



Clinical Study Protocol

Study Title: A Multi-Centric, Open label, Two Arm Randomized, Pivotal Phase 2 Trial to Study the Efficacy and Safety of Itolizumab in COVID-19 Complications

Protocol Number:	ITOLI-C19-02-I-00
Version Number and Date	5.0, Dated 04-Jun-2020
Superseded Version and Date	4.0, Dated 20-May-2020
Investigational Product	Itolizumab (ALZUMAb™)
Phase of Development	Pivotal Phase 2
Study type	Prospective randomized two arm study
CTRI Number:	CTRI/2020/05/024959
Sponsor	Biocon Biologics India Limited, Biocon House, Semicon Park, Bengaluru- 560100, Karnataka, India

The study information described in this protocol will be performed according to the ethical principles described in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6(R2), and New Drugs and Clinical Trials 2019 issued by the Government of India.

1. Investigator's Declaration

Title: A Multi-Centric, Open label, Two Arm Randomized, Pivotal Phase 2 Trial to Study the Efficacy and Safety of Itolizumab in COVID-19 Complications

Study Drug: ALZUMAb™ (Itolizumab injection)

I, the undersigned have read and understood this protocol and hereby agree to conduct the study in accordance with this protocol and to comply with all requirements regarding the obligations of investigators and all other pertinent requirements of the ICH-E6 (R2) 'Guidance on Good Clinical Practice', Indian Good Clinical Practices and New Drugs and Clinical Trials 2019.

Appropriate signatories at this site have signed the Investigator Agreement. As the Site Principal Investigator, I agree to:

- Comply with any authorized protocol amendments, formal instructions and training;
- Maintain local ethics committee approval for this protocol and related consent materials;
- Maintain medical records to document study data, including supplemental records, worksheets or notes with study data;
- Promptly submit adverse event reports as per post marketing reporting requirements;
- Ensure that only coded study identifier(s) are associated with submitted study data, and that personally-identifying information (e.g., names, address, etc.) are not transmitted to other parties.

I further agree to ensure that all associates assisting in the conduct of this study are informed regarding their obligations.

Investigator's Name:

Investigator's Affiliations:

Investigator's Signature with Date:

2. Sponsor's Signature

This protocol reflects the Sponsor's current knowledge of investigational product- itolizumab as applicable to this study. It has been designed to achieve the stated objectives whilst minimizing exposure to, and risk from, both the products being used and the assessments. The protocol has been designed according to the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP), Good Clinical Practices for Clinical Research in India published by Central Drugs Standard Control Organization, Indian Council of Medical Research guidelines for biomedical research on human subjects and the Declaration of Helsinki. It has undergone both medical and scientific review by the Sponsor.

- We hereby agree to conduct the study in accordance with this protocol and the above-mentioned guidance/ regulation.
- We agree to comply with all relevant standard operating procedures (SOP) required for the conduct of this study.
- We further agree to ensure that all associates assisting in the conduct of study are informed regarding their obligations.

Reviewed and Approved by:

Sandeep

Nilkanth Athalye

Digitally signed by
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Head, Clinical Development and Medical Affairs
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Date:

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3. Background

Coronavirus disease 2019 (COVID-19) progresses to respiratory complications as consequence of the exaggerated immune response of the host, producing a pro-inflammatory cytokine storm syndrome (i.e.: IL-6, TNF) and cytopenia, with a high mortality rate.

Emergency treatments aiming to reduce individual cytokines (IL-6 and IL-1) specifically [or indirectly (JAK inhibitors and CCR5 antagonists) have shown survival benefit in patients with hyperinflammation, without increased adverse events.

However, not being sufficient to reduce the rising mortality by COVID-19 other interventions to immunomodulate the life-threatening hyperinflammation are urgently needed.

Therefore, the proposal for use of an anti-CD6 monoclonal antibody (Itolizumab) for the treatment of the COVID-19 cytokine storm syndrome complication.

Why CD6?

