Itolizumab Injection

Biocon Biologics

ALZUMAb®

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1. GENERIC NAME
Itolizumab Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient: Itolizumab
Excipients: monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride, polysorbate 80 and water for injection
For full list of excipients, See Description (Section 7) for details.

3. DOSAGE FORM AND STRENGTH
Each vial contains
Itolizumab 25 mg
(r-DNA Origin)
For i.v. infusion only. Single use vial.
Itolizumab is a humanized recombinant anti-CD6 monoclonal antibody.
See Description (Section 7) for details.

4. CLINICAL PARTICULARS
4.1 Therapeutic indication
ALZUMAb®(Itolizumab injection) is indicated for the:

- Treatment of patients with active moderate to severe chronic plaque psoriasis who are candidates for systemic therapy.
- Treatment of Cytokine release syndrome (CRS) in moderate to severe Acute Respiratory distress syndrome (ARDS) patients due to Coronavirus disease 2019 (COVID-19).

Limitations of Use
The safety and efficacy of ALZUMAb® has not been studied in, (a) pediatric patients <18 years old; (b) patients with hepatic and renal impairment; (c) pregnancy and, (d) nursing mothers.

4.2 Posology and method of administration
Pre-Medication
Hydrocortisone 100 mg IV (or equivalent short acting glucocorticoid) and pheniramine 30 mg IV are given about 30 ± 10 minutes prior to each infusion. ALZUMAb®is intended for use under the guidance and supervision of a physician. The diluted infusion solution should be prepared by a trained medical professional using an aseptic technique, as follows:

- Calculate the dose and number of ALZUMAb® vials needed. ALZUMAb® is provided as preservative-free single-use vial for IV infusion. Each vial contains 25 mg of itolizumab (5 mg/mL) in a sterile, clear, colorless, preservative-free buffer solution at pH 7.0±0.5 [see Pharmaceutical Particulars sections].
- ALZUMAb®should be administered via IV infusion in 250 mL of 0.9% Sodium Chloride solution (normal saline). For this, dilute the appropriate dose of ALZUMAb®to 250 mL with sterile normal saline. Gently mix.

Note: Itolizumab infusion is not to be prepared in dextrose solution.

- Fully diluted ALZUMAb® solution should be allowed to reach room temperature prior to infusion. Before use, the fully diluted ALZUMAb®solution may be stored at room temperature or refrigerated at 2°C-8°C (36°F-46°F) protected from light. ALZUMAb®is stable in an infusion bag containing 250 mL of normal saline for up to 10 hours at room temperature. Do not administer as IV push or bolus.
- The infusion must be administered using an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size of 1.2 µm or less).
- The infusion period can be extended up to 8 hours for medical reasons.

Note: Prior to initiating ALZUMAb® and periodically during therapy patients should be evaluated for active tuberculosis and tested for latent infection and history of severe allergy. History of known hypersensitivity reaction to any component of ALZUMAb® or any murine proteins should be evaluated [see Special Warnings and Precautions for Use and Contraindications sections].

1) Plaque Psoriasis
The recommended dose of ALZUMAb® for the treatment of plaque psoriasis is 1.6 mg/kg given as IV infusion once every 2 wks for 12 wks, followed by 1.6 mg/kg every 4 wks up to 24 wks.
Approximately 50 mL of diluted ALZUMAb®solution should be administered during the first hour, followed by remaining solution in the next hour.

2) Treatment of Cytokine release Syndrome (CRS) in moderate to severe Acute Respiratory Distress Syndrome (ARDS) patients due to COVID-19
The recommended dose of ALZUMAB®is 1.6 mg/kg given as IV infusion as a starting dose. Based on the clinical status and serum inflammatory markers, additional dose of 0.8mg/Kg can be administered after 7 days based on the physician's discretion.
First infusion of itolizumab at 1.6mg/ kg must be initiated at 25 ml/h for the first hour. If well tolerated it can be increased to 50 mL/h to infuse the remaining amount. The infusion is to be completed over a period of 5-6h.
In case the dose had to be interrupted due to an infusion reaction, the dosing must be restarted very slowly after constant monitoring and appropriate management of vital signs and symptoms. If reaction appears upon re-challenge, dosing must be terminated.
If required, a second infusion of itolizumab at 0.8mg/Kg is to be given after one week. The infusion can be completed over 3- 4 h.
The clinical trial data supports safety of up to 4 doses.

- The vials do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse [see Pharmaceutical Particulars sections].
- No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of ALZUMAb®with other agents. ALZUMAb®should not be infused concomitantly in the same IV line with other agents.
- Prior to administration, the solution in the vial should be carefully inspected visually for particulate matter and discoloration. If visible opaque particles, discoloration or other foreign particulates are observed, the product should not be used.

4.3 Contraindications
ALZUMAb®should not be administered to patients having a history of severe allergy or known hypersensitivity reaction to any component of ALZUMAb®or any murine proteins *(see Qualitative and Quantitative Composition).*

4.4 Special warnings and precautions for use

Warning: Itolizumab is not recommended to be administered to patients who are on an invasive mechanical ventilator. No trials have been done on such patients

Infusion-related reactions and hypersensitivity reactions
During administration of ALZUMAb® some patients may develop acute infusion reactions. Symptoms may include chills/ rigors (common), nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, wheezing, dyspnoea, oxygen desaturation (in ARDS patients), dizziness, headache and hypertension. Infusion reactions are most likely to occur during the first cycle of dosing and tend to decrease in severity and frequency upon subsequent infusions.

