▼This medicinal product is subject to additional monitoring in Australia due to provisional approval. 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

MINJUVI® (TAFASITAMAB)
POWDER FOR SOLUTION FOR INFUSION

1 NAME OF THE MEDICINE

MINJUVI 200 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 200 mg of tafasitamab.

After reconstitution each mL of solution contains 40 mg of tafasitamab.

Excipient with known effect
Each vial of MINJUVI contains 7.4 mg of sodium. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to slightly yellowish lyophilised powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MINJUVI is indicated in combination with lenalidomide followed by MINJUVI monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT).

This indication was approved via the **provisional approval** pathway, based on objective response rate and duration of response in a single arm trial. Continued approval for this indication depends on verification and description of clinical benefit in a confirmatory trial.

4.2 DOSE AND METHOD OF ADMINISTRATION

MINJUVI must be administered by a healthcare professional experienced in treatment of cancer patients.

Recommended pre-medication

A pre-medication to reduce the risk of infusion-related reactions should be administered 30 minutes to 2 hours prior to tafasitamab infusion. For patients not experiencing infusion-

related reactions during the first 3 infusions, pre-medication is optional for subsequent infusions.

The pre-medication may include antipyretics (e.g. paracetamol), histamine H1 receptor blockers (e.g. diphenhydramine), histamine H2 receptor blockers (e.g. cimetidine), or glucocorticosteroids (e.g. methylprednisolone).

Treatment of infusion-related reactions

If an infusion-related reaction occurs (Grade 2 and higher), the infusion should be interrupted. In addition, appropriate medical treatment of symptoms should be initiated. After signs and symptoms are resolved or reduced to Grade 1, MINJUVI infusion can be resumed at a reduced infusion speed (see Table 1).

If a patient has experienced a Grade 1 to 3 infusion-related reaction, pre-medication should be administered before subsequent tafasitamab infusions.

Dosage

The recommended dose of MINJUVI is 12 mg per kg body weight administered as an intravenous infusion according to the following schedule:

- Cycle 1: infusion on day 1, 4, 8, 15 and 22 of the cycle.
- Cycles 2 and 3: infusion on day 1, 8, 15 and 22 of each cycle.
- Cycle 4 until disease progression: infusion on day 1 and 15 of each cycle.

Each cycle has 28 days.

In addition, patients should self-administer lenalidomide capsules at the recommended starting dose of 25 mg daily on days 1 to 21 of each cycle. The starting dose and subsequent dosing may be adjusted according to the lenalidomide Product Information.

MINJUVI plus lenalidomide in combination is given for up to twelve cycles.

Treatment with lenalidomide should be stopped after a maximum of twelve cycles of combination therapy. Patients should continue to receive MINJUVI infusions as single agent on day 1 and 15 of each 28-day cycle, until disease progression or unacceptable toxicity.

<u>Dose modifications</u>

Table 1 provides dose modifications in case of adverse reactions. For dose modifications regarding lenalidomide, please also refer to the lenalidomide Product Information.

Table 1: Dose modifications in case of adverse reactions

Adverse reaction	Severity	Dosage modification
Infusion-related reactions	Grade 2 (moderate)	• Interrupt MINJUVI infusion immediately and manage signs and symptoms. • Once signs and symptoms resolve or reduce to Grade 1, resume MINJUVI infusion at no more than 50% of the rate at which the reaction occurred. If the patient does not experience

Adverse reaction	Severity	Dosage modification
		further reaction within 1 hour and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to the rate at which the reaction occurred.
	Grade 3 (severe)	• Interrupt MINJUVI infusion immediately and manage signs and symptoms. • Once signs and symptoms resolve or reduce to Grade 1, resume MINJUVI infusion at no more than 25% of the rate at which the reaction occurred. If the patient does not experience further reaction within 1 hour and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to a maximum of 50% of the rate at which the reaction occurred. • If after rechallenge the reaction returns, stop the infusion immediately.
	Grade 4 (life-threatening)	• Stop the infusion immediately and permanently discontinue MINJUVI.
Myelosuppression	Platelet count of less than 50,000/µL	• Withhold MINJUVI and lenalidomide and monitor complete blood count weekly until platelet count is 50,000/µL or higher. • Resume MINJUVI at the same dose and lenalidomide at a reduced dose if platelets return to ≥ 50,000/µL. Refer to the lenalidomide SmPC for dosage modifications.
	Neutrophil count of less than 1,000/µL for at least 7 days or Neutrophil count of less than 1,000/µL with an increase of body temperature to 38 °C or higher or Neutrophil count less than 500/µL	• Withhold MINJUVI and lenalidomide and monitor complete blood count weekly until neutrophil count is 1,000/µL or higher. • Resume MINJUVI at the same dose and lenalidomide at a reduced dose if neutrophils return to ≥ 1000/µL. Refer to the lenalidomide Product Information for dosage modifications.

