12 December 2024
EMA/8692/2025 corr.1[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kavigale

International non-proprietary name: sipavibart

Procedure No. EMEA/H/C/006291/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] 18 December 2024

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List of abbreviations

Abbreviation or special term	Definition
ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibodies
ADE	Antibody-dependent enhancement
ADME	Adsorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AZD3152	Sipavibart
AZD7442	Evusheld
BLQ	Below limit of quantification
BMI	Body mass index
C1q	complement C1q
CAD	Coronary artery disease
CHF	Chronic heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CV%	Coefficient of variation percentage
DC	Discontinuation
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EMA	European Medicines Agency
ETF	Emergency Task Force
Fc	Fragment crystallisable
FcRn	Neonatal Fc receptor
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
GCP	Good clinical practice
Geomean	Geometric mean
HCP	Healthcare provider
HLT	High-level term
IC50	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation
ICU	Intensive care unit
Ig	Immunoglobulin
IM	Intramuscular
IMP	Investigational medicinal product
INN	International non-proprietary name
IV	Intravenous
kD	Equilibrium dissociation constant
LAAB	Long-acting antibody
MAA	Marketing authorisation application
MAAE	Medically attended adverse event
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NA	Not applicable
nAb	Neutralising antibody
PD	Pharmacodynamics
PDCO	Paediatric Committee

PE	Pulmonary embolism
PK	Pharmacokinetics
PT	Preferred term
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PVD	Peripheral venous disease
RBD	Receptor binding domain
RR	Relative risk
RRR	Relative risk reduction
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SE	Standard error
SMQ	Standardised MedDRA Queries
SOC	System organ class
TM	L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding
UK	United Kingdom
US	United States
WHO	World Health Organization
YTE	M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 1 June 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Kavigale, through the centralised procedure falling within the Article 3(1) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 February 2023.

The applicant applied for the following indication:

KAVIGALE is indicated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg and:

- *who are immunocompromised due to a medical condition or receipt of immunosuppressive medications or treatments or*
- *for whom COVID-19 vaccination is not recommended.*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0504/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0504/2023 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's requests for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance with Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active Substance status

The applicant requested the active substance sipavibart contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	ETF co-ordinators
14 June 2022	EMA/SA/0000091770	Sol Ruiz
14 July 2022	EMA/SA/0000097659	Sol Ruiz
31 August 2022	EMA/SA/0000097668	Ingrid Schellens
12 May 2023	EMA/SA/0000134467	Filip Josephson, Edwige Haelterman Brenneisen
14 December 2023	EMA/SA/0000157231	Mair Powell

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Concurrence with the module 3 data package submitted at time of MAA
- Pre-clinical virology plan
- Initial immunobridging approach to support a pre-exposure prophylaxis indication
- Evidence base to support IV dosing with AZD3152
- Agreement on the dual primary efficacy endpoint and corresponding testing strategy for SUPERNOVA
- Eligibility for rolling review with expedited assessment

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Jan Mueller-Berghaus

For the appointed CHMP rapporteur it was considered exceptionally justified that the individual had previously been acting as coordinator for Scientific advice on the development relevant for the indication subject to the present application. The justification was as follows:

- The individual possesses a deep understanding of the scientific and regulatory landscape pertinent to the indication
- No other member or alternate with a comparable or equally adequate expertise for that product in that indication was available.

Accelerated assessment procedure was agreed-upon by CHMP on	30 May 2024
The application was received by the EMA on	1 June 2024
The procedure started on	20 June 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	20 August 2024
The CHMP Co-Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	n/a
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	27 August 2024
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
ETF discussion	3 September 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	5 September 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	17 September 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	10 October 2024
GMP inspections were carried out at: – WuXi Biologics Co., Ltd. , 108 Meiliang Road, Mashan, Binhu District, Wuxi, Jiangsu 214092, China, on March 2024. The outcome of the inspection was issued on 15/03/2024.	15 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	4 November 2024
ETF discussion	5 November 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 November 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	19 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	28 November 2024
ETF discussion	29 November 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	12 December 2024

a marketing authorisation to Kavigale on	
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	12 December 2024

The (Co-) Rapporteurs assessment reports have been discussed and supported by the Emergency Task Force (ETF) in the context of its public health preparedness activities.

During the assessment of the application for the marketing authorisation of Kavigale, the following non-EU authorities were allowed to participate as part of the OPEN framework and contribute to the scientific discussions of the ETF and CHMP: PMDA and Swissmedic. These authorities did not participate in the overall benefit/risk determination, which was decided by the CHMP.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

SARS-CoV-2, a coronavirus, is the causative agent of COVID-19. Like other viruses, SARS-CoV-2 continues to evolve over time. Important historical variants, present when early interventional clinical trials to prevent infection and/or treat disease were conducted, belonged to the Alpha, Beta, Delta, and Gamma lineages, while contemporary variants belong to the Omicron lineage.

Although Omicron variants are known to cause less severe disease compared to previous variants, they are highly transmissible and have multiple mutations. Immune evasion is one of the notable consequences of these mutations.

Several different vaccines are available for immunisation against SARS-CoV-2, some of which are anticipated to be updated yearly based on viral strain evolution. Still, an unmet medical need with regards to pre-exposure prophylaxis may be considered for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to vaccination (Evans et al 2023, Lee et al 2022, Parker et al 2022). Notably, there are presently no products in the EU indicated for passive immunisation which are anticipated to be efficacious given the currently circulating viral variants.

2.1.2. Epidemiology

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 in Wuhan, in Hubei Province of China, and subsequently spread worldwide, causing a global pandemic.

World Health Organization (WHO) declared an end to the coronavirus disease 2019 (COVID-19) global health emergency in May 2023. SARS-CoV-2 transitioned to endemicity remaining as an important cause of illness especially in subjects at increased risk of severe disease such as immunocompromised patients.

Along the time, SARS-CoV-2 has evolved and therefore, mutated. Some of these mutations or combinations of mutations provide the virus with a selective advantage, e.g. increased transmissibility, the ability to evade the host immune response, etc. In such cases, these mutations or combinations of mutations (also called variations) can increase the risk to human health, and the virus strains (or variants) that carry those mutations are classified as variants of concern (VOCs), (ECDC; 2023)

ECDC continuously assesses new evidence on the emergence and circulation of VOCs in the EU and reports its findings on the evolution of SARS-CoV-2 (ECDC; 2024).

2.1.3. Biologic features

SARS-CoV-2 infection is initiated by binding of the viral transmembrane spike glycoprotein to angiotensin converting enzyme 2 (ACE2) on the surface of host cells. The receptor binding domain of the spike glycoprotein is, consequently, the main target for neutralising antibodies.

Sipavibart (AZD3152) is being developed for the prophylaxis of COVID-19. AZD3152 binds to the receptor binding domain of the spike protein and blocks its interaction with the hACE2 host cellular receptor, resulting in a blockade of virus entry, effectively neutralizing the SARS-CoV-2 virus.

2.1.4. Clinical presentation

The infection caused by SARS-CoV-2 may be asymptomatic or it may cause a wide spectrum of illness, ranging from a mild upper respiratory tract infection to severe acute respiratory distress syndrome and multiple organ failure (Wiersinga et al., 2020). The majority of patients with SARS-CoV-2 infection exhibit relatively mild to moderate symptoms or are asymptomatic (Hu et al., 2020; Oran and Topol, 2020) and make a full recovery without needing hospital treatment. However, for some patients, the SARS-CoV-2 infection leads to hypoxemia and other serious respiratory conditions that require hospitalisation and can be fatal (Guan et al., 2020; Richardson et al., 2020; Wu and McGoogan, 2020). Infection is more likely to lead to hospitalisation and severe disease among patients with pre-existing risk factors or comorbidities, such as older age, obesity, diabetes mellitus, cardiovascular disease, chronic lung disease, and immunocompromised status (CDC 2023c; Lighter et al., 2020).

Another aspect of the disease is the post COVID-19 condition, commonly known as long COVID, which can affect anyone exposed to SARS-CoV-2, regardless of age or severity of original symptoms. This occurs beyond 3 months from the initial SARS-CoV-2 infection, with symptoms lasting for at least 2 months with no other explanation (WHO, 2021) and can include symptom such as fatigue, bodily pain or mood swings, cognitive problems, and ongoing respiratory problems. Studies show that around 10–20% of people infected by SARS-CoV-2 may develop symptoms that can be diagnosed as long COVID although exact numbers are uncertain (WHO, 2024)

2.1.5. Management

COVID-19 vaccines continue to be the first line of protection against COVID-19-related hospitalisation (and severe outcomes), especially for patients at increased risk of severe disease.

Currently, there are also some available therapies which have different benefit-risk considerations depending on the stage of illness and disease manifestations. On the other hand, unfortunately, nowadays, none of the approved monoclonal antibodies are effective against the SARS-CoV-2 variants of concern currently in circulation.

2.2. About the product

Sipavibart is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody that provides passive immunisation by binding the SARS-CoV-2 spike protein receptor binding domain (RBD).

The applicant seeks approval of sipavibart (300 mg i.m. or i.v. as a single dose) *for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg and:*

- *who are immunocompromised due to a medical condition or receipt of immunosuppressive medications or treatments or*
- *for whom COVID-19 vaccination is not recommended.*

2.3. Type of application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest.

This was based on the fact that still in the omicron-era, the disease burden due to SARS-CoV-2 in immunocompromised individuals is of public health significance. Due to anticipated lower response to vaccination in this population, passive immunisation strategies with monoclonals may address an unmet need provided that efficacy is demonstrated.

On the other hand, top line results of the SUPERNOVA study in immunocompromised patients show a 35% reduced risk of any symptomatic COVID-19 and a 43% reduced risk of symptomatic COVID-19 due to "matched variants" (without a 456-position mutation in the spike protein).

2.4. Quality aspects

2.4.1. Introduction

The active substance in Kavigale is sipavibart, also referred to as AZD3152. Sipavibart is a human IgG1-TM-YTE, λ monoclonal antibody directed against the receptor binding domain (RBD) within the spike (S) protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The antibody was engineered to contain two sets of three amino acid substitutions in the fragment crystallisable region (Fc) that are referred to as TM (triple mutation) and YTE. The TM mutations were introduced to reduce Fc-mediated effector functions and the YTE substitutions were introduced to enhance affinity to neonatal Fc receptor (FcRn) and, thus, extend serum half-life.

Sipavibart is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

The finished product is a sterile, preservative-free, liquid dosage form (pH 6.0) intended for intravenous or subcutaneous administration. It is supplied as a single-dose vial in one presentation: 300 mg of AZD3152 per vial with a 2 mL label-claim volume (2.28 mL target fill volume which includes a 0.28 mL overfill). The finished product composition contains 150 mg/mL AZD3152 in histidine/L-histidine hydrochloride monohydrate, arginine hydrochloride, polysorbate 80 (PS80) (0.8 mg per vial) and water for injections.

2.4.2. Active Substance

2.4.2.1. General information

Sipavibart is an IgG1 monoclonal antibody composed of two identical heavy chains (HC) (containing four intra-chain disulfide bonds each) and two identical light chains (LC) (containing two intra-chain

disulfide bonds each), with a molecular mass of approximately 148 kDa including glycosylation. Sipavibart contains intra-chain and inter-chain disulfide bonds.

The antibody was engineered to contain two sets of three amino acid substitutions in the fragment crystallisable region (Fc), denoted triple mutation TM (L242F/L243E/P339S) and YTE (M260Y/S262T/T264E). TM sites were introduced to reduce Fc-mediated effector functions, whereas the YTE substitutions extend the serum half-life of sipavibart by enhancing the affinity to the neonatal Fc receptor (FcRn). Each of the heavy chains possesses an N-linked glycosylation site (Asn-305) with predominantly biantennary complex-type glycans attached.

The mode of action for sipavibart relies on the specific binding to the RBD of the S protein of SARS-CoV-2. This binding blocks the SARS-CoV-2 virus from binding to the human angiotensin-converting enzyme 2 (ACE2) receptor and, thereby, inhibits viral infection by inhibiting viral fusion to the host cell membrane.

2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

All sites involved in manufacture and control of the active substance operate in accordance with GMP.

Sipavibart (AZD3152) is manufactured in CHO cells. The manufacturing process for 2K and 4K is the same except for minor changes required to fit equipment.

An overview of the process is presented. It is divided into 14 steps and includes the upstream and downstream process. The upstream process consists of five steps: vial thaw, inoculum expansion in shake flasks and rocker bags, seed bioreactor(s) for further expansion of inoculum, production bioreactor to generate AZD3152, and harvest. Nutrient feed preparation, filtration and storage of media and nutrient feeds are also described.

The downstream process consists of three chromatography steps. There are two dedicated virus clearance steps: a low-pH treatment step for virus inactivation and a virus filtration step for virus removal. The active substance is frozen for storage and shipment to the finished product manufacture

In addition to the overview, more thorough descriptions are provided describing each step with classified critical and non-critical process parameters (CPPs or NCPPs) and acceptable ranges, in-process controls (IPCs), and for performance attributes output measurements and action limits. Flow rates, buffers, solutions, protein loads, start and end criteria for collection of active substance are all defined. Representative chromatograms were provided.

The batch numbering systems, using unique numerical digits, have been described.

The applicant has described procedures for two steps that might be subject to reprocessing, i.e. the virus filtration step, and the 0.2-micron bulk active substance filtration.

The microbial controls and a summary of process intermediate hold times are included in Section S.2.4.

Control of materials

Raw materials

A table of raw materials used in the manufacturing process is included with type of material and if used for cell banking, cell culture, purification or as excipients. The materials are either of pharmacopeial grade or have internal standards. The latter are raw materials that are purchased from approved suppliers in accordance with the vendor's and/or applicant's written specifications. Filters used in the

manufacturing process are also included in S.2.3 with supplier, materials and surface areas. The medium powder and nutrient feed have short descriptions of contents and quantitative information is not required, in line with the BWP Q&A for biological medicinal products. The applicant has confirmed that there is a contract in place with the supplier that any changes to the medium or feed will be communicated to the applicant to enable control.

Source history and generation of the cell substrate

An overview of the stages in the identification and optimisation of the lead antibody sequence is shown. The DNA sequences of the variable domains were combined with constant domain and used to prepare an expression plasmid for production of AZD3152 in CHO cells. The nucleotide and corresponding amino acid sequences for AZD3152 HC and LC genes are shown as are the plasmid construction and the structure of the final expression plasmid. Origins of the DNA elements within the expression plasmid with DNA element, component and origin and function is provided.

The history and generation of the host cell line is described.

The generation and transfection of the production cell line is described including the process to demonstrate clonality. This was tested for the presence of bacteria, fungi, mycoplasma and virus contamination. None were detected.

The preparation of the MCB and WCB is acceptably described. Information on the background, generation and testing also of this MCB was also provided.

The applicant has prepared an end-of-production cell bank (EOPCB) with 30 population doubling limit (PDL) from the bioreactor that produced unprocessed bulk lot. In addition, a limit of *in vitro* cell age (LIVCA) cell bank with 62 PDLs was manufactured at pilot scale.

Safety testing of cell banks complies with ICH Q5A and is found acceptable. Phenotypic characterisation at different cell ages is presented with end points of process performance and product quality. In accordance with ICH Q5B and ICH Q5D, genetic stability with gene copy number and structure of expression vector has also been demonstrated (LIVCA). No large insertions or deletions within the construct were reported.

Certificates or reports of analyses for all safety testing of MCB, WCB, EOPCB and LIVCA cells are provided as is a report on genetic stability. Methods for cell bank identity and genetic stability testing are briefly described. Method descriptions for cell bank safety testing are found in Module 3.2.A.2.

A protocol is included describing requirements for future WCB qualification with tests for identity, safety and purity as well as cell culture process outputs with action limits. A commitment for a lifetime and storage stability of cell banks is also included. The applicant is reminded that ICH Q5A revision 2 encourages to replace the *in vivo* test with next-generation sequencing (NGS) testing for future qualifications of cell banks, in line with the 3R principles.

Control of critical steps and intermediates

The process control strategy is explained with definitions of process parameters and classifications as critical or non-critical. Process outputs are divided into IPCs, microbial controls and performance attributes. The applicant explains the control criteria and what are the outcomes, i.e. what is the consequence if a defined acceptance criterion, action limit or acceptable range is exceeded, both for CPPs and NCPPs.

Bioburden and endotoxin action limits for process intermediates and solutions in the active substance process are provided. Buffers and solutions are routinely tested for bioburden and endotoxin unless extremes of pH or when media simulation studies have confirmed the integrity of the buffer hold vessels. It is agreed that microbial safety is satisfactorily controlled.

Hold times for process intermediates have been validated through a combination of small-scale studies for biochemical stability and also at commercial scale for microbial control. The information provided in section S.2.4 is accepted.

The control strategy is found acceptable.

Process validation and/or evaluation

The applicant declares that the validations were successfully executed. Deviations with root cause and impact assessments are listed as are change controls. All required data are assessed as being in place, and it is agreed that the validation studies demonstrates that the upstream and downstream processes are reproducible and under control.

Protocols and reports are listed in process validation overviews. Small-scale process intermediate hold time validation for biochemical stability, filter validation studies, the active substance shipping qualification, and validations for reprocessing are joint reports for the 2K and 4K processes.

Generic commercial-scale microbial validation studies have been performed to establish the microbial control process intermediate hold times. A growth promoting solution was held in representative hold vessels used in the process to demonstrate microbial integrity at 2-26°C. Details for the microbial validation study design at commercial scale are summarised in the dossier. The report for the at-scale microbial hold studies is also submitted. The validation approach at small and commercial scale to demonstrate biochemical stability and commercial scale microbial control is found acceptable.

Resin lifetime studies have been conducted. The resin lifetimes are confirmed at commercial scale following an ongoing protocol.

Sanitisation and storage conditions were subjected to a microbial challenge that demonstrated that the solutions used for the sanitisation and storage of the resins met acceptable levels of antimicrobial efficacy.

An ultrafiltration/diafiltration (UF/DF) membrane lifetime study was performed at commercial scale to establish the maximum number of product-contacting cycles.

Shipping qualification with the shipping container was performed to assess that the shipping system can withstand anticipated physical rigors (journey hazard operational qualification (OQ)). A performance qualification (PQ) study was performed.

Reprocessing for virus and active substance filtration has been prospectively validated. Protocols for commercial scale are in place. This is accepted.

Resin lifetime and carry over studies are also presented as interim reports and will continue according to submitted protocol; this is accepted.

Overall, the active substance manufacturing process is considered validated.

Manufacturing process development

FMEA and criticality assignments to quality attributes and process parameters

Quality attributes and their criticality as critical quality attribute (CQA) or non-CQA have been assessed. The criticality relates to the importance of the attribute to clinical performance (biological activity), pharmacokinetics (PK), safety, and immunogenicity. Quality attributes, assigned criticality with severity score, impact category, impact, uncertainty and severity are presented. A rationale for criticality assignment with literature references (supplied in the dossier) is provided Some attributes related to formulation, presentation, identity, and potency are routinely assessed to have a high impact on safety and/or efficacy.

A comprehensive failure modes and effects analysis (FMEA) has been performed that covers all process steps concludes the severity, detectability and occurrence scores. The scoring process is explained with acceptable rationales for the chosen levels. Process parameters that can have an impact on CQAs and how to control them through process controls, analytical testing or by other means are shown for each process step. The residual risk to patient is presented to confirm control for each quality attribute and that identified risks have been mitigated. The CPPs with the impacted CQAs are summarised.

Scale down models

The methodology for scale-down model verification is explained. Product performance and/or quality is compared between the commercial scale and scale-down model, either as independent runs or as parallel satellite runs. The latter means that the scale-down runs use the same starting materials and solution preparation lots as the corresponding commercial-scale lots (e.g. load materials, buffers and media). For some steps, the predictive ability of the scale down model is well understood and is supported by literature, vendor data and prior knowledge with similar monoclonal antibodies with data from prior model verification studies. In those cases, no product specific scale-down model verification experiments were performed.

The statistical evaluation between scales is using a 90% confidence interval of the difference in output measurements between scales and is compared to an equivalence limit. Using the 90% confidence interval is equivalent to the two one-sided test (TOST). A description on the methodologies to calculate the equivalence limits and the 90% confidence intervals is provided. The approach for scale down models has been explained and is found acceptable.

Process characterisation

A risk assessment was performed on each process step, upstream and downstream, including freezing of active substance and in-process hold times. Scale-down models were developed, and the models were verified through output comparisons to commercial scale data and statistically evaluated. Multivariate or univariate experimental designs were developed with process parameters and ranges to test. CPP or NCPP assignments were made as a result of the experimental designs. Acceptable rationales and risk assessments for criticality classification, process ranges and studied parameters have been provided, also for the parameters that were excluded from experimental studies, deemed as not required. All is supported by data and it is found that the active substance manufacture and the criticality assignments are adequately characterised.

Manufacturing process history and comparability

Two manufacturing processes were used during the development of AZD3152: Process 1 that was used for non-clinical toxicology and initial clinical manufacturing, and Process 2 that was used for both clinical and commercial manufacturing.

Lot genealogy for the manufactured active substance batches with their use is outlined. The site of manufacture, process version (1 or 2), cell bank used, scale, identification of active substance and finished product lots, use of lots, and clinical study number where applicable are provided. Three more active substance lots were manufactured using process 2, one at 500 L scale used for development and two 2000 L (2K) scale lots used in clinical studies. Process 2 was then transferred for commercial active substance manufacture. Four lots at 2000 L and four lots at 4000 L (4K) scale were manufactured for process validation.

A summary of the active substance manufacturing development is provided.

Scale up has been limited from 500 L to 2000 L and 4000 L. This was confirmed through a risk assessment and following characterisation studies using worst case formulations. This is accepted.

Development lot used for toxicology studies, was derived from clinical lot and was compared to process 1 material with lot release results and characterisation tests, CE-SDS, peptide mass spectrometry, N-glycan profile and deglycosylated intact mass. The data supports comparability.

Comparability exercises in line with ICH Q5E were performed. The comparison included lot release results, side by side profile comparisons, extended characterisation and stressed degradation trend studies. The approach for setting comparability acceptance criteria was explained. The data presented verifies that comparability in line with ICH Q5E has been demonstrated in all three comparisons as outlined.

Leachables risk assessments are provided. It was concluded that potential leachables from in-process product contact materials used to manufacture active substance pose a minimal safety risk to the patient). The materials had estimated leachable exposure below the SCT of 10 µg/patient/day, demonstrating negligible safety risk.

Overall, manufacturing process development has been adequately documented and justified.

Characterisation

Elucidation of structure and other characteristics

Characterisation of sipavibart (AZD3152) has been performed with regards to primary structure higher order structure, carbohydrate structure, charge and size heterogeneity and biological functions. The characterisation analyses were mostly performed on reference standard prepared from representative Process 2 active substance. This is found acceptable.

The methods used for characterisation are considered state-of-the-art, with evaluation of most relevant characteristics. The provided results are complemented with relevant chromatograms, electropherograms and dose-response curves, where applicable, and the methods used throughout the characterisation are briefly described.

Primary structure and post-translational modifications

Mass spectrometry was used to confirm the primary sequence of sipavibart. For intact mass analysis, liquid chromatography mass spectrometry (LC-MS) analysis was performed on sipavibart for deglycosylated (PNGase F) full-length protein, light chain and heavy chain, respectively. Deconvoluted mass spectra and theoretical and detected molecular weights can be found in the dossier. The detected masses for full-length protein, LC and HC were demonstrated to be consistent with theoretical masses. This is found acceptable.

For peptide mapping, protein cleavage using trypsin was performed prior to MS analysis. For each detected tryptic peptide, relevant information such as retention time and detected mass have been provided.

Furthermore, it is reported that a sequence coverage of 100% of the theoretical heavy and light chain sequences of sipavibart was obtained from peptide mapping.

The presence of post-translational modifications (PTMs) in sipavibart was explored by mass spectrometry (LC-MS/MS) peptide mapping of peptides after trypsin treatment. The chemical modifications observed, with most of them at site-specific positions, include deamidation, oxidation, complementarity-determining region (CDR) glycation, N-terminal cyclisation, C-terminal Lys, and C-terminal amidation. The relative level of modified to unmodified peptide have been presented in the dossier, and the data revealed. The approach to use peptide mapping to reveal PTMs is acknowledged and the determined levels of the PTMs are in found acceptable.

Protein glycation of sipavibart was determined by analysis of intact mass using mass spectrometry (LC-MS), and a total glycation of 21% was revealed. This level of glycation was demonstrated to have low impact on efficacy and safety, as shown by additional data in the dossier. This is found acceptable.

Glycosylation

Peptide mapping was used to reveal that sipavibart contains one N-linked glycosylation site located at the position N305 in the CH2 domain of each heavy chain. The approach to explore carbohydrate content is supported, and the information provided is found acceptable.

Higher-order structure

Higher-order structures (secondary and tertiary structure) of sipavibart were analysed by the five different methods, disulfide bond determination using non-reducing peptide mapping, free thiol (denatured), differential scanning calorimetry (DSC), far UV circular dichroism (FUV CD), and near UV circular dichroism (NUV CD). Relevant spectra and thermograms are provided, and acceptable higher-order structure has been shown.

Purity, size and charge heterogeneity

The purity and presence of high and low molecular-weight species (HMWS, LMWS) were analysed by high performance size exclusion chromatography (HPSEC), including multi-angle light scattering (MALS) for molecular-weight determination, analytical ultracentrifugation, capillary electrophoresis sodium dodecyl sulfate (CE-SDS) (reducing, non-reducing). Overall, a thorough analysis of purity and product-related substances, including analysis of sub-visible and visible particles, has been presented, and this is found acceptable.

Biological function

The mode of action for sipavibart relies on the specific binding to the RBD of the S protein of SARS-CoV-2. This binding blocks the SARS-CoV-2 virus from binding to the ACE2 receptor and, thereby, inhibits viral infection by inhibiting viral fusion to the host cell membrane. The proposed mode-of-action of sipavibart is sufficiently described.

To characterise the biological function of sipavibart, several orthogonal methods were employed, including both Fab binding, *in vitro* virus neutralisation assays and Fc binding, an approach which is acknowledged. An ELISA-based RBD binding assay, also used for release and stability testing, demonstrated binding of sipavibart to RBD of the S protein of SARS-CoV-2, B.1.1.529 strain. All presented biological activity assays demonstrated a neutralising activity of sipavibart, with provided examples of dose-response curves. The approach to deduce the biological activity of sipavibart is endorsed and is considered sufficiently described and justified.

Sipavibart is engineered to contain two sets of amino acid substitutions in the Fc region (Fc), TM and YTE, to reduce Fc-mediated effector functions (not part of mode-of-action) and to extend the serum half-life of sipavibart by enhancing the affinity to the neonatal Fc receptor (FcRn), respectively. For that reason, Fc binding characterisation was restricted to binding of sipavibart to FcγRIIIa and neonatal Fc receptor (FcRn), a strategy which is supported. Binding of sipavibart to FcγRIIIa was evaluated with surface plasmon resonance (SPR) and revealed a 73-fold reduction in binding compared to unmodified IgG1 Fc. In addition, an AlphaLISA binding assay was utilised to demonstrate a 30-fold increase in FcRn binding for AZD3152, due to the YTE mutation in the Fc domain, compared to an IgG1 with a wild-type Fc domain. The evaluation and conclusions from the FcγRIIIa and FcRn binding is found acceptable.

Impurities

Product variants have been categorised as product-related substances or product-related impurities based on their potential impact on safety and efficacy, a categorisation which is supported. Furthermore, platform knowledge has been utilised for characterisation and severity assessment of product-related substances and product-related impurities, and in cases where platform knowledge cannot be applied to a quality attribute, product-specific studies are conducted to characterise the attribute and elucidate the structure-function relationship.

Product-related impurities

Extended characterisation has been performed using various chromatographic and electrophoretic methodologies to characterise product-related impurities of sipavibart active substance generated from manufacturing and/or stressed conditions. The approach to reveal product-related impurities is found acceptable.

Process-related impurities

The process-related impurities are residual host cell DNA, residual host cell protein (HCP), residual Protein A, glucans and peptides from the yeast extract in the cell-culture medium, antifoam emulsion, 2-mercaptoethanol, methionine sulfoximine (MSX), monothioglycerol, and Pluronic F-68. Results presented confirm efficient removal of all the process-related impurities. This is found acceptable.

In the method description for HCP, it is stated that residual HCP in the active substance is determined using a platform sandwich immunoassay (ELISA). Further, it is explained that the HCP antigen standard is generated from an in-house null CHO cell line, representative of the production CHO cell line, using the platform upstream process, and that HCP antibodies are generated by immunising animals with the HCP antigen, followed by affinity purification of the animal serum. Moreover, it is revealed in section 3.2.S.3.2 that the HCP coverage was 69%. The platform strategy as such is endorsed.

Overall, the active substance is considered adequately characterised.

2.4.2.3. Specification

Specification

The release specifications for active substance are provided and include control of identity, purity and impurities, biological activity and other general tests.

To control the sipavibart active substance prior to lot release and for stability testing, a set of analytical methods are used, including appearance (colour, clarity), bioburden, bacterial endotoxin, pH, charge heterogeneity by cIEF, purity by HPSEC and non-reducing CE-SDS, host cell proteins by sandwich immunoassay, identity by peptide mapping, PS80 by gas chromatography (GC), total protein content by UV absorbance at 280 nm, and biological activity by target-binding ELISA. The set of chosen analytical methods is acceptable.

For compendial methods, references are made in the specification to the corresponding Ph. Eur. chapters. Moreover, for all non-compendial methods, in-house method identifiers have been defined and provided. This is endorsed.

Justification of specifications

To set the specification limits for sipavibart active substance, the applicant has used a strategy based on a combination of approaches, including published limits approach, stability limits approach and non-

stability limits approach. In addition, acceptance criteria for potency have been established by using a different approach.

The specification limits for general tests are based on active substance batch release and stability data and Ph. Eur. requirements. This strategy is found acceptable.

Overall, the active substance specifications are acceptable.

Analytical procedures

The compendial methods stated in the active substance specification include tests for appearance (colour, clarity), bioburden, bacterial endotoxin and pH. Reference to relevant Ph. Eur. chapters is made for each compendial method, which is endorsed. For bacterial endotoxin testing, the compendial LAL test based on the Limulus Amebocyte lysate (Ph. Eur. 2.6.14) is used, and the applicant has briefly revealed the plans for future transitioning to Ph. Eur. 2.6.32 "Test for bacterial endotoxins using recombinant factor C", or other alternatives, eliminating the need for horseshoe crab derived material. This is found acceptable.

Method descriptions for all non-compendial analytical procedures are provided in the dossier. For all methods, the method principle is described and the equipment, method parameters and samples to be analysed are listed. Calculation and reporting of results are sufficiently described, and examples of typical chromatograms and electropherograms are provided, where applicable, for a majority of the methods. The method descriptions are found acceptable.

For determination of residual CHO HCP, a platform sandwich immunoassay (ELISA) is used. This is found acceptable.

Validation of analytical procedures

For the compendial methods appearance (colour), appearance (clarity) and pH, it is acknowledged that validation of the corresponding methods can be considered fulfilled *per se*. In addition, specific data and validation summaries for sipavibart have been provided in the dossier for the methods bacterial endotoxin (inhibitory and enhancement effects) and bioburden (recovery of microorganisms) to support the suitability of the respective method. This is found acceptable.

Validation summaries have been provided for all non-compendial methods, including descriptions of validation approaches and parameters. Relevant validation parameters have been evaluated. Furthermore, relevant calculations, acceptance criteria, description of results obtained for individual samples have been presented. This is found acceptable.

Batch analysis

Results from analysis of lots (n=12) from the different manufacturing processes including Process 1 Development, Process 2 Clinical, Process 2 Commercial are presented in the dossier. It is acknowledged that the release results from all presented lots comply with the proposed specification limits in place at the time of testing, and that the provided release data from the commercial process is in support of a consistent manufacture of active substance.

Reference Standards or Materials

The reference standard system for sipavibart is described in terms of source material, preparation, storage, qualification, stability, history, and future replacement. Two different reference standards have been used during the development of the sipavibart active substance. The primary reference standard (PRS) currently in, for routine lot release and stability testing of active substance and finished product, is prepared from active substance (Process 2 Clinical) and stored at ≤ -65°C. It is stated that a two-tiered reference standard system, including primary and working reference standards, will be

implemented for sipavibart, which is highly encouraged, and that the working reference standard (WRS) will be prepared in the same way as for the PRS, but from a different lot compared to PRS. It is understood from the dossier that there is currently no working reference standard in use. The preparation of the reference standards (PRS and WRS) is found sufficiently described.

Methods used for qualification, as well as the corresponding acceptance criteria have been summarised in the dossier. Furthermore, qualification data for PRS have been provided, including data for structural integrity, purity, and biological activity. Moreover, all acceptance criteria for qualification of PRS were met and, thus, it is considered that the current reference standard has been adequately qualified.

The primary reference standard is re-evaluated for stability annually by testing for purity, charge heterogeneity, and binding potency. The results will be evaluated against the acceptance criteria. In addition, the qualified working reference standard will be routinely monitored via data generated from routine GMP testing. Re-evaluation of is performed annually, and the expiry is extended for an additional year upon successfully meeting the acceptance criteria. This strategy is acceptable.

Historically, one initial reference standard lot from manufacturing Process 1, has been used earlier in the development process of sipavibart, and this lot has been described with regards to source material, batch number, manufacturer, date of fill, storage conditions, and qualification results.

For future primary and working reference standards, preparation, storage conditions, and qualification acceptance criteria are stated in the dossier, and the presented approach is endorsed. For qualification of total protein content and binding potency, a sufficient number of replicates (12 and ≥12, respectively) have been suggested. Further, the strategy to assign binding potency for future primary and working reference standards has been clearly stated in the dossier and is agreed to.

Overall, the information provided in this section on reference standards can be considered acceptable.

Container Closure System

The container closure system (CCS) used for sipavibart active substance is the 16/20 L CryoVault Freeze and Thaw Platform. The components of the CryoVault container and the corresponding materials are clearly described. A schematic drawing of the CryoVault container and its components is included. A vendor certificate of quality for the CryoVault container is provided, as well as a qualification guide document including information for the container on, for example, characterisation, specification, gamma irradiation. The applicant explains that the CryoVault storage containers are tested and monitored by the vendor to meet the requirements for USP <661> "Plastic Packaging Systems and their Materials of Construction". This is also confirmed by the vendor's certificate provided in the dossier.