In the clinical trial infusion reactions were mild to severe in intensity. All of them resolved with appropriate symptomatic management. Acute infusion reactions should be treated using the standard of care; and physicians may need to delay dosing till the patient is stabilized.
Infections
In the psoriasis trial, overall, ALZUMAb® did not appear to increase the rate of infections in patients compared to placebo, during the study. However, physicians should exercise caution before and during ALZUMAb® treatment in patients with a history of recurrent infections or underlying conditions which may predispose them to serious infections. Patients should be closely monitored closely for the development of signs and symptoms of an infection during and after the treatment with ALZUMAb®, including patients who were evaluated negative for latent tuberculosis infection prior to initiating the therapy. In case of new infections or reactivation of latent infections during the treatment, ALZUMAb® should be discontinued and immediate treatment in accordance with standard medical practice should be instituted. During the TREAT-PLAQ study, one case of tubercular lymphadenitis was reported after 4 wks of itolizumab treatment, in a patient who had prior history of tuberculosis. The patient was withdrawn for safety reasons. During the study, one case of septic arthritis was reported; bacterial culture and acid-fast bacilli (AFB) culture of synovial fluid were negative and causality was inconclusive [see Undesirable Effects]. Overall, ALZUMAb®did not appear to increase rate of infections in patients compared to placebo, during the study.
ALZUMAb®has not been studied in patients with a history of serious infections such as HIV-AIDS or active tuberculosis. The effect of ALZUMAb® in these special populations is unknown. Caution should be exercised while administering itolizumab to immunocompromised patients with Human Immunodeficiency Virus (HIV), Hepatitis B, Hepatitis C infection and patients receiving or received chronic steroid therapy.
Prior to initiating the ALZUMAb®administration, patients should be screened for active or latent tuberculosis infection using Mantoux test and or chest X-ray and or IGRA.

Transient Lymphopenia
In the COVID-19 trial, patients with ALC < 500mm3 were excluded. lymphopenia was observed post infusion; however, the lymphopenia was transient in nature and in general reversed within 7 days.

Use with other biologics
ALZUMAb®has not been studied in combination with other biological agents.

Vaccination
No data are available on the response to vaccination with live/attenuated vaccines or on the secondary transmission of infection by live vaccines in patients receiving ALZUMAb®therapy. Based on its mechanism of action, ALZUMAb®may blunt the effectiveness of some immunizations. It is recommended that live/attenuated vaccines not be given concurrently with ALZUMAb®. The patient's vaccination record and the need for immunization prior to receiving ALZUMAb® should be carefully investigated. The interval between vaccination and initiation of ALZUMAb® therapy should be in accordance with current vaccination guidelines. Caution is advised in the administration of live vaccines to infants born to female patients treated with ALZUMAb®during pregnancy, since ALZUMAb®may cross the placenta.

Malignancies
None of the patients on itolizumab treatment developed malignancies during the clinical trials.

4.5 Drugs interactions
Drug interaction studies have not been performed with ALZUMAb®.

4.6 Use in special populations
Pregnancy
As with other IgG antibodies, itolizumab may cross the placenta during pregnancy. It is not known whether ALZUMAb® can cause fetal harm when administered to a pregnant woman, or whether it can affect reproductive capacity or fertility. Animal reproduction studies have not been conducted with ALZUMAb® as it does not recognize peripheral blood mononuclear cells within species other than humans, baboons and chimpanzees (see Nonclinical Properties section).
The available clinical experience is too limited to exclude a risk, and administration of ALZUMAb® is therefore not recommended during pregnancy.

Lactation
It is not known whether itolizumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulin are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ALZUMAb®, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines
Treatment with ALZUMAb®, is not expected to effect patient's ability to drive or use machines.

4.8 Undesirable effects
Clinical trial experience in patients
Safety data of ALZUMAb®has been derived from 2 randomized, multicentre studies in patients with chronic plaque psoriasis and 1 randomized, multicentre study in COVID-19 complications. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs and may not predict the rates observed in the broader patient population in clinical practice.

Study I was a randomized, single-blind, parallel-group, phase 2 study in 40 patients. Overall, 123 adverse events (AEs) were reported during the study. The most common AE was chills (5.69%), followed by pyrexia (4.88%). There was a relatively higher incidence of AEs with higher frequency of dosing at each dose. Numerically, the largest number of AEs (n=24) was reported for the highest dose administered in the trial (1.6 mg/kg every 2 wks).

Twenty nine out of 40 (72.50%) patients in the study reported at least one AE during the study. Seventy-three out of 123 (59.35%) AEs were graded as mild, 46 (37.39%) were graded as moderate and 4 (3.25%) were graded as severe. There were 4 SAEs reported during the study. Three out of 4 SAEs reported were related to musculoskeletal and connective tissue disorders (e.g. arthralgia, other musculoskeletal pain and osteonecrosis) and one was erythrodermic psoriasis. There were 16 acute and 4 possible delayed infusion reactions. All these reactions were mild to moderate and the patients recovered completely. The incidence of infusion reactions was higher during the initial doses and decreased with subsequent dosing. All infusion reactions were mild to moderate in severity. There were no significant changes in general examination and vital signs from baseline to the end of trial. Immunogenicity analysis detected one sample from one patient (0.4 mg/kg once in 2 wks) with high-titre antibody response at week 12. However, the immunogenic response did not correlate with any clinical adverse event or impact the PK profile.

