

Any clinically significant abnormalities on 12-lead electrocardiogram at screening, as judged by the investigator.

Eligibility Criteria for the SUPERNOVA Substudy

Inclusion Criteria

Substudy Sentinel Safety Cohort

Healthy, defined according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the investigator.

Participants must be 18 to 55 years at the time of signing the informed consent.

Weight ≥ 45 kg and ≤ 110 kg at screening.

Full Substudy Cohort

Immunocompromised or immunocompetent, including healthy participants, with all degrees of SARS-CoV-2 infection risk, will be enrolled following completion of sentinel safety cohort enrollment.

Participants must be ≥ 18 years of age at the time of signing the informed consent form.

Weight ≥ 40 kg at screening.

Substudy Sentinel Safety Cohort and Full Substudy Cohort

Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act in the United States) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.

Negative rapid antigen test for SARS-CoV-2 prior to dosing at visit 1.

Medically stable defined as disease not requiring significant change in maintenance therapy or hospitalization for worsening disease or any recent cardiovascular event (e.g., acute myocardial infarction, thromboembolic event) during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the investigator and no expected changes at the time of the enrollment.

Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined), based on the assessment of the investigator.

Exclusion Criteria

Substudy Sentinel Safety Cohort

Active infection with hepatitis B or C.

Serum creatinine, aspartate aminotransferase, or alanine aminotransferase > 1.5 × ULN at screening.

History of malignancy other than treated nonmelanoma skin cancers or locally treated cervical cancer in previous 5 years.

Substudy Sentinel Safety Cohort and Full Substudy Cohort

Receipt of tixagevimab–cilgavimab within 12 months prior to visit 1.

Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from ≥ 4 weeks prior to study intervention administration and until ≥ 6 months after study intervention administration.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

- Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone levels in the postmenopausal range.
- Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of < 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a nonsterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until ≥ 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.

- All female participants of childbearing potential must have a negative urine or serum (β human chorionic gonadotropin) pregnancy test result at screening and visit 1.

- Highly effective birth control methods include: Total sexual abstinence, provided it is the usual lifestyle of the participant (defined as refraining from

heterosexual intercourse during the entire period of risk associated with the study treatments [periodic abstinence {e.g., calendar, ovulation, symptothermal, post-ovulation methods}, declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception]), a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

Known hypersensitivity to any component of the study intervention.

Previous hypersensitivity or severe adverse reaction following administration of a mAb.

Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to visit 1.

Clinically significant bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder) or prior history of significant bleeding or bruising following intramuscular injections or venipuncture.

Has human immunodeficiency virus infection.

Receipt of intravenous or subcutaneous immunoglobulin or blood products within

6 months prior to visit 1 and expected to receive intravenous or subcutaneous immunoglobulin or blood products 6 months after dosing.

Receipt of a COVID-19 vaccine within 3 months prior to visit 1.

Receipt of a COVID-19 antiviral for prophylaxis within ≥ 2 weeks prior to visit 1.

COVID-19 within 3 months prior to visit 1 (confirmed either by laboratory reverse transcription-polymerase chain reaction testing or a rapid antigen test [including at home testing]).

Receipt of any investigational medicinal product in the preceding 90 days or expected receipt of an investigational medicinal product during the period of study follow-up, or concurrent participation in another interventional study (except where the participant ceased investigational medicinal product treatment > 90 days and is in the follow-up period of the study and not expected to receive further investigational medicinal product).

Alcohol or substance abuse that, in the opinion of the investigator, might interfere with the trial conduct or completion.

Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

Any condition that, in the opinion of the investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the sipavibart program, clinical study site staff, or any other individuals

involved with the conduct of the study, or family members of such individuals.

Definitions of Antidrug Antibody Responses

Little DIPPER: Treatment-emergent ADA positivity was defined as either ADA negative at baseline and ADA positive at one or more post-baseline assessments with ADA titers ≥ 200 (treatment-induced ADA positive), or ADA positive at baseline with titers that were increased four-fold or more during the study period (treatment-boosted ADA positive).