To demonstrate safety of the CryoVault storage containers, and to ensure that the product contact components do not leach undesirable amounts of potentially harmful species into the sipavibart active substance, an extractables and leachables assessment was performed. The assessment was using a 3-stage, risk-based approach, and the results are presented in the dossier. The approach is considered acceptable. The data revealed low risk of compromising patient safety due to potential leachables. It is agreed to that the presented data supports the safety of the CryoVault containers for frozen storage of sipavibart active substance with regards to extractables and leachables.

To demonstrate compatibility of the 16/20 L CryoVault containers, stability studies of sipavibart active substance were conducted with scaled-down 30 mL CryoVault containers having a fill volume of 21-30 mL. This is representative of the full-scale storage closure system, as the scaled-down containers exhibit a considerably higher surface-to-volume area (2.5-3.5 cm^2/mL) compared to the full-scale storage closure system (0.4-1.5 cm^2/mL). Both types of CryoVault containers he same manufacturing

method, materials of construction, and product contact parts. To conclude, the CCS can be considered adequate and acceptably described.

2.4.2.4. Stability

The presented stability programme includes stability studies under long-term, accelerated and stressed storage conditions. The aim of the stressed stability studies is to promote degradation to help identifying stability-indicating methods. This approach is endorsed.

Long-term stability data, obtained at -50°C to -30°C, for one Process 1 Clinical lot covering 12 months (completed) and one Process 1 Clinical lot covering 18 months (ongoing, 18 of 24 months) is provided. For Process 2 Clinical, long-term stability data are available for two lots covering 18 months (ongoing, 18 of 36 months). The stability studies for the supportive process validation stability lots are ongoing and available data, obtained at -45°C to -35°C, are available for three lots covering 6 months and three lots covering 9 months, respectively. All results met the stability acceptance criteria in place at the time of testing and no trends was observed for any of the attributes. It is noted that the long-term stability studies for the supportive Process 2 Commercial lots are planned to continue for up to 60 months.

Accelerated stability studies were performed at 2°C–8°C for all lots, and available data obtained so far revealed that all time points analysed met the current stability acceptance criteria in place at the time of testing and no trends was observed for any of the attributes. This supports the comparability of Process 1 Clinical and Process 2 Clinical, and of Process 2 Clinical/Commercial in terms of degradation trends.

In addition, data were presented for accelerated studies (23°C–27°C/55–65% RH) and stressed studies (28°C–32°C/60–70% RH) showed that further elevated temperatures had an impact on certain attributes. Based on these results from elevated temperatures, stability-indicating methods for sipavibart active substance were defined. No significant changes in attributes were observed after three cycles of freeze/thawing.

It is acknowledged that one batch per year, for those years in which manufacture is undertaken, will be placed into the stability programme. Approval of this type of annual stability studies is a matter of GMP and not within the remit of the current assessment. The applicant is reminded that the stability protocol may need to be revised due to post-approval process changes, depending on the nature of the changes.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product is a sterile, preservative-free, liquid dosage form intended for intravenous administration. It is supplied as a single-dose vial in one presentation: 300 mg of AZD3152 per vial with a 2.0 mL label-claim volume (2.28 mL target fill volume which includes a 0.28 mL overfill). The finished product composition contains 150 mg/mL AZD3152 in L- histidine/L-histidine hydrochloride monohydrate, L-arginine hydrochloride, PS80, pH 6.0. The finished product is aseptically filled into 2R glass vials and closed with an elastomeric stopper. The stoppered finished product vial is then capped with an aluminium seal and packaged.

Pharmaceutical development

Components of the finished product and formulation development

Components of the finished product is described with active substance and excipients. Main routes of degradation are aggregation, fragmentation, and changes in charged species. The development summary describes process 1 and 2, clinical and process 2 commercial.

The rationale behind the formulation is described. A risk-based approach was used with multivariate experimental designs, platform knowledge and scientific understanding. Agitation studies were done following ASTM D4169 (shipping studies), data is provided. There is no overage used. Physical properties of the finished product are described.

Manufacturing process development

Manufacturing process flow diagrams over the three processes is shown for comparison and an overview of changes to the finished product manufacturing processes. There were no changes during process 1 and process 2 clinical finished product manufacturing. There were no significant changes between process 2 clinical and process 2 commercial.

Comparability

The comparability exercise was performed through lot release tests and comparison of analytical and degradation profiles, side by side. No extended characterisation was performed at finished product level as it was for active substance, this is found acceptable however considering that active substance is final formulated and essentially the same as finished product. The approach for setting comparability acceptance criteria is presented and based on process capability, clinical experience and clinically relevant range (impact on potency or PK) and the specification. It is acknowledged that the release data and the analytical and degradation trends all support comparability. This is further supported by comparability following ICH Q5E including extended characterisation and demonstrated at the active substance level.

Manufacturing process characterisation studies

A process FMEA was performed making use of prior knowledge from earlier clinical manufacture and characterisation. Process risks were identified for, thawing, pooling, mixing, shear stress, bioburden reduction filtration, in-process holds, sterile filtration, aseptic filling with line pause duration, stoppering and capping. For each step a criticality classification of studied process parameters was made. Assigned CPPs were for the sterile filtration, flow rate and pressure, and for container closure integrity (CCI), crimp pressure. The other parameters studied were not deemed as critical with justifications derived from process characterisation studies and when kept within acceptable process ranges. The applicant explained what the consequence would be if a defined acceptance criterion, action limit or acceptable range were exceeded, both for CPPs and NCPPs. The control strategy is found acceptable.

A material compatibility study was performed for all product contacting materials. Data are presented. Room temperature hold in facility, photosensitivity, risk assessment on in-process extractables and leachables have also been performed and are acceptable.

Container closure

The type, manufacturer and quality of the vial, stopper and seal is provided. The product contacting vial, 2R borosilicate, and stopper are of pharmacopeial quality. The same container closure has been used throughout process versions. Suitability for intended use has been demonstrated as protection, physicochemical and biological reactivity tests. Safety by extractables and leachables studies including analysis of elemental impurities has been shown using orthogonal methods of analysis. This is

endorsed. After an accelerated simulation test (species identified) and a risk-based approach, it was concluded that the leachables study could be limited to testing for elemental impurities. This, on three process validation finished product batches at 2-8°C and tested at 0, 6, 12, 24, and 36 months. The results are summarised in the dossier.

Microbiological attributes

The finished product is a sterile liquid solution dosage form manufactured using sterile filtration and aseptic fill-finish process. The finished product is intended for single dose only and does not contain a preservative. Sterility and endotoxin of the finished product are tested as part of lot release, and CCI is tested as part of the finished product stability programme.

Compatibility

Undiluted finished product at target concentration of 150 mg/mL (IM or IV administration), was assessed using latex-free, polycarbonate (PC) and polypropylene (PP) plastic syringes. The study components were materials, hold temperatures, finished product concentration, agitation and hold time and duration of contact with all components, including IV injection administration set with needle. Material types were selected based on prevalence at clinical settings. Finished product was withdrawn from a vial using an 18.5 G syringe, a small IV injection catheter was attached to the syringe. Finished product was expelled through the catheter and this was time zero. The samples were placed on orbital shaker for 15 minutes at ambient temperature. Following agitation, two hold time conditions were evaluated to support refrigeration (24 hours) and at 28–32°C, for 6 hours with exposure to light.

For diluted finished product, in 0.9% (w/v) sodium chloride or 5% (w/v) dextrose, the study components were materials, hold temperatures, finished product concentration, IV bag diluent, hold time and duration of contact with all components, including administration set and in-line filter. The IV bags were prepared with 3 mg/mL and of either 20 or 30 mg/mL finished product. Two hold temperature conditions were evaluated, 28–32°C (4 hours) and 2–8°C (24 hours). The temperatures and hold times were combined as worst-case conditions. The initial time zero sample of diluted finished product was removed through the dosage injection port for testing. The remaining diluted finished product admixture was slowly infused via an administration line with in-line filter to assess the compatibility of an IV line (Post infusion sample). Samples were collected manually at each timepoint through a syringe port. At the final timepoint, the dose was expelled through the infusion line simulating the clinical infusion rate of approximately 30 minutes for the delivery of the entire dose. Compatibility was assessed by the quality attributes of appearance, sub-visible particles, purity (aggregation, fragmentation), cIEF (charged species), potency and total protein. The results were that the quality attributes met specifications and were found compatible under the studied conditions. The study design and results for compatibility are found acceptable and support the information in the SmPC, section 6.3, that chemical and physical in-use stability has been demonstrated for 24 hours at 2ºC to 8ºC and 4 hours up to 25ºC.

Microbial challenge study

Two microbial challenge studies for undiluted finished product were designed to support the intended hold times of 24 hours at 2–8°C and 4 hours at 28–32°C aligning with the duration of the physicochemical stability studies. The challenge organisms used in the study were S. *aureus*, P. *aeruginosa*, E. *coli*, S. *epidermidis*, C. *albicans*, and A. *brasiliensis*. The microbial challenge study for the undiluted finished product demonstrated no growth at both 2–8°C and 28–32°C for up to 48 hours, demonstrating the growth inhibition of this finished product in intended formulation.

2.4.3.2. Manufacture of the product and process controls

Manufacturing process and controls

AstraZeneca (AZ) AB, Gärtunavägen, SE 152 57 Södertälje, Sweden is responsible for EU batch release. All sites involved in manufacture and control of the finished product operate in accordance with GMP.

The manufacturing process starts with receipt of the active substance. The active substance is then thawed and pooled into a mixing vessel and further filtered into a holding bag. The active substance is sterile filtered and aseptically filled into sterile vials, closed with sterile stoppers, and sealed with aluminium caps. The finished product is 100% visually inspected, labelled and packaged.

An overview is provided with material inputs, CPPs, NCPPs, IPCs and performance attributes. Thaw time, number of active substance containers, volume of active substance transferred with flow rate (pump setting), mixing time and speed. For bioburden reduction, flush volume, volume filtered, flow rate, in-process hold time, refrigerated and room temperature are presented with ranges. These are classified as NCPPs.

The visual inspection, bulk packaging, shipping, labelling and packaging as well as the batch numbering system are briefly described.

Control of critical steps and intermediates

The CPPs and IPCs with acceptance criteria are summarised. In-process hold times have been validated as part of process validation to demonstrate effective microbial control for bioburden reduction filtered refrigerated active substance (≤24 hours) and room temperature (17-25°C) ≤48 hours and classified as NCPPs. A bioburden sample is taken at the end of the in-process hold.

Process validation

Three consecutive finished product lots using different combinations of active substance lots are presented. Batch sizes ranged from 226 kg to 772 kg. All CPPs and IPCs were within acceptance criteria. Homogeneity and quality were demonstrated for post-mixing, end of intermediate hold, and for the filling process, the beginning, middle and end. Data is presented and found acceptable. Acceptable data is also shown for NCPPs confirming thawing, pooling, mixing, bioburden reduction filtration, mixing after optional in-process hold, sterile filtration, stoppering and capping.

Aseptic filling time ranged from 11 to 46 hours. In-process hold was calculated from the end of bioburden reduction to the start of the sterile filtration and were challenged to ensure maximum hold duration to be covered (hold times in the Mobius bag). There was no impact on quality including bioburden results as a result of mixing and in-process hold (<1 CFU/100 mL all three batches). Total wetted time is calculated from the start to the end of sterile filtration and ranged from 12 to 47 hours. Approved fill weight performance was shown. Mixing data is presented for quality and homogeneity also after in-process hold. No major deviations were found throughout the finished product validation.

Media fills are performed semi-annually on the filling line with not less than two media fills per calendar year. Four media fill lots support qualification of the AZD3152 aseptic process. All the steps and parameters of the manufacturing process under evaluation were challenged. No microbial contamination was observed in any of the incubated vials. The studied aseptic processing elements were, vial size, filling line speed, quantity, duration of media fill and number of personnel during operation.

The process of CCI testing has been described in detail with all samples as pass and is found acceptable. Filter validation studies on the polyvinylidene difluoride (PVDF) 0.2 µm filters used for

sterile filtration. Data is provided on product specific bubble point integrity testing for finished product and rinsing bubble point wetted with DS and rinsed out with purified water. A chemical compatibility study showed no compatibility issues.

Microbial retention studies has been performed determining B. *diminuta* retention capability of the sterilising- grade Durapore 0.2 µm hydrophilic filter, used in the sterile filtration process. Validated for up to 60 hours. flowrate of 3 LPM and a total batch volume of 1,000 L. The original reports on filter compatibility, bubble point determination and bacterial retention tests are provided.

Information and validation data on sterilisation methods including sites are presented. Data is shown on depyrogenation of vials, autoclavation for manufacturing equipment and caps, and gamma irradiation for filtration and filling assembly. The information provided includes load configurations and thermocouple positionings (dose mapping for irradiation), the equipment used is identified.

The results from the filter extraction study were less than the SCT and acceptable.

Shipping qualifications studies are described using a cumulative testing approach for the shipping qualification of the bulk and final pack for finished product. Once the units were exposed to transportation stress in bulk configurations, they were packed into the commercial secondary packaging configuration, and further exposed to transportation stress via simulation in accordance with ASTMD4169. Shipping routes and stress exposure with results summary and packaging and pallet configurations are given with sufficient detail.

No reprocessing is claimed for finished product. The manufacture section can be approved once the raised concern is solved.

Overall, the finished product manufacturing process is considered validated.

Control of excipients

Excipients are all compendial, none of human or animal origin.

2.4.3.3. Product specification

Specifications

The finished product specifications include control of identity, purity and impurities, biological activity and other general tests.

Justification of specification

Justifications have been made for appearance, visible particles, osmolality, sterility, sub-visible particles, extractable volume, CCI and lateral flow identity. These are finished product specific and are found acceptable.

The applicant explains the approaches to set acceptance criteria through published, stability and non-stability limits approach. The specification is found acceptable.

The compendial methods of visible and sub-visible particles, clarity, colour and pH have the same acceptance criteria for release and end of shelf life. The visible particles acceptance criteria is "practically free from visible particles". This is endorsed. Identity, extractable volume, sterility and endotoxin are tested at release and not at end of shelf life and container closure is tested only as end of shelf life and not release. This is found acceptable. The limits for total protein, potency are also the same for release and end of shelf life.

Overall, the finished product specifications are acceptable.

Analytical methods and validation

The analytical methods used for both active substance and finished product are described. Information on the compendial methods has been provided for the two finished product specific non-compendial methods. The information is accepted.

Validation reports and results demonstrating the suitability of analytical methods used for lot release and stability testing of finished product is provided. Where the same tests are used for both active substance and finished product, validation studies applicable to both are summarised in the dossier. Tests for endotoxin and sterility have been verified as they are specific to AZD3152. Appearance, clarity, colour, visible particles, pH, osmolality, extractable volume, and sub-visible particles, were verified according to the corresponding compendial procedure. Reports for analytical transfers during development have been provided.

An acceptable report investigating Low Endotoxin Recovery (LER) has been submitted and is acceptable.

Batch analysis

Batch data is provided

Characterisation of impurities

Concerning potential finished product impurities, reference is made to corresponding the active substance section, which is considered adequate as no new impurities are expected.

Furthermore, a risk assessment concerning the potential presence of nitrosamines, in line with the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products 03 August 2020 EMA/409815/2020, has been provided. The conclusion that the risk of nitrosation or the presence of nitrosating reagents during the active substance and finished product manufacturing is very low is endorsed.

A risk assessment on elemental impurities in accordance with ICH Q3D indicates that the levels of metal impurities will be below 30% control threshold of the permitted daily exposure (PDE) limits. The risk assessment considered the potential for introducing elemental impurities from all reagents, water, excipients, manufacturing equipment, and CCS.

Reference standard

For information on reference standards, reference is made to corresponding active substance section, which is considered adequate, as the same materials are used for active substance and finished product.

Container closure system

The AZD3152 finished product CCS consists of a glass vial made of type I clear borosilicate glass, a stopper made of D21-7S chlorobutyl elastomer, with a FluroTec coating and an aluminium seal cap with a removable plastic button. The glass vial and stopper are in immediate contact with the finished product and comply with applicable compendial requirements. Descriptions and manufacturers are given with criteria for incoming inspection for vial, stopper and seal. Representative images of vial, stopper and seal are provided. Measures are found in the material specifications including also examples of sterilisation and quality control certificates. Sterilisation procedures and validations have been provided in section for auxiliary studies. The information provided on the CCS is acceptable.

2.4.3.4. Stability of the product

The applicant refers to a holistic approach to consider stability data from all representative lots. As support, the applicant has performed statistical modelling based on available stability data showing that specifications will be fulfilled at 2 years of storage at a 95% confidence level. Actual data in support of 2 years is expected in December 2024, which is not within the review process. The longest available data for both process 1 and 2 is 18 months at the long-term storage condition of 2°C-8°C.

No overall trends are seen for the reported data at intended storage.

There have been no changes in formulation or CCS. It has been assessed that comparability between active substance processes 1 and 2 and process 2 clinical and commercial has been sufficiently demonstrated as concluded in S.2.6 and P.2.3, i.e. meeting the same quality and specification as that intended for marketing.

The applicant's position was to not include PS80 in the finished product and end-of-shelf-life specification referring to the fact that there are no process steps after release of active substance that are expected to impact the level of PS80 and that no degradation was observed over 24 months of storage at 2-8°C. The provided data cover a storage time period of 24 months which is above the current shelf-life assigned. However, if the applicant intends to expand the shelf life above 24 months, further data demonstrating sufficient PS80 stability would be needed.

A confirmatory photostability study was conducted in accordance with ICH Q1B to demonstrate that the design of finished product secondary packaging protects the product from potential light exposure during product storage and transportation activities in line with the wording in section 6.4 in the SmPC.

The applicant commits to continue the stability studies of the finished product through scheduled duration of 36 months. Stability studies are performed based on ICH Q5C.

Overall, the acceptable finished product shelf life at the time of CHMP Opinion for the present marketing authorisation application is 18 months when stored at 2°C - 8°C protected from light.

Regarding in-use stability of prepared syringes and prepared infusion bags, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C and 4 hours up to 25°C. From a microbiological point of view, unless the method of preparation precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C and 4 hours up to 25°C, unless preparation has taken place in controlled and validated aseptic conditions.

2.4.3.5. Adventitious agents

TSE/BSE

No materials of human or animal origin were used in development of the AZD3152 manufacturing cell line after host cell culture, including the MCB and WCB. One material of animal origin (FBS) was used in culture of the CAT-S host cell line and relevant certificates have been provided. Furthermore, materials not directly used in the process, but which may come into contact with the product during manufacture or primary packaging (eg, tubing, cryovials), were assessed for TSE transmission risk. For those materials manufactured using animal tallow derivatives, the processing conditions meet the processes criteria defined in the Note for Guidance EMA/410/01 Rev. 3. It is agreed that the risk for TSE is negligible.

Microbial contamination

The MCB and WCB have been tested for mycoplasma and sterility. Unprocessed bulk samples were tested for mycoplasma and bioburden, and no contaminating microorganisms were detected for any of the lots manufactured. The active substance and finished product were tested for bioburden and sterility, respectively, and no microbial contamination was detected. It is agreed that the control approach for microbial contamination for the AZD3152 manufacturing is acceptable.

Endogenous and adventitious viral agents

There are short descriptions of the testing performed and it is found to be in line with ICH Q5A requirements. The test results of viral adventitious agents for the MCB, WCB and LIVCA cell banks is presented in section S.2.3. No infectious viral agents were detected in the cell banks. The testing of unprocessed bulk is presented in S.2.5.2 and no infectious adventitious virus were detected.

Virus clearance capability was studied for the purification process using scale-down models representative of manufacturing. Information on process parameter settings in the virus validation studies is shown. Four model viruses were studied in spiking experiments to cover a broad range of virus types: XMuLV (Retro), PRV (Herpes), Reo-3 (Reo), and MVM (Parvo).

A virus validation report is included in the dossier. Proper controls were part of the studies such as hold, cytotoxicity and viral interference. Test articles (load material) that virus was spiked into are identified and were obtained from regular GMP manufacture.

For the low-pH step, samples were withdrawn so as to determine virus inactivation kinetics.

Carry-over was part of the studied chromatography steps as is outlined in ICH Q5A. This is to demonstrate that the cleaning and regeneration procedures inactivate or remove virus. Although high reduction values were obtained for the non-enveloped viruses MVM and Reo, some virus could be detected after the columns were sanitised with 1N NaOH. Considering the experimental set up with high titres of virus loaded onto the columns, these results are not unexpected and no issue is raised.

For virus clearance and resin reuse the applicant leveraged, for this product, sufficient prior knowledge from earlier in-house products and justifications to not perform product specific studies. This is stated in ICH Q5A (R2) to be a possibility if sufficient in-house data is available.

Both the Viresolve Pro and the Planova BioEX filters were studied using duplicate MVM spiking experiments, at pressure levels of 30 psi and 50 psi (one for each run) with a 60-minute pause at 0 psi prior to buffer chase. No effect of the pause could be seen. It is acknowledged that the validation of MVM only for the virus retentive steps is adequate and that results can be extrapolated for larger viruses.

The lower reduction values obtained in the duplicate runs have been used in the calculation of overall log reduction as a conservative approach. A RVLP safety factor of greater than 14 log10 was calculated which is acceptable.

Overall, adventitious agents safety is considered sufficiently assured.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The dossier is appropriately structured. A new active substance claim (NAS) is accepted and all GMP aspects have been satisfactorily covered.

The active substance manufacturing process is adequately described. Description of origin and control of cell banks and gene constructs is acceptable. Characterisation of sipavibart was performed using an extensive panel of appropriate methods. The control of active substance is found acceptable.

The development and manufacture of the finished product has been at large sufficiently described and justifies the chosen formulation as well as the commercial manufacturing process. The control of the finished product has been presented in an acceptable way.

The strategy to set finished product end-of-shelf-life specification limits is supported.

Data presented for the viral clearance studies indicate robust reduction of a broad spectrum of virus.

From a quality perspective, a positive CHMP opinion can be granted.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Kavigale is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Kavigale is considered approvable from the quality point of view.

2.4.6. Recommendations for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Sipavibart and cilgavimab were derived from B cells isolated from convalescent patients. They were engineered with substitutions in the Fc: YTE to extend mAb half-life and TM to reduce Fc receptor and C1q binding.

The 2 mAbs bind to distinct epitopes on the spike protein RBD and do not bind to other human Coronaviruses (CoVs), cilgavimab and sipavibart (derived from the parental mAb Omi-42) bind to the SARS-CoV-2 spike trimer ectodomain, specifically recognizing the RBD).

Sipavibart showed a binding affinity to the SARS-CoV-2 spike trimer in the IgG format with a KD value of 14.81pM) confirm that it recognises the spike protein with high affinity.

Table 1. Cilgavimab, sipavibart and AZD5156 Binding Kinetics to SARS-CoV-2 Spike Trimer and RBD

Test Article	Antigen	ka (1/Ms)	kd (1/s)	KD (pM)	χ2 (RU2) a
Cilgavimab	Spike Trimer [b]	5.096E+05	2.109E-05	41.39	0.0420
sipavibart	Spike Trimer [b]	2.339E+06	3.463E-05	14.81	0.1410
AZD5156	Spike Trimer [b]	2.406E+05	4.620E-05	192.0	0.0447
ACE2	Spike Trimer [b]	1.336E+05	3.210E-03	24030	0.2300

[a] χ^2 values indicate goodness of fit

[b] SARS-CoV-2 BA.2 spike trimer ectodomain protein

Source: Study EVI5156-0001

Cilgavimab and Omi-42, the parental antibody of sipavibart, sterically block virus recognition of the ACE2 receptor by binding the spike RBD at or proximal to the ACE2 interface (MCBS7442-0001). To further study the potential mechanism of the inhibitory activity of sipavibart or CR3022 (a control mAb that does not significantly inhibit RBD), binding to ACE2 was evaluated in an ACE2/RBD binding assay. Sipavibart blocked RBD binding to ACE2, with average IC50 value of 102.4 ng/mL (0.6829 nM). In contrast, CR3022 did not fully inhibit RBD binding to ACE2 up to the highest concentration tested (20 μg/mL). The results of these experiments demonstrate that sipavibart can potently block RBD binding to ACE2.

Table 2. Summary of Antibody Inhibition of RBD-ACE2 Interaction

Test Article	Inhibition	
	IC50 (ng/mL)	IC50 (nM)
sipavibart	102.4	0.6829
CR3022	> 20,000	> 133.3

Note: Mean IC_{50} values and standard deviation averaged from two independent operators; inhibition which did not reach a curve capable of calculating a IC_{50} is reported as greater than the highest concentration used in the assay (20,000 ng/mL).

Source: Study EVI5156-0001

Sipavibart includes YTE amino acid substitutions in the heavy chain CH2 constant region of the Fc. The YTE substitutions increase antibody affinity for the human neonatal Fc receptor (huFcRn) at a lower endosomal pH, resulting in enhanced recirculation of the antibody and an extended half-life in serum.

The introduction of TM substitutions in sipavibart is designed to reduce binding to FcγR and complement proteins. This may reduce virus-antibody complex mediated FcγR crosslinking or viral uptake to prevent potential over-activation of immune cells.TM and YTE substitutions also result in strongly reduced binding of the sipavibart component mAbs to huFcγRs and huC1q, which should mitigate Fc-mediated immune cell activation.

When bound to SARS-CoV-2 spike RBD, sipavibart prevents interaction of the virus with human angiotensin converting enzyme 2 (ACE2) host cellular receptor), and thus should effectively neutralise the virus by blocking its entry.

To confirm this effect, the in vitro viral neutralisation activity of sipavibart was assessed against authentic SARS-CoV-2 virus variants in a research-grade focus reduction neutralisation test (FRNT) assay. the FRNT assay data showing that sipavibart has strong neutralisation breadth against all tested variants; IC50 values were between 8.3 ng/mL (BA.1.1 variant) and 110.9 ng/mL (D614G variant). Thus, the FRNT assay confirms that sipavibart retains broad and potent coverage against all tested viral variants.

The results of pseudovirus neutralisation assay testing of the mAbs against SARS-CoV-2 variants confirm the FRNT assay data showing that sipavibart has strong neutralisation breadth against all tested variants; IC50 values were between 3.6 ng/mL (XBB.1 variant) and 25 ng/mL (BA.2.75 variant). Thus, the pseudovirus neutralisation assay confirms that sipavibart retains potent coverage against all tested viral variants.

To understand the sipavibart interactions that are responsible for recognition of spike, the structure of the sipavibart Fab was determined in co-complex with the BA.2 RBD. Sipavibart binds the back of the RBD along the "left shoulder" according to the RBD anatomical torso analogy. Defining a binding site as any RBD residue with at least one of its atoms within a 5 Å radius of the Fab, the sipavibart binding site was observed to comprise 28 non-contiguous residues (AA 403, 405, 409, 414-418, 420, 421, 453-460, 473-477, 486, 487, 489, 493, 505). The specificity of sipavibart for its RBD epitope is explained by its structure. The sipavibart paratope involves contacts by both heavy and light chains. High affinity binding between sipavibart and its RBD epitope is aided by shape and charge complementarities of these two molecules at the interface.

Recombinant GFP-expressing SARS-CoV-2 XBB.1.5 viruses were generated by reverse genetics wherein the mutations identified (T415I, K458E, F456L, and V991E) were individually introduced into the XBB.1.5 spike protein. The neutralisation potency of sipavibart against these recombinant viruses was then evaluated in the FFRNT neutralisation assay. A 103-fold reduction in susceptibility to sipavibart (EC50, 2672 ng/mL) was observed for recombinant virus encoding the T415I substitution compared to the parental virus. A >769-fold reduction in susceptibility to sipavibart (EC50, >20000 ng/mL) was observed for recombinant viruses encoding the K458E or F456L substitutions compared to parental virus. The V991E mutation resulted in a <2-fold reduction in potency (EC50, 47 ng/mL), in agreement with the observation that mock passaged virus, which also acquired V991E, was still sensitive to sipavibart. Therefore, T415I, K458E, and F456L were confirmed as sipavibart escape mutations, while V991E does not result in escape.

Table 3. Susceptibility of Recombinant Virus Encoding Escape Mutations to sipavibart

Sipavibart Potency	**XBB.1.5 parent**	**T415I**	**K458E**	**F456L**	**V991E**
Neutralisation EC_{50} (fold change)	26	2672 (103x)	>20000 (>769x)	>20000 (>769x)	47 (1.8x)

Top number indicates neutralisation EC_{50} in ng/mL in the FFRNT assay; bottom number in parentheses indicates the EC_{50} fold change of each mutant relative to the XBB.1.5 parental virus
Source: Study EVI5156-0009

The 3 RBD escape positions (T415, K458, and F456) were analysed for their importance to sipavibart binding from a structural perspective. The escape residues T415, K458, and F456 are at positions that form key interactions between sipavibart and the RBD, thus lending a structural explanation for these mutations conferring viral escape from sipavibart neutralisation.

The in vivo efficacy of sipavibart alone was evaluated in the Syrian hamster model of SARS-CoV-2 infection, in the prophylactic setting. As was used with AZD5156, Sipavibart-TM (which incorporates only the TM without the YTE substitution) was tested because the YTE substitution that extend mAb half-life in human serum causes rapid elimination of the antibody in rodent species.

Female/male Syrian hamsters (80-120g, 6-8 weeks old) received a single 0.6 mL intraperitoneal (IP) injection containing 6.0 mg isotype control mAb (R347-TM), or sipavibart-TM, ranging from 0.67 to 6.0 mg.

Then hamsters were challenged intranasally (I.N.) with 6 x 103 PFU of SARS-CoV-2 strain USA-WA1/2020 by aspiration, with 50 µL diluted virus (6 x 104 PFU/mL in PBS) delivered to each nostril. Hamsters were weighed and monitored daily.

One cohort of hamsters (n = 8) was euthanised on Day 3 post-challenge, which correlates with peak virological measurements. A second cohort of hamsters (n = 8) was euthanised on Day 7 post-challenge, which correlates with peak lung pathological findings associated with SARS-CoV-2 infection.

Serum samples were collected on Day 0 before challenge and at time of euthanasia (Day 3 and Day 7 post challenge) were assessed for mAb concentrations.

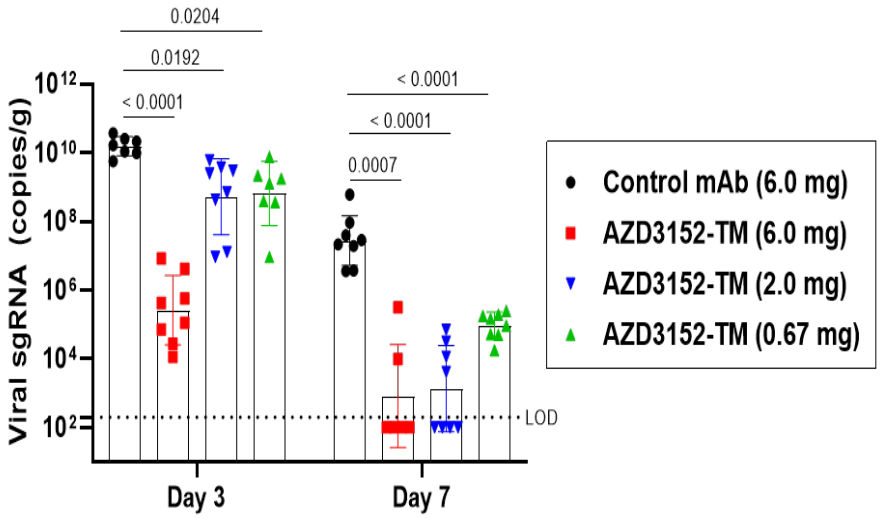
Animals that received the isotype control mAb lost on average 14.6% of their body weight over the week following SARS-CoV-2 challenge relative to their respective body weights recorded on Day 0 (day of challenge). In contrast, animals that received 6.0, 2.0 or 0.67 mg sipavibart-TM were statistically significantly protected from weight loss during the course of the experiment ($p<0.0001$) and gained approximately 3% in body weight relative to their respective starting weights by the end of the study (Day 7 post-challenge). These data demonstrate that a single prophylactic administration of ≥0.67 mg sipavibart-TM was sufficient to protect hamsters from weight loss associated with SARS-CoV-2 infection.

There was a dose-dependent decrease in sipavibart-TM serum concentrations at all time points. These data indicated that most animals were appropriately dosed. However, three animals were mis-dosed and thus were removed from virology and pathology analyses. Importantly, the Day 0 serum concentration of sipavibart-TM was negatively correlated with lung sgRNA levels at Day 3, demonstrating that prophylactic administration of sipavibart-TM protects hamsters from SARS-CoV-2 challenge.

Hamsters that received 6.0, 2.0 or 0.67 mg sipavibart-TM had a statistically significant reduction in mean viral sgRNA of 5.41 ($p<0.0001$), 8.72 ($p=0.0192$) and 8.81 ($p=0.0204$) log10 copies/g, respectively. By Day 7, animals dosed with the isotype control had mean viral sgRNA levels of 7.44 log10 copies/g, while animals that received 6.0, 2.0, or 0.67 mg sipavibart-TM showed a statistically significant reduction in mean viral sgRNA levels of 2.91 ($p=0.0007$), 3.13 ($p<0.0001$) and 4.97 ($p<0.0001$) log10 copies/g.

The lungs of SARS-CoV-2 infected hamsters were evaluated for inflammation and alveolar damage using haematoxylin and eosin (H&E)-stained sections. On Day 3, animals administered 6.0 mg isotype control mAb had a mean pathology score of 12. In contrast, those that received 6.0, 2.0, or 0.67 mg sipavibart-TM had mean pathology scores of <1, 4.6, and 5.9, respectively. On Day 7, animals that received 6.0 mg isotype control mAb had a mean pathology score of 8 while animals that received 6.0, 2.0, or 0.67 mg sipavibart-TM had mean pathology scores of 0, <1, and 2.5, respectively. The data demonstrate that sipavibart-TM protects hamsters from SARS-CoV-2 induced alveolar damage and inflammation in a dose-dependent manner.

Figure 1. Prophylactic Sipavibart-TM (AZD3152-TM) Administration Reduced SARS-CoV-2 Burden in the Lungs of Infected Hamsters



Lung SARS-CoV-2 viral load on Day 3 and Day 7 post-challenge. Homogenates of lung sections collected on Day 3 and Day 7 post-challenge were assessed for viral sgRNA. Data represent geometric means ± geometric standard deviation.
Source: Study EVI5156-0008

2.5.2.2. Secondary pharmacodynamic studies

Secondary pharmacodynamic studies of sipavibart have not been conducted as no binding to any human tissue was observed in the tissue cross reactivity studies and the product is specific for the RBD antigen of the spike protein target.