Study II (TREAT-PLAQ) was a double-blind, placebo-controlled, one-way crossover phase 3 study in 225 patients. Overall, there were 289 AEs reported in 111 (49.8%) of the 223 patients in the safety population (i.e. patients who received at least one infusion) during 52-week treatment period. Sixty-six patients (29.6%) patients had mild AEs, 34 (15.2%) had moderate AEs, and 11 (4.9%) had severe AEs. The overall incidence of AEs and related AEs was not meaningfully different between patients randomized to treatment arms A, B and C. Overall incidence of AEs was 50%, 47.8% and 53.5% in treatment arm A, B and C, respectively. Incidence of related AEs was 26.7%, 28.9% and 30.3%, respectively. The most frequently reported AEs (in ≥5% of patients) were infusion-related reactions, pyrexia, upper respiratory tract infection and pruritus (Table 1). Study drug related SAEs were anaphylactic reaction, bacterial arthritis, lung infection, hyponatremia, and decreased appetite.
A total of 30 (13.5%) patients had AE that led to change in administration of study drug. Two (0.9%) patients had a decrease in dosage, 19 (8.5%) temporarily discontinued the study drug, 2 (0.9%) patients permanently stopped the study drug and 7 (3.1%) patients were withdrawn from the study.
Study III (ITOLI-C19-02-I-00) was a multi-centric, open label, two arm, randomized trial study of itolizumab in COVID-19 complications in 30 patients. The most common adverse events reported were transient lymphopenia and infusion reactions that were moderate to severe in intensity and were managed conservatively. Drug related TEAEs were lymphocyte count decreased, chills, infusion related reaction, and anaphylactic reaction.

Most frequently reported adverse events (Chronic Plaque Psoriasis)
In the trial conducted in plaque psoriasis patients, the most frequently reported AEs (those that occurred in >5% of patients overall or in any individual treatment arm), in decreasing order, were infusion-related reactions, pyrexia, upper respiratory tract infection and pruritus (Table 1). In addition to these, diarrhea was reported in 6 (6.7%) patients in arm B. Of the total enrolled 223 patients, 3 (15.2%) patients had at least one acute infusion reaction during 52-week of treatment period. The treatment arms A and B had a slightly higher rate of acute infusion reactions (20% and 16.7%, respectively) compared to arm C (11.6%) during 52-week treatment period [see Special Warnings and Precautions for Use].

Table1 Most Frequently Occurring Adverse Events (in >5% of Patients) in the TREAT-PLAQ Study (Wks 1-52)

Preferred Term	Arm A n (%)	Arm B n (%)	Arm C n (%)	Total n (%)
	N=90	N=90	N=43	N=223
All Adverse Events				
Gastrointestinal disorders				
Diarrhoea	0	6 (6.7)	1 (2.3)	7 (3.1)
General disorders and administration site conditions				
Infusion related reaction (acute)	18 (20)	15 (16.7)	5 (11.6)	38 (15.2)
Infusion related reaction (delayed)	2 (2.2)	5 (5.6)	1 (2.3)	8 (3.6)
Pyrexia	9 (10)	8 (8.9)	5 (11.6)	22 (9.8)
Infections and infestations				
Upper respiratory tract infection	2 (2.2)	10 (11.1)	5 (11.6)	17 (7.6)
Skin and subcutaneous tissue disorders				
Pruritus	3 (3.3)	5 (5.6)	4 (9.3)	12 (5.4)

Infection
Several immunomodulatory agents approved for psoriasis (such as anti-TNF monoclonal antibodies) are known to increase the risk of infections. In the TREAT-PLAQ study, patients were monitored for infections (summarized in Table 2). In general, itolizumab did not appear to increase the rate of infections as compared to placebo. During the placebo-controlled period, (wks 1-12) the proportion of patients with at least one infection was higher in the placebo arm (18.6%) than in arms A (11.1%) or B (8.9%). Over the course of the study, a total of 40 (17.9%) patients had at least one infection; 26 (11.7%) patients in the first 12 wks and 19 (8.5%) patients in wks 13 to 52 (5 patients had an infection in both periods).

Table2 Incidence of Infections in TREAT-PLAQ Study

Study Period	Number of Patients (%)			
	Arm to Which Patient was Initially Randomized			Total
	Arm A	Arm B	Arm C	
Overall	16 (17.8)	16 (17.8)	8 (18.6)	40 (17.9)
Weeks 1-12	10 (11.1)	8 (8.9)	8 (18.6)	26 (11.7)

During the TREAT-PLAQ study, one case of septic arthritis was reported 8 months after the start of treatment, which was deemed related to the study drug by the investigator. However, bacterial culture and AFB culture of synovial fluid were negative. Total and differential counts of the patient were stable and in normal range throughout the study.
There was 1 case of tubercular lymphadenitis was observed after 4 wks of treatment (5 doses of itolizumab, total dose of 3.2 mg/kg) in a patient who had a history of tuberculosis (15 years prior). The patient had WBC and differential counts in the normal range throughout the study participation. The patient was withdrawn from the study for safety reasons. All other infections reported were either mild or moderate in severity.

Vital signs
Vital signs (systolic and diastolic blood pressure, respiratory rate, mean and median pulse rates and temperature) were stable throughout the study.

Immunogenicity
The human anti-humanized antibody (HAHA) response to itolizumab was evaluated through analysis of immunogenicity of itolizumab at wks 4, 12, 28, and 52 in the TREAT-PLAQ study. Positive HAHA responses were observed in 51 (23.2%) patients through the study (23 from arm A, 19 from arm B and 9 from arm C). In arm C, 7 patients were positive prior to dosing (during the placebo-controlled phase) and 2 patients were positive after the crossover phase. Fourteen patients had positive titre at visit 1 (prior to dosing with itolizumab).
There were a few incidences of positive HAHA response during the study. It is not known whether the HAHA detected were neutralizing or not; although positive immunogenic response in patients did not correlate with either infusion reactions or decreased efficacy.

Clinical laboratory abnormalities
Overall, there were no clinically meaningful differences between treatment arms with respect to the proportion of patients with abnormalities in haematology and clinical chemistry. There were 31 abnormal laboratory values that were reported as AEs in 18 patients. Twenty-six (83.9%) out of the 31 AEs were mild and 5 (16.1%) were moderate. Twenty-two (71%) of the 31 abnormal laboratory values were reported in the first 12 weeks of the study and 20 (64.5%) were related to different lipoprotein findings.