Special populations

Paediatric population

The safety and efficacy of MINJUVI in children under 18 years have not been established.

No data are available.

Elderly

No dose adjustment is needed for elderly patients (≥ 65 years).

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment (see section 5.2). There are no data in patients with severe renal impairment for dosing recommendations.

Hepatic impairment

No dose adjustment is needed for patients with mild hepatic impairment (see section 5.2). There are no data in patients with moderate or severe hepatic impairment for dosing recommendations.

Method of administration

MINJUVI is a cytotoxic drug. Follow applicable special handling and disposal procedures.

MINJUVI is provided in sterile, preservative-free vials. The vial is for single use (in one patient on one occasion) only. Discard any residue.

MINJUVI is for intravenous use and should be reconstituted and diluted prior to intravenous infusion.

- For the first infusion of cycle 1, the intravenous infusion rate should be 70 mL/h for the first 30 minutes. Afterwards, the rate should be increased to complete the first infusion within a 2.5-hour period.
- All subsequent infusions should be administered within a 1.5 to 2-hour period.
- In case of adverse reactions, consider the recommended dose modifications provided in Table 1.
- MINJUVI must not be co-administered with other medicinal products through the same infusion line.
- MINJUVI must not be administered as an intravenous push or bolus.

Use appropriate aseptic technique for reconstitution and dilution.

Instructions for reconstitution

- Determine the dose of tafasitamab based on patient weight by multiplying 12 mg by the patient weight (kg). Then calculate the number of tafasitamab vials needed (each vial contains 200 mg tafasitamab).
- Using a sterile syringe, gently add 5.0 mL sterile water for injections into each MINJUVI vial. Direct the stream toward the walls of each vial and not directly on the lyophilised powder.

- Gently swirl the reconstituted vial(s) to aid the dissolution of the lyophilised powder. Do not shake or swirl vigorously. Do not remove the contents until all the solids have been completely dissolved. The lyophilised powder should dissolve within 5 minutes.
- The reconstituted solution should appear as a colourless to slightly yellow solution. Before proceeding, ensure there is no particulate matter or discolouration by inspecting visually. If the solution is cloudy, discoloured or contains visible particles, discard the vial(s).

Instructions for dilution

- An infusion bag containing 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection should be used.
- Calculate the total volume of the 40 mg/mL reconstituted tafasitamab solution needed. Withdraw a volume equal to this from the infusion bag and discard the withdrawn volume.
- Withdraw the total calculated volume (mL) of reconstituted tafasitamab solution from the vial(s) and slowly add to the sodium chloride 9 mg/mL (0.9%) infusion bag. Discard any unused portion of tafasitamab remaining in the vial.
- The final concentration of the diluted solution should be between 2 mg/mL to 8 mg/mL of tafasitamab.
- Gently mix the intravenous bag by slowly inverting the bag. Do not shake.

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.

Infusion-related reactions

Infusion-related reactions may occur and have been reported more frequently during the first infusion (see section 4.8). Patients should be monitored closely throughout the infusion. Patients should be advised to contact their healthcare professionals if they experience signs and symptoms of infusion-related reactions including fever, chills, rash or breathing problems within 24 hours of infusion. A premedication should be administered to patients prior to starting tafasitamab infusion. Based on the severity of the infusion-related reaction, tafasitamab infusion should be interrupted or discontinued and appropriate medical management should be instituted (see section 4.2).

Myelosuppression

Treatment with tafasitamab can cause serious and/or severe myelosuppression including neutropenia, thrombocytopenia, and anaemia (see section 4.8). Complete blood counts should be monitored throughout treatment and prior to administration of each treatment cycle. Based on the severity of the adverse reaction, tafasitamab infusion should be withheld (see Table 1). Refer to the lenalidomide Product Information for dosage modifications.