SUPERNOVA Substudy: Treatment-emergent ADA positivity was defined as either ADA negative at baseline and ADA positive at one or more post-baseline assessments with ADA titers ≥ 200 for sipavibart, ≥ 80 for cilgavimab or ≥ 160 for tixagevimab (treatment-induced ADA positive) or ADA positive at baseline with titers that were increased four-fold or more during the study period (treatment-boosted ADA positive).

Pharmacokinetic, Antidrug Antibody, and SARS-CoV-2 Neutralizing Antibody Analyses and Assays

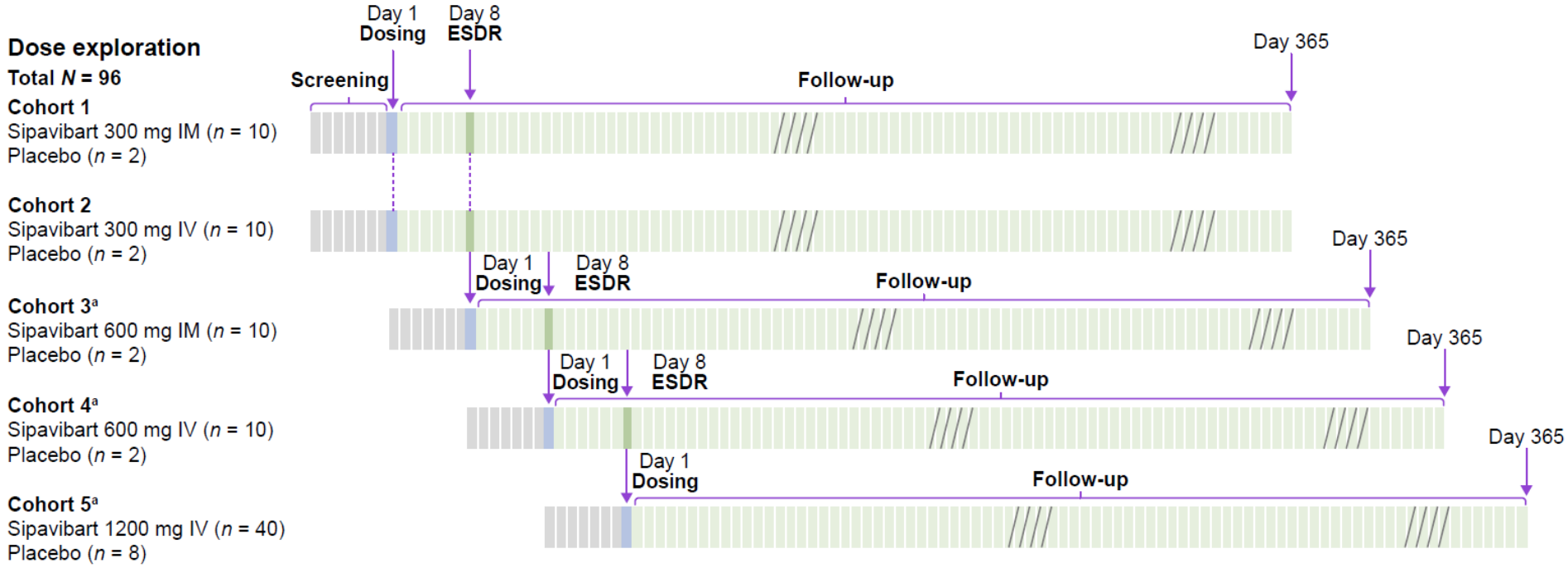
Bioanalytical analyses of sipavibart and tixagevimab–cilgavimab in serum were performed by PPD Laboratories (Richmond, VA, USA), using immunocapture to the SARS-CoV-2 receptor-binding domain followed by denaturation and detection of mAb-specific peptides by liquid chromatography–mass spectrometry [1].

