AusPAR - Kavigale - Sipavibart - AstraZeneca Pty Ltd - PM-2024-03590-1-2
Date of finalisation: 7 April 2026. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-pi**>**

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

KAVIGALE®
(sipavibart) solution for injection/infusion

1 NAME OF THE MEDICINE

Sipavibart

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear to opalescent, colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

KAVIGALE is not recommended as a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.

4.2 DOSE AND METHOD OF ADMINISTRATION

KAVIGALE must be administered by a healthcare professional.

Individuals should be monitored after administration according to local medical practice.

Dosage

The dosage in adults and adolescents aged 12 years and older weighing at least 40 kg is 300 mg of KAVIGALE administered as an intramuscular injection or intravenous infusion. Subsequent doses of 300 mg KAVIGALE administered as an intramuscular injection or intravenous infusion may be given every 3 months until no longer required.

Special patient populations

Renal impairment

No dose adjustment is required (see Section 5.2).

Hepatic impairment

No dose adjustment is required (see Section 5.2).

Use in the elderly

No dose adjustment is required (see Section 5.2).

Paediatric use

No dose adjustment is required in adolescents aged 12 years and older and weighing at least 40 kg (see Section 5.2). The safety and efficacy of KAVIGALE in children aged <12 years have not been established.

Method of administration

KAVIGALE may be administered via an intramuscular injection or via intravenous infusion using an infusion bag or a syringe pump.

Intramuscular injection

Intramuscular injection of KAVIGALE should be made preferably in the anterolateral aspect of the thigh. The solution for injection should be prepared and administered by a healthcare professional, using aseptic technique as follows:

1. Remove KAVIGALE vial from refrigerated storage.
2. Inspect the vial visually for particulate matter and discolouration. KAVIGALE is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.
3. Withdraw 2 mL sipavibart into a syringe. For storage conditions of the prepared syringe, see Section 6.3.
4. Administer the intramuscular injection, preferably in the anterolateral aspect of the thigh.
5. Discard any unused portion left in the vial.
6. Individuals should be monitored after administration according to local medical practice.

Intravenous infusion

KAVIGALE may be administered diluted in a 50 mL or 100 mL infusion bag over approximately 20 minutes, or undiluted using a syringe pump over at least 6 minutes. The solution for infusion should be prepared and administered by a healthcare professional, using aseptic technique as follows:

Preparation of solution

1. Remove KAVIGALE vial from refrigerated storage.

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

3. 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).

4. Do not freeze or shake the solution. For storage conditions of the prepared syringe or prepared infusion bag, see Section 6.4.

5. Discard any unused portion left in the vial.

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 50 mg/mL (5%) dextrose injection to ensure delivery of the required dose.

4. Individuals should be monitored after administration according to local medical practice.

Administration – syringe pump

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

2. It is recommended to use administration set components of the lowest volume possible to ensure sufficient dose delivery prior to flushing.

3. 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 50 mg/mL (5%) dextrose injection to ensure that the full dose has been administered.

4. Individuals should be monitored after administration according to local medical practice.

If signs and symptoms of an infusion-related reaction occur, interrupt, slow or stop the infusion and administer appropriate medicinal products and/or supportive therapy (see Section 4.4).

4.3 CONTRAINDICATIONS

Individuals with a history of severe hypersensitivity reactions, including anaphylaxis, to the active substance or to any of the excipients listed in Section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity including anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have not been observed with KAVIGALE in clinical trials, but have been observed with other 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.

Cardiovascular and/or thrombo-embolic events

In the SUPERNOVA Parent Study, Main Cohort, more participants in the KAVIGALE arm experienced cardiac or thrombo-embolic adverse events as compared to those in the comparator (EVUSHELD or placebo) arms 181 days after the first dose (3.8% versus 2.9%). The majority of participants had cardiovascular risk factors and/or history of cardiovascular disease that could explain the occurrence of such events.

A causal relationship between KAVIGALE and these events has not been established.

Patients should be advised of signs or symptoms suggestive of cardiovascular event (notably chest pain, dyspnoea, malaise, feeling lightheaded or faint) and to seek immediate medical attention if such symptoms occur.

Infusion-related reactions

Infusion-related reactions (IRRs) were observed in clinical trials with intravenous administration of sipavibart and were mild in severity (see Section 4.8). If an IRR occurs, consider interrupting, slowing or stopping the infusion, and initiate appropriate medicinal products and/or supportive therapy.

