ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

KAVIGALE 300 mg solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 300 mg of sipavibart in 2 ml (150 mg/ml).

Sipavibart is a recombinant human immunoglobulin (Ig) G1 based antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipient with known effect

Each vial contains 0.8 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion (injection/infusion)

Clear to opalescent, colourless to slightly yellow, pH 6.0 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

KAVIGALE must be administered by a healthcare professional.

Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored after administration according to local medical practice.

Posology

The recommended dose in adults and adolescents 12 years of age and older weighing at least 40 kg is 300 mg of sipavibart administered as an intramuscular injection or intravenous infusion.

Special populations

Elderly
No dose adjustment is required (see section 5.2).

Renal impairment
No dose adjustment is required (see section 5.2).

Hepatic impairment
No dose adjustment is required (see section 5.2).

Paediatric population
No dose adjustment is required in adolescents 12 years of age and older weighing at least 40 kg (see section 5.2).

The safety and efficacy of sipavibart in children less than 12 years of age and children 12 years of age and older but less than 40 kg have not been established. No data are available.

Method of administration

For intramuscular injection or intravenous infusion.

Intramuscular injection
This medicinal product should be administered as a single intramuscular injection in the anterolateral aspect of the thigh.

Intravenous infusion
Other medicinal products should not be administered through the same infusion line.

After infusion, the administration set should be flushed with sufficient sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection to ensure delivery of the required dose.

Infusion using an infusion bag
Following dilution with sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection, this medicinal product should be administered as an infusion by gravity or with an infusion pump over approximately 20 minutes using an administration set with a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Undiluted infusion using a syringe pump
This medicinal product should be administered with a syringe pump as a 2 ml (300 mg) undiluted intravenous infusion over at least 6 minutes.

If signs and symptoms of an infusion-related reaction (IRR) occur, the infusion should be interrupted, slowed, or stopped and appropriate medicinal products and/or supportive therapy should be administered (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Antiviral resistance

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).

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 shown in Table 2 (see section 5.1).

Patients who receive sipavibart should be informed of the potential for breakthrough infections to occur. If signs or symptoms of COVID-19 occur (the most common symptoms include fever, chills, sore throat, cough, tiredness, and new loss of taste or smell; the most serious symptoms include difficulty breathing or shortness of breath, loss of speech or mobility, or confusion and chest pain), advise individuals to promptly seek medical attention.

Hypersensitivity including anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with human immunoglobulin G1 (IgG1) monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration, and initiate appropriate medicinal products and/or supportive therapy.

Infusion-related reactions

IRRs were observed in clinical trials with intravenous administration of sipavibart and were mild in severity (see section 4.8). If signs and symptoms of an IRR occur, the infusion should be interrupted, slowed, or stopped and appropriate medicinal products and/or supportive therapy should be administered.

Clinically significant bleeding disorders

As with any other intramuscular injections, sipavibart should be given with caution to patients with thrombocytopenia or any coagulation disorder.

COVID-19 vaccines

Pre-exposure prophylaxis with sipavibart is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.

Excipient with known effect

This medicinal product contains 0.8 mg of polysorbate 80 in each vial. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Sipavibart is not expected to be renally excreted or metabolised by cytochrome P450 enzymes (see section 5.2). Therefore, interactions with concomitant medicinal products that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of sipavibart in pregnant women.

Non-clinical reproductive toxicity studies have not been performed with sipavibart. In a tissue cross reactivity study with sipavibart, no binding was detected to human foetal tissue or reproductive tissues.

Human IgG1 antibodies are known to cross the placenta barrier; therefore, sipavibart has the potential to be transferred from the mother to the developing foetus. It is unknown whether the potential placental transfer of sipavibart provides any treatment benefit or risk to the developing foetus.

Sipavibart should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus.

Breast-feeding

It is unknown whether sipavibart is excreted in human milk. In humans, excretion of IgG antibodies in milk occurs during the first few days after birth, decreasing to low concentrations soon afterwards. Consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, sipavibart could be used during breast-feeding if clinically needed.

Fertility

There are no data on the effects of sipavibart on human fertility.

4.7 Effects on ability to drive and use machines

KAVIGALE has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In patients receiving sipavibart by intramuscular injection, the most common adverse reaction is injection site reaction (4.1%). In patients receiving sipavibart by intravenous infusion, the most common adverse reactions are infusion site reactions (1.9%) and infusion-related reactions (1.9%).