In vitro IC_{50} values for sipavibart and serum nAb ID_{50} titers were determined from the sera of study participants using the PhenoSense SARS-CoV-2 nAb assay (Monogram Biosciences, San Francisco, CA). The PhenoSense SARS-CoV-2 nAb assay, which is based on previously described methodologies [2, 3], uses a lentivirus system where human immunodeficiency virus (HIV) pseudovirus virions express the SARS-CoV-2 spike protein of the variant of interest. HEK293 cells were transfected with a HIV genomic vector that contained a luciferase report gene plus an envelope expression vector carrying the SARS-CoV-2 spike protein open reading frame. Neutralizing titers or IC_{50} values were measured by assessing inhibition of luciferase activity, following preincubation of pseudovirions with serial dilutions of sera from trial participants or from in vitro dilutions of mAbs.

Serum samples for the detection of ADAs were processed by PPD Laboratories (Richmond, VA, USA), using a three-tier testing scheme. Samples were screened for ADAs against sipavibart, tixagevimab, or cilgavimab using an enhanced chemiluminescence (ECL) solution-phase bridging method, validated by PPD Laboratories (VA, USA). Diluted samples were incubated in a solution phase with biotinylated tixagevimab or cilgavimab and ruthenium ([sulfo-TAG]-labeled tixagevimab or cilgavimab). Samples were reported screen positive for ADA in the

screening assay if the mean ECL value was at or above the ECL value of the plate-specific cut point factor. Screen positive samples were retested in a confirmation assay, where samples are analyzed both in the absence and presence of excess drug to determine if the sample's positive response is specific to tixagevimab or cilgavimab. Titers were measured in confirmed positive samples and were reported as the reciprocal of the highest two-fold dilution that measured positive in the assay, before returning a negative response. Titers for negative samples were reported as < 80 for tixagevimab, < 40 for cilgavimab, or < 100 for sipavibart in relation to the minimum required dilution of each assay.