2.5.2.3. Safety pharmacology programme

No dedicated safety pharmacology study was conducted. Safety pharmacology was assessed as part of the repeat dose GLP toxicology study.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were not conducted based on the high affinity, selectivity, and specificity of sipavibart.

2.5.3. Pharmacokinetics

Kinetics of sipavibart were evaluated after single IV administration in mice transgenic for human FcRn and in cynomolgus monkeys as part of the single-dose toxicity study after IV and IM administration. This is in line with the intended clinical administration.

Methods of analysis

The concentration of sipavibart in cynomolgus monkey serum was measured using a validated LC-MS/MS method. The method was validated for both sipavibart and cilgavimab since the toxicity study was conducted with both antibodies. The range of the assay was 9.00 ng/mL to 1000 ng/mL for both antibodies. The presented data show that the assay was sufficiently validated. Potential impact of high concentrations of sipavibart and cilgavimab and vice versa was assessed, no impact was detected.

Studies in mice

Mice transgenic for human FcRn are considered a suitable model to assess target-independent PK parameters of human IgG molecules; changes in the mAb's Fc region affecting binding to FcRn will be adequately reflected in these animals. The YTE substitutions in the Fc were shown to enhance binding to FcRn at low pH and thereby enhance the mAb half-life in vivo (see PD section). In general, PK parameters for sipavibart and cilgavimab were comparable.

Studies in cynomolgus monkeys

In general, the toxicokinetic data were as expected and thus, no anti-drug antibodies analysis has been conducted. No gender difference was noted.

Dedicated studies for distribution, metabolism, excretion and PK drug interactions were not conducted, which is acceptable for monoclonal antibodies.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No formal single-dose toxicity study of sipavibart was performed as a repeat dose toxicology study (section 4.2) was completed.

2.5.4.2. Repeat dose toxicity

The repeat dose toxicology study was conducted to evaluate the potential toxicity and toxicokinetics of AZD5156 (combination of sipavibart and AZD1061) in monkeys when administered once weekly for 3 weeks at 300 mg/kg (150 mg/kg each antibody) by intramuscular (IM) or intravenous (IV) route of administration followed by an 8-week treatment free period.

The cynomolgus monkey was chosen as a suitable nonclinical toxicity species from a pharmacokinetics perspective. As both sipavibart and AZD1061 are directed at foreign targets that are not endogenously expressed in animals or humans, species selection was not based on target binding considerations but based on binding of the antibodies to cynomolgus monkey FcRn.

Dose levels were selected based on available clinical and nonclinical data for other similar antiviral and antibacterial mAbs with extended half-life modification, for which the nonclinical safety has been demonstrated. Further, one of the component mAbs, AZD1061, in combination with AZD8895, has been tested previously in cynomolgus monkeys at a single dose of 300 mg/kg IV and 75 mg/kg IM with no toxicity findings of concern. The selected IM and IV dose levels were intended to provide the minimum safety margin (10x using the Human Equivalent Dose calculation) over the proposed IM clinical dose level of 300 mg.

There were no adverse AZD5156-treatment related findings. Microscopic findings in AZD5156-treated animals were observed in the brain (meninges) and IM and IV administration sites. In the brain, perivascular mononuclear cell infiltration was observed and generally characterised by minimal, multifocal, predominantly lymphocytic infiltrates around meningeal blood vessels in one or more of the brain sections examined. The infiltrates in the brain were not associated with any evidence of tissue injury and were considered non-adverse.

At the IM administration sites, a higher incidence and/or severity (as compared with controls) of mixed cell inflammation and eosinophilic infiltration were observed intramuscularly and/or subcutaneously. All findings were considered non-adverse. At the IV administration site, vascular/perivascular

inflammation, perivascular degeneration/necrosis, acute thrombus, and a higher severity (as compared with controls) of perivascular fibroplasia were observed in one Group 3 male.

In recovery group animals at the end of the 8-week treatment-free period, no AZD5156-related microscopic findings were observed in any tissues, including brain and sites of administration, consistent with full reversibility of these findings.

Toxicokinetics were evaluated following Day 1 and Day 15 dose administration to assess exposure to AZD5156 component mAbs AZD1061 and sipavibart. TK results confirmed that systemic exposure to AZD1061 and sipavibart were very similar following IM injection and IV infusion of AZD5156.

The PK data for sipavibart is very similar to that of cilgavimab, which is currently approved for clinical use. This would be anticipated as both drugs exhibit similar Fc-modifications and would be expected to behave similarly within the body.

Table 4. Summary of TK Results of AZD1061 and Sipavibart in Male and Female Cynomolgus Monkeys Following IM and IV Administration of AZD5156

Analyte and Dose	**150 mg/kg AZD1061**			
Route	**IM**		**IV**	
Day	**1**	**15**	**1**	**15**
Mean C_{max} ±SD (µg/mL)	2220 ±267	4840 ±75	4010 ±773	5940 ±824
Mean $AUC_{0\text{-}72hrs}$ (±SD) hr*µg/mL	136000 ±14100	318000 ±44100	175000 ±18200	342000 ±32300
Mean $AUC_{0\text{-}168hrs}$ (±SD) hr*µg/mL	280000±24900	NC	346000±30000	691000±44900
Analyte and Dose	**150 mg/kg sipavibart**			
Route	**IM**		**IV**	
Day	**1**	**15**	**1**	**15**
Mean C_{max} ±SD (µg/mL)	2510 ±514	4470 ±974	3990 ±918	6390 ±608
Mean $AUC_{0\text{-}72hrs}$ (±SD) hr*µg/mL	147000 ±23500	289000 ±51700	165000 ±23600	353000 ±26100
Mean $AUC_{0\text{-}168hrs}$ (±SD) hr*µg/mL	296000±36900	NC	322000±38200	701000±40800

$AUC_{0\text{-}72hr}$, area under the concentration-time curve from time 0 to 72 hours; $AUC_{0\text{-}168hrs}$ = area under the concentration-time curve from time 0 to 168 hours; C_{max} = maximum concentration; hr = hour; IM = intramuscular; IV = intravenous; NC = not calculated; SD = standard deviation; TK = toxicokinetic

2.5.4.3. Genotoxicity

In accordance with ICH S6 (R1), genotoxicity testing has not been conducted with sipavibart as it is not applicable to biotechnology-derived large protein products. sipavibart is not expected to cross the nuclear or mitochondrial membranes to interact directly with DNA or other chromosomal materials.

2.5.4.4. Carcinogenicity

In accordance with ICH S6 (R1), carcinogenicity studies have not been conducted with sipavibart and are not planned given that the target for this product is a virus-specific target which is not expressed in nonclinical animal models or in humans and based on the proposed intermittent dosing regimen.

2.5.4.5. Reproductive and developmental toxicity

In accordance with ICH S6 (R1), the reproductive and developmental toxicity studies with sipavibart have not been conducted and are not planned. AZD5156 did not show any adverse effects on reproductive tissues evaluated in the repeat-dose toxicity study in cynomolgus monkeys. Further, sipavibart did not demonstrate binding to any of the evaluated human reproductive tissues (including placenta) in the GLP TCR study. To support inclusion of pregnant women in the clinical trials, a GLP tissue cross-reactivity study assessing off target binding to a limited panel of human foetal tissues was performed. Results showed no binding of sipavibart was present in the foetal human tissue panel examined.

2.5.4.6. Toxicokinetic data

See above (repeat dose study)

2.5.4.7. Local tolerance

A dedicated local tolerance study sipavibart was not conducted. Injection sites were evaluated as part of the repeat-dose toxicity studies with AZD5156 in cynomolgus monkeys.

2.5.4.8. Other toxicity studies

Tissue cross-reactivity studies were carried out to confirm that the product did not react with any human adult or foetal tissue.

The toxicology package consists of a repeat dose toxicity study in cynomolgus monkeys (Q1W for 3 weeks and recovery period, GLP) and two tissue cross reactivity studies (adult and fetal tissue, GLP).

The combination sipavibart and cilgavimab given by intravenous infusion or intramuscular injection of 300 mg/kg was well tolerated. No adverse changes were noted. Slightly higher globulins, and microscopic findings in the brain and administration site for both dosing routes were noted upon sipavibart/cilgavimab administration. These findings were not observed during the recovery phase, suggesting reversibility. The NOAEL was set to be 300 mg/kg (150 mg/kg sipavibart) which is agreed. Samples for Anti-drug-Antibody (ADA) evaluation were apparently collected but not analysed which is acceptable given that continuous exposure in the toxicity study was observed and there was no evidence for increased sipavibart clearance.

2.5.5. Ecotoxicity/environmental risk assessment

Sipavibart (AZD3152) is being developed for the prophylaxis of COVID-19. AZD3152 binds to the receptor binding domain of the spike protein and blocks its interaction with the hACE2 host cellular receptor, resulting in a blockade of virus entry, effectively neutralising the SARS-CoV-2 virus. AZD3152 was designed to provide broad and potent coverage across viral variants.

Antibodies are considered naturally-occurring products (i.e., they are proteins), which are not expected to remain either stable or biologically active in the environment for any significant period of time because of their high susceptibility to rapid chemical (e.g., oxidation, deamidation, proteolysis, beta elimination and disulfide scrambling) and physical (e.g., denaturation (protein unfolding), aggregation, precipitation, and surface adsorption), degradation, as well as biodegradation by a wide range of microflora, and various physical removal mechanisms. Degradation may be easily triggered from

exposure to uncontrolled ambient environmental conditions (e.g., due to desiccation, suboptimal pH or temperature, and light exposure).

AZD3152 is considered to be a non-hazardous, biodegradable product. As such, the environmental risk in terms of use and disposal is considered to be negligible and in accordance with the guideline on the environmental risk assessment of medicinal products for human use. A justification for not performing ERA studies was submitted. Furthermore, the assessment performed does not indicate a requirement to take special precautions during the release to the environment that will result from use in patients or disposal of the product.

As indicated in the section 6.6 of the SmPC, any unused medicinal product or waste material should be disposed of in accordance with local requirements.

2.5.6. Discussion on non-clinical aspects

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, sipavibart (AZD3152) is not expected to pose a risk to the environment.

Sipavibart was designed to be effective against early omicron strains, with pseudovirus neutralisation IC50 values ranging from 3.6 ng/mL (XBB.1 variant) to 25.0 ng/mL (BA.2.75 variant). Sipavibart binds to the spike protein RBD of SARS-CoV-2 (BA.2) with equilibrium dissociation constant of KD = 20.95 pM, blocking RBD binding to the human ACE2 receptor.

The YTE substitutions increase antibody affinity for the human neonatal Fc receptor (huFcRn) at a lower endosomal pH, resulting in enhanced recirculation of the antibody and an extended half-life in serum. This resulted in an increased binding to HuFcRn. The introduction of TM substitutions in sipavibart reduced binding to huFcγRIIa with the potential to decrease-activation of immune cells.

A screen of a number of SARS-CoV-2 virus variants was carried out. The results of the pseudovirus neutralisation assay showed that sipavibart has strong neutralisation breadth against tested variants, which include XBB.1, BA.2.75, Gamma, BA.1.1, BA.4.6, BA.4.7, BA.5.9, BA.2.75.2, BF.7, BQ.1, BQ.1.1, XBB and XBB.1.

Sipavibart was also evaluated for potency against individual amino acid RBD substitutions that were experimentally derived in cilgavimab and tixagevimab viral escape experiments. Sipavibart showed potent activity against pseudoviruses carrying RBD mutations that decreased susceptibility to cilgavimab (R346G, R346I, R346S, K444E, K444N, K444Q, K444R, K444T, V445A, N450D or S494L) or tixagevimab (F486S or F486V).

Virus variants that escape sipavibart neutralisation were selected in vitro by serially passaging a recombinant GFP-expressing SARS-CoV-2 XBB.1.5 virus in the presence of increasing antibody concentrations. Four separate selections (replicates) were performed in the presence of antibody with corresponding control selections without antibody treatment (mock).

Three of the mutations identified which showed reduced susceptibility are found within the RBD: T415I, K458E, and F456L. This is particularly relevant as emerging variants KP.2, KP.3 and LP.1 exhibit the F456L mutation and are therefore not anticipated to be susceptible to sipavibart. Moreover, this is in line with pseudovirus neutralisation data against SARS-CoV-2 variants containing the F456L mutation (SmPC section 5.1).

Administration of the mAb prevented weight loss associated with SARS-CoV-2 infection in Syrian hamsters. This was carried out using the sipavibart-TM form which incorporates only the TM because the YTE substitution that extend mAb half-life in human serum causes rapid elimination of the antibody

in rodent species. There was a dose dependency in the efficacy of the sipavibart-TM at both days 3 and 7 on the attenuation of viral sgRNA burden in the alveolar tissue as well as on H&E staining of alveolar tissue damage as determined by immunohistochemistry followed by pathological scoring. These studies demonstrated that sipavibart-TM had an antiviral effect as well as decreasing alveolar viral burden and tissue damage, with the latter two being in a dose-dependent manner.

The cynomolgus monkey is considered as an appropriate species to carry out the repeat dose toxicity study due to the similar binding of human antibodies containing YTE mutations. The doses used were appropriate and were 10x the Human Equivalent Dose calculation. While there was minor evidence of some local inflammation and eosinophilic infiltration intramuscularly and/or subcutaneously, this was largely transient and could be attributed to the administration procedure. One explanation for the sporadic finding at the IV administration site could be related to the placement of the cannula, which was used for the dosing procedure as the animals received three separate IV administrations. There was one individual incidence of perivascular degeneration/necrosis, acute thrombus and perivascular fibroplasia in a single animal, but this was considered as not severe.

There was no evidence of long-term toxicity in the recovery animals.

Overall, IM or IV administration of AZD5156 once weekly for 3 weeks was well tolerated and the NOAEL was 300 mg/kg of AZD5156 (150 mg/kg of sipavibart). No specific toxicity issues were highlighted in the results submitted and given the sporadic nature of the injection site findings; the clinical significance is considered low.

The tissue cross reactivity study demonstrated that the antibodies are specific for the RBD region of the spike protein of the SARS-CoV-2 virus and do not bind to human tissue.

Issues of viral susceptibility are further discussed under the headings of PK/PD and efficacy.

2.5.7. Conclusion on the non-clinical aspects

Overall, the combined pharmacological evidence suggests that sipavibart is selective for the RBD domain of the spike protein of the SARS-CoV-2 virus. It effectively neutralises early omicron variants. However, its ability to neutralise is abolished by the F456L mutation which is present in so called FLiRT viral variants.

Evaluation of sipavibart susceptibility against variants included in the SmPC has been conducted using a pseudotyped VLP assay. This assay has remained consistent across variants, with the only change being the pseudovirus. Details of this neutralisation assay has been provided; however, study reports for each individual variant have not been generated. The applicant agreed to provide individual variant study reports as soon as they are available. This is also applicable for future testing of upcoming variants (REC).

In a Syrian hamster disease model, sipavibart showed dose dependent antiviral effects and prevention of alveolar tissue damage.

The pharmacokinetic profile of sipavibart is as would be expected, including the prolonged half-life previously described for the Evusheld components. No specific issues have been raised in the results that have been provided.

A repeat dose toxicity study of sipavibart was carried out in cynomolgus monkeys. There were no specific adverse events reported apart from local inflammatory effects, largely due to the administration of the drug which were acute, and which did not persist during the recovery period. This information has been included in the SmPC.

Non-clinical recommendation:

A study report for variants tested that were circulating during the SUPERNOVA study (XBB.1.5, BA.2.86, and JN.1) should be provided no later than Q2 2025. (REC)

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study identifier	Study design	Population (incl. number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
D7000C00001 Supernova Parent Study Sentinel safety cohort	Sentinel Safety Cohort (Phase I portion of the Phase I/III study) Phase I First-Time-In-Human, Randomised, Double- Blind Study to Evaluate the Safety and PK of AZD5156 / AZD3152 in Healthy Participants	healthy adults, 18 to 55 years of age, weighing ≥ 45 kg and ≤110 kg. screened 87 randomised 57 (41 – AZD5156; 16 – placebo) median age 32 years all aged ≥18 - ≤55 years The majority of participants were White (63.2%); 26.3% of participants were Black or African American, 7.0% were of Other race, and 3.5% were Asian.	AZD5156 600 mg IM(300 mg sipavibart + 300 mg cilgavimab) compared to placebo administer-ed to gluteal region	serum PK analysis After a single dose IM administration of AZD5156 600 mg (sipavibart 300 mg and cilgavimab 300 mg, in separate vials) to the gluteal region (2 sequential injections on contralateral sides) in healthy adult participants, the serum concentration-time profiles of sipavibart and cilgavimab through 180 days post-dose (Day 181) were comparable

Study identifier	Study design	Population (incl. number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
				After a single dose IM administration of AZD5156 600 mg (sipavibart 300 mg and cilgavimab 300 mg, in separate vials) to the anterolateral thigh (2 sequential injections on contralateral sides) in healthy adult participants, the serum concentration-time profiles of sipavibart and cilgavimab through 180 days post-dose (Day 181) were also similar
D7000C00001 Supernova Parent Study Main Cohort	Phase III	patients 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at higher risk of developing severe COVID-19. Total randomised – 3349 Total dose – 3335 Negative SARS-CoV-2 rapid test at Visit 1	sipavibart 300 mg IM compared to 600 mg IM Evusheld / placebo sipavibart 300 mg or comparator administered IM in the anterolateral thigh on Day 1. Participants are to receive a second dose of their original randomised IMP (i.e., active treatment or comparator) 6	serum PK parameters

Study identifier	Study design	Population (incl. number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
		median age 60 years 15 participants age 12 – 18 years Female participants – 56.8% Most participants were white (74.1%), while 12.1% were Black or African American and 6.5% were Asian. A total of 21.5% were Hispanic/Latino.	months after Day 1 followed for 15 months randomisation 1:1	
D7000C00004 Little DIPPER	Phase I double-blind, placebo-controlled, multicentre, dose exploration study	healthy volunteers aged 18 to 55 years (and weighing ≥ 45 kg and ≤110 kg) across different dose levels 300 mg, 600 mg, and 1200 mg) and routes of administration (i.e. IM injection and IV infusion) 98 randomised 96 patients treated mean age 31 years male 56.3% Most participants (60/96; 62.5%) were White; 32/96 (33.3%) were Black or African American.	different dose levels (300 mg, 600 mg, and 1200 mg) and routes of administration (i.e., IM injection and IV infusion). single dose IMP was administered IM in the anterolateral thigh or IV (infusion rate: 50 mg/minute).	serum PK analysis
D7000C00001 Supernova substudy	A Phase II Open Label Sub-study to Evaluate the Safety, PK, and Neutralizing Activity of AZD3152 for Pre-exposure Prophylaxis of COVID-19	immunocompromised or immunocompetent participants (including healthy volunteers) ≥ 18 years of age with a minimum weight of 40 kg with all	single dose of sipavibart 1200 mg sipavibart 1200 mg IV infusion (infusion rate: 50 mg/minute)	serum PK parameters

Study identifier	Study design	Population (incl. number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
		degrees of SARS-CoV-2 infection risk. recruited and randomised 476 drug received by 468 mean age of participants was 48.8 years. female (56.2%). majority of participants (448 of 468 [95.7%]) were immune-competent / healthy and 20 (4.3%) were immunocompromised (16 [5.2%] participants in the sipavibart group, 2 [1.3%] in the Evusheld group, and 2 [100%] in the crossover group)	or Evusheld 300 mg IM (gluteal region) on Day randomisation 2:1	

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Sipavibart has been developed to provide efficacy similar to that of Evusheld (also referred to as AZD7442; AZD8895 [tixagevimab] and AZD1061 [cilgavimab]), but with greater breadth against SARS-CoV-2 omicron variants. Evusheld, which was granted marketing authorisation in the European Union and globally for pre-exposure prophylaxis of COVID-19, serves as an active comparator in sipavibart and AZD5156 (sipavibart and cilgavimab) clinical studies.

Results of PK analysis in four study groups are included in the application:

1) D7000C00001 (SUPERNOVA Parent Study Main Cohort) – pivotal study for efficacy and safety
2) D7000C00001 (SUPERNOVA Parent Study Sentinel Safety Cohort)
3) D7000C00004 (Little DIPPER)
4) D7000C00001 (SUPERNOVA Sub Study).

Methods

Bioanalysis

To measure sipavibart concentrations in human serum, an approach employing immunoaffinity enrichment using streptavidin magnetic beads coated with biotinylated RBD of SARS-CoV-2, followed by LC-MS/MS detection was used. The captured proteins are subjected to "on-bead" proteolysis with trypsin, following standard protein denaturation, reduction, and alkylation processing steps. Proteotypic peptides are quantified as surrogates for the component mAb serum concentrations.

Population PK analysis

A population PK analysis was conducted on pooled data from studies SUPERNOVA (parent study main cohort, parent study sentinel safety cohort, and sub study) and Little DIPPER, to characterise the PK of sipavibart and to evaluate the impact of covariates. In total, 4039 PK samples from 1091 participants were included in the analysis. Very few adolescents (N=8/1669) were randomised to the sipavibart arm in the SUPERNOVA parent study main cohort, and no PK information were collected from them.

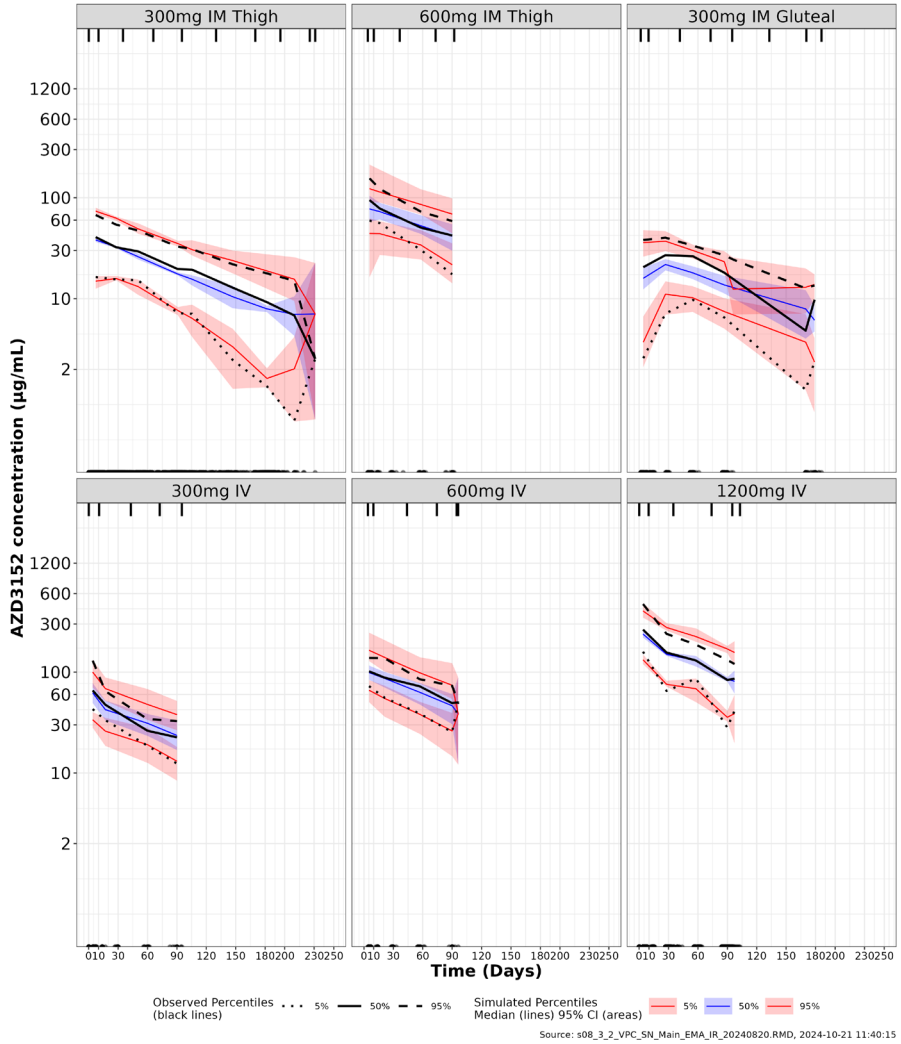
Sipavibart PK following IV and IM administration was described using a 2-compartmental model with first-order absorption (for IM) and first-order elimination. Final parameter estimates are presented in table below and a prediction corrected visual predictive check (pcVPC) of the final model stratified by dose and route of administration is presented in the figures below.

Table 5. Parameter estimates for the final sipavibart population PK model

PARAMETER	VALUE (RSE%)	COMMENT
Typical parameters		
ka	0.157 (16.8%)	(1/day) First order IM absorption rate parameter
CL	0.044 (0.90%)	(L/day) Clearance
Vc	4.59 (1.33%)	(L) Volume of central compartment
FIM	0.62 (13.89%)	(fraction) Absolute IM bioavailability for gluteal administration
Q	0.486 (7.38%)	(L/day) Intercompartmental clearance
Vp	0.403 (19.59%)	(L) Volume of peripheral compartment
Inter-individual variability		
ka CV%	104.4 (9.82%)	LogNormal
CL CV%	44.27 (1.64%)	LogNormal
Vc CV%	24.29 (2.11%)	LogNormal
FIM CV%	0 (FIX)	-
Q CV%	0 (FIX)	-
Vp CV%	133.9 (5.18%)	LogNormal
Correlation of random effects		
corr(ka,CL)	-0.4107	Correlation coefficient
corr(ka,Vc)	0.1663	Correlation coefficient
corr(CL,Vc)	0.2319	Correlation coefficient
Parameter-Covariate relationships		
beta ka(SEXM 1)	0.665 (25.5%)	Sex Male on ka
beta_ka(AGECAT_1)	-0.416 (43.7%)	Age category >65 years on ka
beta_ka(BMICAT_1)	-0.033 (487.8%)	BMI category >=30 kg/m2 on ka
beta ka(DIAB 1)	-0.6 (31.8%)	Diabetes Yes on ka
beta_CL(BWT)	0.75 (FIX)	Baseline weight in kg on CL (centered around: 70 kg)
beta_CL(DIAB_1)	0.208(18.9%)	Diabetes Yes on CL

beta_Vc(BWT)	1 (FIX)	Baseline weight in kg on Vc (centered around: 70 kg)
beta_Vc(RACEB_1)	-0.08 (36.8%)	Black Race Yes on Vc
beta_Q(BWT)	0.75 (FIX)	Baseline weight in kg on Q (centered around: 70 kg)
beta_Vp(BWT)	1 (FIX)	Baseline weight in kg on Vp (centered around: 70 kg)
beta_FIM(Thigh)	0.263 (24.8%)	Thigh injection Yes on FIM (relative to gluteal)
beta_ka(Thigh)	1.083 (31.4%)	Thigh injection Yes on ka (relative to gluteal)
beta_ka(ETHNIC)	-0.351(46.3%)	Hispanic or Latino Yes on ka
Residual variability		
error_ADD1	0.181 (0.82%)	Additive Error (log(ug/mL)) - IM data
error_ADD2	0.142 (2.07%)	Additive Error (log(ug/mL)) - IV data

Figure 2. Prediction-Corrected Visual Predictive Check: Prediction of Sipavibart Serum Concentrations, Stratified by Dose and Route of Administration

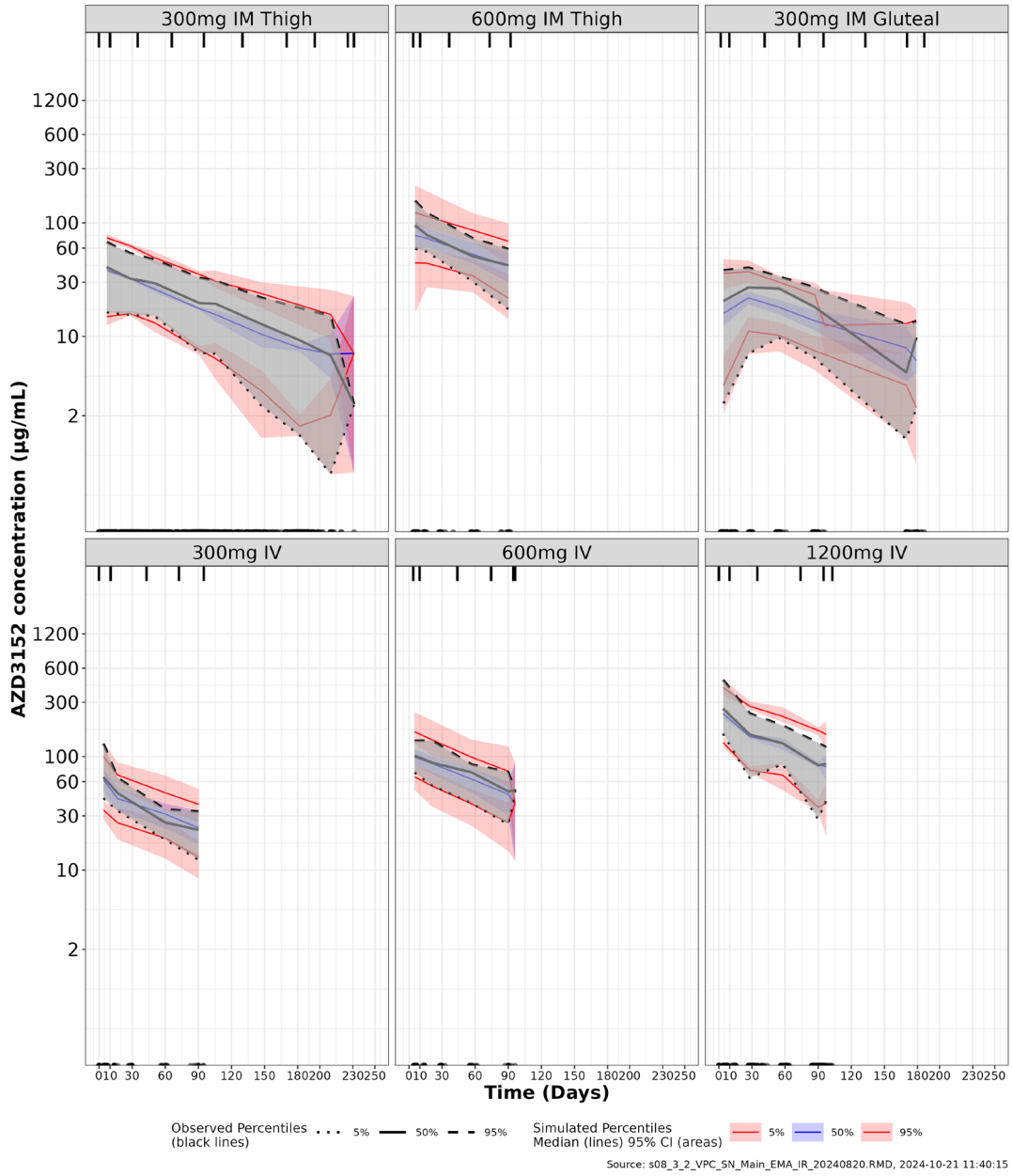


pcVPCs of sipavibart were performed with 1,000 simulated datasets using parameters from 2024 sipavibart popPK model. The upper and lower red shaded areas represent the 90% CI of the 95th percentile and 5th percentile of the predicted values with the predicted median (red solid line), respectively. The middle blue shaded area represents the 90% CI of the predicted median values with the median of the predicted median values (blue solid line).

The black dashed and dotted lines represent the respective 95th percentile and 5th percentile of the observed data. The black solid line represents the observed prediction-corrected median serum concentration.

The x-axis indicates time after dose. AZD3152 = sipavibart

Figure 3. Prediction-Corrected Visual Predictive Check: Prediction of Sipavibart Serum Concentrations, Stratified by Dose and Route of Administration



pcVPCs of sipavibart were performed with 1,000 simulated datasets using parameters from 2024 sipavibart popPK model. The upper and lower red shaded areas represent the 90% CI of the 95th percentile and 5th percentile of the predicted values with the predicted median (red solid line), respectively. The middle blue shaded area represents the 90% CI of the predicted median values with the median of the predicted median values (blue solid line).

The black dashed and dotted lines represent the respective 95th percentile and 5th percentile of the observed data. The black solid line represents the observed prediction-corrected median serum concentration. Grey shaded area represents the 90% range (5th percentile to 95th percentile) of the observed data.

The x-axis indicates time after dose. AZD3152 = sipavibart

The graphs indicate that overall, the model describe the sipavibart plasma concentration-time profiles reasonably well. It is noted that the IM Gluteal PK-profile is less well captured, however this model discrepancy is not further pursued since the recommended IM administration is in the thigh.

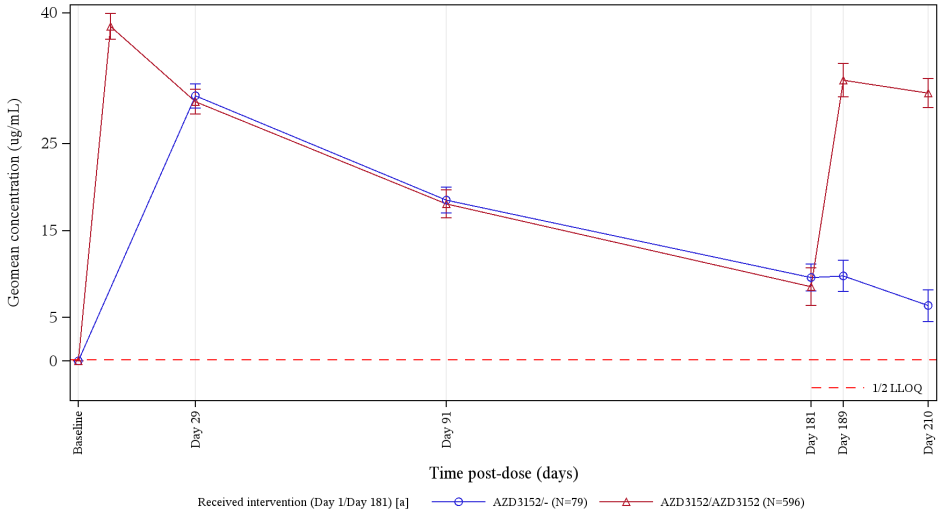
Absorption

Following a single 300 mg IM administration of sipavibart to the anterolateral thigh and the gluteal region, the geometric mean (geometric CV%) of sipavibart Cmax was 47.97 (25.23%) µg/mL and 25.44 (51.65%) µg/mL, respectively (Supernova - Sentinel Safety Cohort). The corresponding median time (range) to Cmax was 7.5 (3.9, 53) days and 52.0 (4.9, 86) days in Healthy Adult Participants in the Supernova Sentinel Safety Cohort.