Tabulated list of adverse reactions

Table 1 presents the adverse reactions identified from the clinical studies.

The adverse reactions in Table 1 are listed by MedDRA system organ class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency, and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), and not known (cannot be estimated from the available data).

Table 1 Tabulated list of adverse reactions

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

[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 flushing, coughing, chest discomfort, dizziness, and shortness of breath.

Description of selected adverse reactions

Hypersensitivity
Hypersensitivity reactions occurred within 14 days post-dose, were mild to moderate in severity, and most resolved within a few days.

Injection site reactions
Injection site reactions occurred within 7 days post-dose, were mild in severity, and most resolved within a few days.

Infusion site reactions
Infusion site reactions occurred within 7 days post-dose, were mild to moderate in severity, and resolved within a few days.

Infusion-related reactions
Infusion-related reactions occurred during or on the same day of infusion, were mild to moderate in severity, and resolved within a few days.

Paediatric population

There are limited safety data available for paediatric patients ≥ 12 years to < 18 years of age (n=8). No data are available for paediatric patients < 12 years of age. The safety profile in paediatric participants ≥ 12 years of age was similar to the safety profile in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for overdose with sipavibart.

In clinical trials, sipavibart doses up to 1 200 mg have been administered intravenously without dose-limiting toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immune sera and immunoglobulins, antiviral monoclonal antibodies, ATC code: J06BD09

Mechanism of action

Sipavibart is a recombinant human IgG1 monoclonal antibody that provides passive immunisation by binding the SARS-CoV-2 spike protein receptor binding domain (RBD). Sipavibart is long-acting, with amino acid substitutions to extend antibody half-life (YTE) and to reduce antibody effector function and potential risk of antibody-dependent enhancement of disease (TM). 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. This results in a blockade of virus entry.

Antiviral activity

In a SARS-CoV-2 pseudovirus neutralisation assay, sipavibart had antiviral activity through direct neutralisation.

Antiviral resistance

Evaluation of neutralisation susceptibility of variants identified through global surveillance and in participants who received sipavibart is ongoing.

Neutralisation activity of sipavibart against pseudovirus SARS-CoV-2 variants are shown in Table 2.

Table 2 Sipavibart pseudovirus neutralisation data against SARS-CoV-2 variants

Lineage with spike protein substitutions		**Characteristic RBD substitutions tested**	**Fold reduction in susceptibility[a]**	**IC_{50} (ng/ml)**
Pango lineage (origin)	**WHO label**		**Pseudovirus[b]**	
BA.2 (Multiple countries)	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

Lineage with spike protein substitutions		Characteristic RBD substitutions tested	Fold reduction in susceptibility[a]	IC_{50} (ng/ml)
Pango lineage (origin)	WHO label		Pseudovirus[b]	
BA.4/5 (Multiple countries)	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 countries)	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 countries)	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 countries)	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

Lineage with spike protein substitutions		Characteristic RBD substitutions tested	Fold reduction in susceptibility[a]	IC_{50} (ng/ml)
Pango lineage (origin)	WHO label		Pseudovirus[b]	
XBB.1.5/XBB.1.9 (Multiple countries)	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 countries)	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
XBB.1.5.10/EG.5 (Multiple countries)	Omicron XBB.1.5.10/EG.5	XBB.1.5 + F456L	> 50-fold	> 1 000[c]
EG.5.1 (Multiple countries)	Omicron EG.5.1	XBB.1.5 + Q52H + F456L	> 50-fold	> 1 000[c]

Lineage with spike protein substitutions		Characteristic RBD substitutions tested	Fold reduction in susceptibility[a]	IC_{50} (ng/ml)
Pango lineage (origin)	WHO label		Pseudovirus[b]	
BA.2.86[d] (Multiple countries)	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 countries)	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
KP.2, KP.3, LB.1, KP.3.1.1 (Multiple countries)	Multiple	Defining mutation: F456L	> 50-fold[c]	> 1 000[c,e]

[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 (IC_{50}) of monoclonal antibody required for a 50% reduction in infection compared to ancestral reference strain (Wuhan D614G).

[b] Pseudoviruses expressing the entire SARS-CoV-2 spike variant protein and individual characteristic spike substitutions.

[c] Sipavibart is not deemed 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.

[e] Presumed IC_{50} based on presence of F456L mutation in the variant.

