1. NAME OF THE MEDICINAL PRODUCT

Enjaymo
50 mg/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for infusion contains 50 mg of sutimlimab*.
One vial contains 1100 mg of sutimlimab in 22 mL

* Sutimlimab is an immunoglobulin G4 (IgG4) monoclonal antibody (mAb) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipient with known effect

Each mL of solution for infusion contains 3.5 mg sodium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion (infusion)

Opalescent, colorless to slightly yellow solution essentially free of visible particles, with a pH of approximately 6.1 and osmolality of 268-312 mOsm/Kg.

Patient safety information Guide and Guide for Healthcare Professionals

The marketing of Enjaymo is subject to a risk management plan (RMP) including a 'Patient safety information guide' and “Guide for Healthcare Professionals”.

The 'Patient safety information guide', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the guide before starting treatment.

Guide for Healthcare Professionals
This product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enjaymo is indicated for the treatment of haemolysis in adult patients with cold agglutinin disease (CAD).

4.2 Posology and method of administration

Enjaymo must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological disorders.

Posology

Patients should be vaccinated according to the most current local recommendations for patients with persistent complement deficiencies (see section 4.4).

The recommended dose is based on body weight. For patients weighing 39 kg to less than 75 kg, the recommended dose is 6500 mg and for patients weighing 75 kg or more, the recommended dose is 7500 mg. Administer Enjaymo intravenously weekly for the first two weeks, with administration every two weeks thereafter. Enjaymo should be administered at the recommended dose regimen time points, or within two days of these time points (see section 4.4). Enjaymo is intended for continuous use as chronic therapy only, unless the discontinuation of Enjaymo is clinically indicated.

Missed dose

If a dose is missed, the missed dose should be administered as soon as possible. If the duration after the last dose exceeds 17 days, therapy should be reinitiated with weekly administrations for the first two weeks followed by administration every two weeks thereafter.

Special populations

Elderly
No dose adjustment is required for patients with CAD aged 65 years and over (see sections 5.1 and 5.2).

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment.

Renal impairment
No dose adjustment is required in patients with renal impairment.

Pediatric population
There is no relevant use of Enjaymo in children < 18 years of age in the treatment of CAD.

Method of administration

Enjaymo is for intravenous infusion only. Do not administer as an intravenous push or bolus. For instructions on preparation and administration, see section 6.6.

Following preparation, Enjaymo infusion solution should be administered intravenously at the infusion rate presented in Table 1.

Table 1 - Infusion reference table

Body weight range	Dose (mg)	Number of vials needed	Volume (mL)	Maximum infusion rate
Greater than or equal to 39 kg to less than 75 kg	6500	6	130	130 mL/hour
75 kg or greater	7500	7	150	150 mL/hour

Patients with cardiopulmonary disease may receive the infusion over 120 minutes.

If an adverse reaction occurs during the administration of Enjaymo, the infusion may be slowed or stopped at the discretion of the physician. If hypersensitivity reactions occur, discontinue Enjaymo and initiate appropriate treatment. Monitor the patient for at least two hours following completion of the initial infusion for signs or symptoms of an infusion and/or hypersensitivity reaction. Monitor the patient for one hour following completion of subsequent infusions for signs or symptoms of an infusion reaction.

Home infusion

Home infusions should be performed by a healthcare professional.
The decision to consider home infusion should be based on individual clinical characteristics of the patient and individual needs of the patient. Transitioning the infusion from a clinical facility to home administration includes ensuring that adequate infrastructure and resourcing is in place and consistent with treating physician orders. Infusion of Enjaymo at home may be considered for patients who have tolerated their infusion well in a clinical facility and have not had infusion related reactions. A patient's underlying co-morbidities and ability to adhere to the home infusion requirements need to be considered when evaluating the patient for eligibility to receive home infusion. In addition, the following criteria should be considered:

- The patient must have no ongoing concurrent condition that, in the opinion of the physician, may place the patient at greater risk when receiving an infusion in the home setting rather than in the clinic setting. A comprehensive evaluation should be completed before the initiation of home infusion to ensure that the patient is medically stable.
- The patient must have successfully received Enjaymo infusion in a clinical setting (hospital or outpatient) for at least three months under the supervision of a physician or care provider experienced in the management of patients with CAD.
- The patient must be willing and able to comply with home infusion procedures and recommendations of the treating physician or care provider.
- The healthcare professional administering the infusion at home should be available at all times during the home infusion and for at least 1 hour after infusion.