Other AEs that do not appear in Special Warnings and Precautions for Use or Undesirable effects sections that occurred at a rate of at least 1% and at a higher rate in the itolizumab treated patients than the placebo group during the placebo-controlled period of TREAT-PLAQ study (Study II) irrespective of relationship to the study products are listed below:

Gastrointestinal disorders: diarrhoea, toothache, vomiting, gastritis, gastrointestinal inflammation.
General disorders and administration site conditions: Infusion-related reactions (acute and chronic), oedema peripheral, pain, chest pain.

Immune system disorders: Hypersensitivity, anaphylactic reaction.

Infections and infestations: abscess, folliculitis, gastroenteritis, lymphadenitis bacterial, lymph node tuberculosis, oral herpes, pyrexia, urinary tract infection, rhinitis, tooth abscess.

Metabolism and nutrition disorders: dehydration, hepatic steatosis, hypertriglyceridemia.

Musculoskeletal and connective tissue disorders: musculoskeletal pain, pain in extremity, arthralgia, back pain.
Nervous system disorders: headache, neuropathy peripheral, cerebrovascular accident.

Psychiatric disorders: Adjustment disorder with anxiety.

Renal and urinary disorders: dysuria.

Respiratory, thoracic and mediastinal disorders: cough, oropharyngeal pain, rhinorrhoea Skin and subcutaneous tissue disorders: psoriasis, keloid scar, dermatitis exfoliative, pruritus, erythrodermic psoriasis.

Study III (ITOLI-C19-02-I-00) (COVID-19 with moderate to severe ARDS): In the trial conducted in moderate to severe ARDS patients with COVID-19 infection, where up to a maximum of 4 doses of itolizumab were received, the most frequently reported treatment related emergent adverse event were lymphocyte count decrease, that was transient, and infusion related reaction.
The infusion reaction occurred only during the first infusion. Six patients reported with infusion related reaction during the first infusion. Most of the infusion reaction presented as chills and were mild to moderate in severity except for two events that were severe. The events were managed conservatively and were resolved. These infusion reactions occurred when they were given over 2 hours. However, the reaction were abated when the infusion was given over 5-6 hours For Infusion related reaction see section on Posology and Method of Administration.
There were 11 events of grade III Lymphopenia occurring post infusion and were transient in nature. They reversed spontaneously. The lymphopenia is to be followed up. If persisting has to be managed appropriately.

4.9 Overdose
Doses up to 1.6 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. During the TREAT-PLAQ study (study II), one patient was overdosed by 23.2 mg with the cumulative dose of 50 mg during the first week of itolizumab treatment. However, no AE was observed, and the patient was normal. In case of an overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

4.10 Clinical Studies
Psoriasis
The efficacy and safety of ALZUMAb®was assessed in 2 randomized, multicentric studies (Study I and II) in patients 18 years of age and older with chronic, stable plaque psoriasis involving ≥10% body surface area, a minimum Psoriasis Area and Severity Index (PASI) score of ≥10. All patients had either failed or were intolerant to or had a contraindication to at least one prior systemic anti-psoriatic therapy.
The claim of efficacy is supported primarily by data from pivotal phase 3 trial (TREAT-PLAQ; Study II) in moderate to severe plaque psoriasis. Supporting efficacy data from this patient population was also collected from the phase 2 trial (Study I).

Pivotal Safety and Efficacy Study in Moderate to Severe ARDS patients due to COVID-19
The safety and efficacy of ALZUMAb®was assessed in Moderate to Severe ARDS patients due to COVID-19 in a multi-centric, randomized trial in patients 18 years of age and older with confirmed virological diagnosis of SARS-CoV2 infection (RT-PCR) (Study III).

Study I (Study T1hAb-CT1-001-07) was a 32-week, randomized, single-blind, parallel, phase 2 study to evaluate the efficacy and safety of itolizumab in 40 patients of plaque psoriasis. Patients were randomized into 8 groups (5 patients per group), who received 0.4 or 0.8 mg/kg [once every week, once in 2 weeks (wks), once in 4 wks]; or 1.6 mg/kg (once in 2 wks or once in 4 wks). Patients were treated for 8 wks and were followed up for 24 wks. Efficacy parameters of the study included PASI, Physician's Global Assessment (PGA), Psoriasis Severity Scale (PSS); the Short Form-36 (SF-36), Dermatology Life Quality Index (DLQI) questionnaires to assess changes in patient quality of life; and reductions in epidermal as well as rete thickness.
In the overall study cohort (n=40), the mean PASI score decreased consistently for all patients from baseline visit to week 12. The mean PASI score at baseline was 22.32±8.84 which was significantly reduced to 7.62±7.80 at week 8 and 6.23±7.14 at the end of week 12 (p<0.0001). Overall, 72.5% of patients achieved PASI 50 and, 45% achieved PASI 75 at week 12. The reduction in mean PASI scores observed at the end of treatment phase (week 8) continued to persist till the end of week 12 in all dosing cohorts, 62.16% of patients improved or maintained their PASI improvement achieved at week 8 till week 12 after stopping the study drug. The PGA and PSS scores reduced consistently from baseline to week 12 (p<0.0001) for all groups in the study. Moreover, 65% of the patients achieved a score of "minimal" or "clear" by PGA scoring criteria. The proportion of patients with improvement in PASI and PGA scores at wks 8 and 12 is shown in Table 3. In addition, DLQI and SF-36 assessment suggested improvement in the quality of life in the patients owing to improvement of their skin lesions. Lastly, there were

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significant reduction in mean epidermal (p=0.0005) and rete thickness (p<0.0001) at week 12 compared to baseline; with maximal reduction in both epidermal and rete thickness seen at week 8.