Immunogenicity

Treatment-emergent anti-drug antibodies (ADA) were uncommonly (0.8% (5/604)) detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. However, data are still limited.

Clinical efficacy

SUPERNOVA parent study, main cohort

The SUPERNOVA parent study, main cohort is a Phase III, randomised (1:1), double-blind, comparator-controlled clinical trial studying sipavibart for the pre-exposure prophylaxis of COVID-19 in immunocompromised adults and adolescents ≥ 12 years of age. 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.

A total of 1 669 adults and adolescents ≥ 12 years of age and weighing at least 40 kg were randomised to receive a single dose of sipavibart 300 mg via intramuscular injection, and 1 666 were randomised to receive a comparator (tixagevimab 300 mg + cilgavimab 300 mg or placebo). Participants received a second dose of sipavibart 300 mg or placebo 6 months after the initial dose. The study excluded participants who received COVID-19 vaccine or those with a history of laboratory-confirmed or rapid-test confirmed SARS-CoV-2 infection within 3 months prior to the first visit. At interim analysis, the median follow-up time post-second dose was 61 days (range 1 to 180 days).

The baseline demographics were balanced across the sipavibart and comparator treatment arms. The median age was 60 years [36.3% 65 years of age or older, 15 participants 12 years to less than 18 years (including 8 who received sipavibart)], 56.8% of participants were female, 74.1% were Caucasian, 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 but not limited to:

- taking immunosuppressive medication (74.3%)
- haematologic malignancy (15.3%)
- moderate/severe secondary immunodeficiencies (predominantly haemodialysis) (15.1%)
- solid organ transplant (14.2%)
- within one year of receiving B-cell depleting therapies (13.3%)
- solid tumour cancer and on treatment (3.4%)
- haematopoietic stem-cell transplantation (2.0%)
- moderate/severe primary immunodeficiencies (1.6%)
- advanced or untreated HIV infection (1.1%), and
- received chimeric antigen receptor T-cell therapy (0.3%)

The study included dual primary efficacy endpoints, comparing the efficacy of sipavibart to a comparator in the prevention of symptomatic COVID-19 (1) caused by any SARS-CoV-2 variant up to 181 days post last dose confirmed by RT-PCR and (2) attributable to matched variants (variants that do not contain the F456L mutation based on viral sequencing data and are expected to be susceptible to sipavibart) up to 181 days post last dose confirmed by RT-PCR. For each of the dual primary endpoints, a superiority test was performed to compare the relative risk of symptomatic COVID-19 between treatment arms.

Relative risk reduction where events were counted regardless of receipt of COVID-19 vaccinations / medicinal products or unblinding is presented in Table 3.

Table 3 Relative risk reduction of symptomatic COVID-19

	N	Number of events, n (%)	Relative risk reduction, % (CI)[b]
Overall primary efficacy endpoint over 6 months post-dose			
Sipavibart	1 649	151 (9.2%)	29.9% (95% CI: 13.4, 43.3)
Comparator[a]	1 631	207 (12.7%)	
Matched variant primary efficacy endpoint over 6 months post-dose			
Sipavibart	1 649	72 (4.4%)	35.3% (95% CI: 12.7, 52.0)
Comparator[a]	1 631	108 (6.6%)	

CI = Confidence Interval, N = number of participants in the analysis.

[a] The comparator was either tixagevimab + cilgavimab or placebo.

[b] Not multiplicity controlled.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with sipavibart in one or more subset of the paediatric population in the pre-exposure prophylaxis of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following a single dose, sipavibart demonstrated approximately dose proportional increase in serum exposure as doses increased in the range of 300 mg to 600 mg for intramuscular injection or 300 mg to 1 200 mg for intravenous infusion.

Absorption

Following a single 300 mg intramuscular dose of sipavibart in the anterolateral thigh, the geometric mean (geometric coefficient of variation (CV%)) of the maximum serum concentration (C_{max}) of sipavibart was 48.0 (25.2%) µg/ml. The median time (range) to C_{max} was 7.5 (3.9, 53) days.

Based on population PK analysis, the estimated absolute bioavailability of sipavibart following intramuscular administration in the anterolateral thigh is 80.7%.

Following the first and second dose of 300 mg sipavibart administered intramuscularly in the anterolateral thigh, the geometric mean serum sipavibart concentrations (CV%) at one-month post-dose were 29.8 (36.2%) µg/ml and 30.8 (54.3%) µg/ml, respectively. Doses were administered 6 months apart.