If the patient experiences adverse reactions during the home infusion, the infusion process should be stopped immediately, appropriate medical treatment should be initiated (see section 4.4) and the treating physician should be notified. In such cases, the treating physician should decide if subsequent infusions should occur and if so, whether the infusions should be administered in a hospital or supervised outpatient care setting.

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.

Infections

Enjaymo targets the classical complement pathway (CP) specifically binding to complement protein component 1, s subcomponent (C1s) preventing the cleavage of complement protein C4. Although the lectin and alternate pathways remain unaffected, patients may have an increased susceptibility to serious infections, especially infections caused by encapsulated bacteria such as *Neisseria meningitides, Streptococcus pneumoniae,* and *Haemophilus influenza*. Patients should be vaccinated against encapsulated bacteria before treatment with Enjaymo is started, please see "Vaccinations" below.

In clinical studies with CAD, serious infections, including sepsis, have been reported in patients receiving treatment with Enjaymo (see section 4.8). Enjaymo should not be initiated in patients with active, serious infections. Patients should be monitored for early signs and symptoms of infections and should be informed to seek immediate medical care if such symptoms should occur.

Patients with viral hepatitis and HIV were excluded from the clinical studies. Before and during treatment, patients must notify their physician if they have been diagnosed with hepatitis B, hepatitis C, or HIV infection. Be cautious when treating patients with a history of hepatitis B, hepatitis C, or HIV infection.

Vaccinations

Vaccinate patients according to the most current local recommendations for patients with persistent complement deficiencies, including meningococcal and streptococcal vaccines. Revaccinate patients in accordance with local recommendations.

Immunize patients without a history of vaccination against encapsulated bacteria at least 2 weeks prior to receiving the first dose of Enjaymo. If urgent Enjaymo therapy is indicated in an unvaccinated patient, administer vaccine(s) as soon as possible. The benefits and risks of antibiotic prophylaxis for prevention of infections in patients receiving Enjaymo have not been established.

Hypersensitivity reactions

As with other protein products, administration of Enjaymo may result in hypersensitivity reactions, including anaphylaxis. In clinical studies, no serious hypersensitivity reactions were observed with Enjaymo. If hypersensitivity reactions occur, discontinue Enjaymo and initiate appropriate treatment.

Infusion-related reactions

Administration of Enjaymo may result in infusion-related reactions during the infusion or immediately after the infusion (see section 4.8). Patients should be monitored for infusion-related reactions, infusion interrupted if a reaction occurs and appropriate treatment initiated.

Systemic lupus erythematosus (SLE)

Individuals with inherited classical complement deficiency are at a higher risk for developing SLE. Patients with SLE were excluded from clinical studies with Enjaymo. Patients being treated with Enjaymo should be monitored for signs and symptoms of SLE and evaluated appropriately. Use Enjaymo with caution in patients with SLE or those who develop signs and symptoms of SLE.

Monitoring CAD manifestations after Enjaymo discontinuation

The effects on haemolysis diminish after end of treatment. Patients should therefore be monitored for signs and symptoms of haemolysis in case of treatment discontinuation.

Sodium

This medicinal product contains 3.5 mg per mL or 77 mg sodium per vial, equivalent to 3.85% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Enjaymo is an unlikely candidate for cytochrome P450 mediated drug-drug interactions as it is a recombinant human protein. The interaction of sutimlimab with substrates of CYPs has not been studied. However, sutimlimab decreases the levels of proinflammatory cytokines in patients, such as IL-6 which is known to supress the expression of specific hepatic CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4). Therefore, caution should be exercised when starting or discontinuing sutimlimab treatment in patients also receiving substrates of CYP450 3A4, 1A2, 2C9 or 2C19, particularly those with a narrow therapeutic index (such as warfarin, carbamazepine, phenytoin and theophylline), and doses adjusted if needed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no available data on sutimlimab from the use in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Human IgG antibodies are known to cross the placental barrier; therefore, sutimlimab may be transmitted from the mother to the developing fetus.

As a precautionary measure, it is preferable to avoid the use of sutimlimab during pregnancy. Sutimlimab should be given during pregnancy only if clearly indicated.

Breast-feeding

Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. It is unknown whether sutimlimab/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sutimlimab therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Effects of sutimlimab on male and female fertility have not been studied in animals. In repeat-dose studies with sutimlimab with exposures at up to approximately 4 times the recommended human dose, no effects on reproductive organs were observed in cynomolgus monkeys.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The most frequently reported adverse reactions with Enjaymo in CADENZA and CARDINAL clinical studies were headache, hypertension, urinary tract infection, upper respiratory tract infection, nasopharyngitis, nausea, abdominal pain, infusion-related reactions and cyanosis (reported as acrocyanosis).