Table 3 Summary of Itolizumab Efficacy Data in Phase 2 Study: Proportion of Patients Achieving Improvement in PASI and PGA Scores, at Week 8 and 12

Response achieved at:	Proportion of patients achieving PASI and PGA response [n/N (%)]				
	PASI 50	PASI 75	PASI 90	PASI 100	PGA score ("clear" or "minimal")
Week 8 (N=40)	27/40 (67.50%)	17/40 (42.50%)	8/40 (20%)	3/40 (7.50%)	24/40 (60%)
Week 12 (N=40)	29/40 (72.50%)	18/40 (45%)	12/40 (30%)	3/40 (7.50%)	26/40 (65%)

PASI: psoriasis area and severity index; PGA: physician's global assessment
n=number of patients with response; N=total number of patients

Study II ("TREAT-PLAQ"; Study T1hAb-CT3-002-09) was a 52-week, randomized, double-blind, placebo-controlled, one-way cross over, pivotal phase 3 study to assess the efficacy and safety of itolizumab.
The study was conducted in three double blind phases post screening (2 wks) and washout phases (if necessary, up to 8 wks depending on current treatment):

- Placebo controlled phase (12 wks),
- Crossover of Placebo and consolidation treatment phase (16 wks) and,
- Randomized withdrawal phase (24 wks).

In this study, 225 patients were treated as follows:
Wks 1-12 (double-blind, placebo-controlled): Patients were randomized in a 2:2:1 ratio to following treatment arms: (A) itolizumab 0.4 mg/kg every week for 4 wks, followed by 1.6 mg/kg every 2 wks for 8 wks; (B) itolizumab 1.6 mg/kg every 2 wks for 12 wks; or (C) placebo for 12 wks.

Wks 12-24 (double-blind): Patients from arms A and B continued to receive itolizumab at the dose of 1.6 mg/kg every 4 wks till wks 24; and patients from arm C received itolizumab at 1.6 mg/kg every 2 wks till wks 24.
Wks 24-52: Week 24-28 was a treatment-free period.
Patients from arm C received itolizumab at the dose of 1.6 mg/kg every 12 wks, and patients from arm A and B were re-randomized based on their PASI response:

- Patients who achieved ≥PASI 75 were randomized (1:1) to receive either itolizumab 1.6 mg/kg every 12 wks or placebo (double-blind) till week 52;
- Patients who achieved ≥PASI 50 but <PASI 75 response received itolizumab 0.4 mg/kg every week for 4 wks followed by 1.6 mg/kg every 4 wks (open-label);
- Patients failing to achieve PASI 50 were withdrawn from the study.

The last dosing visit (at wks 48) was followed by a 4-wks treatment-free follow-up period.
In the TREAT-PLAQ study, the primary endpoint was the proportion of patients achieving ≥PASI 75 at wks 12 in each itolizumab cohort as compared to placebo. Other evaluated outcomes measured at different intervals were, (a) proportion of patients achieving PASI 50, 75, 90 and 100 from baseline in each itolizumab cohort; (b) proportion of patients with PGA score in Table 4"clear" or "minimal" and, (c) change in health-related quality of life as assessed by SF-36 and DLQI.

Two hundred and twenty patients were included in the efficacy population (full analysis set - intent-to-treat [FAS-ITT] population). The proportions of patients who achieved PASI 50, 75, 90 and 100 scores at week 12, 28 and 52 are displayed in Table 4. In the primary analysis, at week 12 both itolizumab treatment arms A and B demonstrated significant efficacy over arm C (placebo from wks 1-12): 27% of patients from arm A, 36.4% from arm B and 2.3% from arm C achieved PASI 75 at week 12. The proportion of PASI 50 responders followed the same trend as for PASI 75. Thus, itolizumab produced improvements in PASI 50 and PASI 75, both clinically meaningful outcomes for psoriasis patients.

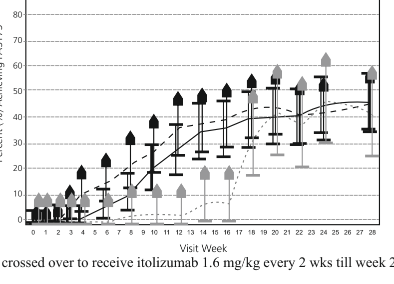
Table 4 Summary of Itolizumab Efficacy Data in the TREAT-PLAQ Study: Proportion of Psoriasis Patients Achieving PASI 50, 75, 90 and 100 at Week 12, 28 and 52

Response achieved at:	Treatment arm	Proportion of patients achieving PASI response [n/N (%)]			
		PASI 50	PASI 75	PASI 90	PASI 100
Week 12 (N=220)	A	52/89 (58.4%)	24/89 (27.0%)	10/89 (11.2%)	2/89 (2.2%)
	B	59/88 (67.0%)	32/88 (36.4%)	15/88 (17.0%)	3/88 (3.4%)
	C (placebo)	10/43 (23.3%)	1/43 (2.3%)	0/43	0/43
	p values	0.0003 (A vs. C): <0.0001 (B vs. C): 0.2160 (A vs. B)	0.0172 (A vs. C): 0.0043 (B vs. C)	0.0234 (A vs. C): 0.0046 (B vs. C): 0.2477 (A vs. B)	-
Week 28 (N=220)	A	70/89 (78.7%)	41/89 (46.1%)	17/89 (19.1%)	2/89 (2.2%)
	B	71/88 (80.7%)	40/88 (45.5%)	19/88 (21.6%)	4/88 (4.5%)
	C (itolizumab 1.6 mg/kg every 2 weeks)	34/43 (79.1%)	18/43 (41.9%)	12/43 (27.9%)	0/43
Week 52 (N=177)	Open label arm	52/59 (88.1%)	33/59 (55.9%)	16/59 (27.1%)	5/59 (8.5%)
	Placebo arm	28/40 (70.0%)	21/40 (52.5%)	12/40 (30.0%)	4/40 (10.0%)
	Itolizumab (from arm A and B)	33/39 (84.6%)	26/39 (66.7%)	12/39 (30.8%)	3/39 (7.7%)
	Itolizumab (from arm C)	27/39 (69.2%)	16/39 (41.0%)	11/39 (28.2%)	2/39 (5.1%)