Following a single infusion of 300 mg and 1 200 mg sipavibart (infusion rate: 50 mg/min), the geometric mean (CV%) serum concentration of sipavibart at 20 minutes post-infusion was 101.6 (7.6%) µg/ml and 452.1 (25.8%) µg/ml, respectively.

Distribution

The geometric mean (CV%) apparent volume of distribution for sipavibart was 6.3 (19.4%) L following a single 300 mg intramuscular administration in the anterolateral thigh.

Based on population PK analysis, the estimated central and peripheral volume of distribution (relative standard error, RSE%) for sipavibart was 4.6 (1.3%) L and 0.4 (19.6%) L, respectively, following intravenous administration.

Biotransformation

Sipavibart is expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

Elimination

Following a single 300 mg intramuscular dose in the anterolateral thigh, the geometric mean (CV%) clearance of sipavibart was 0.053 (43.1%) L/day, and the estimated mean terminal elimination half-life (standard deviation) of sipavibart was 87.3 (26.5) days.

Based on population PK analysis, the estimated clearance (RSE%) of sipavibart following intravenous administration was 0.044 (0.9%) L/day.

Special populations

Renal impairment
No specific studies have been conducted to examine the effects of renal impairment on the PK of sipavibart.

Sipavibart has a molecular weight (MW) of approximately 148 kDa and is not expected to be excreted intact in the urine. Renal impairment is not expected to significantly affect the exposure of sipavibart. Similarly, dialysis is not expected to impact the PK.

Hepatic impairment
No specific studies have been conducted to examine the effects of hepatic impairment on the PK of sipavibart.

Sipavibart is expected to be catabolised by multiple tissues through proteolytic degradation into amino acids and recycling into other proteins, therefore hepatic impairment is not expected to affect the PK of sipavibart.

Elderly
Exposure to sipavibart in older adults ≥ 65 years of age (n=233) was comparable to that in younger adults 18 to < 65 years of age (n=354).

Paediatric population
The recommended dose regimen is expected to result in comparable serum exposures of sipavibart in adolescents 12 years of age or older who weigh at least 40 kg as observed in adults, since adults with similar body weight have been included in the clinical studies with sipavibart.

Other special populations
There were no clinically meaningful differences in serum exposures to sipavibart based on sex, age (12 to 85 years of age), race, or ethnicity.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, and reproductive toxicology studies with sipavibart have not been conducted.

Non-clinical data reveal no special hazard for humans based on studies of tissue binding and a repeat dose toxicity study in cynomolgus monkeys, including assessment of safety pharmacology and local tolerance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine monohydrochloride
Arginine hydrochloride
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

2 years

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.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze. Do not shake.

Keep the vial in the outer carton in order to protect from light.

For storage conditions of prepared syringes and prepared infusion bags, see section 6.3.

6.5 Nature and contents of container

2 ml of solution for injection/infusion in a clear glass vial closed by a chlorobutyl elastomeric stopper sealed with a light green aluminium flip-off top.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

KAVIGALE is supplied as a single-dose vial. KAVIGALE may be administered via an intramuscular injection or via an intravenous infusion using an infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection or a syringe pump. The solution for injection/infusion should be prepared and administered by a healthcare professional, using aseptic technique as follows:

Preparation of the solution before administration

1. Remove the vial from refrigerated storage.

2. Visually inspect the vial for particulate matter and discolouration. The solution is clear to opalescent, colourless to slightly yellow. Discard the vial if the solution is cloudy, discoloured, or visible particles are observed. Do not shake the vial.

For storage conditions of the prepared syringe or prepared infusion bag, see section 6.3.

Intramuscular injection

1. Withdraw 2 ml from the vial into a syringe.

2. Administer the intramuscular injection in the anterolateral aspect of the thigh.

Intravenous infusion – infusion bag or syringe pump

Preparation of solution
1. Withdraw 2 ml from the vial and prepare an admixture for infusion by transferring into a 50 ml or 100 ml infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection, or administer using a syringe pump (see below).

2. Do not freeze or shake the solution.

Administration – infusion bag
1. Do not co-administer other medicinal products through the same infusion line.

2. Administer the infusion solution intravenously via infusion pump or gravity over approximately 20 minutes through an intravenous line containing a sterile, low protein-binding 0.2 or 0.22 micron in-line filter.