Tabulated list of adverse reactions

The safety evaluation of Enjaymo in patients with CAD was primarily based on data from 66 patients who participated in the phase 3, randomized, placebo-controlled study (CADENZA) and in an open-label single-arm study (CARDINAL).

Listed in Table 2 are adverse reactions observed in the CADENZA and CARDINAL studies presented by system organ class and frequency, using the following categories: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 List of adverse reactions in CADENZA and CARDINAL studies

MedDRA System Organ Class	Very common	Common
Infections and infestations	Urinary tract infection Cystitis Upper respiratory tract infections[a] Nasopharyngitis[b] Gastroenteritis Rhinitis	Lower respiratory tract infections[c] Urosepsis Escherichia urinary tract infection Urinary tract infection bacterial Cystitis bacterial Oral herpes Herpes simplex viraemia Herpes zoster Herpes simplex
General disorders and administration site conditions		Pyrexia[f] Feeling cold[f] Infusion related reactions[f]
Nervous system disorders	Headache	Aura[f] Dizziness[f*]
Vascular disorders	Hypertension[d] Cyanosis (reported as acrocyanosis) Raynaud's phenomenon	Hypotension[f*] Stress cardiomyopathy[f]
Gastrointestinal disorders	Abdominal pain[e] Nausea	Diarrhoea[f] Dyspepsia[f] Aphthous ulcer[f]
Respiratory, thoracic and mediastinal disorders		Chest discomfort[f*]
Skin and subcutaneous tissue disorders		Pruritus[f*]

[a]**Upper respiratory tract infections:** upper respiratory tract infection, bronchitis, and viral upper respiratory tract infection
[b]**Nasopharyngitis**: nasopharyngitis, pharyngitis
[c] **Lower respiratory tract infections:** pneumonia klebsiella, COVID-19 pneumonia, lower respiratory tract infection, respiratory tract infection viral, respiratory tract infection, pneumonia
[d]**Hypertension**: hypertension, blood pressure increased, essential hypertension, hypertensive crisis, white coat hypertension
[e]**Abdominal pain:** abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness
[f]**Infusion related reaction:** All occurred within 24 hours of start of Enjaymo infusion. *Events suggestive of hypersensitivity reactions are included in the table.

Serious infections

Of the 66 patients who participated in CADENZA and CARDINAL studies, serious infections were reported in 10 (15.2%) patients. Serious infections listed in the ADR table include respiratory tract infection [pneumonia klebsiella (n=1), respiratory tract infection (n=1), COVID-19 pneumonia (n=1)], urinary tract infection [urosepsis (n=1), urinary tract infection (n=1), urinary tract infection bacterial (n=1)], herpes zoster (n=1). Sutimlimab was discontinued in one patient due to a serious infection of Klebsiella pneumonia with fatal outcome. No other fatal events of infections were reported. See section 4.4 for information on vaccination recommendations for serious infections and for monitoring early signs and symptoms of infections.

Immunogenicity

Immunogenicity of sutimlimab was assessed in CAD patients in the CARDINAL and CADENZA studies at baseline, during the treatment period, and at end of treatment (Week 26). Two of the 24 patients (8.3%) enrolled in the CARDINAL study who received at least one dose of sutimlimab developed treatment-emergent ADAs. In CADENZA, 6 of 42 patients treated with sutimlimab (14.3%) developed treatment-emergent ADAs. These ADAs were transient in nature with low titre and were not associated with changes in the pharmacokinetic profile, clinical response, or adverse events.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

In patients who experience overdose, immediate interruption of infusion and close monitoring is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, complement inhibitors, ATC code: L04AJ04.

Mechanism of action

Sutimlimab is an IgG, subclass 4 (IgG4) monoclonal antibody (mAb) that inhibits the classical pathway (CP) and specifically binds to complement protein component 1, s subcomponent (C1s), a serine protease that cleaves C4. The activities of the lectin and alternative complement pathways are not inhibited by sutimlimab. Inhibition of the classical complement pathway at the level of C1s prevents deposition of complement opsonins on the surface of red blood cells, resulting in inhibition of haemolysis in patients with CAD, prevents generation of proinflammatory anaphylatoxins C3a and C5a and the downstream terminal complement complex C5b-9.

Clinical efficacy and safety

Greater than 90% inhibition of CP was observed after the first Enjaymo infusion and C4 levels were restored to normal levels (0.2 g/L) in CAD patients within one week following the first dose of Enjaymo.