Based on population PK analysis, the estimated absolute bioavailability of sipavibart following IM dose administration in the anterolateral thigh and gluteal region, is 80.7% and 62.0%, respectively.

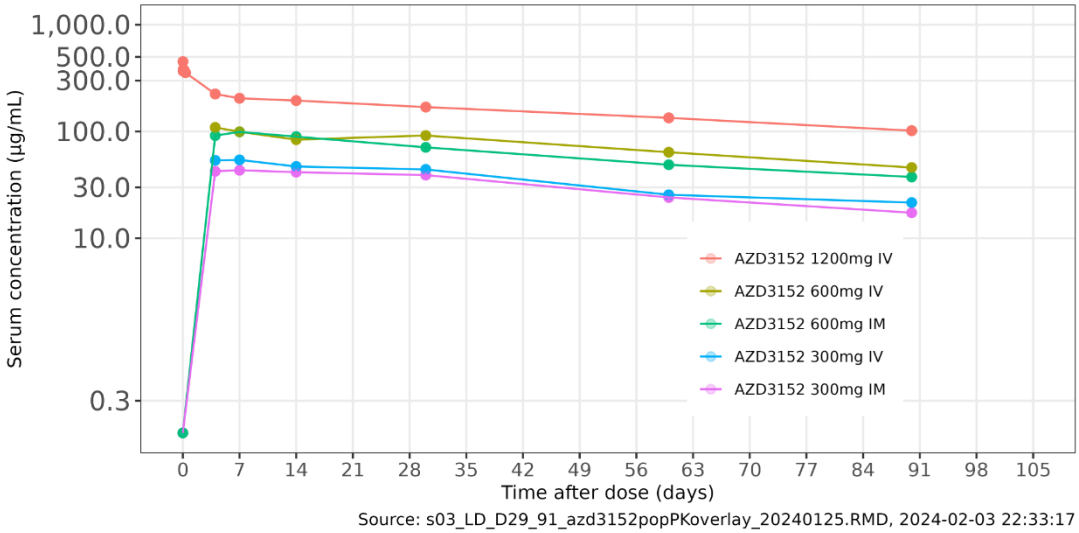
Following the first and the second dose (administered 6 months apart) of 300 mg sipavibart IM administration in the anterolateral thigh, the geometric mean (geometric CV%) serum sipavibart concentration at one-month post-individual doses was 29.81 (36.23%) µg/mL and 30.78 (54.30%) µg/mL, respectively Supernova – Main Cohort).

Figure 4. Geometric Mean (± gSD) Serum Concentration of Sipavibart (AZD3152) Over Time up to Day 210 (Linear Scale) – Main Cohort (Pharmacokinetic Set)



In order to estimate absorption parameters from IM gluteal and anterolateral thigh injections, the applicant provides data from the Little DIPPER study and from a population PK analysis, which includes all available PK data from all the sipavibart studies.

Figure 5. Geometric Mean Serum Concentration (µg/mL) of Sipavibart Over Time (semi-logarithmic scale) (PK Analysis Set), Little DIPPER.



Simulations were performed with 15 replicates per individual in the population PK dataset (all treatment arms, N = 2104), to represent the variability in the target population. The table below reports the simulated geometric mean and 90% PI values for Cmax, Tmax, and AUC0-360days in 1-year simulations of 300 mg IM (thigh) or IV single dose, every 3 months (Q3M), or every 6 months (Q6M). The second table below reports the simulated geometric mean and 90% PI values for serum concentrations at days 28, 90, 180, and 360 in 1-year simulations of 300 mg IM (thigh) or IV single dose, Q3M, or Q6M.

Table 6. Sipavibart serum exposure statistics by dosing regimen, based on simulations from the final population PK model

Treatment	Cmax [µg/mL]	AUC0-360day [µg*days/mL]	Tmax [days] (IM only)
SD IM thigh 300 mg	35.95(19.51-64.17)	4252.41(2015.63-8511.62)	7.8(2-32)
SD IV 300 mg [a]	56.42(31.75-99.41)	5281.69(2502.55-10571.5)	-
Q3M IM thigh 300 mg	36.07(19.5-64.49)	14036.35(7118.31-26617.99)	7.74(2-31)
Q3M IV 300 mg [a]	56.55(31.95-99.17)	17574.17(8954.16-33246.16)	-
Q6M IM thigh 300 mg	36.07(19.5-64.49)	7706.18(3821.7-14900.32)	7.74(2-31)
Q6M IV 300 mg[a]	56.55(31.95-99.17)	9605.46(4763.99-18531.74)	-

[a] Cmax: serum concentration at 4.8 hour from the start of infusion (first sampling timepoint).

Data presented as geometric mean (5^{th} to 95^{th} percentiles)

AUC0-360day was approximated by integrating the sipavibart concentration in the central volume over the simulation duration of 360 days, corresponding to AUClast at time point of 360 day. Simulations were conducted with a pre-dose time-point, 5 time steps per day for the first day after each dose, then 1 step per day for the next 40 days, and last timepoint day 360 post-dose. Cmax and Tmax reported for the first dose. IV infusion rate: 20 mg/min

Table 7. Sipavibart serum concentrations on days of interest by dosing regimen, based on simulations from the final population PK model

Treatment	Day 31 [a]	Day 91 [a]	Day 181 [a]	Day 361 [a]
SD IM thigh 300 mg	29.79(15.76-53.49)	17.41(8.03-33.96)	7.46(1.81-20.28)	1.36(0.07-8.87)
SD IV 300 mg	36.33(19.47-65)	20.5(8.89-41.15)	8.71(1.86-24.84)	1.57(0.07-10.93)
Q3M IM thigh 300 mg	29.86(15.71-53.76)	17.41(8.06-34.06)	25.29(10.35-53.79)	31.11(11.09-74.13)
Q3M IV 300 mg	36.41(19.41-65.18)	20.5(8.84-41.41)	29.73(11.23-65.46)	36.55(11.84-90.6)
Q6M IM thigh 300 mg	29.86(15.71-53.76)	17.41(8.06-34.06)	7.43(1.81-20.28)	9.14(1.89-28.8)
Q6M IV 300 mg	36.41(19.41-65.18)	20.5(8.84-41.41)	8.67(1.86-24.82)	10.66(1.93-35.43)

[a] Beginning of Study Day 1 corresponds to TIME=0. Thus 'Day N' corresponds to TIME=(N-1) days for the purpose of derivation of the sipavibart concentrations on selected study days

Concentrations in µg/mL. Data presented as geometric mean (5^{th} to 95^{th} percentiles)

Distribution

Estimates of the volumes of distribution pertaining to the 2-compartment linear model adopted (central Vc and peripheral Vp) have been obtained from the final popPK model developed for sipavibart and they are 4.59 L and 0.403 L respectively.

The geometric mean (geometric CV%) apparent volume of distribution for sipavibart was 6.33 (19.35%) L and 7.76 (15.72%) L following 300 mg IM administration in the anterolateral thigh and gluteal region, respectively.

Elimination

The arithmetic mean elimination t½ for sipavibart and cilgavimab were 91 days and 78 days, respectively (with gluteal administration – Supernova Sentinel Cohort)).

The arithmetic mean elimination t½ for sipavibart and cilgavimab were 87 days and 80 days, respectively (with thigh administration – Supernova Sentinel Cohort). Coefficients of variation for Cmax and AUCs ranged from 22.21% to 55.97%.

Sipavibart is not expected to be excreted intact into urine due to its large molecular size (molecular weight approximately 148 kDa), as mAbs with molecular weight > 69 kDa do not undergo renal excretion.

Due to extremely large molecular weight of Sipavibart (based on a human antibody structure) it cannot be excreted by the kidney nor can it be metabolised by the liver - drug metabolising enzymes. It can only be eliminated by intracellular enzyme degradation.

A mass balance ADME study was not conducted, because sipavibart is a human IgG mAb with known metabolism and elimination pathways based on basic pharmacology.

Dose proportionality and time dependencies

Sipavibart demonstrates an approximately dose-proportional increase in exposure as doses increase in the range of 300 mg to 600 mg for IM administration or 300 mg to 1200 mg for IV administration. At

D 14, sipavibart concentration was 42.6 µg/mL for 300 mg IM and 89.5 µg/mL for 600 mg IM (Little DIPPER).

At the time of data cut-off, no TE-ADAs had been observed in the SUPERNOVA Parent Study Sentinel Safety Cohort, Little DIPPER and SUPERNOVA Sub-study. In the SUPERNOVA Parent Study Main Cohort, the incidence of sipavibart-induced ADA responses was low (0.8%). Across studies, ADA at baseline were up to 5%. The low rate of ADA-positive participants does not allow for complete assessment of the impact of ADA on the PK or safety of sipavibart.

The reported results suggest that there is no apparent difference in serum mAb exposures in immunocompromised and immunocompetent individuals, and therefore, dosage adjustment in individuals with immunocompromised conditions is not considered necessary.

Special populations

Body weight

The body weight of participants in the pooled dataset ranged from 44.5 kg to 178 kg (mean: 84.5 kg). Body weight was included as a covariate on distribution (Vc, Vp, and Q) and elimination (CL) parameters in the population PK analysis, using fixed theoretical allometric exponents (1.0 for Vc and Vp, and 0.75 for CL and Q).

Upon request, the applicant provided boxplots for four quartiles of body weight. For the 4th quartile (143-180 kg), there is a significant decrease in AUC-180 days (ca. 40% lower than the predicted geometric mean AUC0-180days for a typical participant (80 kg). However, given limitations in the understanding of PK/PD (see below), this is not considered actionable.

Body mass index was included as a covariate on absorption rate in the population PK analysis. Subjects with a BMI ≥30 kg/m2 were found to have a 3.3% slower absorption than subjects with a BMI <30 kg/m2.

Age

Exposures to sipavibart were found to be comparable in elderly (≥ 65 years old) compared to younger adults (< 65 years old).

Table 8. Number of Participants 65 Years of Age and Older by Study and age Subgroup-PK Analysis Set

Study	Treatment	Age 65-74 years (Older participants number/ total number)	Age 75-84 years (Older participants number/ total number)	Age 85+ years (Older participants number/ total number)
SUPERNOVA - Main cohort	Sipavibart	198/677	65/677	1/677
	Evusheld and/or placebo	195/670	56/670	7/670
SUPERNOVA - Sub-study	Sipavibart	46/302	14/302	0/302
	Evusheld	20/152	10/152	0/152

Paediatric subjects

Although paediatric participants 12 to < 18 years of age were enrolled into the Main Cohort of SUPERNOVA Parent Study (n = 8 dosed with sipavibart), no PK data were collected from these

participants, as they were not among the first 1200 participants that were scheduled to have PK samples collected per study protocol specification.

Exposure-matching has been conducted as requested based 2024 sipavibart population PK model for the planned sipavibart dose regimen (300 mg IM in anterolateral thigh).

Prediction was presented for AUC 0 to 180 days, AUC 0 to 360 days, serum concentration at days 90, 180 and 360 as well as Cmax. Due to the lower body weight, and the fix dose regimen, slightly higher exposure is expected and was predicted for the adolescent subpopulation. Considering the broad safety margins of the 300 mg dose based on preclinical and available human studies, a slightly higher exposure is assumed not to result in safety problems. The presented analyses provide reassurance that no dose adjustment in the adolescent age group is necessary.

Pharmacokinetic interaction studies

Sipavibart is not renally excreted or metabolised by cytochrome P450 enzymes, therefore interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors or cytochrome P450 enzymes are unlikely. Interaction studies are neither expected nor have been reported due to the nature of this mAb.

Pharmacokinetics using human biomaterials

Not applicable

2.6.2.2. Pharmacodynamics

Mechanism of action

Sipavibart was designed to provide broad and potent coverage across Omicron and ancestral viral variants, by neutralizing spike protein interaction with the host receptor ACE2.

Primary and secondary pharmacology

Sipavibart binds to an epitope on the RBD of the SARS-CoV-2 spike protein. It binds to the BA.2 spike with nanomolar affinity (KD value of 14.81 pM). AZD3152 is capable of sterically blocking RBD interaction with the ACE2 receptor, with calculated IC50 value 0.6829 nM.

AZD3152 has been engineered with the YTE (M257Y/S259T/T261E) substitution to extend the mAb half-life, and the TM (L234F/L235E/P331S) substitution to reduce effector function through reduced human FcRn or complement component 1q (C1q) binding, which is expected to reduce potential risk of antibody dependent enhancement of infection.

The following in vitro neutralisation data has been provided. Notably, sipavibart does not retain in vitro neutralisation activity against SARS-CoV-2 subvariants containing the F456L mutation. This includes KP.2, KP.3 and LB.1 variants.

Table 9. Sipavibart Pseudovirus Neutralisation Data Against SARS-CoV-2 Variants

Lineage with spike protein substitutions		Characteristic RBD substitutions tested	Fold reduction in susceptibility [a]	IC50 (ng/mL)
Pango lineage (origin)	WHO label		Pseudovirus [b]	
BA.2 (Multiple country)	Omicron BA.2	T19I:del24-26:A27S:G142D:V213G: G339D:S371F:S373P:S375F:T376A: D405N:R408S:K417N:N440K:S477N:T478K:E484A:Q493R:Q498R:N501Y:Y505H:D614G:H655Y:N679K:P681H:N764K:D796Y:Q954H:N969K	0.8	10.7
BA.4/5 (Multiple country)	Omicron BA.4/5	T19I:del24-26:A27S:del69-70:G142D: V213G:G339D:S371F:S373P:S375F: T376A:D405N:R408S:K417N:N440K:L452R:S477N:T478K:E484A:F486V: Q498R:N501Y:Y505H:D614G:H655Y:N679K:P681H:N764K:D796Y:Q954H:N969K	0.4	4.7
BQ.1 (Nigeria)	Omicron BQ.1	T19I:del24-26:A27S:del69-70:G142D: V213G:G339D:S371F:S373P:S375F: T376A:D405N:R408S:K417N:N440K:K444T:L452R:N460K:S477N:T478K: E484A:F486V:Q498R:N501Y:Y505H:D614G:H655Y:N679K:P681H:N764K:D796Y:Q954H:N969K	0.9	11.6
BQ.1.1 (Multiple country)	Omicron BQ.1.1	T19I:del24-26:A27S:del69-70:G142D: V213G:G339D:R346T:S371F:S373P: S375F:T376A:D405N:R408S:K417N: N440K:K444T:L452R:N460K:S477N: T478K:E484A:F486V:Q498R:N501Y:Y505H:D614G:H655Y:N679K:P681H:N764K:D796Y:Q954H:N969K	0.7	9.2
XBB (Multiple country)	Omicron XBB	T19I:del24-26:A27S:V83A:G142D: Y144-:H146Q:Q183E:V213E:G339H: R346T:L368I:S371F:S373P:S375F: T376A:D405N:R408S:K417N:N440K:V445P:G446S:N460K:S477N:T478K: E484A:F486S:F490S:Q498R:N501Y: Y505H:D614G:H655Y:N679K:P681H:N764K:D796Y:Q954H:N969K	0.3	3.8
XBB.1 (Multiple country)	Omicron XBB.1	T19I:del24-26:A27S:V83A:G142D: Y144-:H146Q:Q183E:V213E:G252V: G339H:R346T:L368I:S371F:S373P: S375F:T376A:D405N:R408S:K417N: N440K:V445P:G446S:N460K:S477N: T478K:E484A:F486S:F490S:Q498R: N501Y:Y505H:D614G:H655Y:N679K:P681H:N764K:D796Y:Q954H:N969K	0.3	3.6
XBB.1.5/ XBB.1.9 (Multiple country)	Omicron XBB.1.5/ XBB.1.9	T19I:L24S:del25-27:V83A:G142D: del144:H146Q:Q183E:V213E:G252V:G339H:R346T:L368I:S371F:S373P: S375F:T376A:D405N:R408S:K417N: N440K:V445P:G446S:N460K:S477N: T478K:E484A:S486P:F490S:Q498R: N501Y:Y505H:D614G:H655Y:N679K:P681H:N764K:D796Y:Q954H:N969K	0.4	5.8
XBB.1.16 (India)	Omicron XBB.1.16	T19I:del24-26:A27S:V83A:G142D: Y144-:H146Q:E180V:Q183E:V213E: G252V:G339H:R346T:L368I:S371F: S373P:S375F:T376A:D405N:R408S: K417N:N440K:V445P:G446S:N460K:S477N:T478R,E484A:F486P:F490S: Q498R:N501Y:Y505H:D614G:H655Y:N679K:P681H:N764K:D796Y:Q954H:N969	0.1	1.3
XBB.2.3 (Multiple country)	Omicron XBB.2.3	T19I:L24-:P25-:P26-:A27S:V83A: G142D:Y144-:H146Q:Q183E:V213E: D253G:G339H:R346T:L368I:S371F: S373P:S375F:T376A:D405N:R408S: K417N:N440K:V445P:G446S:N460K:S477N:T478K:E484A:F486P:F490S: Q498R:N501Y:Y505H:P521S:D614G:H655Y:N679K:P681H:N764K:D796Y:Q954H:N969K	0.3	3.4

Table 9. Sipavibart Pseudovirus Neutralisation Data Against SARS-CoV-2 Variants

Lineage with spike protein substitutions		Characteristic RBD substitutions tested	Fold reduction in susceptibility [a]	IC50 (ng/mL)
Pango lineage (origin)	WHO label		Pseudovirus [b]	
XBB.1.5.10/EG.5 (Multiple country)	Omicron XBB.1.5.10/EG.5	XBB.1.5 + F456L	> 50-fold	> 1000 [c]
EG.5.1 (Multiple country)	Omicron EG.5.1	XBB.1.5 + Q52H + F456L	> 50-fold	> 1000 [c]
BA.2.86 [d] (Multiple country)	Omicron BA.2.86	T19I:R21T:L24-:P25-:P26-:A27S: S50L:H69-:V70-:V127F:G142D:Y144-: F157S:R158G:N211-:L212I:V213G: L216F:H245N:A264D:I332V:G339H: K356T:S371F:S373P:S375F:T376A: R403K:D405N:R408S:K417N:N440K:V445H:G446S:N450D:L452W:N460K:S477N:T478K:N481K:V483-:E484K: F486P:Q498R:N501Y:Y505H:E554K:A570V:D614G:P621S:H655Y:I670V: N679K:P681R:N764K:D796Y:S939F: Q954H:N969K:P1143L	0.3	3.8
JN.1 (Multiple country)	Omicron (JN.1)	T19I:R21T:L24-:P25-:P26-: A27S:S50L:H69-:V70-: V127F:G142D:Y144-:F157S: R158G:N211-:L212I:V213G: L216F:H245N:A264D:I332V: G339H:K356T:S371F:S373P: S375F:T376A:R403K:D405N: R408S:K417N:N440K:V445H: G446S:N450D:L452W:L455S: N460K:S477N:T478K:N481K:V483-:E484K:F486P:Q498R: N501Y:Y505H:E554K:A570V: D614G:P621S:H655Y:I670V: N679K:P681R:N764K:D796Y: S939F:Q954H:N969K:P1143L	6.2	83.1

a Range of reduced in vitro potency across multiple sets of co-occurring substitutions and/or testing labs using research-grade assays; mean fold change in half maximal inhibitory concentration (IC50) of monoclonal antibody required for a 50% reduction in infection compared to ancestral reference strain.
b Pseudoviruses expressing the entire SARS-CoV-2 spike variant protein and individual characteristic spike substitutions.
c Sipavibart is unlikely to be active against this variant.
d BA.2.86 includes BA.2.86, BA.2.86.1, JN.2 and JN.3, which have the same SARS-CoV-2 spike protein sequence.

Observed SARS-CoV-2 nAb Titres

Table 10. SARS-CoV-2 Adjusted Neutralizing Antibodies (1/Dilution) Over Time by Variant in Participants Receiving a Single Dose of Sipavibart - Main Cohort (SARS-CoV-2 nAb Set)

	Baseline	Day 29		Day 91	
Variant	GMT	GMT	Fold rise [b]	GMT	Fold rise [b]
Alpha/B.1.1.7					
n	682	642	631	480	470
Adj geomean [a]	2490.36	6272.56	2.50	4317.67	1.62
95% CI [a]	NC, NC	5668.89, 6940.51	2.26, 2.77	3793.19, 4914.67	1.42, 1.84
BA.2					
n	664	641	616	476	457

Variant	Baseline	Day 29		Day 91	
	GMT	GMT	Fold rise [b]	GMT	Fold rise [b]
Adj geomean [a]	900.89	2882.78	3.15	2533.72	2.54
95% CI [a]	NC, NC	2605.79, 3189.22	2.85, 3.49	2221.92, 2889.28	2.22, 2.89
BA.4/5					
n	655	641	606	477	448
Adj geomean [a]	694.17	4096.70	5.78	3134.33	4.02
95% CI [a]	NC, NC	3702.42, 4532.97	5.23, 6.40	2727.35, 3602.04	3.50, 4.63
XBB.1.5					
n	604	633	551	424	363
Adj geomean [a]	146.52	2545.10	16.79	1877.28	12.02
95% CI [a]	NC, NC	2248.90, 2880.30	14.83, 19.00	1569.14, 2245.93	10.04, 14.38

a The point estimate and 95% CI of the geometric means are calculated from an ANCOVA of the log-transformed value of the titres and fold rises, including baseline nAb concentrations on the log-scale, age (< 65 years, ≥ 65 years), and Coronavirus disease 2019 (COVID-19) vaccination and SARS-CoV-2 infection prior to randomisation, as fixed effects. Only participants with non-missing covariates are included in the analysis.
b The fold rise is calculated for participants with a titre result at baseline and at the relevant time point. Post baseline assessments include assessments after the first dose of the investigational product up to the second dose or the scheduled Day 181 pre-dose visit if the second dose was missed

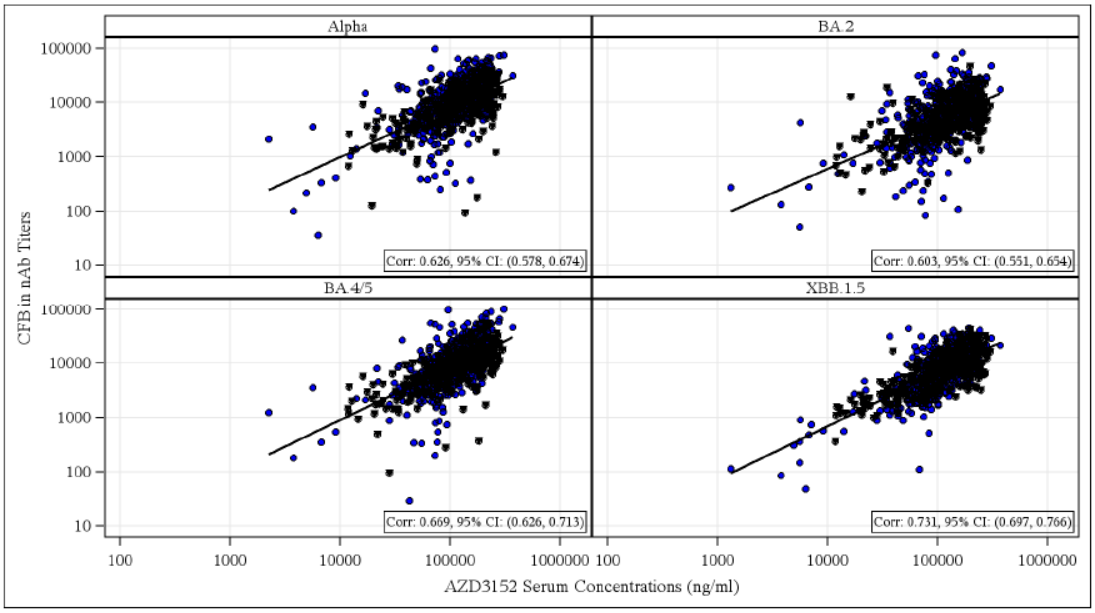
titres below the LLOQ are imputed to half of the LLOQ. titres above the ULOQ are imputed to the ULOQ (787339). Geomean is calculated as the antilogarithm transformation of the mean of the log10-transformed titre. Baseline is the last non-missing measurement taken on or before the first dose of IMP.

SARS-CoV-2 nAb titers in pseudovirus assays from study SUPERNOVA were not presented for JN.1 + subvariants or for variants carrying F456L mutations.

Relationship between plasma concentration and effect

Correlation Between mAb Serum Concentration and Change from Baseline in Observed SARS-CoV-2 nAb titres

Figure 6. Correlation Plot of Sipavibart Serum Concentrations vs Change from Baseline nAb titres Among Participants Receiving Sipavibart in SUPERNOVA Sub-study and Little DIPPER (PK/SARS-CoV-2 nAb Analysis Set



Note: Includes post-dose assessments on Study Day 29 and 91 from SUPERNOVA Sub-study (Blue filled circle) and Study Day 5, 8, 31, and 91 from Little DIPPER (Black filed upside-down triangle) when available.
The correlation coefficient estimate for the repeated measurement data are calculated following the methods by Hamlett et al 2004, accommodating for instances where data pairs are not simultaneously available at each timepoint, and the 95% CI for the correlation coefficient was estimated using the normal approximation method by Shen and Lu 2006.
A simple linear regression model was fit to the data to generate the regression line shown.
Post-baseline SARS-CoV-2 nAb titre measurements or serum PK concentration measurements reported as either (1) below the LLOQ or (2) above the ULOQ had this measurement excluded from the analysis.
Source: IEMT 15, Figures 1.1, 1.2, 1.3 and 1.4,

In overall assessment of available data from Little DIPPER and SUPERNOVA studies, sipavibart serum concentrations did at least moderately correlate with neutralizing antibody titres analysed in pseudovirus assay.

For individuals who received sipavibart but went on to get a symptomatic COVID-19 infection nonetheless, their nAb titre values against the XBB.1.5 variant were shown compared to individuals who received sipavibart but did not get an infection. There were no meaningful differences in titre values against the XBB.1.5 variant between these 2 groups. Thus, given the available information, titre level archived in humans seems not to correlate with efficacy against breakthrough infections – infections occurred also in patients with high titre level infected with variants susceptible for sipavibart in pseudovirus assay.

Exposure-response analyses for efficacy

An understanding of what quotient of plasma concentration over SARS-Cov-2 variant IC50 is required for protection against symptomatic disease, is required to inform labelling regarding proper use in the following respects:

a) What variants are susceptible to sipavibart?

b) What is the duration of protection against susceptible variants?

c) Under what epidemiological conditions might Kavigale be used?

d) If relevant, when might a second dose be given?

Another way of phrasing this question, is what neutralising titre is required for protection?

To address this, the applicant provided an M&S exercise based on PROVENT data (from the registrational study for Evusheld), to which SUPERNOVA data are added.

The model describes % protection as a function of "prevalence-adjusted nAb titres". Placebo nAb titres were imputed to zero.

A Cox model treating prevalence-adjusted nAb titres as a time-dependent covariate was then fit for time to RT-PCR--confirmed symptomatic COVID-19 through day 366, adjusted for treatment and its interaction with the time-dependent predictor X(t) defined as log10(prevalence adjusted titres + 1).

Participant-level data were bootstrapped 1,000 times and the model was fit for each bootstrap sample. The quantile approach was used to estimate the one-sided 95% confidence interval (CI).

So called "prevalence adjusted Nab titres" were imputed as follows:

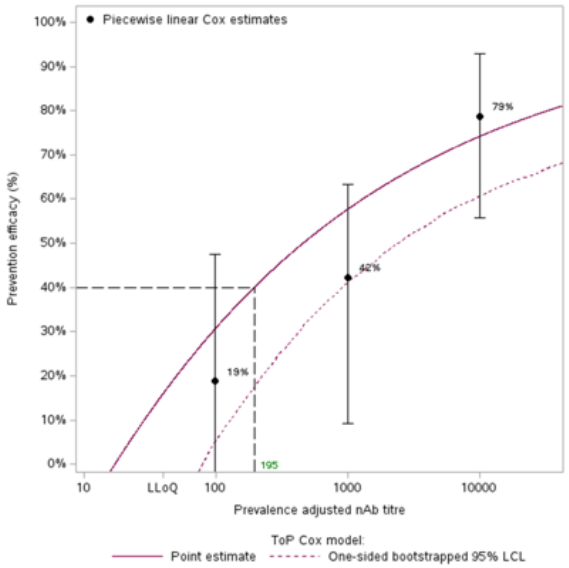
SARS-CoV-2 genomic sequencing data from GISAID database was used to infer region-specific variant prevalence of SARS-CoV-2 by calendar date. Variants with at least 5% prevalence were included.

Where the IC50 values were unable to be determined in vitro due to reduced binding of sipavibart to the spike protein, the values were imputed to 1,000, which is the upper limit of pseudovirus neutralisation assay.

Variant prevalence data were combined with individual-level predicted nAb titre data by country and calendar date.

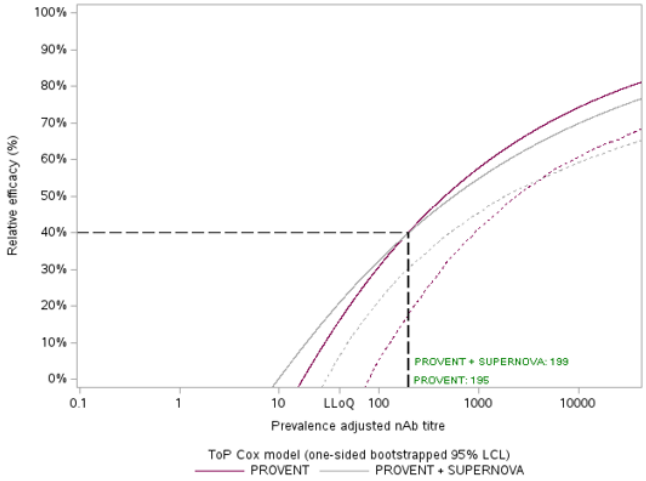
For each participant and day, a prevalence-adjusted nAb titre level was calculated as a weighted geometric mean of predicted nAb titres, based on regional variant prevalence (country-level).

The following graph portrays Cox Model Estimates of Efficacy as a Function of Prevalence-Adjusted nAb titres from the PROVENT study for Evusheld.



The solid line gives the point estimate from the model showing the change in efficacy as a function of prevalence adjusted nAb titre level. The dotted line shows the lower bound of the confidence interval. Black points represent point estimates from a piecewise linear Cox model. Error limits on point estimates from the piecewise linear Cox model correspond to 95% bootstrapped confidence intervals. The model indicates that a threshold of 195 corresponds with 40% efficacy (approximately the level of protection conferred over 3 months against JN.1)

Below is a comparison of Cox Model Estimates of Efficacy as a Function of Prevalence-Adjusted nAb titres in the PROVENT study versus the addition of SUPERNOVA data to the PROVENT study model.



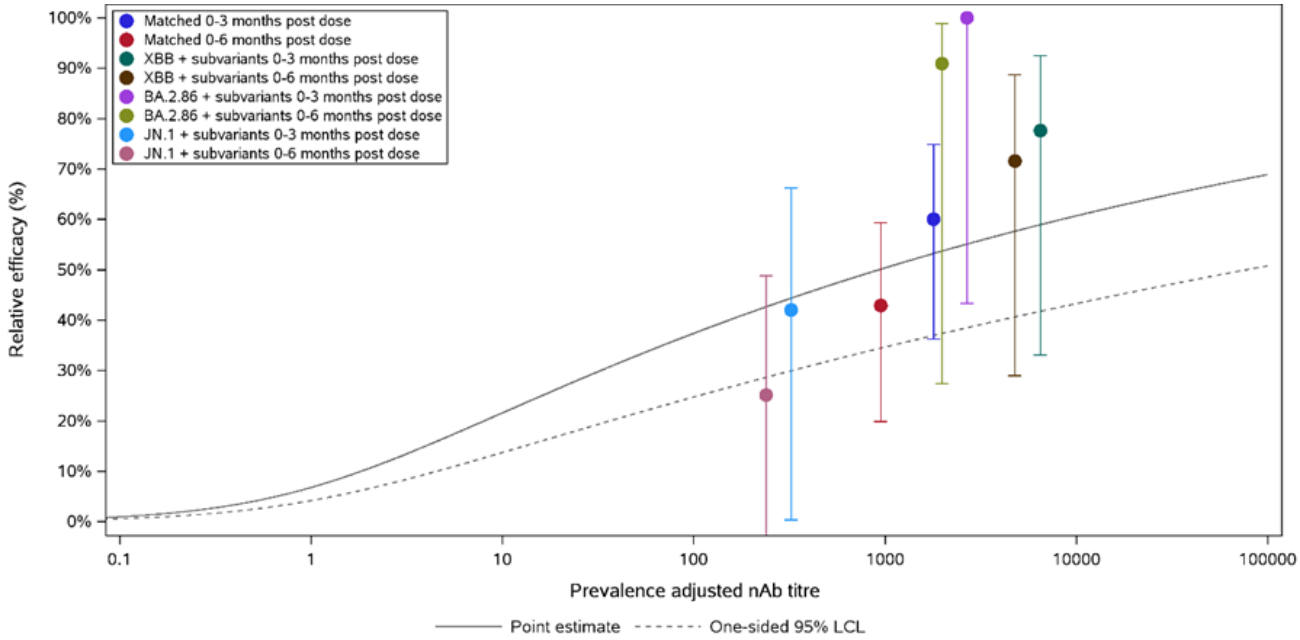
The solid lines represent the point estimate from each model (PROVENT – purple; PROVENT and SUPERNOVA – grey) showing the change in efficacy as a function of prevalence adjusted nAb titre level. The dotted lines show the lower bound of the confidence intervals for each model. The PROVENT only model indicates that a threshold of 195 corresponds with 40% efficacy. The updated model incorporating data form both PROVENT and SUPERNOVA indicates that a threshold of 199 corresponds with 40% efficacy

The modelling presumes similar PK/PD in the PROVENT and SUPERNOVA studies. Caveats to this include viruses with different pathogenic features (pre-omicron/omicron) and different study populations (immunocompetent at elevated risk/immunocompromised. Thus, the appropriateness of this dataset pooling remains subject to doubt.