3. Once the infusion is complete, flush the tubing with sufficient sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection to ensure delivery of the required dose.

Administration – syringe pump
1. Administer 2 ml (300 mg) as an undiluted intravenous infusion using a syringe pump over at least 6 minutes.

2. After the entire contents of the syringe have been administered, flush the administration set with a sufficient volume of sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection to ensure that the full dose has been administered.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER

EU/1/24/1900/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 January 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Wuxi Biologics Co. Ltd.
108 Meiliang Road,
Binhu, Wuxi, Jiangsu 214092,
China

Name and address of the manufacturer responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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 (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

KAVIGALE 300 mg solution for injection/infusion
sipavibart

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 300 mg of sipavibart in 2 ml (150 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride, arginine hydrochloride, polysorbate 80 (E 433), water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection/infusion
1 vial
300 mg/2 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular or intravenous use
Read the package leaflet before use.
For single use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the vial in the outer carton in order to protect from light.
Do not freeze.
Do not shake.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER

EU/1/24/1900/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

KAVIGALE 300 mg injection/infusion
sipavibart

IM/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg/2 ml

6. OTHER

AstraZeneca

B. PACKAGE LEAFLET

Package leaflet: Information for the user

KAVIGALE 300 mg solution for injection/infusion
sipavibart

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before the medicine is given because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What KAVIGALE is and what it is used for

KAVIGALE is a medicine called a monoclonal antibody. It contains the active substance sipavibart.

KAVIGALE is used to help prevent COVID-19 (pre-exposure prophylaxis). It is used in adults and adolescents aged from 12 years and weighing at least 40 kg who are at increased risk of infection because they have a weakened immune system caused by a medical condition or by treatments.

The active substance in KAVIGALE (sipavibart) is designed to recognise and attach to a specific protein of the SARS-CoV-2 virus that causes COVID-19. This prevents the virus from entering into your cells and from spreading between cells. This may help your body to resist the infection.

2. What you need to know before you are given KAVIGALE

You must not be given this medicine
- if you are allergic to sipavibart or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or nurse before you are given KAVIGALE
- if you have low numbers of blood platelets (components which help blood clotting), any blood clotting problems or if you are taking a medicine to prevent blood clots (an anticoagulant).

This medicine may cause an allergic reaction, which may be severe or life-threatening. **If you notice any signs or symptoms of an allergic reaction, get medical help immediately.** Signs and symptoms of an allergic reaction include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue, or throat
- severe itching of the skin, with a red rash or raised bumps.

KAVIGALE may cause a reaction to the infusion (drip). This could happen immediately or within a few hours of the infusion. Symptoms may include:
- feeling sick (nausea)
- joint pain
- headache
- fever and chills
- upset stomach
- pain
- feeling lightheaded or faint
- red, warm face
- coughing
- chest discomfort
- dizziness
- shortness of breath.

Talk to a doctor or nurse if you notice any of these symptoms.

You may still get COVID-19 after you receive KAVIGALE. The SARS-CoV-2 virus that causes COVID-19 changes over time and KAVIGALE may not protect you against every circulating variant of the virus. COVID-19 affects different people in different ways, but the most common symptoms include:
- fever
- chills
- sore throat
- cough
- tiredness
- new loss of taste or smell.

The most serious symptoms of COVID-19 include:
- difficulty breathing or shortness of breath
- loss of speech or mobility
- confusion
- chest pain.

Talk to a doctor right away if you get symptoms of COVID-19.

Children and adolescents
KAVIGALE should not be given to children under 12 years of age and children 12 years of age and older weighing less than 40 kg. It has not been studied in these populations.

Other medicines and KAVIGALE
It is not known if this medicine affects other medicines, or if it is affected by them. Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
Tell your doctor or nurse if you are pregnant, think you may be pregnant or are planning to have a baby.

This medicine has not been studied in pregnant women. It is not known if it can affect the unborn child. Your doctor will only give this medicine if the potential benefits of treatment to the mother outweigh the potential risks to the unborn child.

Tell your doctor or nurse if you are breast-feeding. It is not yet known whether this medicine passes into human breast milk, and what the effects might be on the baby. Your doctor will help you decide whether you can breast-feed or not.

Driving and using machines
It is unlikely that KAVIGALE will affect your ability to drive or use machines.