Neutropenia

Neutropenia, including febrile neutropenia, has been reported during treatment with tafasitamab. Administration of granulocyte colony-stimulating factors (G-CSF) should be considered, in particular in patients with Grade 3 or 4 neutropenia. Any symptoms or signs of developing infection should be anticipated, evaluated, and treated.

Thrombocytopenia
Thrombocytopenia has been reported during treatment with tafasitamab. Withholding of concomitant medicinal products that may increase bleeding risk (e.g. platelet inhibitors, anticoagulants) should be considered. Patients should be advised to report signs or symptoms of bruising or bleeding immediately.

Infections

Fatal and serious infections, including opportunistic infections, occurred in patients during treatment with tafasitamab. Tafasitamab should be administered to patients with an active infection only if the infection is treated appropriately and well controlled. Patients with a history of recurring or chronic infections may be at increased risk of infection and should be monitored appropriately.

Patients should be advised to contact their healthcare professionals if fever or other evidence of potential infection, such as chills, cough, or pain on urination, develops.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported during combination therapy with tafasitamab. Patients should be monitored for new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing of tafasitamab must be immediately suspended. Referral to a neurologist should be considered. Appropriate diagnostic measures may include MRI scan, cerebrospinal fluid testing for JC viral DNA and repeat neurological assessments. If PML is confirmed, tafasitamab must be permanently discontinued.

Tumour lysis syndrome

Patients with high tumour burden and rapidly proliferative tumour may be at increased risk of tumour lysis syndrome. In patients with DLBCL, tumour lysis syndrome during treatment with tafasitamab has been observed. Appropriate measures/prophylaxis in accordance with local guidelines should be taken prior to treatment with tafasitamab. Patients should be monitored closely for tumour lysis syndrome during treatment with tafasitamab.

Immunisations

The safety of immunisation with live vaccines following tafasitamab therapy has not been investigated and vaccination with live vaccines is not recommended concurrently with tafasitamab therapy.

Excipient

This medicinal product contains 37.0 mg sodium per 5 vials (the dose of a patient weighing 83 kg), equivalent to 1.85% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Treatment with tafasitamab in combination with lenalidomide should not be initiated in female patients unless pregnancy has been excluded. Please also refer to the Product Information of lenalidomide.

Women of childbearing potential/Contraception in females

Women of childbearing potential should be advised to use effective contraception during and for at least 3 months after end of treatment with tafasitamab.

Effects on fertility

No specific studies have been conducted to evaluate potential effects of MINJUVI on human fertility. No dedicated animal fertility studies have been conducted with tafasitamab. No adverse effects on reproductive organs in males and females and no effects on menstrual cycle length in females were observed in cynomolgus monkeys at intravenous doses up to 100 mg/kg/week for 13 weeks (8 times the exposure (AUC) at maximum recommended human dose (MRHD)).

Use in pregnancy - Pregnancy Category C

There are no data on the use of MINJUVI in pregnant women. Animal reproductive and developmental toxicity studies have not been conducted with tafasitamab.

Human IgG is known to cross the placenta and tafasitamab may cause fetal B-cell depletion based on the pharmacological properties (see section 5.1). In case of exposure during pregnancy, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B-cell count has recovered (see section 4.4).

Tafasitamab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lenalidomide (Pregnancy Category X) can cause embryo-fetal harm and is contraindicated for use in pregnancy and in women of childbearing potential unless all of the conditions of the lenalidomide pregnancy prevention programme are met.

Use in lactation

There are no data on the presence of tafasitamab in human milk, the effects on the breastfed infant, or the effects on milk production. However, maternal IgG is known to be excreted in human milk. There are no data on the use of MINJUVI in breast-feeding women and a risk for breast-feeding children cannot be excluded. Women should be advised not to breast-feed during and for at least 3 months after the last dose of tafasitamab.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MINJUVI has no or negligible influence on the ability to drive and use machines. However, fatigue has been reported in patients taking tafasitamab and this should be taken into account when driving or using machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting of suspected adverse reactions

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 and drugsafety-STA@stbiopharma.com.