Clinically significant bleeding disorders

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

Risk of breakthrough infection due to SARS-CoV-2 viral variants not neutralised by sipavibart

Certain SARS-CoV-2 viral variants may not be neutralised *in vitro* by monoclonal antibodies such as sipavibart. KAVIGALE may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. 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 KAVIGALE 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.

Use in the elderly

See Section 5.2 Pharmacokinetic properties.

Paediatric use

The safety and efficacy of sipavibart in children aged <12 years has not been studied and no data is available. There is limited clinical trial evidence supporting the safety and efficacy of sipavibart in children 12-18 years of age due to the low number of trial participants in this age group (See SUPERNOVA study in Clinical Trials).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been conducted.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Category B2

There are no data from 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 fetal tissue or reproductive tissues (e.g., placenta).

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

KAVIGALE should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Use in lactation

It is not known whether sipavibart is excreted in human milk, but maternal IgG is known to be present in human milk. Exposure to the breast-fed child cannot be excluded.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for KAVIGALE and any potential adverse effects on the breast-fed child from KAVIGALE or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Sipavibart is expected to have no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Overall, 2061 participants (1691 via intramuscular injection and 370 via intravenous administration) have been exposed to sipavibart in clinical trials.

In the Phase III SUPERNOVA Parent Study, Main Cohort 1671 immunocompromised adult and adolescent participants ≥ 12 years of age and weighing at least 40 kg were exposed to an initial dose of sipavibart 300 mg administered by intramuscular injection and 1485 were exposed to two doses (see Section 5.1).

The Phase II SUPERNOVA Sub-Study, a randomised, open-label study, 310 participants ≥ 18 years of age and weighing at least 40 kg, who were either immunocompromised or immunocompetent with all degrees of SARS-CoV-2 infection risk, were exposed to sipavibart 1200 mg via intravenous infusion.

The Phase I Little DIPPER study (n=80), a double-blind, placebo-controlled study, enrolled 80 healthy adults 18-55 years of age with a minimum weight of 45 kg. Participants received KAVIGALE 300 mg (n=10) or 600 mg (n=10) by intramuscular injection, or 300 mg (n=10), 600 mg (n=10), or 1200 mg (n=40) by intravenous infusion. The safety profile of KAVIGALE observed in this study was consistent with the safety profile in other trials of KAVIGALE.

Adverse Drug Reactions

Table 1 presents the adverse reactions identified from the Phase II and Phase III studies.

Adverse drug reactions (ADRs) are organised 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 <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 1 Adverse reactions

MedDRA SOC	MedDRA Preferred Term	Frequency
Intramuscular administration		
Immune system disorders	Hypersensitivity[a]	Common (1.9%)
General disorders and administration site conditions	Injection site reaction[b]	Common (5.6%)
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 Preferred Terms pruritus, erythema, hypersensitivity, urticaria, dermatitis allergic, drug eruption, rash and hypotension.

[b] Including the 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, injection site warmth, injection site discomfort, and injection site inflammation.

[c] Including the 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, and hypotension.

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. None of the hypersensitivity reactions were serious.

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

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

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

Repeat dosing

In the SUPERNOVA Parent Study, Main Cohort, 1485 participants who had received an initial dose of 300 mg sipavibart received a second dose of 300 mg sipavibart 6 months after administration of the initial dose. The overall safety profile for participants who received a second sipavibart dose remained similar when compared to the initial dose.

Paediatric population

There are limited safety data available for paediatric patients <18 years old. The safety profile in paediatric participants ≥12 years of age was similar to the safety profile in adults.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific treatment for overdose with sipavibart.

In clinical trials, sipavibart doses up to 1200 mg have been administered intravenously without dose-limiting toxicity.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Sipavibart is a recombinant human IgG1 monoclonal antibody that provides passive immunisation by binding the 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 K_D = 20.95 pM, blocking RBD binding to the human ACE2 receptor (IC50 102.4 ng/mL, 0.6829 nM). This results in a blockade of virus entry and effective neutralisation of the SARS-CoV-2 virus.

Antiviral activity

In a SARS-CoV-2 research-grade focus reduction neutralisation test (FRNT) assay, sipavibart had antiviral activity with IC_{50} values of 110.9, 53.6, 25.9, 13.1, 8.3, 32.2, 26.5 and 15.3 ng/mL for SARS-CoV-2 variants D614G, Alpha, Delta, BA.1, BA.1.1, BA.2, BA.2.12.1 and BA.5, respectively. In Pseudovirus neutralisation assay, sipavibart had antiviral activity through direct neutralisation with IC_{50} values were between 3.6 ng/mL (XBB.1 variant) and 25 ng/mL (BA.2.75 variant).