KAVIGALE contains polysorbate 80
This medicine contains 0.8 mg of polysorbate 80 in each vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How KAVIGALE is given

The recommended dose is 300 milligrams (mg).

KAVIGALE is given by your doctor or nurse as an injection into the muscle of your thigh or as an infusion into your vein. Depending on how you are given the infusion, the procedure lasts from 6 to about 20 minutes.

Your doctor or nurse will decide how long you will be monitored for side effects after you are given the medicine.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Patients receiving medicines similar to KAVIGALE have experienced serious allergic reactions. If you experience symptoms of a serious allergic reaction, immediately contact a doctor or go to the emergency centre. Signs and symptoms of an allergic reaction include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue, or throat
- severe itching of the skin, with a red rash or raised bumps.

Other side effects:

Common (may affect up to 1 in 10 people)
- Injection site reactions (reactions near where the injection in the muscle was given, such as pain, bruising, redness, bleeding, swelling, blood under the skin, itching, numbness and tingling, rash, discolouration, and warm feeling on the skin).
- Infusion site reactions (reactions near where the infusion in the vein was given, such as bruising, pain, itching, redness, and swelling).
- Reactions related to the infusion (reactions that affect the body, such as feeling sick, joint pain, headache, and fever).

Uncommon (may affect up to 1 in 100 people)
- Allergic reaction (hypersensitivity) including itching, skin redness, hives, rash.

Reporting of side effects
If you get any side effects, **talk to your doctor, pharmacist or nurse**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store KAVIGALE

Keep this medicine out of the sight and reach of children.

Your doctor, pharmacist or nurse is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Unopened vials:
- Store in a refrigerator (2°C – 8°C).
- Do not freeze.
- Do not shake.
- Keep the vial in the outer carton in order to protect from light.

Prepared syringes or prepared infusion bags should be used immediately. If necessary, store the prepared syringes or prepared infusion bags for no more than:
- 24 hours at 2°C to 8°C, and
- 4 hours at room temperature up to 25°C.

6. Contents of the pack and other information

What KAVIGALE contains
- The active substance is sipavibart. Each vial contains 300 mg sipavibart in 2 ml of solution.

The other ingredients are histidine, histidine monohydrochloride, arginine hydrochloride, polysorbate 80 (E 433) and water for injections.

What KAVIGALE looks like and contents of the pack
KAVIGALE is a clear to opalescent, colourless to slightly yellow solution for injection/infusion (injection/infusion), provided in a clear glass vial with a light green cap.

Each carton contains 1 vial.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Tel: +46 8 553 26 000

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

KAVIGALE is supplied as a single-dose vial. KAVIGALE may be administered via an intramuscular injection or via an intravenous infusion using an infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection or a syringe pump. The solution for injection/infusion should be prepared and administered by a healthcare professional, using aseptic technique as follows:

Preparation of the solution before administration

1. Remove the vial from refrigerated storage.
2. Visually inspect the vial for particulate matter and discolouration. The solution is clear to opalescent, colourless to slightly yellow. Discard the vial if the solution is cloudy, discoloured, or visible particles are observed. Do not shake the vial.

For storage conditions of the prepared syringe or prepared infusion bag, see Summary of Product Characteristics (SmPC) section 6.3.

Intramuscular injection

1. Withdraw 2 ml from the vial into a syringe.
2. Administer the intramuscular injection in the anterolateral aspect of the thigh.

Intravenous infusion – infusion bag or syringe pump

Preparation of solution
1. Withdraw 2 ml from the vial and prepare an admixture for infusion by transferring into a 50 ml or 100 ml infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection, or administer using a syringe pump (see below).
2. Do not freeze or shake the solution.

Administration – infusion bag
1. Do not co-administer other medicinal products through the same infusion line.
2. Administer the infusion solution intravenously via infusion pump or gravity over approximately 20 minutes through an intravenous line containing a sterile, low protein-binding 0.2 or 0.22 micron in-line filter.
3. Once the infusion is complete, flush the tubing with sufficient sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection to ensure delivery of the required dose.

Administration – syringe pump
1. Administer 2 ml (300 mg) as an undiluted intravenous infusion using a syringe pump over at least 6 minutes.

2. After the entire contents of the syringe have been administered, flush the administration set with a sufficient volume of sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection to ensure that the full dose has been administered.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.