As anticipated, the exclusion of F456L variants in the determination of Nab-titres as well as F456L events, results in a right-shift of the Nab-titre/protection curve, indicating that higher titres are required to produce the same protection.

Modelling based on SUPERNOVA alone resulted in the following prediction:

Figure 7. ToP Cox Model Estimates of Efficacy as a Function of Prevalence-Adjusted nAb titres – SUPERNOVA (excluding F456L variants)



The solid line gives the point estimate from the model showing the change in efficacy as a function of prevalence adjusted nAb titre level. The dotted line shows the lower bound of the confidence interval produced from the quantiles of 1,000 bootstrapped samples. Coloured points represent point estimates from the supernova matched analysis (IEMT 26). For XBB + subvariants an IC50 of 4.15 ng/ml is assumed, calculated as the average of known IC50s from XBB subvariants.

Investigation of anti-drug antibodies

Table 11. Anti-drug Antibody (ADA) Responses to Sipavibart– Main Cohort (Sipavibart ADA Set)

ADA Category	Statistic	Received Intervention (Day 1/Day 181) [a]	
		Sipavibart/Sipavibart (N = 545)	Sipavibart/- (N = 59)
ADA-positive at any visit (ADA prevalence)	n (%)	28 (5.1)	1 (1.7)
	Median of maximum titre	200.0	200.0
	Min of maximum titre, max	100, 800	200, 200
	Q1, Q3	100.0, 400.0	200.0, 200.0
TE-ADA-positive (ADA incidence)	n (%)	4 (0.7)	1 (1.7)
	Median of maximum titre	200.0	200.0
	Min of maximum titre, max	200, 400	200, 200
	Q1, Q3	200.0, 300.0	200.0, 200.0
Non-TE-ADA-positive	n (%)	24 (4.4)	0 (0)
	Median of maximum titre	200.0	NA
	Min of maximum titre, max	100, 1600	NA
	Q1, Q3	100.0, 400.0	NA

a 'Received intervention (Day 1/Day 181)': The terms before and after the slash refer to actually received interventions for Day 1 and Day 181. '-' signifies that the participant had not received a second dose of sipavibart as of the data cut-off. ADA categories are defined in the SAP.

Summary statistics are calculated based on the maximum post-baseline titres for each ADA-positive participant within each group, except for the following categories: 'ADA-positive at baseline and not detected post-baseline' is based on the maximum titre at baseline only, and 'Non-TE-ADA positive' is based on the maximum titre at baseline or post-baseline.

Post-baseline assessments include assessments after the first dose of the investigational product. Baseline is the last non-missing measurement taken on or before the first IMP dose.

Treatment-emergent ADA-positive (TE-ADA+): Either treatment-induced ADA or treatment-boosted ADA in the particular ADA analysis set. The percentage is known as ADA incidence.

- Treatment-induced ADA-positive: ADA-negative at baseline and ADA-positive for at least one post-baseline assessment with ADA titre ≥ 200 for AZD3152.
- Treatment-boosted ADA-positive: Baseline-positive ADA titre boosted to ≥ 4-fold during the study period

The company was asked and agreed to provide as soon as available:

- An analysis of outstanding ADA samples (including day 360 p.a.) as well as analysis of neutralising antibodies (REC).
- Results of nADA assay validation as well as of analysis on neutralizing activity on ADA-positive samples from the main cohort of the SUPERNOVA parent study (Q2 2025)

2.6.3. Discussion on clinical pharmacology

The pivotal study Supernova main cohort was conducted using IM administration in the anterolateral thigh. In the SmPC, the applicant includes the intravenous route as well. For this, data are available from the Little DIPPER study and from the Supernova sub-study, and a comparison of exposure has been conducted in the popPK analysis. The comparison indicates that exposure is consistently similar and somewhat higher after IV as compared to IM in the anterolateral thigh. As there is sufficient safety data available (IV tolerated up to 1200 mg), this is considered to support the IV route at the same dose.

A single bioanalytical method has been developed and validated for the analysis of AZD3152 (sipavibart, Kavigale), AZD1061 (cilgavimab, compound in Evusheld), and AZD8895 (tixagevimab, compound in Evusheld) in human serum. Acceptance criteria required for ligand binding assays by 'ICH guideline M10 on bioanalytical method validation and study sample analyses were applied, which can be accepted for the present Hybrid LBA-LCMS assays. Overall, the method is applicable to quantitation within nominal concentration ranges of 0.300 to 30.0 µg/mL for AZD3152, AZD1061, and AZD8895.

ADA assays: A 3-tiered approach comprising a screening assay followed by a confirmatory assay and the analysis of anti-AZD3152 (sipavibart) antibody titre was developed and validated. A bridging ECL assay was applied. Relevant assay performance parameters were investigated. Overall, the assays seem suitable for its intended purpose. An analysis of outstanding ADA samples (including day 360 p.a.) as well as neutralising antibodies will be provided as soon as available.

IM injection to the gluteus has been used as well, but less data is available, and they indicate a lower exposure when that injection site is used. Thus, injection should only be prescribed in the anterolateral thigh.

The metabolism of sipavibart is similar to that of large peptide molecules – it is degraded into small peptides and amino acids via intracellular protein catabolism by lysosomal degradation, in the same manner as endogenous IgG antibodies.

The estimated absolute bioavailability of sipavibart was 80.7% following IM administration to the anterolateral thigh. IM administration to the anterolateral thigh led to faster absorption and higher bioavailability compared to administration in the gluteal region. Exposure (AUCinf) following thigh administration was approximately 19% higher compared to the gluteal injection. The change in infusion time from 6 minutes to 20 or 60 minutes is not expected to affect the efficacy or safety profile of sipavibart.

The parameter estimates seem reliable and provide insight into the PK characteristics of sipavibart.

A difference in the apparent volume of distribution for sipavibart following IM administration of 300 mg in the anterolateral thigh and gluteal region was minimal and probably not significant.

Following the same 300 mg dose administration to the thigh, exposure to sipavibart and cilgavimab (component of Evusheld), as reflected by geometric mean Cmax and AUCs, were very similar. Variability in exposures was also similar. The t1/2 values were approximately similar for sipavibart and cilgavimab (difference of 13 days).

Sipavibart was designed to provide broad coverage across Omicron and ancestral viral variants through the same mechanism of action as Evusheld, by neutralizing spike protein interaction with the host receptor ACE2, but with improved breadth of coverage. Sipavibart has been engineered using the same antibody scaffold as Evusheld; similar to Evusheld, sipavibart contains the YTE substitution to extend the mAb half-life and TM substitution, which reduces effector function through reduced human FcγR or C1q binding, reducing the potential risk of ADE of disease or ADE of infection. Also similar to Evusheld,

sipavibart binds to the RBD of the SARS-CoV-2 spike protein for neutralisation of the virus but recognises a different spike protein epitope than that recognised by Evusheld.

Notably, sipavibart does not retain in vitro neutralisation activity against SARS-CoV-2 subvariants containing the F456L mutation. This includes KP.2, KP.3 and LB.1 variants (see also section discussion and conclusion in clinical efficacy).

The applicant's approach to modelling the PK/PD relation has been described above. Notably, a common Emax model plotting a steady state plasma concentration over IC50 as dependent variable does not work due to the time-dependency of plasma concentrations as well as IC50 in SUPERNOVA. Notably, events indicate the failure of a Nab-titre. There are no data illustrating the success of a Nab-titre. Therefore, the rationale for the applicant's approach (prevalence adjusted Nab-titres) is agreed. That said, the estimations of duration of protection as well as threshold of IC50 over which efficacy can be expected are derived by combining several data sources and assumptions with underlying uncertainties.

Moreover, this is based on hypothetical IC50's of non-existing viral strains, as the actual viruses in the SUPERNOVA study had IC50s that were either <15 ng/mL OR 83.1 ng/mL OR >1,000 ng/mL. Thus, a considerable portion of the (Nab titre / % protection) curves correspond to no empirical facts. Also, there is no support from the PROVENT study of efficacy against viruses with IC50 above 15 ng/mL.

By excluding F456L variants from the determination of prevalence-adjusted Nab-titres as well as the outcome, it was shown that the imputation of IC50 to 1,000 ng/mL for F456L, given an observed protection rate of 30% results in an under-estimation of the titre required for a given level of protection. Further, it is not clear that the assumption of similar PK/PD in the PROVENT and SUPERNOVA experience can be assumed, given viruses with different cellular tropism (pre-omicron versus omicron), the different clinical presentation of omicron disease, as well as the different patient populations (immunocompetent versus immunocompromised).

It is also noted that confidence limits for predictions are wide, indicating uncertainty and sensitivity to assumptions.

In summary, the proposed threshold for protection is not reliably estimated. Notably, observed data are compatible with no clinically relevant protection at any time against a virus with an IC50 of 80 ng/mL. An agreement on a language in the SmPC appropriately describing all these uncertainties was requested and implemented.

The following statement on "antiviral resistance" is included in section 4.4 of the SmPC:

Sipavibart was designed to be effective against early omicron strains, with pseudovirus neutralisation IC_{50} values ranging from 3.6 ng/ml (XBB.1 variant) to 25.0 ng/ml (BA.2.75 variant). The extent and duration of protective efficacy against viruses with moderately increased IC_{50} (e.g. JN.1, IC_{50} 83.1 ng/ml) is reduced and the clinical relevance of any prophylactic effect unclear. Due to the absence of in vitro neutralising activity, sipavibart is not anticipated to provide any protection against symptomatic COVID-19 due to viral variants containing F456L mutations in the spike protein (see section 5.1).

2.6.4. Conclusions on clinical pharmacology

The PK of sipavibart is generally well described, however, the PK/PD relation has not been adequately described to support appropriate use with respect to what variants are anticipated to be neutralised, and what is the duration of protection against these variants after a single dose.

In summary, despite best efforts, modelling of the complex situation of viral evolution across the PROVENT and SUPERNOVA studies do not result in estimations that are sufficiently reliable to support

labelling language on protection against viruses with higher IC50 than those sipavibart was designed to provide efficacy against, nor the anticipated duration of protection of a given dose.

On the other hand, sipavibart shows effective in vitro neutralisation of early omicron variants but does not neutralise viruses carrying the F456L mutation.

Therefore, an agreement on a language in the SmPC appropriately describing all these uncertainties was requested and implemented prior to approval.

Clinical pharmacology recommendations:

An analysis of outstanding ADA samples (including day 360 p.a.) as well as analysis of neutralising antibodies should be provided as soon as available (Q2 2025) (REC).

Results of nADA assay validation as well as of analysis on neutralizing activity on ADA-positive samples from the main cohort of the SUPERNOVA parent study should be provided as soon as available (Q2 2025) (REC).

2.6.5. Clinical efficacy

The following table outlines the key studies of the clinical study programme. The SUPERNOVA Main Cohort is pivotal to this application.

Study/Phase		Population	Success Criteria	Dose/Route of Sipavibart and Number of Participants Exposed [a]	Comparator	Countries
SUPERNOVA Parent Study	Main Cohort (Phase III)	Participants with negative rapid antigen test prior to dosing at Visit 1 who were ≥ 12 years of age and ≥ 40 kg with conditions causing immune impairment	Prevention of symptomatic COVID-19 caused by any SARS-CoV-2 variant or Prevention of symptomatic COVID-19 attributable to non-F456L-containing variants	300 mg IM (n = 1671) Evusheld [c] 300 mg IM (n = 1102) Placebo [c] IM (n = 561)	Evusheld and/or placebo	Australia, Belgium, Canada, Denmark, France, Germany, Israel, Malaysia, Poland, Singapore, Spain, South Korea, Taiwan, Thailand, United Arab Emirates, United Kingdom, United States, Vietnam
	Sentinel Safety Cohort (Phase I)	Healthy adults 18 to 55 years of age, weighing 45 to 110 kg (inclusive)	Safety	300 mg IM [b] (n = 41) Placebo IM (n = 16)	Placebo	United States and United Kingdom

Study/Phase	Population	Success Criteria	Dose/Route of Sipavibart and Number of Participants Exposed [a]	Comparator	Countries
Little DIPPER (Phase I)	Healthy adults, 18 to 55 years of age, weighing 45 to 110 kg (inclusive)	Safety, pharmacokinetics	300 mg IM (n = 10) 300 mg IV (n = 10) 600 mg IM (n = 10) 600 mg IV (n = 10) 1200 mg IV (n = 40) Placebo IM (n = 4) Placebo IV (n = 12)	Placebo	United States
SUPERNOVA Sub-study (Phase II)	Immuno-compromised or immuno-competent adults (including healthy) ≥ 18 years of age, weighing ≥ 40 kg	Safety, predicted nAb response compared to Evusheld	1200 mg IV (n = 310) Evusheld 300 mg IM (n = 158) *2 participants crossed over from Evusheld to sipavibart on Study Day 29	Evusheld	United States

[a] Numbers of participants exposed to the IMP (i.e., those in the safety analysis set)

[b] Administered in combination with cilgavimab 300 mg IM (as AZD5156)

[c] Participants who received any dose of Evusheld are counted as 'Evusheld' (i.e., those who received Evusheld as their first dose and placebo as their second dose), while those that only received placebo are counted as 'Placebo'.

2.6.5.1. Dose response studies

While there were studies of dose-exposure and safety, there were no studies specifically evaluating the relation between dose and antiviral response or efficacy.

The 600 mg dose of AZD5156 for administration in the Sentinel Safety Cohort was selected based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for Evusheld. Similar PK for AZD5156 and Evusheld have been observed in human FcRn transgenic mice and non-human primates.

Based upon population PK modelling, and assuming the same PK and partitioning into the nasal lining fluid as Evusheld (1.8%), 600 mg of AZD5156 was predicted to maintain nasal lining fluid concentrations of AZD5156 above the IC80 for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

As the AZD5156 600 mg dose comprises sipavibart 300 mg and cilgavimab 300 mg, sipavibart 300 mg was used as the dose in the Main Cohort. A 300 mg dose of sipavibart was predicted to maintain nasal lining fluid concentrations of sipavibart above the IC80 for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

2.6.5.2. Main study

Supernova Main Cohort (D7000C00001)

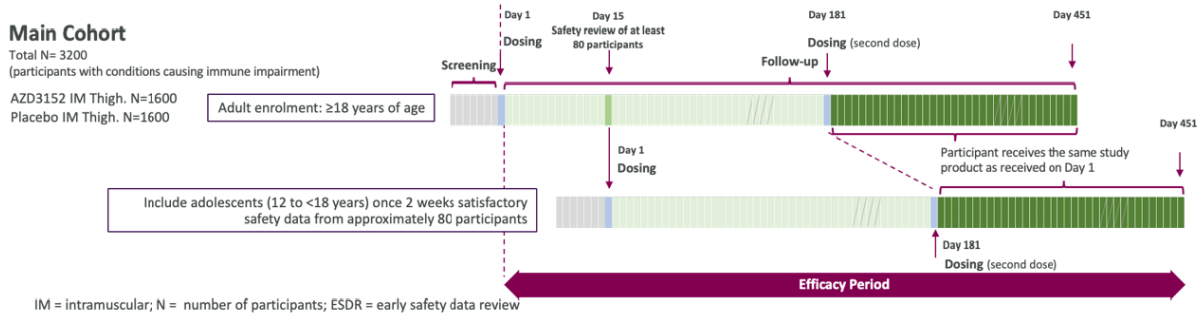
Methods

Table 12. Overview of SUPERNOVA (Study D7000C00001) Main Cohort

Study Number (Acronym) Phase/Sponsor/Countries/CSP	Design/Primary endpoints/IMP	Population/Dose Planned/ No of participants	Duration	Status
D7000C00001 (SUPERNOVA)/Phase III (Main Cohort)/AstraZeneca Australia, Belgium, Canada, Denmark, France, Germany, Israel, Malaysia, Poland, Singapore, South Korea, Spain, Taiwan, Thailand, United Arab Emirates, United Kingdom, United States, Vietnam	Phase III randomised, double-blind study of pre-exposure prophylaxis Demonstrate safety, efficacy, and neutralizing activity of sipavibart in adults and adolescents 12 years of age or older IMP: sipavibart and Evusheld/placebo [a]	12 years of age and older, conditions causing immune impairment; weight ≥ 40 kg, negative SARS-CoV-2 rapid antigen test at randomisation Route = IM Sipavibart 300 mg (N = 1671) or control [a] (N = 1663)	~15 months from first dose of IMP.	Start Date: 31 March 2023 Primary Analysis: the Primary Analysis was triggered when the median follow-up time was greater than 181 days in the SARS-CoV-2-Negative Set and the required number of events was observed for the dual primary endpoints to support the primary efficacy and safety objectives. Clinical data cut-off for the Primary Analysis was 29 March 2024

[c] Prior to implementation of CSP version 7.0, the comparator was Evusheld 300 mg and after implementation the comparator was placebo.

Figure 8. Study Design – Main Cohort



Dosing was staggered, so that no adolescent participants were dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (including at least 40 participants who received sipavibart) were reviewed.
The placebo arm includes participants that were dosed with EVUSHELD prior to the implementation of CSP version 7.0.

Study Participants

Key inclusion criteria were the following:

Participant must be 12 years of age or older at the time of signing the informed consent.

Negative rapid antigen test prior to dosing at Visit 1.

Weight ≥ 40 kg at screening.

Participants must satisfy at least one of the following risk factors at enrolment:

• Have solid tumour 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 within 2 years and/or

− Had a hematopoietic stem cell transplant within 2 years and/or

− Who have chronic graft-versus-host disease

− Participants who previously had a solid organ transplant or hematopoietic stem cell transplant more than 2 years prior to Visit 1 may also be eligible based on the inclusion criterion for immunosuppressive treatment

• Are actively taking immunosuppressive medicines (eg, are using corticosteroids [i.e., ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks]), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive (eg, Bruton's tyrosine kinase inhibitors), tumour-necrosis blockers, or other immunosuppressive biologic agents (eg, for rheumatic diseases)

• Received chimeric antigen receptor T-cell therapy

• Within one year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)

• Have a moderate or severe primary (eg, DiGeorge syndrome) or secondary (eg, haemodialysis) immunodeficiency

• Advanced or untreated HIV infection (people with HIV and CD4 cell counts < 200/mm3 within 6 months of Visit 1, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)

Medically stable defined as disease not requiring significant change in maintenance therapy or hospitalisation for worsening disease or any recent CV event (eg, acute myocardial infarction, thromboembolic event) during the one month prior to enrolment, with no acute change in condition at the time of study enrolment.

Key exclusion criteria included:

Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence.

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

Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

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

Receipt of a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1.

COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

Treatments

Participants in the main cohort were randomised 1:1 to receive sipavibart 300 mg or comparator administered IM in the anterolateral thigh on Day 1.

To allow for immunobridging, the comparator for the main cohort was Evusheld 300 mg i.m prior to CSP version 7.0. At the request of regulatory authorities, a separate immunobridging sub-study was added as an Addendum to the SUPERNOVA study. As a result, the immunobridging endpoint was removed from the main cohort component of the study, the secondary efficacy endpoint became a primary endpoint, and the comparator was changed to placebo.

Participants are to receive a second dose of their original randomised study intervention (i.e., active treatment or comparator) 6 months after the first dose and are to be followed for approximately 15 months from when the first dose was administered.

While participants randomised to comparator could have received either Evusheld or placebo as a first dose, no participant had reached Day 181 before implementation of CSP version 7.0 and, therefore, no participant received Evusheld as a second dose.

Objectives

The study had dual primary objectives:

1. to compare the efficacy of sipavibart to Evusheld and/or placebo in the prevention of symptomatic COVID-19 caused by any SARS-CoV-2 variant.
2. to compare the efficacy of sipavibart to Evusheld and/or placebo in the prevention of symptomatic COVID-19 attributable to matched variants (variants that do not contain the F456L mutation)

Outcomes/endpoints

The dual primary endpoints were:

Confirmed symptomatic COVID-19 case, classified as a binary outcome incorporating the time from the first dose of IMP until a participant develops their first symptoms for COVID-19, which is defined as:

- Positive post-baseline RT PCR at any time up to 181 days after last dose (i.e., Visit 9 [Day 361] for participants who receive both planned treatment administrations) AND
- Satisfying modified WHO definition of symptomatic COVID-19

AND

Confirmed symptomatic COVID-19 case attributable to matched variants, classified as a binary outcome incorporating the time from the first dose of IMP until a participant develops their first symptoms for COVID-19, which is defined as:

- Positive post-baseline RT PCR at any time up to 181 days after last dose (i.e., Visit 9 [Day 361] for participants who receive both planned treatment administrations) AND

- Satisfying the modified WHO definition of symptomatic COVID-19 AND
- Viral sequencing from associated positive RT PCR is attributable to matched variants.

Secondary outcomes included:

GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29)

Incidence of a post treatment:

- Severe COVID-19 caused by any SARS-CoV-2 variant
- Severe COVID-19 caused by any SARS-CoV-2 matched variants
- COVID-19 related hospitalisation (separately)
- COVID-19 related death (separately)

Sample size

The number of participants in the SUPERNOVA part A main cohort were originally approximately n=1200 but changed to approximately n=3200 in v. 4.0 of the CSP. It was estimated that approximately n=40 events were to provide at least 90% power to demonstrate that the lower bound of the 2-sided 95% CI was to be less than 1 under the assumption that the annual event rate was 3.2 in the comparator arm, a hazard ratio of 0.30, an alpha of 0.05, and 10% attrition. The assumptions made were based on data from prior studies with Evusheld.

Additional assumptions were made at the time of implementing the dual primary efficacy endpoints (v. 8.0 of the CSP): that the efficacy for resistant variants such as those with the F456L mutation were 0% and that the efficacy for matched variants was 70%, that the AZD3152-resistant events did not exceed 67%, and that the efficacy for all confirmed events was to be within the range of 30 to 60%. This did not change study target enrolment (n=3200); for the matched variants endpoint, at least n=43 events were required to maintain 90% power and an alpha of 0.025 for both endpoints.

Randomisation and blinding (masking)

Randomisation

Participants (n=3200) were to be randomised 1:1 to receive sipavibart 300 mg or comparator. The participants were to be centrally assigned to the randomised study intervention by using IRT/RTSM. Randomisation was to be stratified for: SARS-CoV-2 vaccination status within six months prior to randomisation (Yes, No), SARS-CoV-2 infection within six months prior to randomisation (Yes, No), and AZD7442 (Evusheld) use within 12 months prior to randomisation (Yes, No).

Blinding

Participants, investigators, and Sponsor staff involved in treatment, clinical evaluation, and in monitoring the participants were to be blinded to the study intervention.

Due to visually distinct differences in the study interventions (including placebo) prior to dose preparation, the study intervention was to be handled by an unblinded pharmacist (or designee) at each study site, respectively, independent of safety evaluations and other trial evaluations. Syringe masking was to be required to maintain the blind. Bioanalytical PK and ADA laboratories, as well as the study personnel carrying out the packaging and labelling of IMP, generating the randomisation list, the Sponsor's supply chain department, and the Sponsor's unblinded monitor or designee, were to have access to the randomisation list during the study.

The randomisation code was not to be broken except in medical emergencies when the appropriate management of the participant required knowledge of the treatment randomisation, or in the instance a participant wished to be considered for a SARS-CoV-2 vaccine.

The study was to maintain a double-blind period until the primary analysis, after which the investigators and participants were to remain blinded. During the evaluation of safety and efficacy, participant level unblinding information was to be kept strictly confidential except for members of the analysis team who were responsible for conducting the primary analysis.

Statistical methods

Primary analysis sets

The primary analysis sets used in the efficacy analyses were:

- SARS-CoV-2-negative set, used for efficacy data including primary analyses of the dual efficacy endpoint, included all participants in the FAS (see below) without evidence of a current SARS-CoV-2 infection at baseline; participants with positive RT-PCR test results at baseline were excluded. If multiple test results were collected and in conflict, the last baseline central RT-PCR available test result was to be used. If not specified otherwise, participants in this population were to be classified according to the assigned treatment.
- FAS/Safety set 1, used for study population, safety, and efficacy data, that included all randomised participants who received part, or all, the study intervention; participants who withdraw consent or assent to participate were to be included up to the date of their study termination. In the FAS, participants were to be classified according to the assigned treatment, while in the Safety set 1, participants were to be classified according to the actual treatment received.

Main analysis methods for primary efficacy endpoints

The primary efficacy analyses were to concern the dual endpoint: 1) confirmed symptomatic COVID-19 and 2) the primary matched variant. The primary analysis set was to be the SARS-CoV-2-Negative Set, see above.

The presence of symptoms at each illness visit were to be considered to link the onset of symptoms with the central RT-PCR test results. This assessment was to be based on the WHO COVID-19 Clinical Progression Scale score; a score of ≥ 2 was indicative of symptomatic COVID-19. Specifically, a positive nasopharyngeal (NP) swab central RT-PCR test must be collected within ten days of the initial onset or during the continuation of COVID-19 symptom and local RT-PCR or rapid antigen tests were not to be used to replace missing central RT-PCR tests. Participants without a positive central RT-PCR test within this window, relative to the ongoing symptoms, were to be considered as not having met the dual primary efficacy endpoint criteria.

The dual primary binary efficacy endpoint was to be analysed by means of Poisson regression models that were to include the covariates study intervention and randomisation stratification factors (see "randomisation and blinding"). This utilised only the first event in a given patient.

The Poisson regression models were to use a log-link function, a robust variance (Zou, 2004), and the log-follow-up time as offset, to adjust for differential follow-up time. The estimated relative risks (RR) with corresponding confidence intervals (CI) for testing superiority of sipavibart vs. comparator were to be calculated from the Poisson regression models, expressed as relative risk reductions (RRR = 100(1-RR)) with corresponding CIs. Participants who died due to COVID-19 or who were hospitalised for COVID-19 were to be considered as having met the "all confirmed events" efficacy endpoint criteria

even if no other qualifying symptoms had been recorded. Any participant who met the dual primary time-to-event efficacy endpoint criteria only after Day 361 was to be considered as having not met the time-to-event efficacy endpoint criteria.

The timing variable to be used for the dual primary COVID-19 outcome was to be the relative day of symptom onset (i.e., symptom onset day = date of symptom onset – date of first IP dose + 1). The timing variable of the "all confirmed events" endpoint were also to include COVID-19-related deaths and the first COVID-19-related hospital admissions.

In addition, Kaplan-Meier curves were to be presented for each dual primary efficacy endpoint per treatment group.

Handling of dropouts, missing data, and censoring

No data were to be considered missing for the dual primary efficacy endpoint; all participants were to be considered as either censored or as having met the dual primary efficacy endpoint.

For the primary confirmed symptomatic COVID-19 endpoint caused by any variant, symptomatic COVID-19 events were to be considered an event when dated on or before the earliest of the following censoring dates:

- Intercurrent events (ICEs), which were to include:
    - Participants becoming unblinded to the study intervention assignment.
    - Receipt of the first dose of any COVID-19 preventive product, including COV-19 vaccinations and/or medications with indications for the prevention of COV-19.
- Death not related to COVID-19.
- Early withdrawal/discontinuation.
- Day 181 for participants who did not receive the second dose of the investigational product (IP) (day 361 analysis only).
- Last assessment date for participants who were lost to follow-up.
- Data cut-off date (DCO).
- End of analysis period (day 361).

For the primary matched variant endpoint, in addition to the above criteria, the following were to be considered an ICE for symptomatic COVID-19 events attributable to matched variants:

- The date of the first occurrence of an RT-PCR confirmed symptomatic COVID-19 case not attributable to a matched variant or undetermined variants, including COVID-19-related hospitalisations and COVID-19-related deaths.

Participants who did not meet the dual primary time-to-event efficacy endpoint criteria on or before the above censoring date were to be right-censored at the earliest of these dates.

Participants were to be allowed to receive additional treatments per the standard of care to manage symptoms or prevent progression to severe COVID-19. Thus, these participants may meet the definition of the COVID-19 endpoint (symptomatic COVID-19) and receiving such treatments would not necessarily lead to exclusion from analysis.

Sensitivity and supplementary analyses

Several sensitivity analyses were specified in the SAP. Key sensitivity analyses performed and presented in the study report included dual primary efficacy endpoint results based on both the original

primary analysis model (Cox proportional hazards model) and new primary analysis model (Poisson regression), the latter implemented in v. 6.0 of the SAP based on feedback from FDA and PMDA. Key supplementary analyses on the primary efficacy endpoints included analysis of the dual primary endpoint by means of treatment policy strategy, instead of while on treatment strategy.

Subgroup analyses

The following subgroup analyses were planned:

Baseline and Demographics:

- Sex (Female, Male)
- Race (Asian, Black, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- BMI: ≥ 30 kg/m2 (Yes, No)
- Region (US, ROW)
- Region 2 (US, EU, ROW)
- ECG interpretation (Normal, Abnormal)
- Age group (≥ 65 years, < 65 years)

Randomisation stratification factors derived from the eCRF:

- COVID-19 vaccination status within six months prior to randomisation (Yes, No)
- Prior SARS-CoV-2 infection within six months prior to randomisation (Yes, No)
- Evusheld use within 12 months prior to randomisation (Yes, No)
- Prior COVID-19 vaccination or prior SARS-CoV-2 infection within six months prior to randomisation (Yes, No)

Immunocompromised conditions:

- Solid organ or stem cell transplants (Yes, No)
- Solid tumour cancer and on active treatment (Yes, No)
- Taking immunosuppressive medicines (Yes, No)
- Haematological malignancies (Yes, No)
- Moderate or severe secondary Immunodeficiency e.g., haemodialysis (Yes, No)

The subgroup analysis models were planned to incorporate both subgroup and subgroup-by-intervention interaction, for the estimation of efficacy measures and the corresponding 95% CIs for each subgroup. The estimated efficacy measures and 95% CIs were to be plotted with forest plots. This model was not to include the stratification factors used in the main analysis. If there are 0 events at any combined level of subgroup and intervention and the Poisson regression with subgroup-by-intervention cannot converge, exact conditional Poisson regression with adjustment of follow-up time were to be used to estimate efficacy for each subgroup. If there is no event in one of two treatment groups in a subgroup, then 97.5% one-sided CI was to be reported.

Error probabilities, adjustment for multiplicity, and interim analyses

To control the type I error for the dual primary efficacy endpoints at 5% significance level, Holm's step-down procedure was to be applied (see figure below). The tests were to concern superiority of AZD3152/AZD3152 over comparator in the SARS-CoV-2-negative analysis set. The analyses were to present the relative risk reduction (RRR) with confidence intervals (CIs) interpreted as follows: the alpha level for the endpoint will the smallest p-value was to be adjusted to 2.5%, and for the endpoint with the largest p-value the alpha level was to be retained at 5%.

A positive study result was to be declared if either one of the two primary endpoints were statistically significant as per above. Following the primary endpoint testing, the secondary efficacy endpoints were to be evaluated hierarchically in the order specified in the figure below, with a sequential testing approach in which each null hypotheses will be tested at the 5% level only if all preceding hypotheses were rejected. If a null hypothesis was not rejected, subsequent tests were to be treated as nominal, as were tests of any endpoints not included in the figure below.

No unblinded interim analyses were planned nor performed. However, there was an option in the SAP for a non-binding blinded sample size re-estimation based on overall symptomatic COVID-19 blinded event rate and the data from external sources (e.g., prophylactic efficacy of other COVID-19-preventive mAbs).

Hierarchical Hypothesis Testing Order of Efficacy Endpoints Controlling Type I Error at 5% (SARS-CoV-2-Negative Set)

*Dual primary endpoint: first occurrence of a symptomatic COVID-19 case up to Month 12 caused by any SARS-CoV-2 variant (Endpoint 1) and/or attributable to matched variants (Endpoint 2)**	Superiority comparison based on Relative Risk (Section 4.4.1)
⇩	
Incidence of post-treatment symptomatic COVID-19 cases in the following order#: 1. Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up 12 months with all observed events at final readout) caused by any SARS-CoV-2 matched variant 2. Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 12 months with all observed events at final readout) caused by any SARS-CoV-2 variants 3. Severe COVID-19 caused by any SARS-CoV-2 variant any time up to 12 months 4. Severe COVID-19 caused by any SARS-CoV-2 matched variants at any time up to 12 months 5. Composite of COVID-19-related hospitalization and/or COVID-19-related death (WHO COVID-19 Clinical Progression Scale score ≥ 4) any time up to 12 months 6. COVID-19-related hospitalization any time up to 12 months 7. COVID-19-related death any time up to 12 months 8. Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 months) caused by any SARS-CoV-2 variant 9. Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 months) caused by any SARS-CoV-2 matched variants	Superiority comparison based on relative risk reduction (Section 4.4.2)

COVID-19 = Coronavirus disease 2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

* Holm's step-down procedure will be applied to manage multiple comparisons arising from the dual primary endpoints and maintain the overall Type I error rate of 5%.

\# Should either of the primary endpoints be non-significant, they will be removed from the testing order.

Changes from protocol-specified analyses

The latest version (8.0) of the CSP was dated 21 December 2023. The SAP was amended five times, with the first version (0.2) dated 29 November 2022 and the last (6.0) April 15, 2024. Clinical data base lock occurred 19 April 2024. Main changes from protocol-specified analyses included change of

primary analysis method, which was implemented in SAP v. 6.0, but not in CSP v. 8.0. The change in primary analysis method was based on feedback from FDA and PMDA. Other main changes from protocol-specified analyses included specification of subgroup analyses in the SAP, which were not specified in the CSP. There were also some changes in subgroup definitions between SAP v. 5.0 and 6.0.