Supplementary Figure S1. Little DIPPER study design

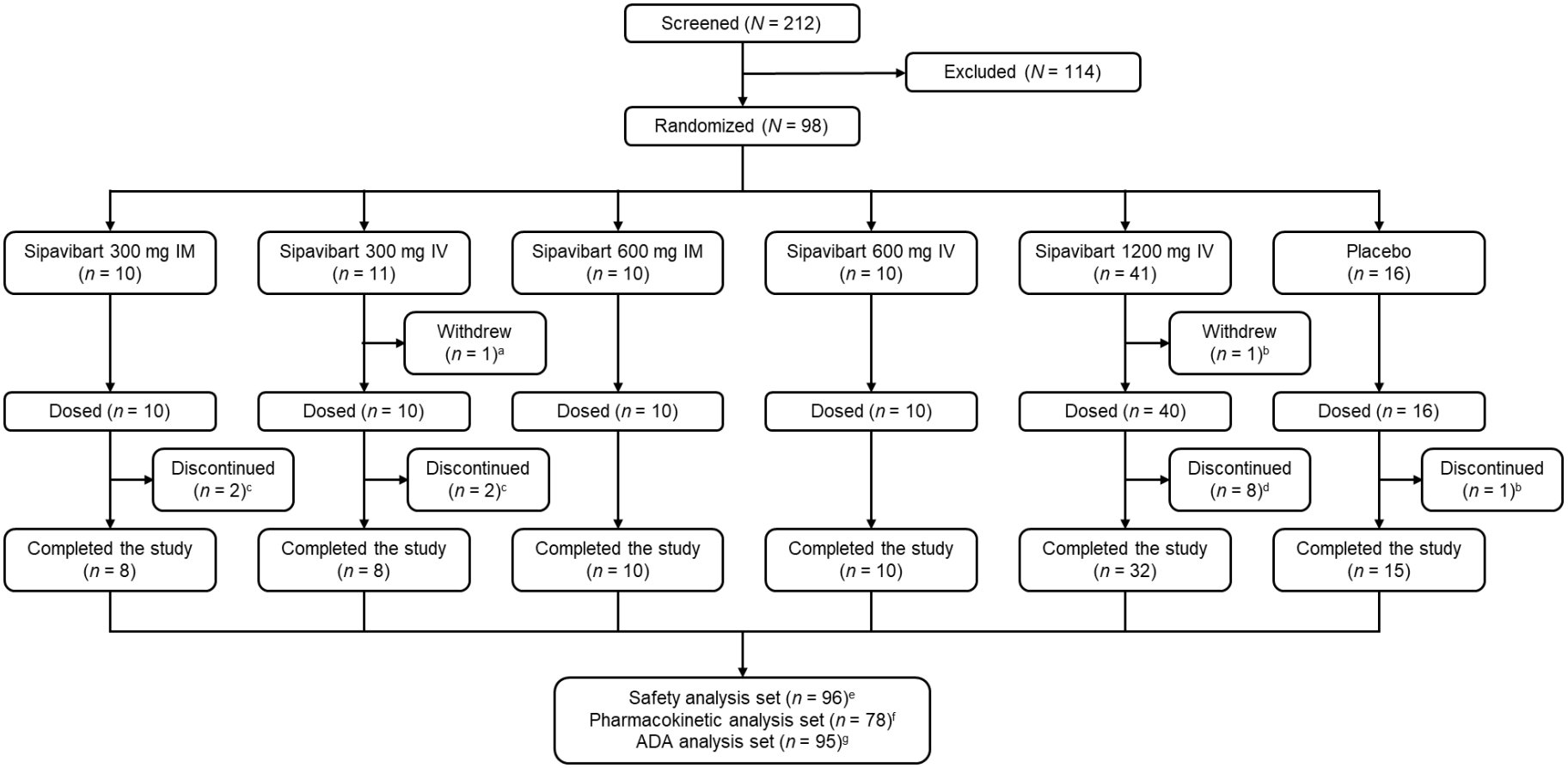


ESDR early safety data review, *IM* intramuscular, *IV* intravenous

Parallel enrollment and randomization occurred in cohorts 1 and 2. An internal Safety Review Committee performed an ESDR of cohorts 1 and 2 (up to day 8) before dosing began in cohort 3, and another ESDR of cohort 3 (up to day 8) before dosing began in cohort 4. An ESDR of cohort 4, planned before dosing began in cohort 5, was not performed.

[a] Sentinel dosing occurred for the first two participants in cohorts 3, 4, and 5 (randomized 1:1 to receive sipavibart or placebo), who were followed for safety for at least 24 h before the remaining participants were dosed.