Summary of the safety profile

The most common adverse reactions are: infections (73%), neutropenia (51%), asthenia (40%), anaemia (36%), diarrhoea (36%), thrombocytopenia (31%), cough (26%), oedema peripheral (24%), pyrexia (24%), decreased appetite (22%).

The most common serious adverse reactions were infection (26%) including pneumonia (7%), and febrile neutropenia (6%).

Permanent discontinuation of tafasitamab due to an adverse reaction occurred in 15% of patients. The most common adverse reactions leading to permanent discontinuation of tafasitamab were infections and infestations (5%), nervous system disorders (2.5%), and respiratory, thoracic and mediastinal disorders (2.5%).

The frequency of dose modification or interruption due to adverse reactions was 65%. The most common adverse reactions leading to tafasitamab treatment interruption were blood and lymphatic system disorders (41%).

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials are listed by MedDRA System Organ Class and by frequency. The frequencies of adverse reactions is based on the pivotal phase 2 trial MOR208C203 (L-MIND) with 81 patients. Patients were exposed to tafasitamab for a median of 7.7 months. The adverse reaction frequencies from clinical trials are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than the medicinal product, such as the disease, other medicines or unrelated causes.

Frequencies are defined as follows: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions in patients with relapsed or refractory DLBCL who received tafasitamab in the clinical trial MOR208C203 (L-MIND)

System organ class	Frequency	Adverse reactions
Infections and infestations	Very common	Bacterial, viral and fungal infections+, including opportunistic infections with fatal outcomes (e.g. bronchopulmonary aspergillosis, bronchitis, pneumonia and urinary tract infection)
	Common	Sepsis (including neutropenic sepsis)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Common	Basal cell carcinoma
Blood and lymphatic system disorders	Very common	Febrile neutropenia+, neutropenia+, thrombocytopenia+, anaemia, leukopenia+
	Common	Lymphopenia
Immune system disorders	Common	Hypogammaglobulinaemia
Metabolism and nutrition disorders	Very common	Hypokalaemia, decreased appetite
	Common	Hypocalcaemia, hypomagnesaemia
Nervous system disorders	Common	Headache, paraesthesia, dysgeusia
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea, cough
	Common	Exacerbation of chronic obstructive pulmonary disease, nasal congestion
Gastrointestinal disorders	Very common	Diarrhoea, constipation, vomiting, nausea, abdominal pain
Hepatobiliary disorders	Common	Hyperbilirubinaemia, transaminases increased (includes ALT and/or AST increased), Gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	Very common	Rash (includes different types of rash, e.g. rash, rash maculopapular, rash pruritic, rash erythematous)
	Common	Pruritus, alopecia, erythema, hyperhidrosis
Musculoskeletal and connective tissue disorders	Very common	Back pain, muscle spasms
	Common	Arthralgia, pain in extremity, musculoskeletal pain
Renal and urinary disorders	Common	Blood creatinine increased
General disorders and administration site conditions	Very common	Asthenia++, oedema peripheral, pyrexia
	Common	Mucosal inflammation
Investigations	Common	Weight decreased, C-reactive protein increased
Injury, poisoning and procedural complications	Common	Infusion related reaction

+Further information on this adverse reaction is provided in the text below.
++ Asthenia includes asthenia, fatigue and malaise.

Compared with the incidences on combination therapy with lenalidomide, the incidences of non-haematological adverse reactions on tafasitamab monotherapy decreased by at least 10% for decreased appetite, asthenia, hypokalaemia, constipation, nausea, muscle spasms, dyspnoea and C-reactive protein increased.

Description of selected adverse reactions

Myelosuppression

Treatment with tafasitamab can cause serious or severe myelosuppression including neutropenia, thrombocytopenia and anaemia (see sections 4.2 and 4.4).

In the L-MIND study, myelosuppression (i.e. neutropenia, febrile neutropenia, thrombocytopenia, leukopenia, lymphopenia or anaemia) occurred in 65.4% of patients treated with tafasitamab. Myelosuppression was managed by reduction or interruption of lenalidomide, interruption of tafasitamab and/or administration of G-CSF (see sections 4.2 and 4.4). Myelosuppression led to interruption of tafasitamab in 41% and to tafasitamab discontinuation in 1.2%.