Note: At week 12, patients in arm C were crossed over to receive itolizumab 1.6 mg/kg every 2 weeks till week 24. Week 24 to 28 was treatment-free period. From week 28 to 52, patients in arm C received itolizumab 1.6 mg/kg every 12 weeks.
n=number of patients with response; N=total number of patients
PASI: psoriasis area and severity index

Figure 1 represents the proportion of patients at each visit up to wks 28 who achieved PASI 75 by treatment arm. The rate of improvement in PASI score was similar in 2 arms (arm A and arm B), though delayed by about 4 wks for arm A, where patients received a lower dose in the first 4 wks compared to patients from arm B. After patients in arm C were crossed over to receive itolizumab at wks 12, they showed rapid improvement, and by wks 20 the proportion of patients achieving PASI 75 was similar in all arms.

Figure 1: Proportion of Patients Achieving PASI 75 by Study Arm and Visit in the TREAT-PLAQ Study. Bars represent exact 95% confidence intervals.



[Note: At week 12, patients in arm C were crossed over to receive itolizumab 1.6 mg/kg every 2 wks till week 24. Week 24 to 28 was treatment-free period].
Similar to the improvement in PASI scores, the proportions of patients who achieved PGA score "clear" or "minimal" were higher at week 12 for arm A (20%) and B (16%) than for arm C (5%); but by week 28, the proportions were similar for all three arms (21%, 26% and 23%) (Table 5). Quality of life, as assessed by the SF-36 and DLQI score, improved throughout the study. Improvement in DLQI scores was consistent with PASI scores. The proportion of patients who reported that the disease had only a small or negligible effect on their lives increased in each arm up to week 28.

Table5 Summary of Itolizumab Efficacy Data in the TREAT-PLAQ Study: Proportion of Patients with PGA Score of "clear" or "minimal" at Week 12, 28 and 52

Response achieved at:	Proportion of patients achieving PGA response [n/N (%)]					p values
	Arm A	Arm B	Arm C	-	Total	
Week 12	16/80 (20%)	14/87 (16.1%)	2/41 (4.9%)	-	32/208 (15.4%)	0.0310[1] 0.0898[2]
Week 28	16/76 (21.1%)	22/84 (26.2%)	9/39 (23.1%)	-	47/199 (23.6%)	-
-	Open label	Placebo group	Itolizumab (from arm A and B)	Itolizumab (from arm C)	-	-
Week 52	17/58 (29.3%)	12/40 (30%)	17/38 (44.7%)	9/38 (23.7%)	55/174 (31.6%)	-

PGA: physician's global assessment
n=number of patients with response; N=total number of patients
[1]A versus. C; [2]B versus. C

Study III (Study ITOLI-C19-02-I-00) was a multi-centric, open label, two arm randomized trial to study the efficacy and safety of itolizumab in COVID-19 complications in 30 patients. Patients were randomized into 2 groups in 2:1 ratio to receive (Arm A)best supportive care + Itolizumab and (Arm B) best supportive care (eg: Antibiotics, Antiviral, Steroids, LMWH, Hydroxychloroquine, multivitamin, oxygen therapy- as per institutional practice). Itolizumab was initiated at 1.6 mg/kg dose iv infusion, and if well tolerated, a weekly dose of 0.8mg/Kg depending on investigator's discretion for upto 4 doses. Majority of the patients were administered two doses.
A statistically significant difference (p = 0.0098) in the 1-month mortality rate was observed between the 2 treatment arms All patients dosed with itolizumab consistently demonstrated significant improvement in oxygenation parameters.

Overall patients dosed showed decrease in inflammatory markers like ferritin and CRP compared to baseline. There was also a post-dosing reduction in other important markers of organ dysfunction and coagulopathy, such as LDH and D-Dimer, in several patients.
Post administration of Itolizumab, key inflammatory markers like IL-6 and TNF alpha showed a sharp reduction, as evidenced by the mean levels of IL-6 and TNF-alpha in comparison to the control arm which showed an increase.

5. PHARMACOLOGICAL PROPERTIES
5.1 Mechanism of Action
Itolizumab is a humanized recombinant anti-CD6 mAb of immunoglobulin (Ig) G1 isotype that binds to domain 1 of CD6. The CD6 leukocyte differentiation antigen is a membrane glycoprotein mainly expressed on the surface of mature thymocytes, in most peripheral blood CD3+ T-cells and in a subtype of B-lymphocytes called B1a cells. In the peripheral blood T-cells, CD6 participates in cell activation as a co-stimulatory molecule. The ligand of CD6, Activated Leukocyte-Cell Adhesion Molecule (ALCAM) is widely distributed in normal tissues, including the thymus, spleen, lymph nodes and skin. Itolizumab immunomodulates human lymphocytes without interfering with the binding of CD6 to ALCAM.
Preclinical studies with T-cells showed that the antibody blocks intracellular Mitogen Activated Protein Kinase (MAPK) and Signal Transducer and Activator of Transcription-3 (STAT-3) signalling pathways, the secretion of pro-inflammatory cytokines (including tumor necrosis factor-a, interferon-g and interleukin-6) and T-cell proliferation, even when co-stimulated with ALCAM.
In COVID-19 infection, of the 20-25% patients that develop pulmonary symptoms there is a sub-set that develops acute respiratory distress syndrome (ARDS) and rapidly progresses into a critical condition. Marked elevation of cytokines and chemokines is observed in these patients. Other markers of inflammation, coagulation and organ damage such as CRP, D-dimer, LDH, Ferritin, Troponin-I are also elevated. By acting upstream in the pathway, itolizumab significantly reduces / downregulates the cytokine production.