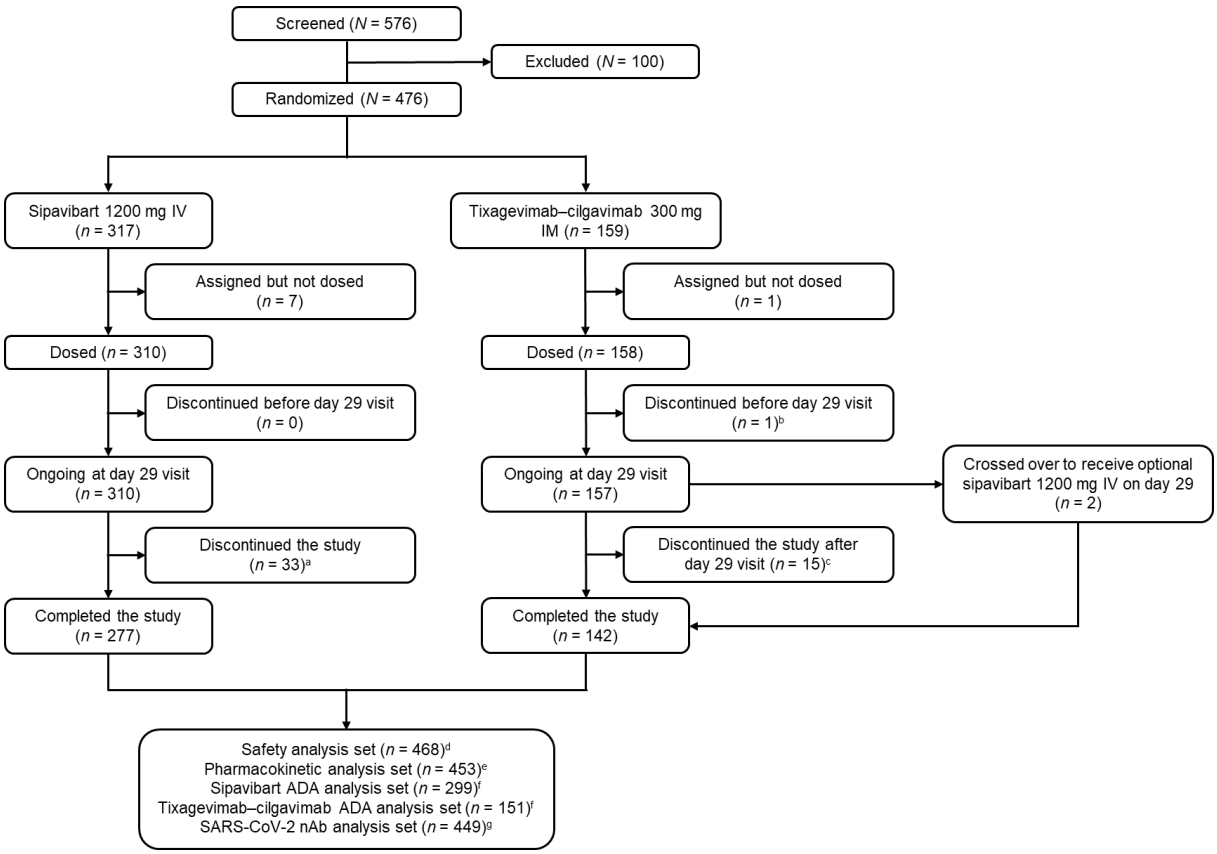
Supplementary Figure S2. Patient flow in the Little DIPPER study



ADA antidrug antibody, *IM* intramuscular, *IV* intravenous

[a] Protocol deviation. [b] Withdrawal by participant. [c] Loss to follow-up (*n* = 1) and withdrawal by participant (*n* = 1). [d] Lost to follow-up (*n* = 5), withdrawal by participant (*n* = 2), and other reason (*n* = 1). [e] All randomized participants who received part or all of study intervention. [f] Subset of the safety analysis set containing those participants who received sipavibart, had at least one post-dose quantifiable serum concentration, and had no protocol deviations that could have impacted the interpretability of data. [g] Subset of the safety analysis set containing those participants with baseline and at least one post-baseline ADA measurements.

Supplementary Figure S3. Patient flow in the SUPERNOVA substudy



ADA antidrug antibody, *IM* intramuscular, *IV* intravenous, *mAb* monoclonal antibody, *nAb* neutralizing antibody

[a] Loss to follow-up (*n* = 15), withdrawal by participant (*n* = 14), death (*n* = 2), physician decision (*n* = 1), or other reason (*n* = 1). [b] Other reason (*n* = 1). [c] Loss to follow-up (*n* = 7), physician decision (*n* = 3), withdrawal by participant (*n* = 3), AE (*n* = 1), or other reason (*n* = 1). [d] All randomized participants who received part or all of study intervention (full analysis set) summarized by intervention actually received. [e] A subset of the full analysis set containing those participants with sufficient data to estimate at least one post-dose quantifiable serum concentration for any mAb component. [f] A subset of the safety analysis set containing those participants with baseline and at least one post-baseline ADA measurements for either sipavibart, or tixagevimab and/or cilgavimab. [g] A subset of the safety analysis set containing those participants with baseline and post-dose antibody measurements with quantifiable SARS-CoV-2 serum nAb titers.