Antibody-dependent cell-mediated cytotoxicity (ADCC) was assessed using target cells that carry SARS-CoV-2 spike protein, with monoclonal antibody concentrations at a range of 1.53 ng/mL to 25 µg/mL. Antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent complement deposition (ADCD) were assessed using spike antigen-functionalised beads. ADCP activity was assessed with primary human neutrophils or THP-1 human monocytic cell line, with antibody concentrations at a range of 2.3 ng/mL to 5 µg/mL. ADCD activity was assessed with antibody concentrations at a range of 45.7 ng/mL to 100 µg/mL. Antibody-dependent NK cell activation (ADNKA) was assessed using primary human NK cells on spike-coated plates with monoclonal antibody concentrations at a range of 9.15 ng/mL to 20 µg/mL Sipavibart showed reduced or no antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or antibody-dependent natural killer cell activation (ADNKA) in cell culture studies. Sipavibart did not mediate antibody-dependent complement deposition (ADCD) activity with guinea pig complement proteins.

Antibody dependent enhancement (ADE) of infection

The potential of sipavibart to mediate antibody-dependent viral entry was assessed in FcγRII-expressing Raji cells co-incubated with recombinant virus pseudotyped with SARS-CoV-2 spike protein, with antibody concentrations at a range of 3125 ng/mL to 12.8 fg/mL. Sipavibart did not mediate entry of pseudovirus into these cells.

Antiviral resistance

Escape variants were identified following serial passage in cell culture of SARS-CoV-2 or recombinant vesicular stomatitis virus encoding SARS-CoV-2 spike protein in the presence of sipavibart. Variants which showed reduced susceptibility to sipavibart included spike protein amino acid substitutions T415I (≥103-fold), K458E (>769-fold), and F456L (>769- fold).

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

Sipavibart neutralises many circulating SARS-CoV-2 variants in pseudovirus neutralisation assays, however it does not retain *in vitro* neutralisation activity against XBB subvariants harbouring an F456L mutation.

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
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

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]**	
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
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

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.1.16 (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	>1000[c]
EG.5.1 (Multiple countries)	Omicron EG.5.1	XBB.1.5 + Q52H + F456L	>50-fold	>1000[c]
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

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]**	
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

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

Pharmacodynamic effects

Following a single intramuscular dose of 300 mg sipavibart, nAb geometric mean titres (GMT) at Days 29, 91, and 181 were higher in the sipavibart group against all tested variants versus placebo.

Immunogenicity

Among participants who received sipavibart, 4.8% (29/604) were ADA-positive at any time and 0.8% (5/604) were treatment-emergent-ADA-positive. The low rate of ADA positive participants does not allow for complete assessment of the impact of ADA on the PK and safety of sipavibart.

Clinical trials

SUPERNOVA Parent Study, Main Cohort

The SUPERNOVA Parent Study, Main Cohort, is an ongoing Phase III, randomised (1:1), double-blind, comparator-controlled clinical trial studying KAVIGALE for the pre-exposure prophylaxis of COVID-19 in immunocompromised adults and adolescents ≥12 years of age. A total of 1669 adults and adolescents ≥12 years of age and weighing at least 40 kg were randomised to receive a single dose of KAVIGALE 300 mg via IM injection and 1666 were randomised to receive comparator (EVUSHELD or placebo). Participants received a second dose of KAVIGALE 300 mg or placebo 6 months after the initial dose. The study excluded participants who received COVID-19 vaccine or with a history of laboratory-confirmed or rapid-test confirmed SARS-CoV-2 infection within 3 months prior to the first visit.

The baseline demographics were balanced across the KAVIGALE and comparator treatment arms. The median age was 60 years (36.3% 65 years of age or older; 15 participants were 12 years to less than 18 years of age), 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 but not limited to:

- 74.3% Taking immunosuppressive medication
- 15.3% Hematologic malignancy
- 15.1% Moderate/severe secondary immunodeficiencies (predominantly hemodialysis)
- 14.2% Solid organ transplant
- 13.3% Within 1 year of receiving B-cell depleting therapies
- 3.4% Solid tumour cancer and on treatment
- 2.0% Hematopoietic stem-cell transplantation
- 1.6% Moderate/severe primary immunodeficiencies
- 1.1% Advanced or untreated HIV infection
- 0.3% Received chimeric antigen receptor T-cell therapy

The study included dual primary efficacy endpoints, comparing the efficacy of KAVIGALE to 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.