Results

Participant flow

Table 13. Disposition – Main Cohort

Disposition	Planned intervention (Day 1/Day 181)			Comparator [a]	Total
	AZD3152/AZD3152 n (%)	AZD7442/Placebo n (%)	Placebo/Placebo n (%)	n (%)	n (%)
Screened	-	-	-	-	3711
Not randomised	-	-	-	-	362
Randomised	1674	1111	564	1675	3349
Randomised, not treated	5	6	3	9	14
Treated	1669 (100)	1105 (100)	561 (100)	1666 (100)	3335 (100)
Received 1st dose	1669 (100)	1105 (100)	561 (100)	1666 (100)	3335 (100)
Received 2nd dose	887 (53.1)	787 (71.2)	94 (16.8)	881 (52.9)	1768 (53.0)
Study ongoing	1569 (94.0)	1012 (91.6)	548 (97.7)	1560 (93.6)	3129 (93.8)
Completed study	0	0	0	0	0
Withdrawn from study	100 (6.0)	93 (8.4)	13 (2.3)	106 (6.4)	206 (6.2)
Adverse Event	2 (0.1)	1 (< 0.1)	0	1 (< 0.1)	3 (< 0.1)
Death	19 (1.1)	11 (1.0)	2 (0.4)	13 (0.8)	32 (1.0)
Failure to Meet Inclusion/Exclusion Criteria	0	0	0	0	0
Lost to Follow-Up	17 (1.0)	19 (1.7)	1 (0.2)	20 (1.2)	37 (1.1)
Physician Decision	5 (0.3)	6 (0.5)	0	6 (0.4)	11 (0.3)
Withdrawal by Subject	52 (3.1)	51 (4.6)	9 (1.6)	60 (3.6)	112 (3.4)
Other	5 (0.3)	5 (0.5)	1 (0.2)	6 (0.4)	11 (0.3)

[d] 'Comparator' includes all participants who received Evusheld and/or placebo.

Screened participants are those who signed informed consent.

Percentages are based on the number of participants who received treatment.

Recruitment

Participants were enrolled at 197 sites in 18 countries: Australia, Belgium, Canada, Denmark, France, Germany, Israel, Malaysia, Poland, Singapore, South Korea, Spain, Taiwan, Thailand, United Arab Emirates, United Kingdom, US, and Vietnam.

Of the 3711 participants screened for the study, 3349 participants were randomised and 3335 were treated.

The first participant was enrolled on 31 March 2023. As of the Primary Analysis data cutoff of 29 March 2024, all treated participants had received the first dose of IMP and 1768 (53.0%) had received the second dose of IMP.

Conduct of the study

The most substantive protocol changes during the study were: (1) the addition of a second (dual) primary endpoint, and (2) the change in the comparator from Evusheld to placebo (see above, *treatments*).

The second primary endpoint (i.e. the matched variant analysis) was added due to the changing variant landscape to ensure that the clinical question of sipavibart efficacy against susceptible variants could be assessed while still allowing for the assessment of efficacy against all events. Randomisation was ongoing and no reviews by the DSMB or AstraZeneca of blinded study data had occurred at the time the addition of the second primary endpoint was proposed to health authorities.

The primary efficacy analysis methodology described in CSP version 8.0 was updated in the final SAP (edition 6.0 dated 15 April 2024). This change occurred before database lock for the Primary Analysis reported in this CSR and before any unblinding of the study data. Based on feedback from FDA and PMDA, the primary efficacy endpoint methodology was updated from a Cox proportional hazard model to a Poisson regression rather than extended Cox model.

Baseline data

Table 14. Demographics - Main Cohort (Full Analysis Set)

Category	Statistic	Planned intervention (Day 1/Day 181)			Comparator [a]	Total
		AZD3152/AZD3152 N = 1669	AZD7442/Placebo N = 1104	Placebo/Placebo N = 561	N = 1665	N = 3334
Age (years)	N	1669	1104	561	1665	3334
	Mean	58.1	58.6	57.7	58.3	58.2
	Min					12
	Median	60.0	60.0	58.0	60.0	60.0
	Max					
Age group (years)						
≥ 12 to < 18	n (%)	8 (0.5)			7 (0.4)	15 (0.4)
≥ 18 to < 65	n (%)	1055 (63.2)			1055 (63.4)	2110 (63.3)
≥ 65	n (%)	606 (36.3)	417 (37.8)	186 (33.2)	603 (36.2)	1209 (36.3)
Sex						

Table 14. Demographics - Main Cohort (Full Analysis Set)

Category	Statistic	Planned intervention (Day 1/Day 181)			Comparator [a]	Total
		AZD3152/AZD3152 N = 1669	AZD7442/Placebo N = 1104	Placebo/Placebo N = 561	N = 1665	N = 3334
Male	n (%)	715 (42.8)	494 (44.7)	232 (41.4)	726 (43.6)	1441 (43.2)
Female	n (%)	954 (57.2)	610 (55.3)	329 (58.6)	939 (56.4)	1893 (56.8)
Race						
Black or African American	n (%)	202 (12.1)	122 (11.1)	78 (13.9)	200 (12.0)	402 (12.1)
Native Hawaiian or Other Pacific Islander	n (%)	5 (0.3)	2 (0.2)	0	2 (0.1)	7 (0.2)
American Indian or Alaska Native	n (%)	1 (< 0.1)	2 (0.2)	2 (0.4)	4 (0.2)	5 (0.1)
Asian	n (%)	111 (6.7)	94 (8.5)	13 (2.3)	107 (6.4)	218 (6.5)
White	n (%)	1239 (74.2)	816 (73.9)	416 (74.2)	1232 (74.0)	2471 (74.1)
Other	n (%)	22 (1.3)	29 (2.6)	9 (1.6)	38 (2.3)	60 (1.8)
Not reported	n (%)	38 (2.3)	8 (0.7)	29 (5.2)	37 (2.2)	75 (2.2)
Multiple	n (%)	42 (2.5)	31 (2.8)	2 (0.4)	33 (2.0)	75 (2.2)
Missing	n (%)	9 (0.5)	0	12 (2.1)	12 (0.7)	21 (0.6)

[e] 'Comparator' includes all participants assigned to Evusheld and/or placebo.

The same participant may belong to more than one race.

Table 15. Baseline Characteristics – Main Cohort (Full Analysis Set)

Characteristic	Statistic	Planned intervention (Day 1/Day 181)			Comparator [a]	Total
		AZD3152/AZD3152 N = 1669	AZD7442/Placebo N = 1104	Placebo/Placebo N = 561	N = 1665	N = 3334
Weight (kg)	N	1665	1101	560	1661	3326
	Mean	83.0	81.6	85.4	82.9	83.0
	Min	41	42	40	40	40
	Median	79.6	79.5	82.6	80.5	80.0
	Max	183	159	182	182	183
COVID-19-vaccinated within 6 months						
Yes	n (%)	198 (11.9)	148 (13.4)	50 (8.9)	198 (11.9)	396 (11.9)
No	n (%)	1471 (88.1)	956 (86.6)	511 (91.1)	1467 (88.1)	2938 (88.1)
SARS-CoV-2-infected within 6 months						
Yes	n (%)	66 (4.0)	58 (5.3)	7 (1.2)	65 (3.9)	131 (3.9)

Table 15. Baseline Characteristics – Main Cohort (Full Analysis Set)

Characteristic	Statistic	Planned intervention (Day 1/Day 181)			Comparator [a]	Total
		AZD3152/AZD3152 N = 1669	AZD7442/Placebo N = 1104	Placebo/Placebo N = 561	N = 1665	N = 3334
No	n (%)	1603 (96.0)	1046 (94.7)	554 (98.8)	1600 (96.1)	3203 (96.1)
Evusheld within 12 months						
Yes	n (%)	191 (11.4)	148 (13.4)	39 (7.0)	187 (11.2)	378 (11.3)
No	n (%)	1478 (88.6)	956 (86.6)	522 (93.0)	1478 (88.8)	2956 (88.7)

[f] 'Comparator' includes all participants assigned to Evusheld and/or placebo.

Table 16. Immunocompromised Conditions – Main Cohort (Full Analysis Set)

Category	Planned intervention (Day 1/Day 181)			Comparator [a]	Total
	AZD3152/AZD3152 N = 1669	AZD7442/Placebo N = 1104	Placebo/Placebo N = 561	N = 1665	N = 3334
	n (%)	n (%)	n (%)	n (%)	n (%)
Received chimeric antigen receptor T-cell therapy					
Yes	4 (0.2)	2 (0.2)	3 (0.5)	5 (0.3)	9 (0.3)
No	1665 (99.8)	1102 (99.8)	558 (99.5)	1660 (99.7)	3325 (99.7)
Taking immunosuppressive medications					
Yes	1228 (73.6)	797 (72.2)	451 (80.4)	1248 (75.0)	2476 (74.3)
No	441 (26.4)	307 (27.8)	110 (19.6)	417 (25.0)	858 (25.7)
Solid organ transplant					
Yes	235 (14.1)	165 (14.9)	72 (12.8)	237 (14.2)	472 (14.2)
No	1434 (85.9)	939 (85.1)	489 (87.2)	1428 (85.8)	2862 (85.8)
Hematopoietic stem-cell transplantation					
Yes	36 (2.2)	21 (1.9)	9 (1.6)	30 (1.8)	66 (2.0)
No	1633 (97.8)	1083 (98.1)	552 (98.4)	1635 (98.2)	3268 (98.0)
Moderate or severe primary immunodeficiencies					
Yes	26 (1.6)	20 (1.8)	9 (1.6)	29 (1.7)	55 (1.6)
No	1643 (98.4)	1084 (98.2)	552 (98.4)	1636 (98.3)	3279 (98.4)
Moderate or severe secondary immunodeficiencies					
Yes	265 (15.9)	181 (16.4)	58 (10.3)	239 (14.4)	504 (15.1)

Table 16. Immunocompromised Conditions – Main Cohort (Full Analysis Set)

	Planned intervention (Day 1/Day 181)			Comparator [a]	Total
	AZD3152/AZD3152 N = 1669	AZD7442/Placebo N = 1104	Placebo/Placebo N = 561	N = 1665	N = 3334
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
No	1404 (84.1)	923 (83.6)	503 (89.7)	1426 (85.6)	2830 (84.9)
Within one year of receiving B-cell depleting therapies					
Yes	235 (14.1)	137 (12.4)	72 (12.8)	209 (12.6)	444 (13.3)
No	1434 (85.9)	967 (87.6)	489 (87.2)	1456 (87.4)	2890 (86.7)
Solid tumor cancer and on treatment					
Yes	55 (3.3)	50 (4.5)	8 (1.4)	58 (3.5)	113 (3.4)
No	1614 (96.7)	1054 (95.5)	553 (98.6)	1607 (96.5)	3221 (96.6)
Hematologic malignancy					
Yes	272 (16.3)	179 (16.2)	60 (10.7)	239 (14.4)	511 (15.3)
No	1397 (83.7)	925 (83.8)	501 (89.3)	1426 (85.6)	2823 (84.7)
Advanced or untreated HIV infection					
Yes	13 (0.8)	0	23 (4.1)	23 (1.4)	36 (1.1)
No	1656 (99.2)	1104 (100)	538 (95.9)	1642 (98.6)	3298 (98.9)

[g] 'Comparator' includes all participants assigned to Evusheld and/or placebo.

Table 17. Concomitant Immunosuppressive Medications by Anatomical Therapeutic Class and Preferred Drug Name - Main Cohort (Full Analysis Set)

ATC Level 2 Preferred drug name (WHODrug GLOBAL 092023 B3)	Planned intervention (Day 1/Day 181)			Comparator [a]	Total
	AZD3152/AZD3152 N = 1669	AZD7442/Placebo N = 1104	Placebo/Placebo N = 561	N = 1665	N = 3334
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any immunosuppressive medication	1298 (77.8)	869 (78.7)	463 (82.5)	1332 (80.0)	2630 (78.9)
Antineoplastic agents	286 (17.1)	194 (17.6)	67 (11.9)	261 (15.7)	547 (16.4)
Rituximab	125 (7.5)	76 (6.9)	28 (5.0)	104 (6.2)	229 (6.9)
Ibrutinib	21 (1.3)	10 (0.9)	7 (1.2)	17 (1.0)	38 (1.1)
Acalabrutinib	12 (0.7)	12 (1.1)	4 (0.7)	16 (1.0)	28 (0.8)
Venetoclax	11 (0.7)	15 (1.4)	1 (0.2)	16 (1.0)	27 (0.8)
Fluorouracil	11 (0.7)	10 (0.9)	3 (0.5)	13 (0.8)	24 (0.7)
Obinutuzumab	10 (0.6)	10 (0.9)	4 (0.7)	14 (0.8)	24 (0.7)
Immunosuppressants	990 (59.3)	642 (58.2)	374 (66.7)	1016 (61.0)	2006 (60.2)
Methotrexate	242 (14.5)	179 (16.2)	80 (14.3)	259 (15.6)	501 (15.0)

Table 17. Concomitant Immunosuppressive Medications by Anatomical Therapeutic Class and Preferred Drug Name - Main Cohort (Full Analysis Set)

ATC Level 2 Preferred drug name (WHODrug GLOBAL 092023 B3)	Planned intervention (Day 1/Day 181)			Comparator [a]	Total
	AZD3152/AZD3152 N = 1669	AZD7442/Placebo N = 1104	Placebo/Placebo N = 561	N = 1665	N = 3334
	n (%)	n (%)	n (%)	n (%)	n (%)
Tacrolimus	192 (11.5)	125 (11.3)	57 (10.2)	182 (10.9)	374 (11.2)
Mycophenolate mofetil	180 (10.8)	120 (10.9)	57 (10.2)	177 (10.6)	357 (10.7)
Hydroxychloroquine	120 (7.2)	62 (5.6)	42 (7.5)	104 (6.2)	224 (6.7)
Adalimumab	72 (4.3)	52 (4.7)	31 (5.5)	83 (5.0)	155 (4.6)
Corticosteroids for systemic use	584 (35.0)	412 (37.3)	178 (31.7)	590 (35.4)	1174 (35.2)

[h] 'Comparator' includes all participants assigned to Evusheld and/or placebo.

Only the 5 most common (and ties) antineoplastic agents and immunosuppressants are included.

Numbers analysed

The SARS-CoV-2-negative set, used for efficacy data was to include all participants in the FAS without evidence of a current SARS-CoV-2 infection at baseline. This was 1649 subjects in the test arm and 1631 subjects in the comparator arm.

Outcomes and estimation

Table 18. Statistical Analysis of Dual Primary Efficacy Endpoints – While-on-Treatment Strategy-Main Cohort (SARS-CoV-2-Negative Set

Endpoint	Statistic	Planned intervention (Day 1/Day 181) [a]		Relative Risk Reduction (%) [c]	p-value	95% CI (%)	97.5% CI (%) [d]	Rank of p-value [e]	Adjusted p-value [f]	Hypothesis testing result [g]
		AZD3152/AZD3152 N = 1649	Comparator [b] N = 1631							
All confirmed events	Participants with events, n (%)	122 (7.4)	178 (10.9)	34.9	< 0.001	17.8, 48.4	15.0, 50.1	1	< 0.001	Significant
	Participants censored, n (%)	1527 (92.6)	1453 (89.1)	-	-	-	-	-	-	-
Matched variant events	Participants with events, n (%)	54 (3.3)	90 (5.5)	42.9	0.001	19.9, 59.3	-	2	0.001	Significant
	Participants censored, n (%)	1595 (96.7)	1541 (94.5)	-	-	-	-	-	-	-

[i] 'Planned intervention (Day 1/Day 181)': The terms before and after the slash refer to planned interventions for Day 1 and Day 181.

[j] 'Comparator' includes all participants assigned to receive Evusheld on Day 1 and placebo on Day 181, or placebo on both Day 1 and Day 181.

[k] Relative risk reduction was defined as 1 - relative risk of sipavibart/sipavibart versus comparator, where relative risk was evaluated with a Poisson regression with robust variance, which includes study intervention, and the randomisation stratification factors as covariates and adjusts follow-up time. Only participants with non-missing covariates are included in the analysis.

[l] The 97.5% CI of efficacy is provided if p-value is first-ranked.

[m] p-values were ranked by ascending order, $p(1) \leq p(2)$.

[n] The adjusted p-value is min (1, 2 × p(1)) for first-ranked p-value, and min(1, max(2 × p(1), p(2))) for second-ranked p-value.

[o] Efficacy is declared statistically significant for the given endpoint if the adjusted p-value is lower than 0.05.

P-values and CIs are 2-sided unless otherwise specified.

Table 19. Incidence of First Symptomatic COVID-19 Cases up to Day 361 Caused by any Variant – While on-Treatment Strategy - Main Cohort (SARS-CoV-2-Negative Set)

Category	Statistic	Planned intervention (Day 1/Day 181) [a]	
		AZD3152/AZD3152 N = 1649	Comparator [b] N = 1631
Event c	n (%)	122 (7.4)	178 (10.9)
Symptomatic COVID-19 case (any variant) [d]	n (%)	120 (7.3)	173 (10.6)
COVID-19-related death	n (%)	0	0
COVID-19-related hospitalisation	n (%)	2 (0.1)	5 (0.3)
Censored	n (%)	1527 (92.6)	1453 (89.1)
Intercurrent events	n (%)	302 (18.3)	309 (18.9)
Became unblinded to IMP assignment	n (%)	14 (0.8)	12 (0.7)
Receipt of any COVID-19 preventive product	n (%)	288 (17.5)	297 (18.2)
Death not related to COVID-19	n (%)	14 (0.8)	8 (0.5)
Early withdrawal	n (%)	43 (2.6)	40 (2.5)
Second IMP dose not received	n (%)	50 (3.0)	50 (3.1)
Lost to follow-up	n (%)	16 (1.0)	18 (1.1)
Data cutoff	n (%)	1102 (66.8)	1028 (63.0)
End of analysis period (Day 361)	n (%)	0	0
Poisson regression	RRR [e] (%)	34.9	-
	95% CI (%)	17.8, 48.4	-
	97.5% CI (%)	15.0, 50.1	-
	p-value	< 0.001	-

[p] 'Planned intervention (Day 1/Day 181)': The terms before and after the slash refer to planned interventions for Day 1 and Day 181.

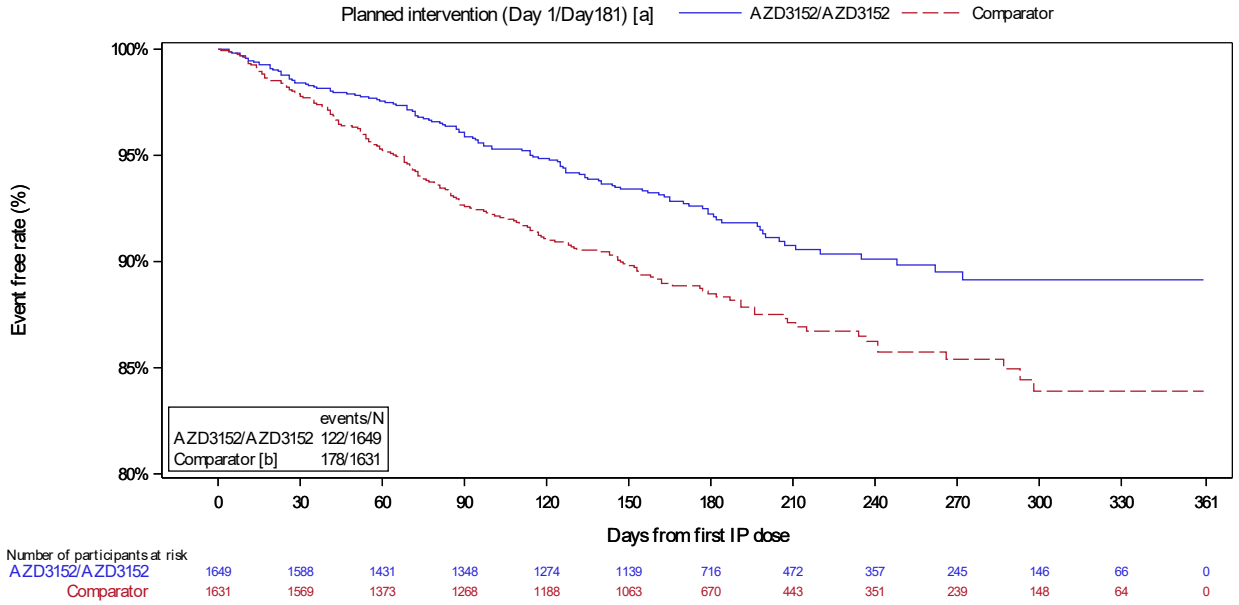
[q] 'Comparator' includes all participants assigned to receive Evusheld on both Days 1 and 181, Evusheld on Day 1 and placebo on Day 181, or placebo on both Days 1 and 181.

[r] Participants may be reported in multiple event categories. The earliest of the events is considered for the analysis.

[s] RT-PCR-confirmed COVID-19 cases.

[t] Relative risk reduction was defined as 1 - relative risk of sipavibart/sipavibart versus comparator, where relative risk was evaluated with a Poisson regression with robust variance, which includes study intervention and the randomisation stratification factors as covariates and adjusts follow-up time. Only participants with non-missing covariates are included in the analysis.

Figure 9. Kaplan-Meier Plot of Time to First Symptomatic COVID-19 Cases up to Day 361 Caused by any Variant – While-on-Treatment Strategy – Main Cohort (SARS-CoV-2-Negative Set)



[u] Planned intervention (Day 1/Day 181)': The terms before and after the slash refer to planned interventions for Day 1 and Day 181.

[v] 'Comparator' includes all participants assigned to receive Evusheld on Day 1 and placebo on Day 181, or placebo on both Days 1 and 181.

Table 20. Time to First Symptomatic COVID-19 Cases Up to Day 361 Attributable to Matched Variants - While-on-Treatment Strategy - Main Cohort (SARS-CoV-2-Negative Set)

Category	Statistic	Planned intervention (Day 1/Day 181) [a]	
		AZD3152/AZD3152 N = 1649	Comparator [b] N = 1631
Event: Symptomatic COVID-19 case (matched variant) c	n (%)	54 (3.3)	90 (5.5)
Censored	n (%)	1595 (96.7)	1541 (94.5)
Intercurrent events	n (%)	370 (22.4)	397 (24.3)
Became unblinded to IMP assignment	n (%)	14 (0.8)	12 (0.7)
Receipt of any COVID-19 preventive product	n (%)	294 (17.8)	303 (18.6)
Events not attributable to matched variant	n (%)	62 (3.8)	82 (5.0)

Table 20. Time to First Symptomatic COVID-19 Cases Up to Day 361 Attributable to Matched Variants - While-on-Treatment Strategy - Main Cohort (SARS-CoV-2-Negative Set)

Category	Statistic	Planned intervention (Day 1/Day 181) [a]	
		AZD3152/AZD3152 N = 1649	Comparator [b] N = 1631
Death not related to COVID-19	n (%)	14 (0.8)	8 (0.5)
Early withdrawal	n (%)	43 (2.6)	40 (2.5)
Second IMP dose not received	n (%)	50 (3.0)	50 (3.1)
Lost to follow-up	n (%)	16 (1.0)	18 (1.1)
Data cutoff	n (%)	1102 (66.8)	1028 (63.0)
End of analysis period (Day 361)	n (%)	0	0
Poisson regression	RRR [d] (%)	42.9	-
	95% CI (%)	(19.9, 59.3)	-
	p-value	0.001	-

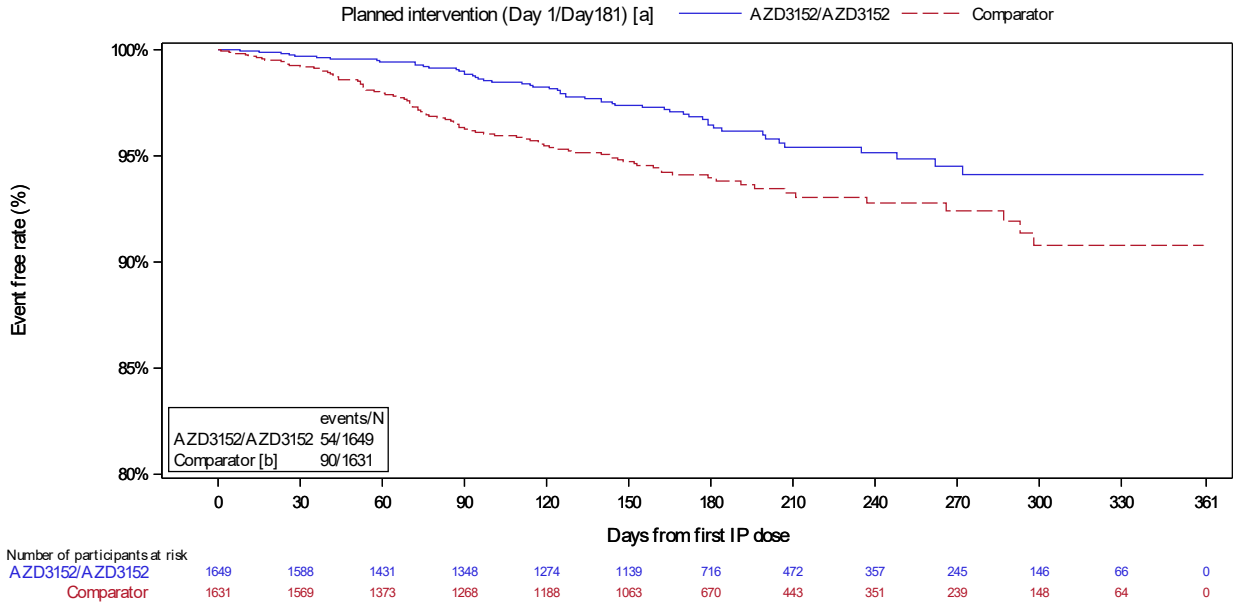
w 'Planned intervention (Day 1/Day 181)': The terms before and after the slash refer to planned interventions for Day 1 and Day 181.

x 'Comparator' includes all participants assigned to receive Evusheld on Day 1 and placebo on Day 181, or placebo on both Days 1 and 181.

y Including symptomatic RT-PCR-confirmed COVID-19 cases, COVID-19-related hospitalisations, and COVID-19-related deaths.

z Relative risk reduction was defined as 1 - relative risk of sipavibart/sipavibart versus comparator, where relative risk was evaluated with a Poisson regression with robust variance, which includes study intervention and the randomisation stratification factors as covariates and adjusts follow-up time. Only participants with non-missing covariates are included in the analysis.

Figure 10. Kaplan-Meier Plot of Time to First Symptomatic COVID-19 Cases Up to Day 361 Attributable to Matched Variants – While-on-Treatment Strategy – Main Cohort (SARS-CoV-2-Negative Set)



[aa] Planned intervention (Day 1/Day 181)': The terms before and after the slash refer to planned interventions for Day 1 and Day 181.

[bb] 'Comparator' includes all participants assigned to receive Evusheld on Day 1 and placebo on Day 181, or placebo on both Days 1 and 181.

A "complementary" post hoc endpoint, including all events that were deemed due to non-matched variants (i.e. including both those due to F456L containing variants by sequencing as well as those that were not sequenced), using similar censoring rules as for the "matched variant" endpoint, was requested. This showed an efficacy estimate of 26.7% (95% CI -0.9-46.7%).

Key sensitivity analysis not censoring for "receipt of any COVID-19 preventative product"

This intercurrent event was largely due to COVID-19 vaccination.

The risk reduction with the sensitivity analysis of the primary any variant endpoint using a treatment policy strategy was slightly lower than the risk reduction with the Primary Analysis using a while-on-treatment strategy: RRR 29.9% (95% CI 13.4, 43.3).

Incidence of symptomatic COVID-19 cases up to Day 361 caused by any variant - treatment policy strategy - Main Cohort (SARS-CoV-2-Negative Set)

		Planned intervention (Day 1/Day 181) [a]	
		AZD3152/AZD3152 N=1649	Comparator [b] N=1631
Event [c]	n (%)	151 (9.2)	207 (12.7)
Symptomatic COVID-19 case (any variant) [d]	n (%)	149 (9.0)	201 (12.3)
COVID-19-related death	n (%)	0	0
COVID-19-related hospitalization	n (%)	2 (0.1)	6 (0.4)
Censored	n (%)	1498 (90.8)	1424 (87.3)
Death not related to COVID-19	n (%)	16 (1.0)	9 (0.6)
Early withdrawal	n (%)	46 (2.8)	47 (2.9)
Second IP dose not received	n (%)	56 (3.4)	62 (3.8)
Lost to follow-up	n (%)	17 (1.0)	18 (1.1)
Data cutoff	n (%)	1363 (82.7)	1288 (79.0)
End of analysis period (Day 361)	n (%)	0	0
Poisson regression	RRR [e] (%)	29.9	
	95% CI (%)	(13.4, 43.3)	
	p-value	0.001	

The result for the sensitivity analysis of the primary matched variants endpoint using a treatment policy strategy was slightly lower than the risk reduction with the Primary Analysis using a while-on-treatment strategy: RRR 35.3% (95% CI 12.7, 52.0).

Incidence of symptomatic COVID-19 cases up to Day 361 attributable to matched variants- treatment policy strategy - Main Cohort (SARS-CoV-2-Negative Set)

		Planned intervention (Day 1/Day 181) [a]	
		AZD3152/AZD3152 N=1649	Comparator [b] N=1631
Event: Symptomatic COVID-19 case (matched variant) [c]	n (%)	72 (4.4)	108 (6.6)
Censored	n (%)	1577 (95.6)	1523 (93.4)
Death not related to COVID-19	n (%)	16 (1.0)	9 (0.6)
Early withdrawal	n (%)	48 (2.9)	50 (3.1)
Second IP dose not received	n (%)	67 (4.1)	65 (4.0)
Lost to follow-up	n (%)	17 (1.0)	18 (1.1)
Data cutoff	n (%)	1429 (86.7)	1381 (84.7)
End of analysis period (Day 361)	n (%)	0	0
Poisson regression	RRR [d] (%)	35.3	
	95% CI (%)	(12.7, 52.0)	
	p-value	0.004	

Severe cases, hospitalisations and COVID-19 related deaths

There were few severe COVID-19 cases or COVID-related hospitalisations through to data cutoff. COVID-related hospitalisations occurred in 20 participants, 10 in each group. Of the 20 hospitalised participants, 4 of the COVID-19 events were classified as severe: 2 in the sipavibart group and 2 in the comparator group nAb Responses to SARS-CoV-2 Variants.

Efficacy by variant

Table 21. Incidence of Symptomatic COVID-19 Cases Up to Day 361 Attributable to Specific Variants - While-on-Treatment Strategy - Main Cohort (SARS-CoV-2-Negative Set)

	Planned intervention (Day 1/Day 181)			
	AZD3152/AZD3152 N = 1649	Comparator [a] N = 1631	Relative risk reduction (%) [b]	95% CI (%)
Variant	n (%)	n (%)		
Any (sequenced)	101 (6.1)	154 (9.4)	37.6	19.6, 51.6
Matched	54 (3.3)	90 (5.5)	42.9	19.9, 59.3
BA.2.86 + subvariants	1 (0.1)	10 (0.6)	90.9	27.4, 98.9
XBB + subvariants	6 (0.4)	20 (1.2)	71.6	29.0, 88.7
JN.1 + subvariants	47 (2.9)	60 (3.7)	25.1	-9.7, 48.8
F456L (sequenced)	47 (2.9)	64 (3.9)	30.4	-1.8, 52.5

[a] 'Comparator' includes all participants assigned to receive Evusheld on Day 1 and placebo on Day 181, or placebo on both Day 1 and Day 181.
[b] Relative risk reduction was defined as 1 - relative risk of sipavibart/sipavibart versus comparator, where relative risk was evaluated with a Poisson regression with robust variance, which includes study intervention and the randomisation stratification factors as covariates and adjusts for follow-up time.
[c] F456L (sequenced) includes all events with the F456L mutation in the sequence regardless of assigned variant.
P-values and CIs are 2-sided unless otherwise specified.

Only participants with non-missing covariates are included in the analysis.

Efficacy over time

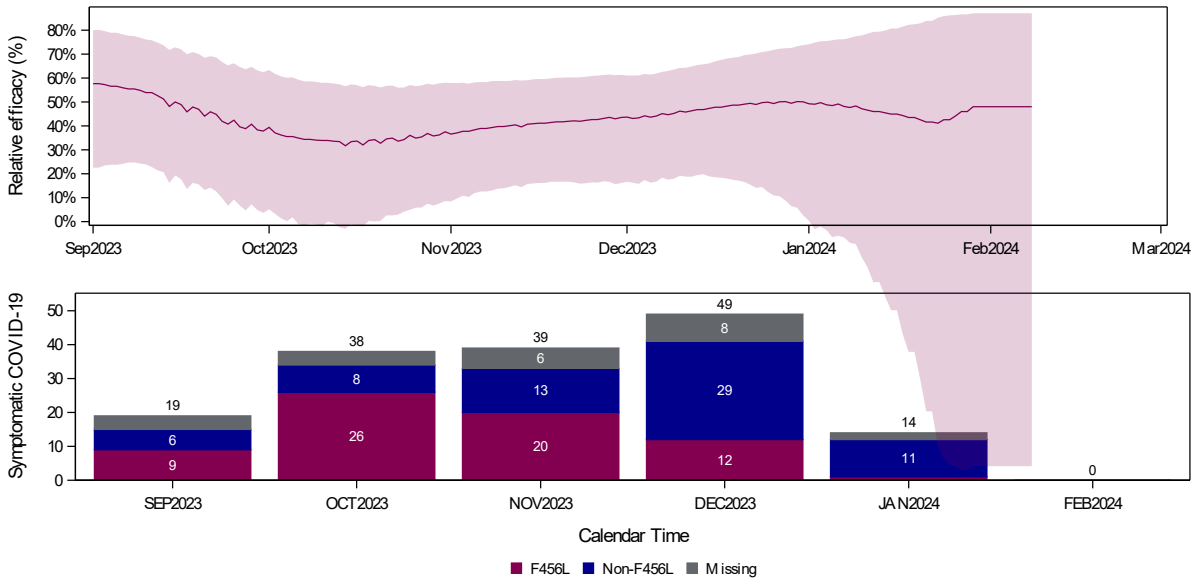
Clinical Outcome: Prevention of symptomatic COVID-19		Overall Endpoint (All Variants) RRR % (95% CI) *% participants reporting events – sipavibart/ % participants reporting events – comparator*		Matched Endpoint (Non-F456L Variants) RRR % (95% CI) *% participants reporting events – sipavibart/ % participants reporting events – comparator*	
		3 months follow-up	6 months follow-up	3 months follow-up	6 months follow-up
Population while on treatment [a]		41.9 (22.5, 56.5) *4.5/7.6*	34.9 (17.8, 48.4) *7.4/10.9*	60.0 (36.2, 74.9) *1.5/3.7*	42.9 (19.9, 59.3) *3.3/5.5*
Variant-specific	Lineage XBB + subvariants	N/A	N/A	77.6 (33.1, 92.5) *0.2/1.0*	71.6 (29.0, 88.7) *0.4/1.2*

Clinical Outcome: Prevention of symptomatic COVID-19		Overall Endpoint (All Variants) RRR % (95% CI) *% participants reporting events – sipavibart/ % participants reporting events – comparator*		Matched Endpoint (Non-F456L Variants) RRR % (95% CI) *% participants reporting events – sipavibart/ % participants reporting events – comparator*	
		3 months follow-up	**6 months follow-up**	**3 months follow-up**	**6 months follow-up**
groupings by lineage	Lineage BA 2.86 + subvariants	N/A	N/A	100.0 (43.3, 100.0) *0/0.5*	90.9 (27.4, 98.9) *0.1/0.6*
	Lineage JN.1 + subvariants	N/A	N/A	42.0 (0.4, 66.2) *1.3/2.1*	25.1 (-9.7, 48.8) *2.9/3.7*

To assess the benefit of sipavibart (300 mg IM, up to 3 months post dose) against any variant between September 2023 and February 2024, when most primary endpoint events accrued in the study, an analysis of efficacy utilizing events due to any variant within 3 months of receiving the first dose was performed. The relative efficacy of sipavibart versus comparator remained above 31% during the entirety of the September 2023 to February 2024 period for those participants who were within 3 months of their first dose.