The safety and efficacy of Enjaymo in patients with cold agglutinin disease (CAD) were assessed in a phase 3, randomized, double-blind, placebo-controlled study (CADENZA) in 42 patients (n=22 on Enjaymo and n=20 on placebo) and in a phase 3, open-label, single-arm study (CARDINAL) in 24 patients for a duration of 26 weeks. Following the completion of the six-month treatment periods (Part A), patients in both studies continued to receive Enjaymo in a long-term safety and durability of response extension phase (Part B) for an additional 12 months (CADENZA) and 24 months (CARDINAL) following last patient out from Part A. Both studies included a 9-week follow-up after the last dose of Enjaymo. Key eligibility criteria were a baseline haemoglobin (Hgb) ≤10 g/dL and active haemolysis with a bilirubin level above the normal reference range. Patients with cold agglutinin syndrome (CAS) were excluded. Patients in the CADENZA study did not have a history of transfusion within 6 months, or more than one blood transfusion in the 12 months prior to enrolment in the study while patients enrolled in the CARDINAL study had a history of at least one

documented blood transfusion within 6 months prior to enrolment in the study. Patients were administered 6500 mg for 39-<75 kg or 7500 mg Enjaymo for ≥75 kg intravenously over approximately 60 minutes on Day 0, Day 7, and every 14 days thereafter. Major baseline characteristics of the study population are summarized in Table 3 below.

Table 3 - Baseline characteristics of patients included in the clinical studies

Parameter	**Statistic**	**CADENZA**		**CARDINAL**
		Placebo N= 20	**Enjaymo N=22**	**Enjaymo N=24**
Age	Mean Min, Max	68.2 51, 83	65.3 46, 88	71.3 55, 85
Sex Male Female	n (%)	 4 (20.0) 16 (80.0)	 5 (22.7) 17 (77.3)	 9 (37.5) 15 (62.5)
Body weight	Mean, Kg Min, Max	64.9 48, 95	66.8 39, 100	67.8 40, 112
Haemoglobin	Mean, g/dL	9.33	9.15	8.59
Bilirubin (total)*	µmol/L	35.77 (1.75 X ULN)	41.17 (2 X ULN)	53.26 (2.6 × ULN†)
History of transfusion Within last 6 months Within last 12 months	Mean number of transfusions (range)	 0 0	 0 0.14 (0, 1)	 3.2 (1, 19) 4.8 (1, 23)
FACIT†-Fatigue scale	Mean	32.99	31.67	32.5

*N=21 in CARDINAL; Placebo N=18 and Enjaymo N= 20 in CADENZA, for bilirubin data excluding patients with either a positive or no available test result for Gilbert's syndrome.
†ULN: Upper limit of normal, FACIT: Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue is measured on a scale of 0 (worst fatigue) to 52 (no fatigue)

CADENZA Study

Forty-two patients were randomized to receive Enjaymo (n=22); or placebo (n=20) through Week 25.

Efficacy was based on the proportion of patients who met the primary endpoint criteria: an increase from baseline in Hgb level ≥ 1.5 g/dL at the treatment assessment time point (mean value from Weeks 23, 25, and 26), no blood transfusion from Week 5 through Week 26, and no treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26. A patient received a blood transfusion if they met the following haemoglobin threshold: Hgb < 7 g/dL or for a Hgb < 9 g/dL with symptoms. Prohibited therapies included rituximab alone or in combination with cytotoxic agents.

Efficacy was further assessed by the following two key secondary endpoints: based on the effect of Enjaymo on the mean change from baseline in Hgb and the FACIT-fatigue score to assess change in quality of life. Additional secondary endpoints were laboratory measures of haemolysis including mean change from baseline in total bilirubin. Supportive efficacy data collected included transfusion

usage after five weeks of treatment.

Efficacy results are described in Tables 4 and 5 below.

Table 4- Efficacy results in patients with CAD in the CADENZA study - Part A

Parameter	Statistic	Placebo N=20	Enjaymo N=22	Treatment effect
Responder [a]	% (95 % CI) Odds Ratio (95% CI) p value	3 (15.0) (3.2, 37.9)	16 (72.7) (49.8, 89.3)	 15.94 (2.88,88.04) <0.001
Haemoglobin	Mean change from baseline (LS† Mean), g/dL	0.09	2.66	2.56
	95% CI of LS Mean	(-0.5, 0.68)	(2.09, 3.22)	(1.75, 3.38)
	p value			<0.001
Mean number of transfusions (Week 5 to Week 26)	n (SD)	0.5 (1.1)	0.05 (0.2)	NC
FACIT†-Fatigue scale	Mean	33.66	43.15	
	Mean change from baseline (LS† Mean)	1.91	10.83	8.93
	95% CI of LS Mean	(-1.65, 5.46)	(7.45, 14.22)	(4, 13.85)
	p value			<0.001
Total bilirubin*	Mean, µmol/L	33.95	12.12	
	Mean change from baseline	-1.83	-22.13	NC
	Number of patients normalized (%)	4 (22.2%)	15 (88.2)	