CD6 is constitutively expressed mainly on effector T cells (Teff) and hardly expressed on regulatory T cells (Tregs). CD6 stimulates the immune response and is overexpressed after lymphocyte activation. CD6 homes inflammatory cells to lesion, and its ligand ALCAM is upregulated after activation and in inflamed tissues.

CD6 and viruses:

CD6 is overexpressed on T-cells during chronic SIV infection, with impaired anti-viral responses, and is associated with SIV disease progression. HTLV-1 induces overexpression of ALCAM facilitating the trafficking of infected lymphocytes through the blood-brain barrier. ALCAM is increased on HIV+ monocytes and anti-ALCAM antibodies and the CCR2/CCR5 dual inhibitor reduce their transmigration.

Why Itolizumab?

Itolizumab is an anti-CD6 humanized IgG1 mAb. Itolizumab is an immune modulatory molecule. Itolizumab accumulates in the inflamed lesion. Itolizumab is used in Psoriasis and evaluated in other inflammatory diseases (Rheumatoid Arthritis) with a good safety profile as monotherapy or in combination with other drugs. Itolizumab has a legacy of therapeutic effect after discontinuation of the treatment period. Itolizumab has a potent anti-inflammatory effect reducing the production of pro-inflammatory cytokines IL-6, TNF, IFN γ , IL-17 and IL-1.

Hypothesis:

Itolizumab in COVID-19 patients will control the pro-inflammatory cytokine storm syndrome, by immunomodulation of Teff function and trafficking to the inflammation site, sparing Tregs and preserving the anti-viral response, reducing the morbidity and mortality.

Summary of Clinical Safety with Itolizumab:

Itolizumab Injection has been administered to 338 patients with RA or psoriasis (including those with psoriatic arthritis) for up to 52 weeks in clinical trials till date and has been found to be well tolerated and safe.

Itolizumab Injection (Alzumab™) was launched in India on 10 Aug 2013, as a solution for IV infusion of 1.6 mg/kg once every two weeks for 12 weeks, followed by 1.6 mg/kg every four weeks up to 24 weeks (each 5 mL vial contains 25 mg of itolizumab) for the treatment of patients with active moderate to severe chronic plaque psoriasis who are candidates for systemic therapy.

Post-marketing, periodic safety update reports (PSURs) have been generated and submitted to the licensing authority. Based on these periodic reviews of safety data, the overall safety profile evaluation for Itolizumab Injection has remained unchanged. No new clinically significant issues arose which warranted changes to the current reference safety information (RSI).

The most commonly (occurring in $\geq 5\%$ patients) reported AEs in the Phase 3 study were infusion reactions (which are managed by premedication), pyrexia, upper respiratory tract infections and pruritus. The majority of the events were mild or moderate in severity. There were small transient reductions observed in the mean ALC during the initial infusions; however ALC increased with continued dosing. The small reduction in ALC did not appear to increase the incidence of infection.

Summary of Contraindications/warning:

ALZUMAB™ should not be administered to patients having history of severe allergy or known hypersensitivity reaction to any component of ALZUMAB™ or any murine proteins. Additionally, ALZUMAB™ is contraindicated in patients with any active serious infection including tuberculosis and HIV-AIDS.

It is recommended that live/attenuated vaccines not be given concurrently with ALZUMAB™.

As with other IgG antibodies, itolizumab may cross the placenta during pregnancy. The available clinical experience is too limited to exclude a risk, and administration of ALZUMAB™ is therefore not recommended during pregnancy.

Infections and Reactivation of Tuberculosis

Physicians should exercise caution before and during Itolizumab Injection treatment in patients with a history of recurrent infections or underlying conditions which may predispose them to serious infections. Patients should be monitored closely for the development of signs and symptoms of infection during and after treatment with Itolizumab.

4. Objectives

Primary Objectives:

To study the efficacy and safety of adding Itolizumab in patients with Moderate to Severe COVID-19 complications (Cytokine Release Syndrome).