5.2 Pharmacodynamic Properties
A range of in-vitro and in-vivo pharmacology studies demonstrated that itolizumab reacts with human CD6 and is therapeutically effective in the severe combined immunodeficiency disease-human (SCID-Hu) xenograft model of psoriasis in mice. In a cross-reactivity study with normal adult human tissues, itolizumab specifically recognized T-cells, but did not show any cross-reactivity to other cells or tissues. In another study, itolizumab was found to have similar reactivity to CD6-expressing cell lines as a commercial anti-CD6 monoclonal antibody.

5.3 Pharmacokinetic properties
The pharmacokinetic (PK) data for itolizumab in psoriasis patients is based primarily on the phase 2 study (Study I). The PK parameters of itolizumab were determined over 8 wks of treatment and 4 wks of treatment-free follow-up. Itolizumab was administered at doses ranging from 0.4 to 1.6 mg/kg as an intravenous (IV) infusion. Enzyme-linked immunosorbent assay (ELISA) method was used to measure itolizumab in the serum samples.
A linear dose-dependent relationship was observed for various PK parameters after the first dose administration of itolizumab. The average maximum drug concentration (C_{max}) and area under concentration-time curve (AUC_{0-t}) values obtained after the first and last infusion of 0.4 mg/kg, 0.8 mg/kg (administered once every week, once in 2 wks or once in 4 wks) and 1.6 mg/kg (administered once in 2 wks or once in 4 wks) increased in proportion to dose (Table 6). Both AUC0-t and serum trough concentration increased with increase in dosage and frequency of administration of itolizumab, indicating more accumulation on frequent administration. With multiple administrations (after administration of all dosages) dose-proportional increase were observed in average Cmin. Volume of distribution and clearance increased marginally with a decrease in the frequency of administration. The median half-life ($t_{1/2}$) obtained after the last dosage ranged from 11.72 to 18.51 days across the different dosage-frequency combinations.

Table 6 Mean pharmacokinetic parameters (C_{max} and AUC_{0-t}) of itolizumab (IV infusion) derived from Phase 2 Study in psoriasis patients

Dose (mg/kg)	Dosing interval	C_{max} (µg/mL)		AUC_{0-t} (hr.µg/mL)	
		First infusion	Last infusion	First infusion	Last infusion
0.4	• Every week • Every 2 weeks • Every 4 weeks	• 8.01 • 10.93 • 14.25	• 20.98 • 15.30 • 12.50	• 569.69 • 897.30 • 4103.77	• 4351.25 • 2750.49 • 1898.20
0.8	• Every week • Every 2 weeks • Every 4 weeks	• 19.95 • 20.03 • 21.12	• 29.75 • 29.19 • 24.37	• 1284.94 • 1833.22 • 3000.40	• 9663.53 • 9205.22 • 4524.04
1.6	• Every 2 weeks • Every 4 weeks	• 39.94 • 41.02	• 49.56 • 41.39	• 4103.77 • 6682.89	• 14017.06 • 10230.29

C_{max}: Maximum drug concentration; AUC_{0-t}: area under the concentration time curve from time 0 to t

6. NONCLINICAL PROPERTIES
6.1 Animal Toxicology or Pharmacology
Carcinogenesis, mutagenesis, impairment of fertility
Long-term animal studies of itolizumab have not been conducted to evaluate carcinogenic potential, mutagenic potential or effect on fertility.

Animal Toxicology and/or Pharmacology
Results in animal studies revealed that itolizumab does not cross-react with rodent CD6. Chimpanzees and baboons were identified as the relevant species as itolizumab recognizes CD6 in these species. However, chimpanzees were not used in further experiments as their use in research is highly restricted as they are considered endangered.
Single- and repeat-dose toxicity studies were conducted in conventional, pharmacologically non-relevant species to evaluate any off-target safety indicators. In the single-dose toxicity study, Sprague-Dawley rats were administered single injection of itolizumab at 1.25 and 2.5 mg/kg (IV). No treatment-related mortalities or clinical toxic signs were observed. Single doses of itolizumab were well tolerated in rats; the maximum tolerated dose (MTD) was found to be 2.5 mg/kg. In the repeat-dose toxicity study, Cenp: SPRD rats (derived from Sprague-Dawley) were treated with itolizumab at 1.6 and 16 mg/kg/day for 14 days (IV). No mortality, toxic signs, changes in body weight, changes in rectal temperature, or alterations at the injection site were seen. Moreover, there were no significant physiological alterations in hematological or biochemical parameters, or macroscopic or histological alterations in parenchymal organs. Itolizumab was found to be well tolerated; no observed adverse effect level (NOAEL) was 16 mg/kg/day. However, as the pharmacological target of itolizumab is absent in rats, clinical relevance of these toxicity findings is unknown.