Neutropenia/febrile neutropenia

Incidence of neutropenia was 51%. Incidence of Grade 3 or 4 neutropenia was 49% and of Grade 3 or 4 febrile neutropenia was 12%. Median duration of any adverse reaction of neutropenia was 8 days (range 1 – 222 days); median time to onset to first occurrence of neutropenia was 49 days (range 1 – 994 days).

Thrombocytopenia

Incidence of thrombocytopenia was 31%. Incidence of Grade 3 or 4 thrombocytopenia was 17%. Median duration of any adverse reaction thrombocytopenia was 11 days (range 1 – 470 days); median time to onset to first occurrence of thrombocytopenia was 71 days (range 1 – 358 days).

Anaemia

Incidence of anaemia was 36%. Incidence of Grade 3 or 4 anaemia was 7%. Median duration of any adverse reaction of anaemia was 15 days (range 1 – 535 days); median time to onset to first occurrence of anaemia was 49 days (range 1 – 1129 days).

When patients in the L-MIND study were switched from tafasitamab and lenalidomide in the combination therapy phase to tafasitamab alone in the extended monotherapy phase, the incidences of haematological events decreased by at least 20% for neutropenia, thrombocytopenia and anaemia; no incidences of febrile neutropenia were reported with tafasitamab monotherapy (see sections 4.2 and 4.4).

Infections

In the L-MIND study, infections occurred in 73% of patients. Incidence of Grade 3 or 4 infections was 28%. The most frequently reported Grade 3 or higher infections were pneumonia (7%), respiratory tract infections (4.9%), urinary tract infections (4.9%) and sepsis (4.9%). Infection was fatal in < 1% of patients (pneumonia) within 30 days of last treatment.

Median time to first onset of Grade 3 or 4 infection was 62.5 days (4 – 1014 days). Median duration of any infection was 11 days (1 – 392 days).

Recommendations for management of infections are provided in section 4.4.

Infection led to dose interruption of tafasitamab in 27% and tafasitamab discontinuation in 4.9%.

Infusion-related reactions

In the L-MIND study, infusion-related reactions occurred in 6% of patients. All infusion related reactions were Grade 1 and resolved on the day of occurrence. Eighty percent of these reactions occurred during cycle 1 or 2. Symptoms included chills, flushing, dyspnoea and hypertension (see sections 4.2 and 4.4).

Immunogenicity

In 245 patients treated with tafasitamab, no treatment-emergent or treatment-boosted anti-tafasitamab antibodies were observed. Pre-existing anti-tafasitamab antibodies were detected in 17/245 patients (6.9%) with no impact on pharmacokinetics, efficacy or safety of tafasitamab.

Special populations

Elderly
Among 81 patients treated in the L-MIND study, 56 (69%) patients were > 65 years of age. Patients > 65 years of age had a numerically higher incidence of serious treatment emergent adverse events (TEAEs) (55%) than patients ≤ 65 years (44%).

4.9 OVERDOSE

In the case of an overdose, patients should be carefully observed for signs or symptoms of adverse reactions and supportive care should be administered, as appropriate.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FX12.

Mechanism of action

Tafasitamab is an Fc-enhanced monoclonal antibody that targets the CD19 antigen expressed on the surface of pre-B and mature B lymphocytes.

Upon binding to CD19, tafasitamab mediates B-cell lysis through:

- engagement of immune effector cells like natural killer cells, γδ T cells and phagocytes
- direct induction of cell death (apoptosis)

The Fc modification results in enhanced antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.

Pharmacodynamic effects

In patients with relapsed or refractory DLBCL, tafasitamab led to a reduction in peripheral blood B-cell counts. The reduction relative to baseline B-cell count reached 97% after eight days

of treatment in the L-MIND study. The maximum B-cell reduction at approximately 100% (median) was reached within 16 weeks of treatment.

Although the depletion of B-cells in the peripheral blood is a measurable pharmacodynamic effect, it is not directly correlated with the depletion of B-cells in solid organs or in malignant deposits.