Supplementary Table S1. Definitions of immunocompetent and immunocompromised participants in the SUPERNOVA substudy

Participants were defined as immunocompetent (healthy) if they satisfied all of the following criteria:
Have no active infection with hepatitis B or C
Have serum creatinine, AST, or ALT ≤ 1.5 × ULN at screening
Have no history of malignancy other than treated non-melanoma skin cancers or locally treated cervical cancer in previous 5 years
Have additional safety laboratory test values within normal range at screening
SARS-CoV-2 vaccines should not be given within 3 months prior to visit 1. SARS CoV-2 vaccines should also not be given during the study until after the day 29 assessments. All routine vaccines are permitted; however, they should not be given within 14 days before or after any dose of study intervention. COVID-19 antivirals for prophylaxis should not be given within at least 2 weeks before visit 1 or during the study until at least after day 29 assessments. If the participant develops COVID-19, standard of care treatment is allowed
Healthy participants on stable medication can be considered for enrollment based on the judgement of the investigator
Participants were defined as immunocompromised if they satisfied one or more of the following criteria:
Have solid tumor cancer and be on active immunosuppressive treatment
Have hematologic malignancy
Transplant participants must satisfy at least one of the following: have had a solid organ transplant and/or had a hematopoietic stem cell transplant within 2 years, and/or have chronic graft-versus-host disease; participants who previously had a solid organ transplant or hematopoietic stem cell transplant may also be eligible based on the inclusion criterion for immunosuppressive treatment
Are actively taking immunosuppressive medications (see **Supplementary Table S2**)
Received chimeric antigen receptor T-cell therapy
Within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
Have a moderate or severe primary (e.g., DiGeorge syndrome) or secondary (e.g., hemodialysis) immunodeficiency

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ULN* upper limit of normal

Supplementary Table S2. Qualifying immunosuppressive medications

Alkylating agents
Bendamustine, busulfan, carboplatin, carmustine, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, melphalan, mitomycin, oxaliplatin, procarbazine, streptozocin, temozolomide, thiotepa, trabectedin
Selective immunosuppressants
General: azathioprine, belumosudil, bortezomib, cladribine, dimethyl fumarate, diroximal fumarate, leflunomide, lenalidomide, mycophenolate, pomalidomide, terifflunomide, thalidomide, antithymocyte immunoglobulin (horse, rabbit) **Calcineurin inhibitors:** cyclosporine, tacrolimus, voclosporin **Antimetabolites:** methotrexate, nelarabine, pemetrexed, pralatrexate, irinotecan, liposome, capecitabine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, fluorouracil, gemcitabine, mercaptopurine **JAK inhibitors:** baricitinib, tofacitinib, upadacitinib, peficitinib, itacitinib **mTOR inhibitors:** everolimus, sirolimus **Sphingosine-1-phosphate receptor modulators:** fingolimod, ozanimod, ponesimod, siponimod
Monoclonal antibodies
General: alemtuzumab (anti-CD52), belimumab, begelomab (anti-DPP-4/CD26), teprotumumab (anti-IGF-1), inebilizumab (anti-CD19), muromonab (anti-CD3), inotuzumab ozogamicin (anti-CD22) **Anti-IFN:** anifrolumab, emapalumab **Anti-CD20:** ibritumomab, obinutuzumab, rituximab, ocrelizumab, ofatumumab **Selective T-cell co-stimulation blockers:** abatacept, belatacept **Integrin receptor agonists:** natalizumab, vedolizumab **Bruton tyrosine kinase inhibitors:** ibrutinib, acalabrutinib, pirtobrutinib, zanubrutinib, deucravacitinib **Complement inhibitors:** pegcetacoplan, eculizumab (anti-C5), ravulizumab (anti-C5), sutimlimab (anti-C1) **TNF-alpha inhibitors:** adalimumab, afelimomab, certolizumab pegol, etanercept, golimumab, infliximab **IL-23 inhibitors:** ustekinumab, guselkumab, tildrakizumab, risankizumab **IL-17 inhibitors:** secukinumab, ixekizumab, bimekizumab, brodalumab, netakimab **IL-1 inhibitors:** anakinra, canakinumab, rilonacept **Other IL inhibitors:** basilximab (anti-IL-2), sarilumab (anti-IL-6), satralizumab (anti-IL-6), siltuximab (anti-IL-6), tocilizumab (anti-IL-6), spesolimab (anti-IL-36)
Steroids
Dexamethasone (≥ 3 mg per day, minimum of 2 weeks of therapy), prednisolone (≥ 20 mg per day, minimum of 2 weeks of therapy), prednisone (≥ 20 mg per day, minimum of 2 weeks of therapy)