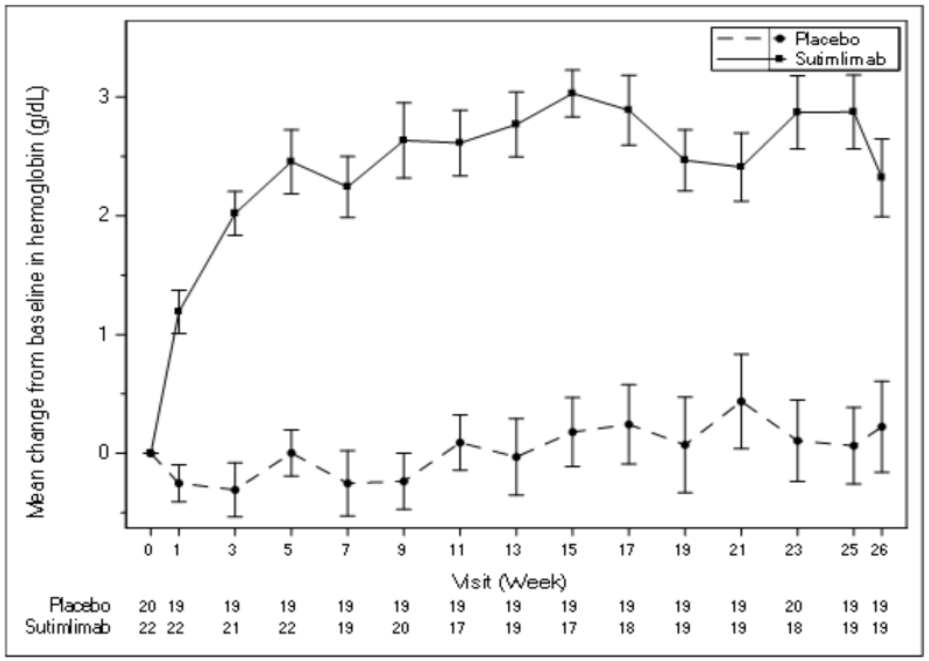
[a]A responder was defined as a patient with an increase from baseline in Hgb level ≥1.5 g/dL at the treatment assessment time point (mean value from Weeks 23, 25, and 26), no blood transfusion from Week 5 through Week 26, and no treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26.

*N=18 for placebo and N=17 for Enjaymo, for bilirubin data excluding patients with either a positive or no available test result for Gilbert's syndrome

†LS: Least Square, FACIT: Functional Assessment of Chronic Illness Therapy, NC= Not calculated

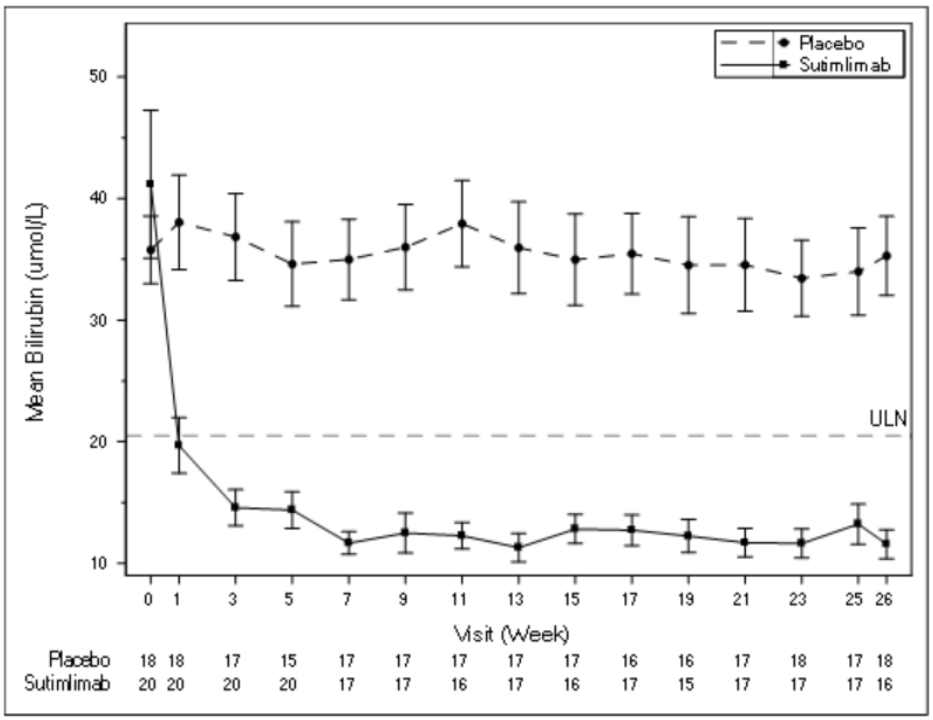
Mean change from baseline in haemoglobin (Hgb) is shown in the Figure 1 below.