Notably, the proportion of F456L variants did not impact the relative efficacy estimate: F456L variants were the predominant event causing variants in September through November (F456L variants accounted for over 57% of events across this period) but were the minority of events in December and January (F456L variants accounted for ~20% of events across this period).

Figure 11. Instantaneous Relative Efficacy Over Calendar Time to First Symptomatic COVID 19 Cases Prior to Day 91 Caused by any Variant – While-on-treatment Strategy – Main Cohort (SARS-CoV-2-Negative Set)



Instantaneous HRs are derived using the Epanechnikov kernel, using a bandwidth of 56 days. All participants were considered at risk at start of follow-up and this set was reduced accordingly when participants had events or were censored.

Relative efficacy is derived as 1 - HR for participants who were planned to receive sipavibart on both Day 1 and 181 vs participants who were planned to receive Evusheld on Day 1 and placebo on Day 181, or placebo on both Days 1 and 181.

Two-sided 95% confidence intervals were derived using the quantile approach from 1,000 bootstrap resamples.

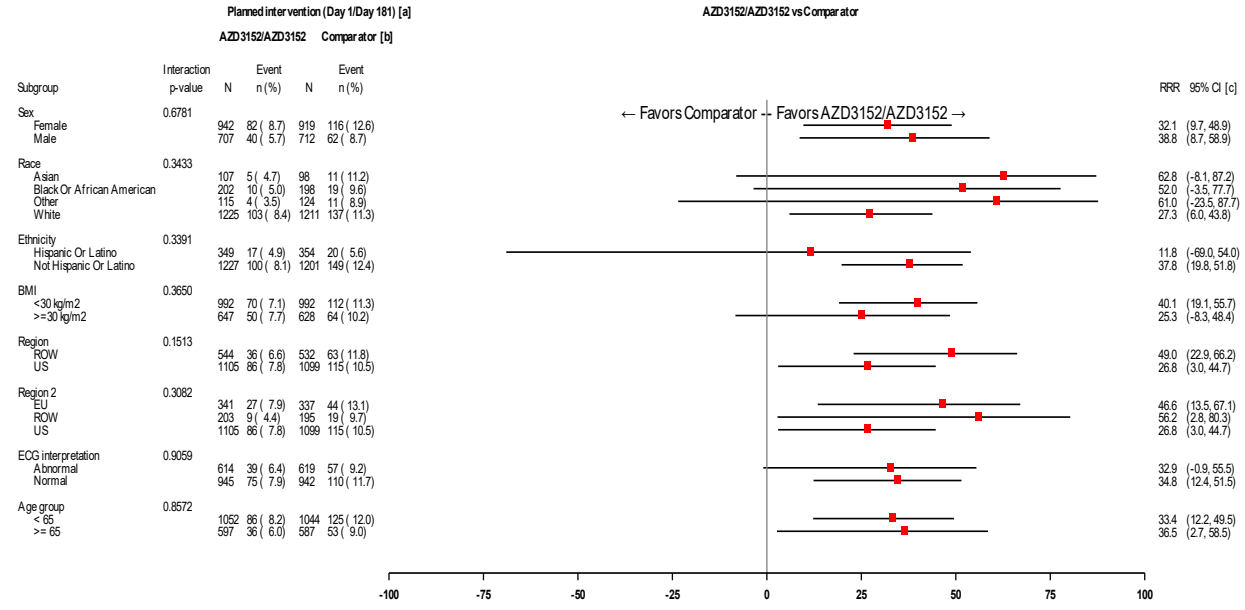
Participants who had not observed an event prior to Day 91 were censored at this time.

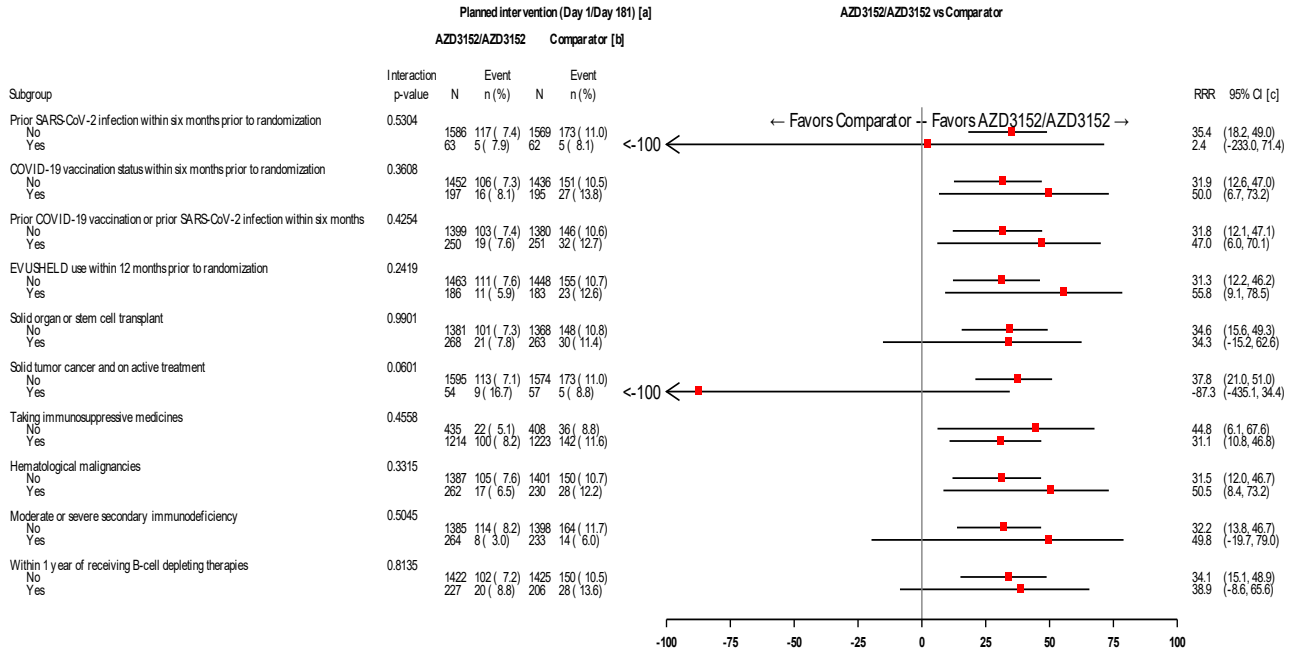
Missing events include those where sequencing result was not available at time of data cutoff or assay failed.

Relative efficacy over this period ranges from 31.7% to 57.7%.

Ancillary analyses

Figure 12. Forest Plot of Prophylactic Efficacy Preventing Symptomatic COVID-19 up to Day 361 Caused by any Variant by Subgroup – While-on-Treatment Strategy – Main Cohort (SARS-CoV-2-Negative Set)





Similar to the any variant endpoint, there was no substantial heterogeneity of response with respect to the matched variant endpoint.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22. Summary of Efficacy for trial SUPERNOVA Main Cohort

Title: Supernova Main Cohort			
Study identifier	Study number: D7000C00001		
Design	Phase III randomised, double-blind international multi-centre study of pre-exposure prophylaxis		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		~15 months from first dose of IMP. Clinical cut-off 12 months for Primary analysis. The study is ongoing. not applicable Follow-up 270 days after the second dose
Hypothesis	Superiority		
Treatments groups	Sipavibart		300 mg IM, two doses on day 1 and day 181, 1671 individuals randomised
	Comparator		1:st dose: Placebo or Evusheld 300 mg IM on day 1 2:nd dose: Placebo on day 181 1663 individuals randomised
Endpoints and definitions	Dual primary endpoint	Symptomatic COVID-19 case (any	Binary outcome incorporating the time from the first dose of IMP until a participant develops

Title: Supernova Main Cohort			
Study identifier	Study number: D7000C00001		
		variant) Symptomatic COVID-19 case (matched variant)	their first symptoms for COVID-19, which is defined as: • Positive post-baseline RT PCR at any time up to 181 days after last dose (i.e., Visit 9 [Day 361] for participants who receive both planned treatment administrations) AND • Satisfying modified WHO definition of symptomatic COVID-19 AND Confirmed symptomatic COVID-19 case attributable to matched variants, classified as a binary outcome incorporating the time from the first dose of IMP until a participant develops their first symptoms for COVID-19, which is defined as: • Positive post-baseline RT PCR at any time up to 181 days after last dose (i.e., Visit 9 [Day 361] for participants who receive both planned treatment administrations) AND • Satisfying the modified WHO definition of symptomatic COVID-19 AND • Viral sequencing from associated positive RT PCR is attributable to matched variants.
	Secondary endpoints	Incidence of post-treatment	• COVID-19 related hospitalisation • COVID-19 related death
Database lock	29 March 2024		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**Full analysis set (FAS):** The primary analysis included of the dual efficacy endpoint included all participants in the FAS without evidence of a current SARS-Cov-2 infection at baseline who received part, or all the study intervention.		
Descriptive statistics and estimate variability	**Treatment group**	**Sipavibart**	**Comparator**
	Number of subjects	1649	1631
	Symptomatic	122 (7.4)	178 (10.9)

Title: Supernova Main Cohort			
Study identifier	Study number: D7000C00001		
	COVID-19 cases, any variant, n (%) Symptomatic COVID-19 cases, matched variant, n (%)	54 (3.3)	90 (5.5)
Effect estimates per comparison	**Primary endpoint:** Symptomatic COVID-19 cases (any variant)	Comparison groups	Sipavibart vs. comparator
		Relative risk reduction (95% CI): Evaluated with Poisson regression with robust variance	34.9 % (17.8, 48.4)
		P value	<0.001
	Primary Endpoint: Symptomatic COVID-19 cases (matched variant)	Comparison groups	Sipavibart vs. comparator
		Relative risk reduction (95% CI): Evaluated with Poisson regression with robust variance	42.9% (19.9, 59.3)
		P-value	0.001
	Secondary endpoint: Covid-related death n (%)	0	0
	Secondary endpoint: Covid-19-related hospitalisation n (%)	2 (0.1)	5 (0.3)

2.6.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number/total number)	**Age 75-84 (Older subjects number/total number)**	**Age 85+ (Older subjects number/total number)**
Controlled Trials (SUPERNOVA Main Cohort, SARS-CoV-2-Negative Set)	857/3280	300/3280	27/3280
Non-Controlled trials	N/A	N/A	N/A

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal Supernova Main Cohort Study recruited patients in EU, UK, USA, Canada, Israel, UAE and East Asia. The start date was March 2023, and the primary analysis was dated March 2024.

This was a randomised double blinded study in adolescents ≥12 year of age or adults with clinically significant immunocompromised.

Subjects were allocated either to receive sipavibart 300 mg i.m or a comparator, which initially was Evusheld 300 mg i.m. During the study, this was changed to placebo. After a first dose, subjects were to receive a second dose of sipavibart or comparator (de facto placebo) 6 months later.

The type 1 error controlled primary endpoint was initially time to RT-PCR confirmed symptomatic Sars-Cov-2 infection due to any variant. In a protocol amendment this was changed to a dual primary endpoint. This included (a) the abovementioned metric as well as (b) one counting only events due to "matched variants" (= not including the F456L mutation, which abolishes the neutralising ability of sipavibart). The type 1 error was controlled over the two primary endpoints with the Holm method. This method rejects the null hypothesis of the endpoint with the smaller p-value if this p-value was below 2.5% (α/2) and the trial was to be considered successful. If that was the case, the primary endpoint with the larger p-value could be tested at full alpha level (5%).

The Primary Analysis was triggered when the median follow-up time was greater than 181 days.

The primary analysis set was the SARS-CoV-2-Negative Set, which included all participants in the FAS without evidence of a current SARS-CoV-2 infection at baseline. Since the exclusion is based on pre-randomisation information, this is ok.

On the change of the comparator from Evusheld to placebo

The basis of sipavibart development is the Evusheld product. This showed high clinical efficacy as pre-exposure prophylaxis in pre-omicron days, reducing the risk of developing symptomatic COVID-19 compared with placebo by 76.7%. The emergence of BQ.1 variants significantly reduced the potency and neutralizing activity of both components of Evusheld, as well as other COVID-19 mAbs.

Sipavibart was designed to provide broad and potent coverage across Omicron and ancestral viral variants. Its development programme was repeatedly discussed with the ETF. Initially, an approval

based on immunobridging was conceived by the company. This prompted the pivotal trial to be a randomised, double-blinded comparison with Evusheld, despite this at the time having little if any neutralising ability against then circulating viral variants.

As a separate immunobridging sub-study was added as an Addendum to the SUPERNOVA study, the company decided to switch the comparator to placebo. In the setting of a superiority study, this is acceptable; moreover, in case Evusheld had some residual activity, this obviously did not incur bias in favour of sipavibart.

One may be tempted to request an analysis of results in patients randomised before and after the switch of the control treatment. However, given concomitant viral evolution, inferences on the residual activity of Evusheld are not likely to be meaningful.

On the changes to the statistical analysis plan

The original endpoint is similar to those that supported the approval of previous products of the same class (any confirmed symptomatic COVID-19 infection). As the study proceeded, viral variants with the F456L mutation in the spike protein emerged. In vitro data indicated that the utility of sipavibart was limited in the same way as that of previous mAbs against Sars-Cov-2. In vitro data indicated that it would not protect against viral variants carrying this mutation.

On this basis, the statistical analysis plan was changed, dividing alpha between dual primary endpoints: any symptomatic COVID-19 infection; and symptomatic COVID-19 infection due to a "matched" variant not exhibiting the F456L mutation.

For both endpoints, the magnitude of effect, as well as external validity will be dependent on the susceptibility of circulating strains where sipavibart is to be used. The "matched variant" endpoint may be understood to approximate the ideal performance of sipavibart when all circulating viral variants are susceptible.

These key protocol amendments were made in a double-blinded study and were accepted by the ETF in repeat scientific advice procedures.

It is noted that from v. 4.0 of the study protocol, the sample size was considerably increased, but as this increase was driven by the addition of the efficacy analyses and performed before start of recruitment in the main cohort, this is acceptable. V. 4.0 of the study protocol also contained information on a non-binding blinded sample size re-estimation which was not implemented.

The primary efficacy endpoint methodology was changed from Cox proportional hazard model to Poisson regression. This change was made in the latest version of the statistical analysis plan, but before data base lock, and was not implemented in any protocol version. The Cox proportional hazard model was, however, also presented, and statistically positive.

In summary, the statistical methodology used in the study appears acceptable and there is no major concern of false conclusions, even though there were some late changes made to the study protocol and statistical analysis plan.

Overall evaluation of the pivotal study design

Given the above considerations, the overall design and conduct of the double-blinded randomised controlled pivotal trial is acceptable. The patient population of immunocompromised individuals may be considered representative of a population anticipated to respond less effectively to active immunisation. The primary endpoints have regulatory endorsement.

Efficacy data and additional analyses

The Supernova Main Cohort recruited 1674 subjects allocated to sipavibart and 1675 subjects allocated to the comparator group (1111 to Evusheld and 564 to placebo).

The median age was 60 years (36.3% 65 years of age or older, 15 participants 12 years to less than 18 years), 56.8% of participants were female, 74.1% were White, 6.5% were Asian, 12.1% were Black/African American, and 21.5% were Hispanic/Latino.

All participants had at least one immunocompromising clinical condition, including e.g. taking immunosuppressive medication (74.3%), hematologic malignancy (15.3%), moderate/severe secondary immunodeficiencies (predominantly haemodialysis) (15.1%), and solid organ transplant (14.2%).

The sipavibart group showed a statistically significant reduction in risk of symptomatic COVID-19 due to any SARS-CoV-2 variant versus comparator (122/1649 [7.4%] events in the sipavibart arm versus 178/1631 [10.9%] events in the comparator arm) with a relative risk reduction of 34.9% (97.5% CI: 15.0, 50.1; $p < 0.001$).

Reduction in risk of COVID-19 was greater for disease attributed to matched (non F456L mutation containing) SARS-CoV-2 variants versus comparator (54/1649 [3.3%] events in the sipavibart arm versus 90/1631 [5.5%] events in the comparator arm) with a relative risk reduction of 42.9% (95% CI: 19.9, 59.3; $p = 0.001$).

Approximately 20% of subjects in each arm in the primary analyses were censored due to "receipt of any COVID-19 preventative product". As anticipated, this was predominantly receipt of vaccination. Key sensitivity analyses according to treatment policy (not censoring for this factor) indicate that the efficacy demonstration is statistically robust.

There was also a quite prominent number of protocol deviations related to the eligibility criteria. However, the applicant has provided an additional analysis on the dual primary endpoint in which patients with protocol deviations based on eligibility criteria were excluded. The outcome of this does not substantially differ from that of the primary analysis.

Thus, efficacy has been demonstrated in a patient group with clinically significant immunosuppression.

That said, it is not agreed that the applicant's pre-determined estimand censoring for intercurrent vaccination, is the most informative with respect to anticipated clinical performance. This is since the target population is, to some extent, likely to also receive vaccines, as did a fifth or so of patients in the SUPERNOVA main cohort.

Notably, the RRR per the any variant endpoint using a treatment policy strategy was 29.9% (95% CI 13.4, 43.3), and for the matched variant endpoint this was 35.3% (95% CI 12.7, 52.0).

The applicant was requested to only present this analysis as a claim in the SmPC section 5.1 where this is reported.

On external validity and the magnitude/duration of effect

The registered effect size, also against "matched variants", is lower than what was seen for Evusheld and other products developed prior to the emergence of omicron variants. In the absence of a clear PK/PD rationale for this, one may speculate whether this is due to the differing pathogenic features of omicron compared to prior variants with greater pulmonary tropism.

Another notable feature is the lower point estimate for efficacy of sipavibart against the JN1 variant (RRR 25.1%; 95% CI: -1.8-52.5). This variant has a higher IC50 than those sipavibart was originally

designed to target (83.1 ng/mL compared to <6 ng/mL for other "susceptible" variants). On the other hand, the point estimate for efficacy against variants carrying the F456L substitution, which are not anticipated to be neutralised by sipavibart, was 30.4% (95%CI: -9.7- 48.8). The true value here is assumed to be 0 based on the absence of any PK/PD rationale for efficacy.

As has been the case for previous products in this class, utility seems short lived due to viral evolution. Notably, variants emerging as epidemiologically dominant at the time of assessment (KP.2, KP.3 and LB.1) are not anticipated to be susceptible to sipavibart, as these exhibit the F456L mutation.

The applicant has presented data indicating that efficacy was greater during the first three months after the sipavibart injection. Time-dependent data are difficult to interpret due to viral evolution during the trial. However, a waning of effect is anticipated over time as sipavibart is eliminated.

A PK/PD analysis is key to the understanding of what variants Evusheld is anticipated to provide protection against, as well as the anticipated duration of that protection. The provided PK/PD modelling and its limitations are discussed above in the section on Clinical Pharmacology.

Overall evaluation

While the efficacy of sipavibart has been established, the magnitude of effect is smaller than would have been anticipated based on experiences of similar drugs in the pre-omicron era. This is true also regarding the "matched variants" analysis outcome. Moreover, the utility of sipavibart in the present viral variant landscape is dubitable and may be very low. The PK/PD relationship remains unclear. The PK of sipavibart is generally well described, however, the PK/PD relation has not been adequately described to support appropriate use with respect to what variants are anticipated to be neutralised, and what is the duration of protection against these variants after a single dose. As indicated in the section for clinical pharmacology, this is reflected in the labelling.

On the other hand, results for the final efficacy analysis have to be submitted, including the evaluation of COVID-19 cases through Day 181 and Day 361, as they become available after the planned data lock in Q2 2025 (REC).

Assessment of paediatric data on clinical efficacy

There were 15 participants 12-18 years of age. While efficacy cannot be evaluated in this subgroup, the overall results are presumed to be relevant also for adolescents.

2.6.7. Conclusions on the clinical efficacy

- The efficacy of sipavibart for ***pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive medications or treatments***, has been established.
- Sipavibart is assumed to have no usefulness in an epidemiological landscape completely dominated by viral variants carrying the F456L mutation. Decisions regarding the use of sipavibart for the prevention of COVID-19 should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viral variants, including geographical prevalence. The *in vitro* neutralisation activity of sipavibart against SARS-CoV-2 viral variants is reflected in section 5.1 of the SmPC.

- The PK/PD relation of sipavibart remains unclear with respect to what variants are anticipated to be neutralised, and what is the duration of protection against these variants after a single dose.
- All these aspects are reflected in the labelling (see also discussion and conclusion in Clinical pharmacology)

Clinical recommendation:

Results for the final efficacy analysis to be submitted, including the evaluation of COVID-19 cases through Day 181 and Day 361, as they become available after the planned data lock in Q2 2025 (REC).

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The extent of exposure and follow up in the safety database was as follows:

Table 23. Disposition, Exposure, and Follow-up

Study/ Data cut-off	IMPs	Number of participants receiving first dose of IMP		Number of participants receiving second dose of IMP		Safety follow-up in sipavibart group (median days)	Participants remaining in the study at data cut-off
		Sipavibart	Comparator	Sipavibart	Placebo		
SUPERNOVA Parent Study Main Cohort / Day 181	Sipavibart 300 mg IM Evusheld 300 mg IM Placebo	1671	1663 a	886	94	183	3129
SUPERNOVA Sub-study/ Day 91	Sipavibart 1200 mg IV Evusheld 300 mg IM	310	158 b	-	-	108	453
Little DIPPER/ Day 91	Sipavibart 1200 mg IV Sipavibart 600 mg IM/IV Sipavibart 300 mg IM/IV Placebo	80 d	16	-	-	114	89
SUPERNOVA Parent Study Sentinel Cohort/ Day 181	AZD5156 600 mg IM Placebo	41 c	16	-	-	181 e	53

[a] N = x received Evusheld as first dose and N = x received placebo as first dose.

[b] Two participants from the Evusheld 300 mg IM group crossed over to the sipavibart 1200 mg IV group after Day 29.

[c] Participants in SUPERNOVA Parent Study Sentinel Safety Cohort were administered 600 mg IM AZD5156 (300 mg sipavibart and 300 mg cilgavimab) in the gluteal region (N = 20) or anterolateral thigh (N = 21).

[d] Forty participants received sipavibart 1200 mg and 40 (10 per group) received either sipavibart 600 mg IM, sipavibart 600 mg IV, sipavibart 300 mg IM, or sipavibart 300 mg IV.

[e] The SUPERNOVA Parent Study Sentinel Safety Cohort CSR evaluated safety data through Day 181. Of the 41 participants in the sipavibart group, 38 completed the Day 181 visit and continued in the study.

The main safety dataset, relevant for the target population with clinically significant immunocompromise, pertains to the Supernova main study. Moreover, the focus of the safety presentation is on events occurring within 90 days of study drug administration.

2.6.8.2. Adverse events

The following table presents an overall summary of AEs from the first dose of IMP through Day 91 for the SUPERNOVA Parent Study Main Cohort.

Table 24. Overall Summary of Adverse Events Up to Day 91 Visit 4 after First Study Intervention Dose – Main Cohort (Safety Set 1)

	Received intervention (Day 1)						Comparator [a] N = 1663	
	sipavibart N = 1671		Evusheld N = 1102		Placebo N = 561			
Category	n (%)	95% CI (%)	n (%)	95% CI (%)	n (%)	95% CI (%)	n (%)	95% CI (%)
AEs	833 (49.9)	(47.43, 52.28)	587 (53.3)	(50.27, 56.25)	270 (48.1)	(43.92, 52.35)	857 (51.5)	(49.10, 53.96)
AE ≥ CTCAE Grade 3	115 (6.9)	(5.72, 8.20)	91 (8.3)	(6.70, 10.04)	38 (6.8)	(4.84, 9.18)	129 (7.8)	(6.52, 9.15)
SAEs leading to death	7 (0.4)	(0.17, 0.86)	4 (0.4)	(0.10, 0.93)	1 (0.2)	(0, 0.99)	5 (0.3)	(0.10, 0.70)
SAEs	120 (7.2)	(5.99, 8.53)	85 (7.7)	(6.21, 9.45)	37 (6.6)	(4.69, 8.98)	122 (7.3)	(6.13, 8.70)
AEs leading to treatment DC	3 (0.2)	(0.04, 0.52)	5 (0.5)	(0.15, 1.06)	2 (0.4)	(0.04, 1.28)	7 (0.4)	(0.17, 0.87)

[a] 'Comparator' includes all participants who received Evusheld or placebo.

Moreover, there were no meaningful differences between the sipavibart and comparator groups following administration of a second dose, including for overall AEs, SAEs, or deaths.

The most commonly reported adverse events after the first dose were as follows:

Table 25. Adverse Events Up to Day 91 Visit 4 after First Study Intervention Dose by Preferred Term with Frequency ≥ 2% - Main Cohort (Safety Set 1)

	Received intervention (Day 1)			
Preferred term (MedDRA Version 26.1)	sipavibart N = 1671	Evusheld N = 1102	Placebo N = 561	Comparator [a] N = 1663
	n (%)	n (%)	n (%)	n (%)
COVID-19	97 (5.8)	78 (7.1)	62 (11.1)	140 (8.4)
Cough	89 (5.3)	75 (6.8)	20 (3.6)	95 (5.7)

Preferred term (MedDRA Version 26.1)	Received intervention (Day 1)			Comparator [a] N = 1663
	sipavibart N = 1671	Evusheld N = 1102	Placebo N = 561	
	n (%)	n (%)	n (%)	n (%)
Headache	84 (5.0)	49 (4.4)	28 (5.0)	77 (4.6)
Fatigue	66 (3.9)	53 (4.8)	27 (4.8)	80 (4.8)
Oropharyngeal pain	66 (3.9)	28 (2.5)	15 (2.7)	43 (2.6)
Rhinorrhoea	53 (3.2)	38 (3.4)	14 (2.5)	52 (3.1)
Upper respiratory tract infection	46 (2.8)	17 (1.5)	21 (3.7)	38 (2.3)
Urinary tract infection	43 (2.6)	27 (2.5)	10 (1.8)	37 (2.2)
Diarrhoea	41 (2.5)	38 (3.4)	15 (2.7)	53 (3.2)
Nasal congestion	38 (2.3)	12 (1.1)	10 (1.8)	22 (1.3)
Nasopharyngitis	36 (2.2)	21 (1.9)	13 (2.3)	34 (2.0)
Pyrexia	34 (2.0)	19 (1.7)	8 (1.4)	27 (1.6)

a 'Comparator' includes all participants who receive Evusheld or placebo.

The table includes AEs that started, worsened, or became serious on or after the first IMP dosing date up to and including 103 days following the first dosing date.

Participants who reported at least one AE for a PT at a frequency of ≥ 2% in any group are summarised.

Participants with multiple occurrences are counted once per PT, regardless of the number of occurrences.

The most common severe adverse events were as follows:

Table 26. Adverse Events of CTCAE Grade ≥ 3 Up to Day 91 Visit 4 after First Study Intervention Dose by Preferred Term - Main Cohort (Safety Set 1)

Preferred term (MedDRA Version 26.1)	Received intervention (Day 1)			Comparator [a] N = 1663
	sipavibart N = 1671	Evusheld N = 1102	Placebo N = 561	
	n (%)	n (%)	n (%)	n (%)
Any AEs	115 (6.9)	91 (8.3)	38 (6.8)	129 (7.8)
Pneumonia	10 (0.6)	5 (0.5)	1 (0.2)	6 (0.4)
Acute myocardial infarction	8 (0.5)	2 (0.2)	2 (0.4)	4 (0.2)
Cardiac failure acute	6 (0.4)	0	1 (0.2)	1 (0.1)
Anaemia	5 (0.3)	1 (0.1)	1 (0.2)	2 (0.1)
Influenza				
Acute respiratory failure	4 (0.2)	4 (0.4)	1 (0.2)	5 (0.3)
Atrial fibrillation	4 (0.2)	2 (0.2)	1 (0.2)	3 (0.2)
COVID-19	4 (0.2)	4 (0.4)	2 (0.4)	6 (0.4)
Cardiac failure congestive	4 (0.2)	1 (0.1)	2 (0.4)	3 (0.2)
Dyspnoea				
Hypervolaemia	4 (0.2)	2 (0.2)	0	2 (0.1)
Hypotension				

Table 26. Adverse Events of CTCAE Grade ≥ 3 Up to Day 91 Visit 4 after First Study Intervention Dose by Preferred Term - Main Cohort (Safety Set 1)

Preferred term (MedDRA Version 26.1)	Received intervention (Day 1)			Comparator [a] N = 1663
	sipavibart N = 1671	Evusheld N = 1102	Placebo N = 561	
	n (%)	n (%)	n (%)	n (%)
Septic shock	4 (0.2)	2 (0.2)	1 (0.2)	3 (0.2)
Urinary tract infection	4 (0.2)	0	1 (0.2)	1 (0.1)
Acute kidney injury	3 (0.2)	5 (0.5)	0	5 (0.3)
Febrile neutropenia	3 (0.2)	2 (0.2)	0	2 (0.1)
Hypertensive emergency	3 (0.2)	3 (0.3)	0	3 (0.2)
Malignant neoplasm progression				
Sepsis	3 (0.2)	1 (0.1)	1 (0.2)	2 (0.1)
Hypertension	1 (0.1)	6 (0.5)	0	6 (0.4)
Hypertensive urgency	1 (0.1)	1 (0.1)	2 (0.4)	3 (0.2)
Hyperkalaemia				

a 'Comparator' includes all participants who receive AZD7442 or Placebo.

The 95% CI for proportions is calculated using the Clopper-Pearson method. The CIs are not presented for categories where the incidence rate is zero (n = 0).

The table includes AEs that started, worsened, or became serious on or after the first investigational product dosing date up to and including 103 days following the first dosing date.

Participants with multiple occurrences are counted once per preferred term regardless of the number of occurrences.

This table includes PTs occurring in ≥ 3 participants in either the sipavibart or comparator groups and is ordered by descending frequency in the sipavibart group.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

Table 27. Serious Adverse Events Up to Day 91 Visit 4 by Preferred Term - Main Cohort (Safety Set 1)

Preferred term (MedDRA Version 26.1)	Received intervention (Day 1)			Comparator [a] N = 1663
	sipavibart N = 1671	Evusheld N = 1102	Placebo N = 561	
	n (%)	n (%)	n (%)	n (%)
Any SAEs	120 (7.2)	85 (7.7)	37 (6.6)	122 (7.3)
Pneumonia	10 (0.6)	5 (0.5)	1 (0.2)	6 (0.4)
Acute myocardial infarction	8 (0.5)	2 (0.2)	2 (0.4)	4 (0.2)
Cardiac failure acute	6 (0.4)	0	1 (0.2)	1 (0.1)
Atrial fibrillation	5 (0.3)	2 (0.2)	1 (0.2)	3 (0.2)
COVID-19	5 (0.3)	2 (0.2)	1 (0.2)	3 (0.2)
Influenza				

Table 27. Serious Adverse Events Up to Day 91 Visit 4 by Preferred Term - Main Cohort (Safety Set 1)

Preferred term (MedDRA Version 26.1)	Received intervention (Day 1)			Comparator [a] N = 1663
	sipavibart N = 1671	Evusheld N = 1102	Placebo N = 561	
	n (%)	n (%)	n (%)	n (%)
Acute respiratory failure	4 (0.2)	4 (0.4)	1 (0.2)	5 (0.3)
Hypervolaemia	4 (0.2)	2 (0.2)	0	2 (0.1)
Hypotension				
Sepsis	4 (0.2)	1 (0.1)	1 (0.2)	2 (0.1)
Septic shock	4 (0.2)	2 (0.2)	1 (0.2)	3 (0.2)
Cardiac failure congestive	3 (0.2)	2 (0.2)	2 (0.4)	4 (0.2)
Dyspnoea				
Hypertensive emergency	3 (0.2)	3 (0.3)	0	3 (0.2)
Syncope				
Urinary tract infection	3 (0.2)	2 (0.2)	1 (0.2)	3 (0.2)
Acute kidney injury	2 (0.1)	4 (0.4)	0	4 (0.2)
Hypertensive urgency	1 (0.1)	1 (0.1)	2 (0.4)	3 (0.2)

a 'Comparator' includes all participants who receive Evusheld or placebo.

The table includes AEs that started, worsened, or became serious on or after the first IMP dosing date up to and including 103 days following the first dosing date.

Participants with multiple occurrences are counted once per SOC regardless of the number of occurrences.

Deaths

In the Supernova main study, deaths during the 90 days after administration of the first dose of IMP were similar between the sipavibart (n = 7 [0.4%]) and comparator (n = 5 [0.3%]) groups. None of the SAEs leading to death were assessed as related to IMP by the Investigator.

For the full study period up to data cutoff there were 33 SAEs leading to death: 20 (1.2%) in the sipavibart group and 13 (0.8%) in the comparator group.

There were no deaths reported in the Supernova substudy or in the Little DIPPER study.

Adverse events of special interest

AESIs for sipavibart and Evusheld were pre-specified as anaphylaxis and other serious hypersensitivity reactions, including immune complex disease, infusion related reactions, and events adjudicated as cardiovascular and thrombotic events.

Notably, in the PROVENT study of Evusheld, a numerical difference was observed between the Evusheld and placebo groups for SAEs in the Cardiac disorders SOC: 40 (1.2%) vs. 8 (0.5%). Therefore, given that sipavibart and Evusheld are structurally very similar, cardiovascular and thrombotic events were included as an AESI for sipavibart.