C complement, *CD* cluster of differentiation, *DPP-4* dipeptidyl peptidase-4, *IFN* interferon, *IGF-1* insulin-like

growth factor 1, *JAK* janus kinase, *IL* interleukin, *mTOR* mammalian target of rapamycin, *TNF* tumor necrosis factor

Supplementary Table S3. Estimates of dose-proportionality following sipavibart administration in the Little DIPPER study (pharmacokinetic analysis set)

Dosing route	Parameter	*n*	Slope	90% CI
IM	C_{max} (*µ*g/ml)	20	0.993	0.706–1.279
	AUC_{last} (day**µ*g/ml)	20	1.008	0.679–1.337
	AUC_{inf} (day**µ*g/ml)	20	0.886	0.573–1.199
IV	C_{max} (*µ*g/ml)	14	0.922	0.651–1.194
	AUC_{last} (day**µ*g/ml)	14	0.663	0.146–1.181
	AUC_{inf} (day**µ*g/ml)	14	0.805	0.467–1.144

AUC_{inf} area under the serum concentration-time curve from time 0 to infinity, *AUC_{last}* area under the serum concentration-time curve from time 0 to the last quantifiable concentration, *CI* confidence interval, *C_{max}* maximum serum concentration, *IM* intramuscular, *IV* intravenous

Supplementary Table S4. Summary of nAb titers following sipavibart administration in the SUPERNOVA substudy (SARS-CoV-2 nAb analysis set)

		Sipavibart 1200 mg (*n* = 297)[a]				
Time parameter	**Statistic**	**Variant alpha/B.1.1.7 (*n* = 297)**	**Variant BA.2 (*n* = 297)**	**Variant BA.4/5 (*n* = 297)**	**Variant XBB.1.5 (*n* = 297)**	**Variant JN.1 (*n* = 297)**
Baseline						
	n	291	289	287	276	260
	Geometric mean (GSD)	2902.9 (5.4)	1227.2 (5.6)	1002.8 (5.9)	163.6 (4.9)	57.4 (4.1)
GMT[b,c]	95% CI	2391.4–3523.8	1006.3–1496.7	816.0–1232.3	135.7–197.4	48.4–68.2
	Min, max	43, 72,536	33, 54,759	33, 50,676	36, 63,527	20, 3801
	< LLOQ, *n* (%)	11 (3.8)	24 (8.3)	29 (10.1)	113 (40.9)	150 (57.7)
Day 29						
	N	288	288	288	287	279
	Geometric mean (GSD)	19,787.4 (2.3)	10,176.1 (2.2)	17,385.9 (2.1)	11,117.3 (2.0)	411.3 (2.3)
GMT[b,c]	95% CI	17,993.0–21,760.7	9294.7–11,141.1	15,960.9–18,938.2	10,245.7–12,063.1	373.8–452.5
	Min, max	43, 140,798	308, 131,418	380, 104,369	301, 45,847	20, 4614
	< LLOQ, *n* (%)	1 (0.3)	NC	NC	NC	2 (0.7)
GMFR[d]	*n*	282	281	278	266	246