Figure 1 CADENZA Study Part A: Plot of mean change from baseline in haemoglobin (g/dL) (+/- SE) by visit



Mean bilirubin levels by visit is shown in the Figure 2 below.

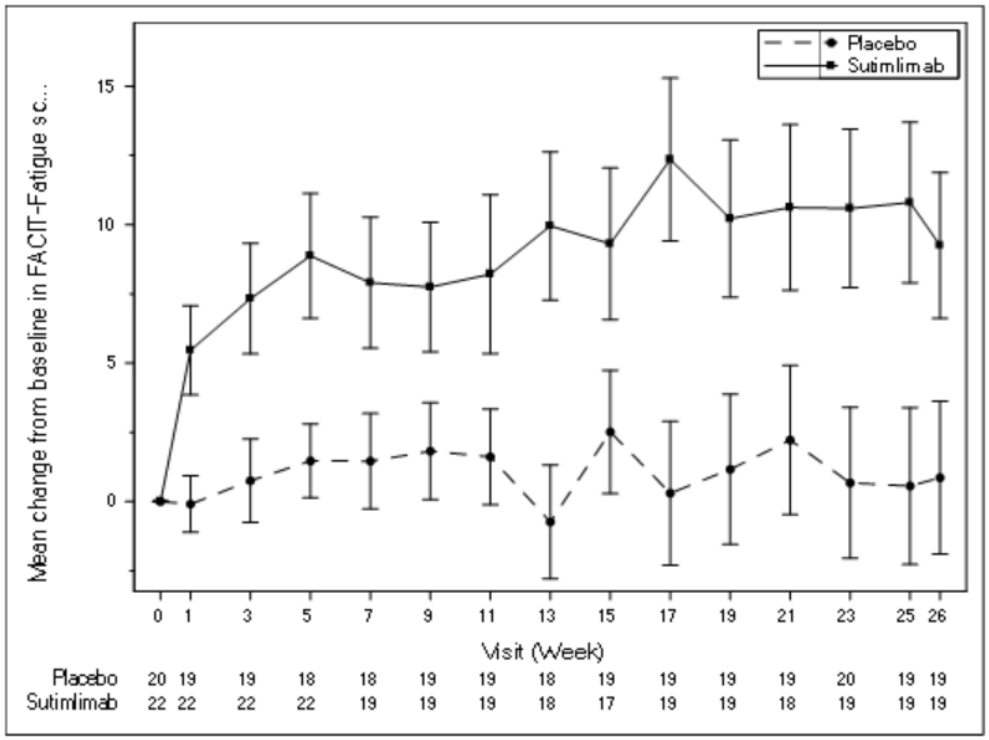
Figure 2- CADENZA Study Part A: Plot of mean bilirubin (µmol/L) (+/- SE) by visit (excluding subjects with positive or unknown Gilbert's syndrome test results)



Health-Related Quality of Life

In Part A, increases in mean FACIT-fatigue scores are presented in the Figure 3 below.

Figure 3 – CADENZA Study Part A: Plot of mean change in FACIT-Fatigue score (SE) by visit – Observed – Full Analysis Set



In Part B, mean haemoglobin levels were maintained >11 g/dL and sustained normalization of mean bilirubin levels were observed indicating a sustained decrease in haemolysis. Improvements in FACIT-Fatigue score observed in Part A were maintained.

After the last dose of Enjaymo in the study, signs and symptoms of recurrent haemolysis were observed. Mean haemoglobin, nine weeks after the last dose in Part B, decreased by 2.41 g/dL standard deviation (SD: 2.21) and mean bilirubin increased by 21.80 µmol/L (SD:18.14) from the last available values during treatment. The mean FACIT-Fatigue score returned to near baseline levels at 31.29, with a mean SD change from baseline of -1.40 (11.48).