Table 28. Adverse Events of Special Interest Up to Day 91 Visit 4 after First Study Intervention Dose by AESI Category and Preferred Term - Main Cohort (Safety Set 1)

AESI category Preferred term (MedDRA Version 26.1)	Received intervention (Day 1)			Comparator [a] N = 1663
	AZD3152 N = 1671	AZD7442 N = 1102	Placebo N = 561	
	n (%)	n (%)	n (%)	n (%)
Any AESIs [b]	18 (1.1)	2 (0.2)	5 (0.9)	7 (0.4)
Serious Hypersensitivity reactions including anaphylaxis	0	1 (0.1)	1 (0.2)	2 (0.1)
Drug hypersensitivity	0	1 (0.1)	0	1 (0.1)
Hypersensitivity	0	0	1 (0.2)	1 (0.1)
Adjudicated cardiovascular and thrombotic events	18 (1.1)	1 (0.1)	4 (0.7)	5 (0.3)
Cardiac Ischemic events	7 (0.4)	0	1 (0.2)	1 (0.1)
Acute coronary syndrome				
Acute myocardial infarction	6 (0.4)	0	1 (0.2)	1 (0.1)
Cerebrovascular events				
Brain stem haemorrhage				
Brain stem infarction				
Cerebral infarction				
Heart Failure events	2 (0.1)	0	2 (0.4)	2 (0.1)
Cardiac failure acute				
Cardiac failure congestive	2 (0.1)	0	2 (0.4)	2 (0.1)
Thromboembolic events	6 (0.4)	1 (0.1)	1 (0.2)	2 (0.1)
Brachiocephalic vein thrombosis				
Deep vein thrombosis	4 (0.2)	1 (0.1)	1 (0.2)	2 (0.1)
Jugular vein thrombosis				
Pulmonary embolism				
Subclavian vein thrombosis				
Vena cava thrombosis				

a 'Comparator' includes all participants who receive Evusheld or placebo.

b AESIs include serious hypersensitivity reactions, including anaphylaxis, immune-complex disease, and adjudicated CV and thrombotic events.

The table includes AEs that started, worsened, or became serious on or after the second IMP dosing date up to and including 103 days following the second dosing date.

Participants with multiple occurrences are counted once per SOC and PT regardless of the number of occurrences.

To further address the potential risk of cardiac and thrombotic events, raised based on Evusheld data (see below, Discussion on Clinical Safety), the applicant presented the following cross study analyses. Notably, based on pharmacology, any such effect, if it exists, is anticipated to be similar for sipavibart and Evusheld, and different from placebo.

Table 29. Summary of positively adjudicated CV results in Evusheld and sipavibart clinical studies

	Evusheld clinical studies				Sipavibart clinical studies		
	PROVENT study		TACKLE study		SUPERNOVA Parent Study Main Cohort		
Population and Indication	Pre-exposure prophylaxis in adults having increased risk for inadequate response to active immunisation [a]		Treatment of COVID-19 in non-hospitalised adults		Pre-exposure prophylaxis in participants ≥ 12 years of age with conditions causing immune impairment		
AESI category [b]	**Evusheld N = 3461**	**Placebo N = 1736**	**Evusheld N = 452**	**Placebo N = 451**	**Sipavibart N = 1671**	**Evusheld N = 1102**	**Placebo N = 561**
Sponsor defined MedDRA search criteria [c]							
Cardiac ischemic events	25 (0.7)	9 (0.5)	2 (0.4)	2 (0.4)	12 (0.7)	2 (0.2)	2 (0.4)
Heart failure events	18 (0.5)	6 (0.3)	0	0	22 (1.3)	8 (0.7)	7 (1.2)
Cerebrovascular events	22 (0.6)	13 (0.7)	1 (0.2)	0	7 (0.4)	1 (0.1)	2 (0.4)
Thromboembolic events	20 (0.6)	10 (0.6)	0	1 (0.2)	9 (0.5)	1 (0.1)	1 (0.2)
CV death [d]	22 (0.6)	10 (0.6)	1 (0.2)	2 (0.4)	NA	NA	NA
Positively adjudicated events							
Cardiac ischemic events	12 (0.3)	3 (0.2)	1 (0.2)	1 (0.2)	8 (0.5)	2 (0.2)	1 (0.2)
Heart failure events	9 (0.3)	1 (0.1)	0	0	5 (0.3)	2 (0.2)	3 (0.5)
Cerebrovascular events	9 (0.3)	4 (0.2)	0	0	5 (0.3)	1 (0.1)	0
Thromboembolic events	9 (0.3)	4 (0.2)	0	0	11 (0.7)	2 (0.2)	2 (0.4)
CV death [c]	5 (0.1)	0	0	0	NA	NA	NA

[a] Adults ≥ 18 years of age who were candidates who may have benefited from passive immunisation with antibodies, defined as having increased risk for inadequate response to active immunisation (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances that put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrolment.

[b] Participants with events in more than one category are counted once in each of those categories.

[c] Events identified based on MedDRA SMQs: Myocardial infarction (narrow), Cardiac failure (broad and narrow), Embolic and thrombotic events, arterial (narrow), Embolic and thrombotic events, venous (narrow), Ischaemic central nervous system vascular conditions (narrow), Haemorrhagic central nervous system vascular conditions (narrow)

[d] Not adjudicated in SUPERNOVA Parent Study Main cohort.

Percentages are based on the total numbers of participants in the treatment group.

Adverse effects related to administration

I.M injection site reactions were uncommon and none were "serious". **Preferred term (MedDRA Version 26.1)**	**Received intervention (Day 1)**			**Comparator [a] N = 1663**
	AZD3152 N = 1671	**AZD7442 N = 1102**	**Placebo N = 561**	
	n (%)	**n (%)**	**n (%)**	**n (%)**
Injection site pain	15 (0.9)	15 (1.4)	4 (0.7)	19 (1.1)
Injection site bruising	12 (0.7)	12 (1.1)	2 (0.4)	14 (0.8)
Injection site erythema	10 (0.6)	6 (0.5)	0	6 (0.4)
Injection site swelling	3 (0.2)	9 (0.8)	0	9 (0.5)

When sipavibart was given i.v. in the SUPERNOVA substudy, mild to moderate infusion reactions were reported in less than 5% of patients.

2.6.8.4. Laboratory findings

The provided information on laboratory findings in the summary of clinical safety as well as in the individual clinical study reports were considered very limited. Therefore, the applicant was asked to present laboratory findings at baseline and over time in tabular format, especially information on potentially clinically significant values and their changes, respectively, throughout day 181 were requested as considerable parts of the study populations had immunocompromising conditions. Data were presented. A review of the available data across the studies did not reveal any clinically significant change from baseline in the safety laboratory parameters. Severe treatment-emergent laboratory abnormalities were observed in a small number of participants in both sipavibart and comparator groups with no notable differences between the treatment groups. The vast majority of the participants with any treatment-emergent laboratory abnormality had presented with a shift of one grade from baseline. Given the underlying conditions of immunosuppression in these participants, these abnormalities were anticipated. No participants had presented with AST or ALT values of ≥ 3 × ULN together with total bilirubin ≥ 2× ULN at any point during the study.

It was concurred that there were no clinically meaningful differences between the treatment groups in haematology, serum chemistry, or coagulation after administration of the first dose of sipavibart.

Referring to the SUPERNOVA Parent Study Main Cohort CSR, 37.2% of the study participants assigned to the sipavibart group presented with abnormal ECG interpretation at baseline (5.3% borderline); in the SUPERNOVA sub-study, 41.9% had abnormal EGC findings (2.3% borderline). In the SUPERNOVA Substudy CSR it is mentioned that no additional ECGs were collected later during the study as here, no CV or TE events were reported. The applicant was asked to provide more detailed information on the abnormal and borderline ECG interpretations at baseline of the clinical studies and to clarify if additional ECGs were performed throughout the studies. (corresponding results should be presented and discussed involving CV Event Adjudication Committee assessments). It was clarified that additional ECG safety assessments may had been performed at Investigator's discretion if deemed necessary. Based on the presented data, it appears plausible that post-dose unscheduled ECG assessments which were performed at Investigator's discretion if indicated, do not give evidence for detrimental effects from sipavibart treatment. In the SUPERNOVA Parent Study Sentinel Safety Cohort, SUPERNOVA Sub-

study and Little DIPPER study none of the participants had a clinically significant ECG at baseline or a post-baseline ECG assessment. Overall, the applicant's conclusion is endorsed that abnormal ECG findings at baseline and unscheduled post-dose ECG assessments do not indicate any specific safety concern in patients treated with sipavibart.

2.6.8.5. Safety in special populations

The safety profile of sipavibart did not meaningfully differ depending on age, gender, race, ethnicity, and BMI.

A total of 15 participants were ≥ 12 to < 18 years, of whom 8 received sipavibart. The incidence of AEs reported up to Day 91 after first study intervention dose were 50.0% and 85.7%, in the sipavibart and comparator groups respectively. No AESIs were reported in either treatment group.

With respect to the elderly, data are as follows. Notably, causality may not be inferred without reference to the comparator frequency.

Table 30. Adverse event summary by treatment arm and age groups from first study intervention dose to end of study for participants in treatment group sipavibart – SUPERNOVA Parent Study Main Cohort (safety set 1)

Treatment Group: Sipavibart	**Age Group (years)**				
Adverse Event	**< 65 N = 1065**	**65-74 N = 428**	**75-84 N = 169**	**85+ N = 9**	**65+ N = 606**
Total AEs Day 1 to end of reporting period [a]	659 (61.9)	265 (61.9)	100 (59.2)	2 (22.2)	367 (60.6)
Serious AEs - Total	109 (10.2)	64 (15.0)	29 (17.2)	2 (22.2)	95 (15.7)
-Fatal	10 (0.9)	4 (0.9)	5 (3.0)	1 (11.1)	10 (1.7)
-Hospitalisation/prolong existing hospitalisation	100 (9.4)	64 (15.0)	26 (15.4)	2 (22.2)	92 (15.2)
-Life-threatening	20 (1.9)	12 (2.8)	3 (1.8)	1 (11.1)	16 (2.6)
-Disability/incapacity	10 (0.9)	0	0	0	0
-Congenital anomaly or birth defect	0	0	0	0	0
-Other (medically significant)	53 (5.0)	29 (6.8)	13 (7.7)	1 (11.1)	43 (7.1)
AE leading to study withdrawal	2 (0.2)	1 (0.2)	0	0	1 (0.2)
Psychiatric disorders	23 (2.2)	9 (2.1)	3 (1.8)	0	12 (2.0)
Nervous system disorders	121 (11.4)	51 (11.9)	16 (9.5)	1 (11.1)	68 (11.2)
Accidents and injuries	46 (4.3)	20 (4.7)	10 (5.9)	0	30 (5.0)
Cardiac disorders	33 (3.1)	14 (3.3)	13 (7.7)	1 (11.1)	28 (4.6)
Vascular disorders	55 (5.2)	23 (5.4)	11 (6.5)	1 (11.1)	35 (5.8)
Cerebrovascular disorders	10 (0.9)	5 (1.2)	1 (0.6)	0	6 (1.0)
Infections and infestations	378 (35.5)	147 (34.3)	50 (29.6)	2 (22.2)	199 (32.8)
Anticholinergic syndrome	41 (3.8)	25 (5.8)	4 (2.4)	1 (11.1)	30 (5.0)
Quality of life decreased	0	0	0	0	0

Treatment Group: Sipavibart	Age Group (years)				
Adverse Event	< 65 N = 1065	65-74 N = 428	75-84 N = 169	85+ N = 9	65+ N = 606
Any of the following: postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	31 (2.9)	22 (5.1)	10 (5.9)	0	32 (5.3)
Other AEs appearing more frequently in older patients [b]					
Urinary tract infection	33 (3.1)	21 (4.9)	5 (3.0)	0	26 (4.3)
Rhinorrhoea	35 (3.3)	15 (3.5)	8 (4.7)	0	23 (3.8)
Diarrhoea	27 (2.5)	12 (2.8)	5 (3.0)	1 (11.1)	18 (3.0)
Influenza	18 (1.7)	14 (3.3)	3 (1.8)	0	17 (2.8)
Nausea	21 (2.0)	11 (2.6)	5 (3.0)	0	16 (2.6)
Bronchitis	19 (1.8)	12 (2.8)	2 (1.2)	0	14 (2.3)
Injection site pain	15 (1.4)	10 (2.3)	3 (1.8)	0	13 (2.1)
Fall	11 (1.0)	6 (1.4)	6 (3.6)	0	12 (2.0)
Rhinitis	19 (1.8)	8 (1.9)	4 (2.4)	0	12 (2.0)
Injection site bruising	14 (1.3)	8 (1.9)	2 (1.2)	0	10 (1.7)
Pain in extremity	12 (1.1)	8 (1.9)	2 (1.2)	0	10 (1.7)
Rheumatoid arthritis	5 (0.5)	7 (1.6)	3 (1.8)	0	10 (1.7)
Atrial fibrillation	5 (0.5)	3 (0.7)	6 (3.6)	0	9 (1.5)
Chronic obstructive pulmonary disease	3 (0.3)	4 (0.9)	3 (1.8)	1 (11.1)	8 (1.3)
Constipation	6 (0.6)	7 (1.6)	1 (0.6)	0	8 (1.3)
Anaemia	8 (0.8)	4 (0.9)	3 (1.8)	0	7 (1.2)
Deep vein thrombosis	1 (0.1)	5 (1.2)	2 (1.2)	0	7 (1.2)
Vertigo	2 (0.2)	5 (1.2)	2 (1.2)	0	7 (1.2)
Cardiac failure congestive	5 (0.5)	4 (0.9)	2 (1.2)	0	6 (1.0)
Osteoporosis	3 (0.3)	5 (1.2)	1 (0.6)	0	6 (1.0)
Skin laceration	2 (0.2)	4 (0.9)	2 (1.2)	0	6 (1.0)

[a] AE that are not serious, AESI, or medically attend are solicited for the first 90 days after either dose.

[b] AEs that were reported in at least 1% of participants > 65 years of age and at a higher frequency than those ≤ 65 years of age are presented.

The table includes AEs that started, worsened, or became serious on or after the first IMP dosing date up to and including the end of the study or DCO date. The table included participants who received first dose and who either received or missed second dose. Participants with multiple occurrences in the same category are counted once per category, regardless of the number of occurrences.

2.6.8.6. Immunological events

In the SUPERNOVA Parent Study Main Cohort, among the participants who received 2 doses of sipavibart, there were 28 (5.1%) participants with any ADA-positive result to sipavibart (ADA prevalence). Of these, 10 (1.8%) participants were ADA-positive at baseline only and 4 (0.7%) had an ADA-positive result post-baseline.

Among participants who received Evusheld, there were 47 (7.9%) with any ADA-positive result to Evusheld. There were also 5 (0.8%) and 3 (0.5%) participants in the sipavibart and Evusheld groups who were treatment emergent (TE)-ADA-positive (ADA incidence). Overall, ADA prevalence and incidence were and similar between sipavibart and Evusheld.

The low rate of ADA positive participants does not allow for complete assessment of the impact of ADA on the safety of sipavibart.

2.6.8.7. Discontinuation due to adverse events

Please refer to the information given above.

2.6.9. Discussion on clinical safety

Sipavibart is a mAb with an exogenous target (The SARS-Cov-2 Spike protein Receptor Binding Domain) Moreover, it has amino acid substitutions in the Fc region to extend the half-life of the antibody and to eliminate Fc-mediated effector function.

The applicant points out that the clinical development programme for sipavibart has built upon the established safety and efficacy of AstraZeneca's Evusheld mAb. For this reason, and since sipavibart and Evusheld both bind to the RBD of the SARS-CoV-2 Spike protein, sipavibart is expected to have a similar safety and PK profile to Evusheld.

The total safety database presented for sipavibart consists of approximately 2,100 patients that received a single dose, among whom approximately half also got a 2nd dose.

The main safety dataset, relevant for the target population with clinically significant immunocompromise, pertains to the Supernova Main Cohort Study. In this, approximately 1,600 patients received at least one dose of sipavibart, whereas in the comparator arm about 1,000 patients received a first dose of Evusheld and approximately 600 received a first dose of placebo.

The focus of the safety presentation is on events occurring within 90 days of study drug administration. It was unclear whether the applicant intended that a second dose would be on label, and if so when it would be given. At any rate, given the nature of sipavibart and the absence of ADA-related concerns, no different safety profile is anticipated after a second dose.

Since sipavibart and Evusheld are anticipated to display a similar safety profile, the comparison with those receiving placebo may be considered more informative.

The median age of patients in the SUPERNOVA Parent Study was 60.0 years and 15 participants were 12 to less than 18 years of age. A substantial proportion (36.3%) were 65 years of age or older.

Most participants were on immunosuppressive medications. Other immunocompromising conditions included hematologic malignancies, solid organ transplant, hematopoietic stem cell transplants, moderate or severe secondary immunodeficiencies (primarily end stage kidney disease/dialysis) and being within one year of receipt of B-cell depleting therapy.

The most common concomitant diseases were hypertension (59.8%), chronic kidney disease (30.2%), and diabetes mellitus (25.0%).

Any AE within 90 days of study drug administration was reported in approximately 50% of participants regardless of treatment arm allocation or whether they received sipavibart, Evusheld or placebo. The rate of CTCAE grade ≥3 severity AEs were around 7% in each arm, as was the rate of SAEs.

The proportion of deaths reported within 90 days was 0.4% and 0.3% in the sipavibart and control arm respectively.

Overall, the safety profile of sipavibart is as anticipated, and appears similar to that of Evusheld.

The methodology used by the applicant to identify adverse drug reactions may be summarised as follows:

All safety data from the SUPERNOVA Main Cohort were reviewed. A quantitative method of statistical assessment was applied based on the risk ratios between sipavibart versus Evusheld and sipavibart versus placebo. The probability of an association was assessed based on a Bayesian framework method used to identify AEs with 95% posterior probability that the relative risk-ratio is >1. A qualitative review was then performed on these PTs/medical concepts. This method was applied for events reported in a total of >10 participants; for laboratory data, vital signs, and AEs reported in ≤10 subjects, only a qualitative review was performed.

On this basis, the applicant proposes the following table for the SmPC section 4.8. This is acceptable.

MedDRA SOC	**MedDRA Preferred Term**	**Frequency**
Intramuscular administration		
Immune system disorders	Hypersensitivity[a]	Uncommon (0.8%)
General disorders and administration site conditions	Injection site reaction[b]	Common (4.1%)
Intravenous administration		
General disorders and administration site conditions	Infusion site reaction[c]	Common (1.9%)
Injury, poisoning and procedural complications	Infusion related reaction[d]	Common (1.9%)

a Including the following preferred terms: pruritus, erythema, hypersensitivity, urticaria, dermatitis allergic, and drug eruption.
b Including the following preferred terms: injection site pain, injection site bruising, injection site erythema, injection site haemorrhage, injection site swelling, injection site haematoma, injection site pruritus, injection site paraesthesia, injection site reaction, injection site rash, injection site discolouration, and injection site warmth.
c Including the following preferred terms: infusion site bruising, infusion site pain, infusion site pruritus, infusion site erythema, infusion site extravasation, and infusion site swelling.
d Including the following symptoms: nausea, arthralgia, headache, pyrexia, chills, dyspepsia, pain, hypotension, facial

In the PROVENT study of Evusheld, a numerical difference was observed between the Evusheld and placebo groups for SAEs in the Cardiac disorders SOC: 40 (1.2%) vs. 8 (0.5%). This prompted a warning in section 4.4. of the SmPC which, however, is agnostic with respect to causality. Given that sipavibart and Evusheld are structurally very similar, cardiovascular and thrombotic events were included as an AESI for sipavibart.

The frequency of "adjudicated cardiovascular and thrombotic events" within 90 days after the first dose was 1.1% of those receiving sipavibart, 0.1% of those receiving Evusheld and 0.7% of those receiving placebo. Comparing sipavibart with the full comparator population, frequencies were 1.1% versus 0.3% Thus, the frequency was numerically higher with sipavibart than with the sum comparator.

However, it is notable that if there was an impact on risk, Evusheld and Sipavibart are anticipated to be similar and different from placebo. However, (a) there is no plausible biological rationale, (b) no suggestive temporal clustering and (c) no clear pattern differentiating Evusheld + Sipavibart from placebo. Therefore, a causal relationship is not considered sufficiently likely for such effects to inform any labelling language.

As the three studies SUPERNOVA Parent Main Cohort, SUPERNOVA Sub-study and Little DIPPER are still ongoing, further long-term safety data until a more recent data cut-off, especially after repeated dosing, are awaited. This data will be submitted in Q3 2025, including the final CSRs of all 3 studies (REC).

Assessment of paediatric data on clinical safety

There are no safety concerns specific to adolescents.

2.6.10. Conclusions on the clinical safety

The safety profile of sipavibart is as anticipated the profile for a monoclonal with an exogenous target. This is acceptable given its proposed use.

Clinical safety recommendation:

Long-term safety data to be submitted including the final CSRs of all 3 studies named SUPERNOVA Parent Main Cohort, SUPERNOVA Sub-study and Little DIPPER (Q3 2025) (REC).

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	None
Important potential risks	None
Missing Information	Use in pregnancy

Pharmacovigilance plan

Table Part III.3: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
A Non-interventional Post-Authorisation Study to Assess Safety of Sipavibart During Pregnancy Study Code: D7000R00017 **Status:** Planned	To evaluate selected pregnancy and offspring health-related adverse outcomes among individuals exposed to sipavibart during pregnancy.	Use in pregnancy	Protocol submission	Q4 2025
			Final report	Q4 2031

2.7.2. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information: Use in pregnancy	Routine risk minimisation measures: SmPC Section 4.6 and Package Leaflet.	Additional pharmacovigilance activities: A Non-interventional Post-Authorisation Study to Assess Safety of Sipavibart During Pregnancy

2.7.3. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Evusheld. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kavigale (sipavibart) is included in the additional monitoring list as *it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.*

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The presently agreed therapeutic indication for Kavigale is:

Kavigale is indicated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments.

Kavigale should be used in accordance with official recommendations where available and based on information on the activity of sipavibart against presently circulating viral variants (see sections 4.4 and 5.1).

Apart from use for "the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive medications or treatments", the applicant initially proposed Kavigale to be also indicated for patients "for whom COVID-19 vaccination is not recommended".

It was however, unclear how the benefit-risk had been shown to be positive in this population or until what extent this does not overlap with the immunocompromised due to a medical condition or receipt of immunosuppressive treatments. The applicant accepted the indication proposed by the Committee.

3.1.2. Available therapies and unmet medical need

Although SARS-CoV-2 Omicron cause less severe disease compared to previous variants, they are highly transmissible and evolve rapidly to achieve immune escape. Vaccination is the key measure to prevent severe COVID-19. However, 2% to 3% of the population may remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to active immunisation. There are presently no approved treatment options for passive immunisation in the EU that are anticipated to be efficacious in preventing infection with presently circulating variants.

3.1.3. Main clinical studies

This application rests on the single pivotal Supernova Main Cohort Study, which recruited patients in EU, UK, USA, Canada, Israel, UAE and East Asia. The start date was March 2023, and the primary analysis was dated March 2024.

This was a randomised double blinded study in adolescents ≥12 year of age or adults with clinically significant immunocompromised.

Subjects were allocated either to receive sipavibart 300 mg i.m or a comparator, which initially was Evusheld 300 mg i.m.. During the study, the comparator was changed from Evusheld to placebo since an initial immunobridging endpoint was diverted to be informed by a different substudy. At that time Evusheld was no longer likely to neutralise circulating viral variants. Moreover, the study had a superiority hypothesis.

After a first dose, subjects were to receive a second dose of sipavibart or comparator (de facto placebo) 6 months later.

The type 1 error controlled primary endpoint was initially time to RT-PCR confirmed symptomatic Sars-Cov-2 infection due to any variant. In a protocol amendment this was changed to a dual primary endpoint with split alpha. This included (a) the abovementioned metric as well as (b) one counting only events due to "matched variants" (= not including the F456L mutation, which abolishes the neutralising ability of sipavibart).

The Primary Analysis was triggered when the median follow-up time was greater than 181 days.

As outlined in the Discussion on Clinical Efficacy both of the key protocol amendments in this double blinded study were acceptable to the CHMP in scientific advice.

3.2. Favourable effects

The sipavibart group showed a statistically significant reduction in risk of symptomatic COVID-19 due to any SARS-CoV-2 variant versus comparator (122/1649 [7.4%] events in the sipavibart arm versus 178/1631 [10.9%] events in the comparator arm) with a relative risk reduction of 34.9% (97.5% CI: 15.0, 50.1; $p < 0.001$).

Reduction in risk of COVID-19 was greater for disease attributed to matched (non F456L mutation containing) SARS-CoV-2 variants versus comparator (54/1649 [3.3%] events in the sipavibart arm versus 90/1631 [5.5%] events in the comparator arm) with a relative risk reduction of 42.9% (95% CI: 19.9, 59.3; $p = 0.001$).

That said, it is not agreed that the applicant's pre-determined estimand censoring for intercurrent vaccination is the most informative with respect to anticipated clinical performance. This is since the target population is, to some extent, likely to also receive vaccines, as did a fifth or so of patients in the SUPERNOVA main cohort.

Notably, the RRR per the any variant endpoint using a treatment policy strategy was 29.9% (95% CI 13.4, 43.3), and for the matched variant endpoint this was 35.3% (95% CI 12.7, 52.0). As these are deemed the most relevant metrics, they are proposed for labelling in the SmPC section 5.1.

3.3. Uncertainties and limitations about favourable effects

No efficacy of sipavibart is anticipated with respect to protection against viral variants containing F456L mutations in the spike protein, since these are not neutralised in vitro. Thus, in the indication, it is reflected to use it considering the available information on the activity of sipavibart against circulating viral variants. "KAVIGALE should be used in accordance with official recommendations where available and based on information on the activity of sipavibart against presently circulating viral variants (see sections 4.4 and 5.1)".

The threshold viral IC50 where any relevant protection may be anticipated remains unclear (see Discussion of Clinical Pharmacology). Correspondingly, it is also not clear what the anticipated duration of protection would be against variants susceptible to sipavibart.

3.4. Unfavourable effects

The total safety database presented for sipavibart consists of approximately 2,100 patients who received a single dose, approximately half of whom also got a 2nd dose.

The main safety dataset, relevant for the target population with clinically significant immunocompromise, pertains to the Supernova Main Cohort Study. In this, approximately 1,600

patients received at least one dose of sipavibart, whereas in the comparator arm about 1,000 patients received a first dose of Evusheld and approximately 600 received a first dose of placebo.

In the Supernova Main Cohort study, any adverse effect within 90 days of the first dose was reported in 50% of subjects receiving sipavibart, 53% of subjects receiving Evusheld, and 48% of subjects receiving placebo. Corresponding figures for SAEs were 7%, 8% and 7%.

The most common AEs reported, regardless of treatment arm, were COVID-19, cough, headache and fatigue, which occurred in 4-10% of subjects.

Identified ADRs include hypersensitivity reactions (0.8% of patient receiving sipavibart and injection site reactions reported in 4%). When sipavibart was given intravenously, 1.9% of subjects had infusion-related reactions. Reactions related to drug administration were mild to moderate.

3.5. Uncertainties and limitations about unfavourable effects

Data on the use of sipavibart in pregnant and breastfeeding patients is absent/limited and it is agreed that this topic should be included as Missing information in the RMP.

3.6. Effects Table

Table 31. Effects table for Kavigale for pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older, who are immunocompromised or for whom COVID-19 vaccination is not recommended.

Effect	Short Description	Unit	sipavibart	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Reduction in risk of symptomatic COVID- 19	Participants with events:	%/n			This analysis censors for the receipt of covid-19 vaccines.	
	Relative risk reduction: All confirmed events		9.2% 151/1649	12.7% 207/1631	RRR 29.9% (95% CI: 13.4, 43.3) (regardless of receipt of COVID-19 vaccinations / medicinal products or unblinding)	SUPERNOVA Parent study Main Cohort*
	Participants with events: Matched variant events, i.e. non-F456 mutation-containing variants		4.4% 72/1649	6.6% 108/1631	RRR 35.3% (95% CI: 12.7, 52.0) (regardless of receipt of COVID-19 vaccinations / medicinal products or unblinding)	SUPERNOVA Parent study Main Cohort*

Effect	Short Description	Unit	sipavibart	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects **						
Immediate AEs *	AEs occurring within 1 hour following study intervention administration.	%	3.1	2.9	Sipavibart: Injection site reactions IM administration: 4.1 % Infusion site reaction IV administration: 1.9% Infusion related reaction IV administration: 2.5% (frequency common)	SmPC/ Little DIPPER
Hypersensitivity	IM administration.	%	0.8	0.2	AE deemed possibly related to by the investigator, within 90 days after the first dose of IMP. (frequency uncommon).	SmPC
SAE frequency	Percentage of subjects with at least one treatment-emergent serious adverse events	%	7.2	7.3	A clearer overview is requested, reporting seems inconsistent	SUPERNOVA Parent study Main Cohort
Related SAE frequency	Percentage of subjects with at least one treatment-related serious adverse events	%	0.1	0.3	Idem (leading to treatment discontinuation 0.1 vs 0.2)	SUPERNOVA Parent study Main Cohort
Related SAE frequency	Percentage of subjects with at least one treatment-related serious adverse events	%	0.1	0.3	Idem (leading to treatment discontinuation 0.1 vs 0.2)	SUPERNOVA Parent study Main Cohort

Effect	Short Description	Unit	sipavibart	Control	Uncertainties/ Strength of evidence	References
AESI	Percentage of subjects with at least one treatment-emergent adverse events of special interest	%	1.1	0.4	Difference mainly driven by CV/TE Events (see below), causality unclear	SUPERNOVA Parent study Main Cohort
Serious AESI frequency	Percentage of subjects with at least one serious treatment-emergent adverse events of special interest	%	0.8	0.4	Idem	SUPERNOVA Parent study Main Cohort

Notes:

* SUPERNOVA Parent study Main Cohort:

- This study started in March 2023 and the primary analysis is dated March 2024 during a period in which mixed variants, including both susceptible and non-susceptible variants, were circulating.

**Anticipated safety profile of sipavibart for a mAb with an exogenous target and no effector functions.

Abbreviations:

Injection site reactions Defined by the following grouped preferred terms at injection site: pain, bruising, erythema, haemorrhage, swelling, haematoma, pruritus, paraesthesia, reaction, rash, discolouration and warmth, occurring within 7 days post-dose.

Infusion site reaction Defined by the following grouped PT:s at infusion site: bruising, pain, pruritus, erythema, extravasation and swelling, occurring within 7 days post-dose.

Infusion related reaction Infusion related reactions occurred within 7 days post-dose.

Hypersensitivity: Defined by the following grouped preferred terms: pruritus, erythema, hypersensitivity, urticaria, dermatitis allergic, and drug eruption, occurring within 14 days post-dose. Hypersensitivity reactions were mild to moderate in severity.

AESI: pre-specified as anaphylaxis and other serious hypersensitivity reactions, including immune complex disease, infusion related reactions, and events adjudicated as cardiovascular and thrombotic events.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The Supernova Main Cohort Study served to establish the efficacy of sipavibart in terms of preventing symptomatic Covid-19 in a patient group with clinically significant immunosuppression. However, the

prespecified primary analysis censors patients upon receipt of COVID-19 vaccines. A treatment policy estimand is deemed more relevant and is presented the SmPC section 5.1.

The effect size, also against "matched variants", is notably lower than what was seen for Evusheld and other products developed prior to the emergence of omicron variants. In the absence of a clear PK/PD rationale for this, one may speculate whether this is due to the differing pathogenic features of omicron compared to prior variants with greater pulmonary tropism.

As previously indicated, sipavibart arm resulted in a statistically significant reduced risk for symptomatic COVID-19 for both primary endpoints investigated, a 35% relative risk reduction against all variants and a 43% relative risk reduction against variants not carrying the F456L mutation, respectively. Variants circulating during the conduct of the trial, where mainly variants without the F456L mutation, with only a minority of variants carrying the F456L mutation.

As has been the case for previous products in this class, the utility of sipavibart is reduced or absent due to viral evolution. Variants emerging as epidemiologically dominant at the time of assessment are not anticipated to be susceptible to sipavibart, as these exhibit the F456L mutation, which abolishes in vitro neutralisation by sipavibart.

Based on data published by ECDC on 25 October 2024, KP.3 is currently the major SARS-CoV-2 variant circulating in the EU/EEA with other variants like BA.2.86, KP.2, KP.1 and KP 3.1.1 co-circulating at low rates (https://www.ecdc.europa.eu/en/covid-19/variants-concern). All these variants, except for BA.2.86, carry the F456L mutation against which sipavibart showed no antiviral activity *in vitro.*

The understanding of PK/PD is not sufficient to provide informative labelling language on what would be the maximal IC50 where sipavibart at the present dose would provide relevant protection, nor what the duration of protection would be. Therefore, the product information remains agnostic as to what viral IC50 is compatible with clinically relevant efficacy, as well as regarding what duration of protection may be anticipated.

The safety profile of sipavibart is as anticipated for a mAb with an exogenous target and no effector functions. There are no specific safety issues.

3.7.2. Balance of benefits and risks

In the Omicron-era, there is still an unmet need with regards to pre-exposure prophylaxis for immunocompromised individuals who can show lower response to vaccination. Therefore, passive immunisation strategies with mAbs may help to address this issue when effective.

The efficacy of sipavibart for the pre-exposure prophylaxis of COVID-19 in immunosuppressed subjects has been demonstrated. Notably, variants circulating during the conduct of the trial, where to a considerable extent without the F456L mutation; however, this is no longer the situation, as the presently predominant variants carry this mutation. Thus, sipavibart is not anticipated to provide clinical benefit in the epidemiological landscape present at the time of approval. The same destiny has befallen all previously approved products in this class.

Several statements are included in the SmPC clearly stating the potential lack of efficacy against SARS-CoV-2 variants harbouring the F456L mutations to ensure that healthcare professionals are aware and do not use sipavibart when these variants are the ones predominantly circulating and therefore to check the national recommendations before using it.

The safety profile is favourable and as anticipated.

The benefit/risk balance is positive.

3.8. Conclusions

The overall benefit/risk balance of Kavigale is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kavigale is favourable in the following indication:

Kavigale is indicated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments.

Kavigale should be used in accordance with official recommendations where available and based on information on the activity of sipavibart against presently circulating viral variants (see sections 4.4 and 5.1).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that sipavibart is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.