Secondary Objectives:

To study the effect of immunomodulation by Itolizumab and its correlation to clinical improvement by evaluating biomarker data (IL6, TNF-a, IL17, IL1, Interferon -A etc.) before and after Itolizumab treatment

5. Outcome Measures

Primary Outcome Measures:

1. Proportion of patients with deterioration of lung function as measured by*:
 - Stable SpO₂ without increasing FiO₂
 - Stable PaO₂ without increasing FiO₂
2. Reduction of endo-tracheal intubation rate, measured as rate of patients needing intubation*
3. Reduction in proportion of patients who need*
 - Non-invasive ventilation
 - Invasive mechanical ventilation
 - High flow nasal oxygen
4. Time of duration of mechanical ventilation or time to end of mechanical, measured as elapsed time from the start date of mechanical ventilation to the weaning date, for patients needing intubation*
5. One-month mortality rate between the two arms* [Time Frame: up to 1 month]

1-month mortality is defined as the ratio of patients who will live after 1month from study start out of those registered at baseline

6. Change in inflammatory markers like CRP (C-reactive protein) level, d-Dimer, ferritin etc. [Time Frame: Arm A; baseline, during treatment (Before every dose and 12 to 24 h after every dose) up to 1 month, Arm B: baseline, 12 to 24 h and approx. 7 and 14 days after randomization]

Secondary Outcome Measures:

1. Biomarkers (IL-6, TNF-a, IL1, IL17, etc...) [Time Frame: Arm A; baseline, during treatment (Before every dose and 12 to 24 h post dose) up to 1 month, Arm B; baseline, 12 to 24 h and approx. 7 and 14 days after randomization]
2. Lymphocyte count [Time Frame: Arm A; baseline and before every dose up to 1 month, Arm B; baseline, approx. 7 and 14 days after randomization]
Lymphocyte count assessed by routinely used determination of blood count
3. PaO₂ (partial pressure of oxygen) / FiO₂ (fraction of inspired oxygen, FiO₂) ratio (or P/F ratio) [Time Frame: Arm A; baseline, during treatment (Before every dose and 48 h post dose) up to 1 month, Arm B: baseline, 48 h and approx. 7 and 14 days after randomization]
calculated from arterial blood gas analyses (values from 300 to 100)
4. Number of participants with treatment-related side effects as assessed by Common Terminology Criteria for Adverse Event (CTCAE) version 5.0 [Time Frame: during treatment and up to 30 days after the last treatment dose]*
graded according to CTCAE criteria (v5.0)
5. Radiological response [Time Frame: at baseline, after seven days and if clinically indicated (up to 1 month)]*
Thoracic CT scan or Chest XR
6. Duration of hospitalization [Time Frame: from baseline up to patient's discharge (up to 1 month)]*
Days of hospitalization and ICU
7. Remission of respiratory symptoms [Time Frame: up to 1 month]*
time to independence from non-invasive mechanical ventilation calculated in days
8. Remission of respiratory symptoms [Time Frame: up to 1 month]*
time to independence from oxygen therapy in days

* Applicable for both arms

6. Population

Patients who have tested positive for virological diagnosis of SARS-CoV2 infection (PCR) are planned to be randomised for enrolment from various centres in India.

Inclusion Criteria:

1. Male or female adults above 18 years (not tested in children yet)
2. Informed consent for participation in the study
3. Confirmed virological diagnosis of SARS-CoV2 infection (RT-PCR)
4. Hospitalized due to clinical worsening of COVID-19 infection
5. Oxygen saturation at rest in ambient air $\leq 94\%$
6. Patients who are in moderate to severe ARDS as defined by PaO₂/Fio₂ ratio of < 200 or more than 25% deterioration from the immediate previous value.
7. Baseline serum ferritin level ≥ 400 ng/mL or IL-6 levels greater than 4 times ULN, if known

Note: Either of Inclusion number 6 or 7 is required for inclusion of the patient into the study. Since there is logistical delay in getting results in time, biomarker data as inclusion criteria may be used if already known.