<u>CARDINAL Study</u>

Twenty-four patients were administered Enjaymo through Week 25.

Efficacy was based on the proportion of patients who met the primary endpoint criteria: an increase from baseline in Hgb level ≥ 2 g/dL or a Hgb level ≥ 12 g/dL at the treatment assessment time point (mean value from Weeks 23, 25, and 26), no blood transfusion from Week 5 through Week 26, and no treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26. A patient received a blood transfusion if they met the following haemoglobin threshold: Hgb < 7 g/dL or for a Hgb < 9 g/dL with symptoms. Prohibited therapies included rituximab alone or in combination with cytotoxic agents.

Efficacy was further assessed by the following secondary endpoints: based on the effect of Enjaymo

on Hgb and laboratory measures of haemolysis including mean change from baseline in total bilirubin. Change in quality of life was assessed by mean change from baseline in the FACIT-fatigue score as a secondary endpoint. Supportive efficacy data collected included transfusion usage after five weeks of treatment.

Table 5 presents efficacy results in patients with CAD in the CARDINAL study.

Table 5 - Efficacy Results in Patients with CAD in the CARDINAL Study - Part A

Parameter	**Statistic**	**ENJAYMO N=24**
Responder[a]	n (%)	13 (54)
Haemoglobin	Mean change from baseline (LS† Mean), g/dL	2.60
	95% CI of LS Mean	(0.74, 4.46)
Mean number of transfusions (Week 5 to Week 26)	n	0.9
Total bilirubin*	Mean, µmol/L	15.48 (0.76 × ULN†)
	Mean change from baseline (LS† Mean)	-38.18
	Number of patients normalized (%)	13 (54.2)
FACIT†-Fatigue Scale	Mean	44.26
	Mean change from baseline (LS† Mean)	10.85
	95% CI of LS Mean	(8.0, 13.7)

[a]A responder was defined as a patient with an increase from baseline in Hgb level ≥ 2 g/dL or a Hgb level ≥ 12 g/dL at the treatment assessment time point (mean value from Weeks 23, 25, and 26), no blood transfusion from Week 5 through Week 26, and no treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26.
*N=21 for bilirubin data excluding patients with Gilbert's syndrome
†LS: Least Square, ULN: Upper limit of normal, FACIT: Functional Assessment of Chronic Illness Therapy

In Part B, mean haemoglobin levels were maintained >11 g/dL and sustained normalization of mean bilirubin levels were observed indicating a sustained decrease in haemolysis.

After the last dose of Enjaymo in the study, signs and symptoms of recurrent haemolysis were observed. Mean haemoglobin, nine weeks after the last dose in Part B, decreased by 2.28 g/dL (SD: 1.80) and mean bilirubin increased by 24.27 µmol/L (SD:13.51) from the last available values during treatment. Mean FACIT-Fatigue scores returned towards baseline, with a mean SD change from baseline pre-treatment values of 1.05 (8.15).

Elderly population

Majority of the patients (43/66, 65%) included in the clinical studies with Enjaymo for CAD were 65 years of age or older. Reported clinical experience has not identified any differences in responses between those over the age of 65 and younger patients.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of sutimlimab were characterized in 24 patients (CARDINAL) and 42 patients (CADENZA), which included 51 patients treated with 6500 mg and 15 patients with 7500

mg as per recommended posology. The total exposures at steady-state of proposed dosing regimen are presented in Table 6.

Table 6 - Mean (SD) steady state exposure parameters

CARDINAL and CADENZA	Dose (mg)	C_{min} (µg/mL)*	AUC_{SS} (µg·h/mL)*
Mean (SD)	6500 (n=51) 7500 (n=15)	1397 (721) 1107 (661)	697449 (256234) 576017 (253776)

* Abbreviations: AUCss = area under the curve between 2 consecutive doses after steady state is achieved; Cmin = trough concentration at steady state defined as 1 hour prior to next dose administration

Steady state was achieved by week 7 after starting sutimlimab treatment, with accumulation ratio of less than 2.

Distribution

The volume of distribution at steady state in central and peripheral compartments was approximately 5.8 L in patients with CAD.

Biotransformation

Sutimlimab is a protein. It is generally recognized that antibodies are metabolized by degradation into small peptides and individual amino acids.

Elimination

The half-life of sutimlimab is dependent on the plasma concentration. The terminal elimination half-life of sutimlimab at steady-state based on the total clearance (linear and non-linear clearance) is 16 days.

Linearity/non-linearity

Following single doses, sutimlimab clearance showed a steep initial decrease at doses less than 30 mg/kg (~ 2 g), becoming independent of dose between 60 and 100 mg/kg of sutimlimab.