Clinical trials

Tafasitamab plus lenalidomide followed by tafasitamab monotherapy was studied in the L-MIND study, an open-label multicentre single-arm study. This study was conducted in adult patients with relapsed or refractory DLBCL after 1 to 3 prior systemic DLBCL therapies, who at the time of the trial were not candidates for high dose chemotherapy followed by ASCT or who had refused ASCT. One of the prior systemic therapies had to include a CD20 targeted therapy. The study excluded patients with severe hepatic impairment (total serum bilirubin > 3 mg/dL) and patients with renal impairment (CrCL< 60 mL/min.), as well as patients with history or evidence of clinically significant cardiovascular, CNS and/or other systemic disease. Patients with a known history of "double/triple-hit" genetics DLBCL were also excluded at study entry.

For the first three cycles, patients received 12 mg/kg tafasitamab via infusion on day 1, 8, 15 and 22 of each 28-day cycle, plus a loading dose on day 4 of cycle 1. Thereafter, tafasitamab was administered on days 1 and 15 of each cycle until disease progression. Pre-medication including antipyretics, histamine H1 and H2 receptor blockers and glucocorticosteroids was given 30 to 120 minutes prior to the first three tafasitamab infusions.

Patients self-administered 25 mg lenalidomide daily on days 1 to 21 of each 28-day cycle, up to 12 cycles.

A total of 81 patients were enrolled in the LMIND study. The median age was 72 years (range 41 to 86 years), 89% were white and 54% were males. Out of 81 patients, 74 (91.4%) had ECOG performance score of 0 or 1 and 7 (8.6%) had ECOG score of 2. The median number of prior therapies was two (range: 1 to 4), with 40 patients (49.4%) receiving one prior therapy and 35 patients (43.2%) receiving 2 prior lines of treatment. Five patients (6.2%) had 3 prior lines of therapies and 1 (1.2%) had 4 prior lines of treatment. All patients had received a prior anti-CD20-containing therapy. Eight patients had a diagnosis of DLBCL transformed from lowgrade lymphoma. Fifteen patients (18.5%) had primary refractory disease, 36 (44.4%) were refractory to their last prior therapy, and 34 (42.0%) were refractory to rituximab. Nine patients (11.1%) had received prior ASCT. The primary reasons for patients not being candidates for ASCT included age (45.7%), refractory to salvage chemotherapy (23.5%), comorbidities (13.6%) and refusal of high dose chemotherapy/ASCT (16.0%).

One patient received tafasitamab, but not lenalidomide. The remaining 80 patients received at least one dose of tafasitamab and lenalidomide. All patients enrolled in the L-MIND study had a diagnosis of DLBCL based on local pathology. However, as per central pathology review, 10 patients could not be classified as DLBCL.

The median duration of exposure to treatment was 9.2 months (range: 0.23, 54.67 months). Thirty-two (39.5%) patients completed 12 cycles of tafasitamab. Thirty (37.0%) patients completed 12 cycles of lenalidomide.

The primary efficacy endpoint was best objective response rate (ORR), defined as the proportion of complete and partial responders, as assessed by an independent review committee (IRC). Other efficacy endpoints included duration of response (DoR), progression-free survival (PFS) and overall survival (OS). The efficacy results are summarised in Table 3.

Table 3: Efficacy results in patients with relapsed or refractory diffuse large B-cell lymphoma in the MOR208C203 (L-MIND) study

Efficacy parameter	**Tafasitamab + lenalidomide** (N = 81 [ITT]*)	
	30-NOV-2019 cut-off (24 months analysis)	**30-OCT-2020 cut-off** (35 months analysis)
Primary endpoint		
Best objective response rate (per IRC)		
Overall response rate, n (%) (95% CI)	46 (56.8) [45.3, 67.8]	46 (56.8) [45.3, 67.8]
Complete response rate, n (%) (95% CI)	32 (39.5) [28.8, 51.0]	32 (39.5) [28.8, 51.0]
Partial response rate, n (%) (95% CI)	14 (17.3) [9.8, 27.3]	14 (17.3) [9.8, 27.3]
Secondary endpoint		
Overall duration of response (complete + partial response) [a]		
Median, months (95% CI)	34.6 [26.1, NR]	43.9 [26.1, NR]

ITT = intention to treat; NR = not reached

*One patient received only tafasitamab

CI: Binomial exact confidence interval using Clopper Pearson method

[a] Kaplan Meier estimates

Overall survival (OS) was a secondary endpoint in the study. After a median follow up time of 42.7 months (95% CI: 38.0; 47.2), the median OS was 31.6 months (95% CI: 18.3; not reached).