Exclusion Criteria:

1. Known severe allergic reactions to monoclonal antibodies
2. Active tuberculosis (TB) infection
3. History of inadequately treated tuberculosis or latent tuberculosis

Note: Latent tuberculosis should be excluded based on history, physical examination and chest x ray before dosing (day 1). QuantiFERON TB also should be performed, however considering criticality of patient condition, patient can be dosed without QuantiFERON TB test results. If QuantiFERON TB test is positive, then continuation of patient in the study is investigator's discretion considering benefit-risk evaluation with the sponsor.

4. In the opinion of the investigator, progression to death is highly probable, irrespective of the provision of treatments
5. Patient on invasive mechanical ventilator support.

6. Have received oral anti-rejection or immune-suppressive drugs within the past 6 months

Note: Patient receiving oral anti-rejection or immune-suppressive drugs regularly in the last 6 months will be excluded. Patient will be included if received short course of steroids.

7. Participating in other drug clinical trials like using anti-IL-6 therapy like tocilizumab (participation in COVID-19 anti-viral trials may be permitted if approved by Sponsor)
8. Patient on treatment of anti-IL-6 or plasma therapy as a part of supportive care

9. Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
10. Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
11. Patients with known history of Hepatitis B, Hepatitis C or HIV
12. Absolute Neutrophils count (ANC) $<1000 / \text{mm}^3$
13. Platelet count $<50,000 / \text{mm}^3$
14. Absolute Lymphocyte count (ALC): $<500/\text{mm}^3$

Note: ANC, ALC and platelet counts can be done in local lab in the hospital.

Planned number of subjects:

Approximately 30 patients are considered sufficient to explore the study objectives and will be included in this study (number of patients may be increased if there is benefit observed in initial cohort of patients. There is no formal sample size calculation estimated).

Method of assigning patient to treatment group:

All eligible patients entering into the study will be randomized in 2:1 ratio to receive the treatment A/ B respectively. A computer derived randomization schedule is planned to be generated using appropriate system e.g. SAS to assign patient to treatment groups. Randomization will be central and appropriate system (e.g. remote telephone based, computer-based email, sealed envelope) will be used to distribute randomization schedule to the site

Note: If the patient is randomised to Arm A and is not initiated itolizumab or not administer one full infusion, is then not considered randomized. The same randomisation code will be used for the subsequent subject in that particular site.

Approximate number of sites:

1-10 sites

7. Treatment

Treatment Intervention and Dose:

Arm A: Best supportive care + Itolizumab

The best supportive care to be given as per the institutions protocol will be administered

(e.g: antivirals /antibiotics/ hydroxychloroquine; oxygen therapy, etc) + **Itolizumab**

Itolizumab

Note: Premedication: Hydrocortisone 100 mg i.v (or equivalent short acting glucocorticoid) and Pheniramine 30 mg per i.v. about 30 ± 10 minutes prior to infusion.

Start at 1.6 mg/kg dose iv infusion, if well tolerated, investigator has the discretion to continue with 1.6 mg/kg dose every 2 weeks or 0.8 mg/kg weekly regimen.

Subsequent dose and frequency can be modified, deferred or stopped if patient recovers as per investigator's discretion. If patients' overall parameters improve (if performed and RT-PCR is negative) further dose need not be given. Total infusion received during study duration can vary from 1 to 4 for each patient.

Arm B: Best supportive care

The best supportive care to be given as per the institutions protocol will be administered

(e.g: antivirals/antibiotics/ hydroxychloroquine; oxygen therapy, etc)

Dosing, Handling and Storage of Itolizumab

- Itolizumab is to be stored in 6R, USP type-1, 10 mL glass vials, refrigerated condition at 2°C to 8°C and is stable at that temperature for 36 months.
- Itolizumab 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 aseptic technique; as follows:
- Calculate the dose and number of itolizumab vials needed. Itolizumab 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, colourless, preservative-free buffer
- Itolizumab should be administered via IV infusion in 250 mL of 0.9% Sodium Chloride solution (normal saline). For this, dilute the appropriate dose of itolizumab to 250 mL with sterile normal saline. Gently mix. The total volume of the infusion will be more than 250 ml due to addition of the drug solution to 250 mL of 0.9% Sodium Chloride solution.
- Fully diluted itolizumab solution should be allowed to reach room temperature prior to infusion. Before use, the fully diluted itolizumab solution may be stored at room temperature or refrigerated at 2-8°C (36°F-46°F) protected from light. Itolizumab 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 over a period of not less than 120 minutes and using an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size of