Special populations

No clinically significant differences were observed in the pharmacokinetics of sutimlimab based on sex, age, hepatic impairment, or renal impairment. Exposure levels (C_{max}, C_{min} and AUC) at steady state were estimated based on 6500 mg (<75 kg) and 7500 mg (>= 75 kg) given Days 0, 7 and every 14 days thereafter. The population pharmacokinetic analysis showed similar exposure parameters between sexes with 101 male and 95 female participants.

The population pharmacokinetic analysis showed similar exposure parameters with participant's race (94 White, 10 Black, 42 Asian).

Population pharmacokinetic analysis showed that body weight and ethnicity (Japanese versus non-Japanese) influenced the pharmacokinetics of sutimlimab. Lower exposure was observed in participants with higher body weight. Based on cross-study comparison, sutimlimab AUC_{0-168} after 30 to 100 mg/kg was up to 38% higher in Japanese subjects than in non-Japanese participants.

Pharmacokinetic/pharmacodynamic relationship(s)

Sutimlimab concentration above 100 μg/mL resulted in maximal CP inhibition. The proposed dosing regimen resulted in adequate sutimlimab exposure at steady state to provide clinically relevant effects on Hgb, bilirubin, and total C4 levels.

5.3 Preclinical safety data

An enhanced pre- and post-natal development (ePPND) study in cynomolgus monkeys revealed no evidence of adverse developmental outcomes with intravenous administration of sutimlimab during organogenesis through delivery, at exposures approximately 2-3 times the AUC in humans at the maximum recommended dose. In repeat-dose studies with sutimlimab with exposures at up to approximately 4 times the recommended human dose, no effects on reproductive organs were observed in cynomolgus monkeys.

No animal studies have been conducted to evaluate the carcinogenic potential of sutimlimab.

Non-clinical data revealed no special hazard for humans based on nonclinical studies in cynomolgus monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, Sodium phosphate monobasic, monohydrate, Sodium phosphate dibasic, heptahydrate Polysorbate 80, Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial:

The expiry date of the product is indicated on the packaging materials.

Storage of the medicinal product after opening:

Chemical and physical in-use stability has been demonstrated for 16 hours at 18°C to 25°C or for 36 hours at 2°C to 8°C. From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be for longer than 24 hours at 2°C to 8°C or 8 hours at room temperature, unless vial opening and pooling into the infusion bag has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Store in the original carton in order to protect from light.
Do not freeze.

For storage conditions after first opening of the medicinal product vial, see section 6.3.

6.5 Nature and contents of container

22 mL solution in vial (type I glass) with a stopper (butyl rubber), seal (aluminium) and a flip-off cap

Each pack contains 1 vial.

6.6 Special precautions for disposal and other handling

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

Enjaymo is provided as a solution in a single-dose vial and should be prepared by a healthcare professional using aseptic technique.

Preparation

1. Remove Enjaymo from the refrigerator. To minimize foaming, do not shake.
2. Inspect vials visually for particulate matter and discoloration prior to administration. The solution is an opalescent and colorless to slightly yellow liquid. Do not administer if discolored or if other foreign particulate matter is present.
3. Withdraw the calculated volume from the appropriate number of vials based on the recommended dose (see Table 1) and add to an empty infusion bag. Discard unused portion remaining in the vial.
4. The prepared solution should be administered immediately. For storage conditions, see section 6.3.

Administration

1. Prior to administration, allow the infusion solution to adjust to room temperature (18°C-25°C). Refer to Table 1 for infusion rate, see section 4.2. The infusion should be administered over 1-2 hours depending on the patient's body weight. Administer the infusion only through a 0.22-micron filter with a polyethersulfone (PES) membrane. Infusion warmers may be used, do not exceed a temperature of 40°C.
2. The infusion catheter and tubing should be primed with the dosing solution immediately before infusion and flushed immediately following completion of the infusion with enough quantity (approximately 20 mL) of sodium chloride 9 mg/mL (0.9%) solution for injection.
3. No incompatibilities have been observed between Enjaymo infusion solution and infusion bags made of Di-(2-ethylhexyl)phthalate (DEHP) plasticized polyvinyl chloride (PVC), Ethyl Vinyl Acetate (EVA) and polyolefin (PO); administration sets made of DEHP-plasticized PVC, DEHP-free polypropylene (PP) and polyethylene (PE); and vial adapters made of polycarbonate (PC) and acrylonitrile-butadiene-styrene (ABS).

7. IMPORTER and MARKETING AUTHORISATION HOLDER

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