KAVIGALE administration resulted in 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; $p=0.001$), see Table 3. The median follow-up time post-second dose was 61 days (range 1 to 180 days). A Kaplan-Meier time to event analysis was conducted to assess the primary endpoint result over time. It shows separation of the sipavibart and comparator curves, suggesting time to first symptomatic COVID-19 event was longer for sipavibart versus comparator, see Figure 1.

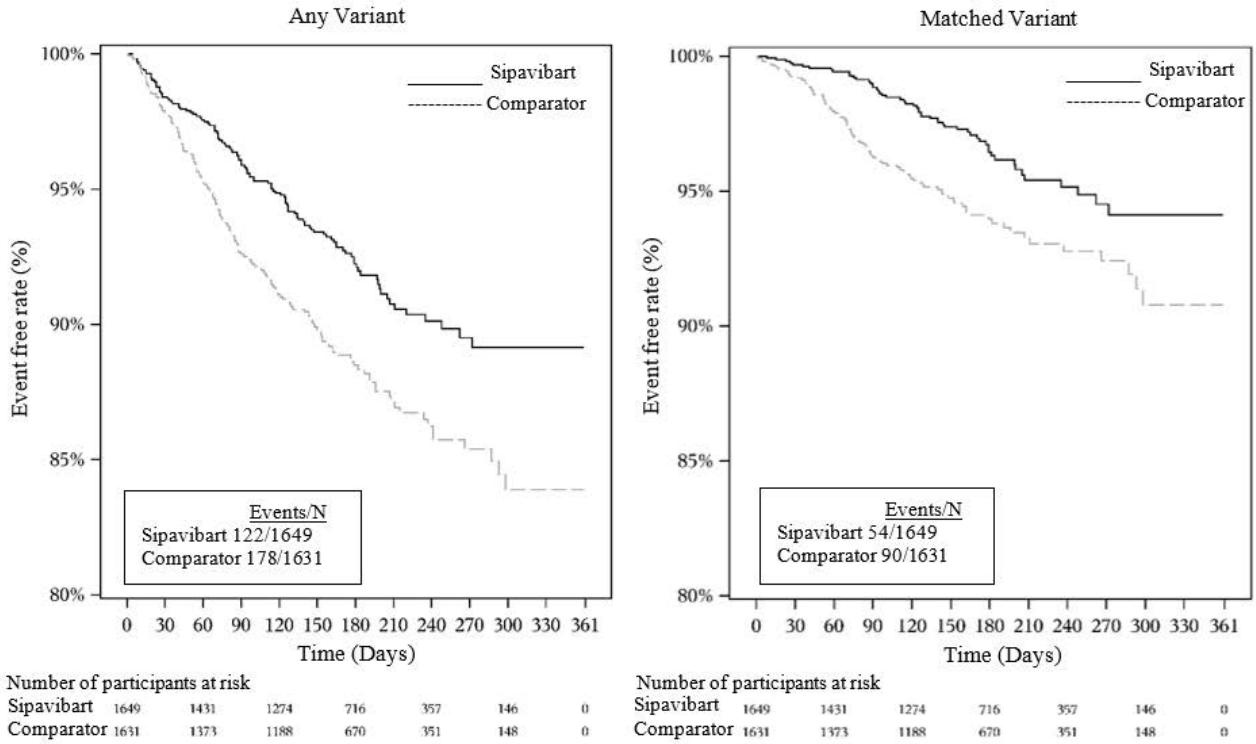
Table 3 Relative risk reduction of symptomatic COVID-19

	N	Number of events, n (%)	Relative risk reduction, % (CI)
Overall primary efficacy endpoint			
Sipavibart	1649	122 (7.4 %)	34.9% (97.5% CI: 15.0, 50.1)
Comparator[a]	1631	178 (10.9 %)	
Matched variant primary efficacy endpoint			
Sipavibart	1649	54 (3.3%)	42.9% (95% CI: 19.9, 59.3)
Comparator[a]	1631	90 (5.5%)	

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

[a] Comparator was either EVUSHELD 600 mg or placebo.