Amongst the eight patients who had a DLBCL transformed from a prior indolent lymphoma, seven patients had an objective response (three patients a CR, four patients a PR) and one patient had a stable disease as the best response to tafasitamab+ lenalidomide treatment.

Elderly

In the ITT set, 36 of 81 patients were ≤ 70 years and 45 of 81 patients were > 70 years. No overall differences in efficacy were observed for patients ≤ 70 years versus patients > 70 years of age.

5.2 PHARMACOKINETIC PROPERTIES

The absorption, distribution, biotransformation and elimination were documented based on a population pharmacokinetic analysis.

Absorption

Based on an analysis of tafasitamab in combination with lenalidomide, tafasitamab average serum trough concentrations (± standard deviation) were 179 (± 53) µg/mL during weekly (plus an additional dose on day 4 of cycle 1) intravenous administrations of 12 mg/kg. During administration every 14 days from cycle 4 onwards, average trough serum concentrations were 153 (± 68) µg/mL. Overall maximum tafasitamab serum concentrations were 483 (± 109) µg/mL.

Distribution

The total volume of distribution for tafasitamab was 9.3 L.

Metabolism

The exact pathway through which tafasitamab is metabolised has not been characterised. As a human IgG monoclonal antibody, tafasitamab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Excretion

The clearance of tafasitamab was 0.41 L/day and terminal elimination half-life was 16.9 days. Following long-term observations, tafasitamab clearance was found to decrease over time to 0.19 L/day after two years.

Special populations

Age, body weight, sex, tumour size, disease type, B-cell or absolute lymphocyte counts, anti-drug antibodies, lactate dehydrogenase and serum albumin levels had no relevant effect on the pharmacokinetics of tafasitamab. The influence of race and ethnicity on the pharmacokinetics of tafasitamab is unknown.

Renal impairment

The effect of renal impairment was not formally tested in dedicated clinical trials; however, no clinically meaningful differences in the pharmacokinetics of tafasitamab were observed for mild to moderate renal impairment (creatinine clearance (CrCL) ≥ 30 and < 90 mL/min estimated by the Cockcroft-Gault equation). The effect of severe renal impairment to end-stage renal disease (CrCL < 30 mL/min) is unknown.

Hepatic impairment

The effect of hepatic impairment was not formally tested in dedicated clinical trials; however no clinically meaningful differences in the pharmacokinetics of tafasitamab were observed for mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or total bilirubin 1 to 1.5 times ULN and any AST). The effect of moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) is unknown.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted with tafasitamab. As tafasitamab is a monoclonal antibody, it is not expected to interact with DNA or chromosomes.

Carcinogenicity

Carcinogenicity studies have not been conducted with tafasitamab. Proliferative changes were not observed in cynomolgus monkeys administered weekly intravenous doses of tafasitamab at 100 mg/kg for 3 months (8 times the exposure (AUC) at the MRHD).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium citrate dihydrate
Citric acid monohydrate
Trehalose dihydrate
Polysorbate 20

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

No incompatibilities have been observed with standard infusion materials.

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.

Unopened vial

4 years

Reconstituted solution (prior to dilution)

The reconstituted solution should be used immediately. If storage is necessary, hold at 2°C – 25°C for not more than 24 hours. Do not freeze or shake.

Diluted solution (for infusion)

The diluted solution should be used immediately. If not used immediately, in-use storage times has been demonstrated for a maximum of 36 hours at 2 – 8 °C, followed by up to 24 hours up to 25 °C. Do not freeze or shake.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2 °C – 8 °C).

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

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

MINJUVI (tafasitamab) powder for solution for infusion is supplied as a sterile, preservative-free lyophilised powder in a 20 mL clear type I glass vial with a butyl rubber stopper, aluminium seal and a plastic flip-off cap.

Each carton contains one single dose vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Tafasitamab is a humanised CD19 specific monoclonal antibody of the immunoglobulin G (IgG) subclass produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology.

CAS number:

1422527-84-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Specialised Therapeutics Alim Pty Ltd
Level 2, 17 Cotham Road, Kew, Victoria 3101
Australia
Ph: 1300 798 820
Fax: 1800 798 829
www.stbiopharma.com

9 DATE OF FIRST APPROVAL

Insert approval date from TGA Approval Letter

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information