1.2 µm or less). Approximately 50 mL of diluted itolizumab solution should be administered during the first hour, followed by remaining solution (more than approximately 200 mL) in the next hour. The infusion period can be extended up to 8 hours for medical reasons.

- The vials do not contain antibacterial preservatives. Therefore, any unused portion of the solution should not be stored for reuse.

Study Drug Discontinuation:

The investigator may decide to terminate the participation and discontinue further study participation of any patient. The recommended withdrawal criteria and dosing interruption criteria are presented below:

1. Protocol violation: If a protocol violation occurs that in the clinical judgment of the investigator and/or after discussion with the sponsor may invalidate the trial, the patient will be withdrawn by the investigator.
2. Consent is withdrawn: Patients have the right to withdraw from the trial at any time for any reason.
3. Serious, life-threatening, or intolerable AEs or laboratory abnormalities in the investigator's opinion, requires withdrawal from the study for safety reasons.
4. Need arises to treat the patient with any medication that is not allowed as concomitant medication during the study; use of which, in the opinion of the investigator and/or medical monitor invalidates the study results or compromises the patient safety if continued on the study drug.
5. The investigator also withdraws a patient if the sponsor terminates the study.

8. Assessments

8.1 Schedule of Study Visits and Procedures

Visit	S1	W1	W2	W3	W4	End of Study
Weeks	-2 to 0	0	1	2	3	4 th week
Days	-14	1 [^]	8 [^]	15 [^]	22 [^]	30 [#]
Event						
Informed Consent	X					
Medical History	X					
Inclusion/Exclusion Criteria ^a	X					
Weight	X	X	X	X	X	X
Physical Examination, Vital signs ^{\$}	X	X	X	X	X	X
Hematology* [;] ^{\$}	X	X	X	X	X	X
Biochemistry** [;] ^{\$}	X	X	X	X	X	X
Chest X Ray/CT scan ##	X	X	X	X	X	
Randomisation	X					
Best Supportive Care		X	X	X	X	
Pre-medication @ in Arm A		X	X	X	X	
ALZUMAb infusion ^b		X	X	X	X	
Cytokines and Immunophenotyping assessment	X	X ^d				
PaO ₂ /FiO ₂ ratio	X	X	X	X	X	
CRP	X	X	X	X	X	X
Daily Morning SOFA Score ^c	X	X	X	X	X	
Concomitant medication check	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

[^] Window period: ± 48 Hours.

^a All inclusion / Exclusion criteria to be reviewed prior to first dosing. Screening period is up to 14 days however screening and baseline visit can happen in one day and screening assessment can be considered as baseline assessments.

^b 1.6 mg/kg dose iv infusion, if well tolerated and improvement in patient observed, investigator has the discretion to continue with 1.6 mg/kg dose every 2 weeks or 0.8 mg/kg weekly regimen in combination therapy with standard of care (anti-viral and antibiotic drugs). Subsequent dose and frequency can be modified, deferred or stopped if patient recovers as per investigator's

discretion. If patients' overall parameters improve (if performed and RT-PCR is negative) further dose need not be given. Total infusion received during study duration can vary from 1 to 4 for each patient. If patient recovers/is discharged earlier than 30 days, then patient should be contacted telephonically to get status of the patient on 30th day after enrolment.

c: Daily SOFA Scoring until patient moved out of ICU/equivalent, and later SOFA score frequency as per investigator discretion. If patient is not admitted in the ICU/equivalent at the time of enrolment, then it is recommended to capture these assessments daily for first 7 days.

Window period for assessment at 4th week or 30th day is \pm 3 days.