Various toxicity studies were conducted with the murine version of itolizumab (ior t1), which is a murine monoclonal antibody with the same antigenic specificity as itolizumab. A single dose acute toxicity was conducted with ior t1 in Wistar rats at the dose levels of 6, 30 and 60 mg/kg (IV). No noticeable difference was found between the control and treatment groups. The MTD was concluded to be 60 mg/kg. In the repeat dose toxicity study Wistar rats were administered with ior t1 at the dose levels of 6, 30 and 60 mg/kg body weight (IV) in 3 cycles of 5 treatment days. No death or toxic alteration was observed even at the highest dose level. The NOAEL of ior t1 was concluded to be 60 mg/kg body weight. In the local cutaneous tolerance test rabbits were administered ior t1 jelly at 0.3 and 3 mg/g topically for 35 days. In this study, no morphological, clinical or histological alterations were observed in the animal skin. In the dermal irritability study, ior t1 was found to be devoid of potential to cause irritation. The significance of results of these nonclinical studies to human risk is unknown.

7. DESCRIPTION
Physicochemical Characteristics
Itolizumab is an IgG1, kappa immunoglobulin containing "murine" light- and heavy-chain complementarity-determining sequences in the variable region. It has human constant-region sequences. Itolizumab is composed of two heavy chains of 449 amino acids and two light chains of 214 amino acids (based on mass spectrometry analysis), and has an approximate molecular weight of 147 kDa. It has a binding affinity for the CD6 antigen in the nanomolar range.
Itolizumab is produced by murine myeloma cells (NS0) in suspension culture in a nutrient medium; and is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures. Itolizumab is supplied as a sterile, clear colorless, preservative-free liquid solution for intravenous (IV) administration.

Dosage Form and Composition of the Drug Product
Itolizumab is formulated at a concentration of 25 mg/5 mL vial in sterile buffer solution (pH7.0±0.5).
The composition of the itolizumab formulation is provided in Table 7.

Table 7 Composition of Itolizumab formulation

Component	Quantity/Vial
Itolizumab (Active substance)	25 mg
Monobasic sodium phosphate (Buffer)	3 mg
Dibasic sodium phosphate (Buffer)	9 mg
Sodium chloride (Buffer)	44 mg
Polysorbate 80 (surfactant)	1 mg
Water for injection q.s.	to 5 ml

Also See *Dosage form and Strength; Pharmaceutical Particulars*.

8. PHARMACEUTICAL PARTICULARS
8.1 Incompatibilities
In the absence of compatibility studies, ALZUMAb®must not be mixed with other medicinal products.

8.2 Shelf-life
Please refer carton/label.

8.3 Packaging information
Pack size: 25 mg/ 5ml.
ALZUMAb® is packed in 6R clear glass vial (USP type 1) closed with a chlorobutyl rubber stopper and sealed with flip-off seals (aluminium rim with plastic flip-off lid).

8.4 Storage and handing instructions
Store at a temperature between 2°C and 8°C.
Keep out of reach of children.

Special Precautions for Disposal and Handling:
Do not administer as IV push or bolus.
Prior to infusion, fully diluted ALZUMAb®solution should be allowed to reach room temperature.
Prior to administration, the product should be visually inspected for opaque particles, discoloration or other particulates.
The product should not be used, and discarded if,

- The seal is broken,
- Visible opaque particles, discoloration or other foreign particulates are observed,
- It may have been accidently frozen, or
- There has been refrigerator failure

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

9. PATIENT COUNSELLING INFORMATION
Infusion related Reactions:
Since Itolizumab is given as intravenous infusion it may be associated with infusion related reactions like any other intravenously given medication. To keep these events at minimum kindly provide adequate pre medications cover as per the prescribing information prior to Itolizumab infusion. Patient should be made aware of the signs and symptoms he is likely to
experience as a part of infusion related reactions. Commonly reported symptoms for infusion related reaction for any intravenously given drug are sensation of vomiting, reddening and itching of skin, skin rash, cough, wheezing or difficulty in breathing, headache, sensation of rotation or increased blood pressure. However as reported in the Study III (ITOLI-C19-02-I-00) (COVID-19 with moderate to severe ARDS) patient is most likely to present with mild to moderate chills. Rarely, he/she may develop severe signs/symptoms. Patient is more likely to experience these signs symptoms with the very 1st Itolizumab infusion which can be managed by the treating physician with routine infusion reaction treatment. During and after administration of Itolizumab, if the patient experiences any of these, he needs to be provided immediate supportive care and management.

Infections:
Patients being treated should be instructed to keep a watch on any sign or symptom of any new infection during and after the treatment with ALZUMAb®and they should report immediately to the treating physician.

Lymphopenia:
Kindly keep patient informed on the possibility of suffering from episodes of lymphopenia (a condition with decreased counts of a type of blood cell which imparts immunity and helps fight infections). Lymphopenia can be of grade III severity, they are usually transient and benign. The patient needs to be adequately monitored. If persisting it has to be managed as per standard of care. The patient could be appraised, that the effect on lymphocyte count could possibly be due to the fact that the drug helps fight COVID-19 infection via modulating these cells.

Hypersensitivity reactions:
Advise patients that allergic/hypersensitivity reactions can occur with Itolizumab therapy ALZUMAb®. Inform patients on the symptoms of hypersensitivity reactions.

10. DETAILS OF MANUFACTURER

Manufactured by:
Biocon Biologics India Limited
Block No. B1, B2, Q13 of Q1 and W20 & Unit S18, 1st Floor, Block B4,
Special Economic Zone, Plot No.: 2, 3, 4 & 5, Phase IV,
Bommasandra-Jigni Link Road, Bommasandra Post,
Bengaluru – 560 099, India.

Marketed by:
M/s Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronic City, Phase - II, Hosur Road,
Bengaluru – 560100, India

BF0720/05

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
- Permission in Form 46 bearing No. MF 378/2012 dated 27.12.2012 and additional indication permission vide File No.: BIO/MA/20/000066 dated 17.07.2020
- Mfg. Lic. No.: KTK/28D/07/2006

12. DATE OF REVISION
Leaflet revised: July 2020.

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **DrugSafety@biocon.com**