Figure 1: Kaplan-Meier: Time to first symptomatic COVID-19 cases up to day 361 caused by any variant and matched variant



Efficacy was consistent across pre-defined subgroups including immunocompromised condition, age, sex, race, ethnicity, BMI, ECG interpretation, and for participants who had previously taken a COVID-19 vaccine (within 6 months of randomisation) and/or EVUSHELD (within 12 months of randomisation).

The efficacy of KAVIGALE in the prevention of symptomatic COVID-19 was higher at 3 months post-dose compared to 6 months post-dose. Sipavibart demonstrated an overall risk reduction of 41.9% (95% CI: 22.5, 56.5) in the three-month period following an intramuscular dose of 300 mg for all variants. Similarly, in the matched non-F456L analysis, sipavibart demonstrated an overall risk reduction of 60.0% (95% CI: 36.2, 74.9) in the three-month period following an intramuscular dose of 300 mg.

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 IM administration or 300 mg to 1200 mg for IV infusion.

Absorption

Following a single 300 mg IM dose of sipavibart in the anterolateral thigh and the gluteal region, the geometric mean (geometric coefficient of variation (CV%)) of the maximum serum concentration (C_{max}) of sipavibart was 48.0 (25.2%) µg/mL and 25.4 (51.7%) µg/mL, respectively. The corresponding median time (range) to C_{max} was 7.5 (3.9, 53) and 52.0 (4.9, 86) days.

Based on preliminary population PK analysis, the estimated absolute bioavailability of sipavibart following IM dose administration in the anterolateral thigh and gluteal region is 83.8% and 70.3%, respectively.

Following the first dose and the second dose of 300mg sipavibart administered intramuscularly in the anterolateral thigh, the geomean 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.

Distribution

The geometric mean (CV%) apparent volume of distribution for sipavibart was 6.3 (19.4%) L and 7.8 (15.7%) L following a single 300 mg intramuscular administration in the anterolateral thigh and gluteal region, respectively.

Metabolism

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

Excretion

The geometric mean (CV%) clearance of sipavibart was 0.053 (43.1%) L/day and 0.063 (47.0%) L/day following 300 mg intramuscular administration in the anterolateral thigh and gluteal region, respectively. The estimated mean terminal elimination half-life (SD) of sipavibart was 87.3 (26.5) days and 91.0 (27.3) days following a single 300 mg IM dose in the anterolateral thigh and gluteal region, respectively.

Special populations

Renal impairment

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

Sipavibart with a molecular weight (MW) of approximately 148 kDa is not expected to be excreted intact in the urine as monoclonal antibodies with MW >69 kDa do not undergo renal excretion. 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.

Immunocompromised condition

No apparent difference in serum sipavibart exposures was observed in individuals with (n=591) or without (n=390) immunocompromised conditions following the same dose and route of administration.

Elderly patients

Exposure to sipavibart in older adults ≥65 years of age (n=217) was comparable to that in younger adults 18 to <65 years of age (n=323).

Paediatric population

The recommended dosing regimen is expected to result in comparable serum exposures of sipavibart in adolescents aged 12 years 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, race, or ethnicity.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with sipavibart.

Carcinogenicity

No carcinogenicity studies have been conducted with sipavibart.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

KAVIGALE solution for injection/infusion contains the excipients histidine, histidine hydrochloride monohydrate, arginine hydrochloride, polysorbate 80 and water for injections.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C to 8°C).

Do not freeze. Do not shake.

Storage of prepared syringes and prepared infusion bags

The solution for injection/infusion does not contain a preservative and therefore, the prepared syringe or prepared infusion bag should be administered immediately. If immediate administration is not possible, and the syringe or infusion bag needs to be stored, the total time from vial puncture to administration should not exceed either:

- 24 hours in a refrigerator at 2ºC to 8ºC
- 4 hours at room temperature up to 25ºC

Keep the vial in the original carton to protect from light. Product is for single use in one patient only. Discard any residue after preparation.

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.

Each pack contains 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Sipavibart is a human immunoglobulin (IgG1) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

CAS number

2768288-97-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4).

8 SPONSOR

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9 DATE OF FIRST APPROVAL

22 May 2025

10 DATE OF REVISION

27 Jan 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Additional text for special warnings and precautions to include cardiovascular and/or thromboembolic events.
4.8	Updated information in Table 1 for the frequency of identified adverse reactions and further clarification of related symptoms. A correction to the safety profile for the paediatric population to include 12-year-olds.
5.1	Minor editorial updates

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