*Hematology assessments (blood test) include: hemoglobin, total leukocyte count, differential count, absolute neutrophil count, absolute lymphocyte count, and platelet count.

**Biochemistry assessments (blood test) include blood urea, liver function tests (i.e. serum bilirubin, AST, ALT, ALP, Serum albumin), Lipid profile (including triglyceride), LDH, serum creatinine, Procalcitonin, d-Dimer, Trop-I, Ferritin. All blood samples for hematology and biochemistry must be collected prior to dosing, and additional as per investigator discretion.

Note: Hematology and Biochemistry including (Procalcitonin, d-Dimer, Trop-I, Ferritin, LDH and CRP) are recommended every 48 to 72 hours.

§: To be recorded daily: TLC; DLC, ANC, ALC; Platelet count; S. creatinine; T. Bilirubin; morning Vitals –pulse, BP, RR; Temperature (highest temperature of the day), PaO₂/FiO₂, MAP, GCS. These daily assessments are mandatory until patient moved out of ICU/equivalent. If patient is not admitted in the ICU/equivalent at the time of enrolment, then it is recommended to capture these assessments daily for first 7 days.

@ Premedication: **In arm A:** Hydrocortisone 100 mg i.v (or equivalent short acting glucocorticoid) and Pheniramine 30 mg per i.v. about 30 \pm 10 minutes prior to infusion.

To be repeated as suggested by the investigator in ICU setting. Earlier chest X ray report may be considered after discussing with sponsor.

d: Cytokine levels in serum: such as IFN- α , TNF- α , IL-17, IL-6, IL-1, IL-4, IL-2, IL-10, GM-CSF, IFN- γ at baseline, before every dose and 12-24 h after dose in Arm A. In Arm B, same panel will be assessed at baseline, 12 to 24 h and approx. 7 and 14 days after randomization. Immunophenotyping in whole blood samples: Teff cells (CD4, CD8, Treg cells), TH17 and macrophage activated cells will be analysed at baseline, 12-24 h after 1st dose and 24h after the second/last dose in Arm A and at baseline, 12-24 h and approx. 7 days after randomization in Arm B.

Timing of administration of Itolizumab:

Patients should be randomized in the trial and given Itolizumab who are in moderate to severe ARDS as defined by PaO₂/Fio₂ ratio of < 200 or more than 25% deterioration from the immediate previous value.

OR

Baseline serum ferritin level \geq 400 ng/mL or IL-6 levels greater than 4 times ULN, if known

Note: Either of Inclusion number 6 or 7 is required for inclusion of the patient into the study. Since there is logistical delay in getting results in time, biomarker data as inclusion criteria may be used if already known.

8.2 Laboratory Procedures

Collection of Biomarker Samples:

Cytokine levels in serum: such as IFN- α , TNF- α , IL-17, IL-6, IL-1, IL-4, IL-2, IL-10, GM-CSF at baseline, weekly before every dose and 12-24 h after dose in Arm A. In Arm B, same panel will be assessed at baseline, 12 to 24 h and approx. 7 and 14 days after randomization.

Immunophenotyping in whole blood samples: T_{eff} cells (CD4, CD8, T_{reg} cells), TH17 and macrophage activated cells will be analysed at baseline, 12-24 h after 1st dose and 24h after the second/last dose in Arm A and at baseline, 12-24 h and approx. 7 days after randomization in Arm B.

Blood sample collections and handling instructions:

Two sets of sample collection are required:

1) Serum Sample

Samples to be collected: Blood 4-5 ml; (approx. 2-2.5 ml serum can be collected from blood)

Time points: Refer to section 8.1: Schedule of Study Visits and Procedures

Storage of sample: Serum separation will be performed at the Site/Clinic.

For each visit, serum samples should be immediately aliquoted into 2 vials of approx. 1 ml each and then stored at -70° C \pm 15° C or dry ice. Transportation should take place in dry ice only. Once at CRO the samples should be stored frozen at -80° C till used for batch analysis. This samples will be used for cytokines/chemokines.

Note: if -20 freezers are only available, then samples to be shipped within 24h in -80° C.