	Geometric mean (GSD)	6.9 (4.1)	8.3 (4.3)	17.3 (5.2)	67.3 (5.2)	7.2 (2.9)
	95% CI	5.9–8.2	7.0–9.9	14.3–21.0	55.1–82.2	6.3–8.3
	Min, max	0.5, 1273.2	0.3, 741.2	0.3, 2175.3	0.2, 1229.1	0.1, 118.3
Day 91						
	n	277	277	277	277	256
	Geometric mean (GSD)	10,200.6 (2.6)	5186.3 (2.5)	7663.7 (2.5)	4473.6 (2.4)	270.8 (2.9)
GMT[b,c]	95% CI	9100.2–11,434.0	4658.5–5773.8	6889.4–8524.9	4025.4–4971.7	237.8–308.5
	Min, max	43, 163,991	163, 123,260	211, 148,468	119, 38,010	20, 8239
	< LLOQ, *n* (%)	1 (0.4)	NC	NC	NC	11 (4.3)
	n	272	270	268	258	227
	Geometric mean (GSD)	3.5 (3.6)	4.1 (4.0)	7.5 (4.9)	26.5 (5.3)	4.2 (3.2)
GMFR[d]	95% CI	3.0–4.1	3.5–4.9	6.2–9.1	21.6–32.5	3.7–4.9
	Min, max	0.2, 337.0	0.1, 383.9	0.1, 512.0	0.1, 814.9	0.1, 132.9
Day 181						
	n	239	240	240	239	199
	Geometric mean (GSD)	7119.3 (3.0)	4119.7 (3.0)	5039.9 (2.9)	2517.5 (2.8)	328.6 (3.3)
GMT[b,c]	95% CI	6201.4–8173.1	3587.9–4730.2	4405.5–5765.7	2204.0–2875.6	278.1–388.3
	Min, max	43, 178,102	33, 113,436	33, 190,390	36, 40,877	20, 16,876
	< LLOQ, *n* (%)	1 (0.4)	1 (0.4)	1 (0.4)	4 (1.7)	12 (6.0)

	n	233	232	230	222	179
GMFR[d]	Geometric mean (GSD)	2.5 (3.3)	3.4 (3.9)	5.1 (4.5)	14.8 (5.1)	5.0 (3.9)
	95% CI	2.1–2.9	2.9–4.1	4.2–6.2	12.0–18.4	4.1–6.1
	Min, max	0.3, 114.4	0.1, 331.1	0.1, 433.2	0.1, 195.2	0.1, 124.6

CI confidence interval, *GMFR* geometric mean fold rise, *GMT* geometric mean titer, *GSD* geometric standard deviation, *LLOQ* lower limit of quantification, *nAb* neutralizing antibody, *NC* not calculable

Identified intercurrent events on or after day 1 are: (1) infection with SARS-CoV-2 and (2) COVID-19 treatment, vaccination, or other prophylactic; data collected on or after the date of an intercurrent event are not included in the analysis

[a]Participants in the tixagevimab–cilgavimab group who crossed over to receive sipavibart on day 29 are included in the tixagevimab–cilgavimab summary statistics through day 29; the data from these participants after crossover are not included in the summary statistics.

[b]GMT is calculated as the antilogarithm transformation of the mean of the $\log_{10}$-transformed titer.

[c]Titers below the LLOQ (40) were imputed to half of the LLOQ (86 for Alpha/B.1.1.7; 66 for BA.2; 66 for BA.4/5; 72 for XBB.1.5; 40 for JN.1).

[d]GMFR are calculated from the number of participants with titers at baseline and at the relevant timepoint

References

1. Loo YM, McTamney PM, Arends RH, et al. The SARS-CoV-2 monoclonal antibody combination, AZD7442, is protective in nonhuman primates and has an extended half-life in humans. Sci Transl Med. 2022;14(635):eabl8124. doi: 10.1126/scitranslmed.abl8124

2. Huang Y, Borisov O, Kee JJ, et al. Calibration of two validated SARS-CoV-2 pseudovirus neutralization assays for COVID-19 vaccine evaluation. Sci Rep. 2021;11(1):23921. doi: 10.1038/s41598-021-03154-6

3. Benkeser D, Fong Y, Janes HE, et al. Immune correlates analysis of a phase 3 trial of the AZD1222 (ChAdOx1 nCoV-19) vaccine. NPJ Vaccines. 2023;8(1):36. doi: 10.1038/s41541-023-00630-0