To be performed at:

Syngene International Ltd.

Tower I, Semicon Park, Phase-II,
Hosur Road, Bangalore 560 100,
Karnataka, India

2)Whole blood Collection:

Additionally, approximately 4ml of blood is to be drawn for immunophenotyping. . Sample should be stored at 2-8 °C. **NOT FROZEN** and shipped to Syngene international Ltd or analysed locally.

The sample has to be shipped and should reach Syngene or local lab for analysis within 48 h.

Time points: Refer to section 8.1: Schedule of Study Visits and Procedures

Specific details will be included in the Laboratory manual/instruction document sent to the sites.

9. Safety Monitoring

Adverse Events and Safety Reporting

For the evaluation of safety, all the evidences of adverse events occurring during the study will be considered. The clinical laboratory tests will be conducted at local labs as and when necessary for safety evaluation. Any investigation, at any time during the study may be conducted at the local lab as per investigator's discretion, in order to monitor safety. Definitions of adverse events and safety reporting for SAEs and SUSARs will be as per regulatory requirements for marketed products (Refer Appendix 3 for details on definitions and reporting that Investigators must follow to satisfy regulatory requirements and ensure patient safety and well-being).

Special Precautions

In general, according to previous data, ALZUMAbTM is safe and well tolerated. However, it is recommended that investigators should exercise caution before administering ALZUMAbTM in subjects with a history of recurrent infections, or underlying conditions which may predispose them to infections. Subjects who develop a new infection while undergoing treatment with ALZUMAbTM should be monitored closely and treated according to standard treatment guidelines. While previous clinical study data has not revealed the incidence of opportunistic infections, it is recommended that Investigators be watchful for occurrence of tuberculosis and opportunistic infections like candidiasis. Administration of ALZUMAbTM should be discontinued if a subject develops a serious infection (other than COVID19). In case a reactivation of latent tuberculosis occurs in study subjects during the clinical study, immediate treatment in accordance with standard medical practice should be instituted and the subjects should be withdrawn from the study.

10.Data Handling Procedures

Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study.

Location of Data

All records and documents pertaining to the study will be maintained in the permanent files of the Investigator and will be available for inspection by the authorized party at any time.

Statistical Analysis

In general, continuous variables is summarized using descriptive statistics such as mean, standard deviation, 95% confidence interval (CI), minimum, and maximum. Categorical variables are summarized using proportions (counts and percentages). All statistical tests will be performed at 5% level of significance (two-sided test) and p-value<0.05 considered statistically significant (if necessary). All statistical analysis will be performed using SAS® (version 9.4 or higher) system software (SAS Institute Inc., USA)/or R/or EAST/or NCSS software.

11.Administrative Procedures

Ethics and Good Clinical Practice

This research will be carried out in accordance with the clinical research guidelines established by the basic principles defined in the revised New Drugs and Clinical Trials 2019, India and the principles enunciated in the Declaration of Helsinki [Ethical Principles for Medical Research Involving Human Subjects, revised, October 2013]. The investigator is responsible for overall activities at the center in accordance with Indian ICH-GCP guidelines, current New Drugs and Clinical Trials 2019 and ethical guidelines for biomedical research on human subjects issued by ICMR.

Interim study report - Data will be provided to DSMB (constituted prior to first patient screened) on a periodic basis. Based on DSMB recommendation, interim clinical study report may be prepared and submitted to DCGI/regulatory agencies.

Subject confidentiality - All reports, CRF and communications relating to subjects in the study will identify each subject only by the subject number, and the protocol number.

Publication of Results

Any formal presentation or publication of data from this trial will be considered jointly between the investigator and the sponsor, as indicated in the contract agreement undersigned by both parties.

References

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12. Appendices

Appendix 1: World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research on Human Patients

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Informed Consent Form

Please see informed consent form.

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Appendix 3: Adverse Event Definitions and Safety Reporting for Investigators (as per requirements for marketed products)

a. Definitions

An Adverse Event/Experience [AE] is any untoward medical occurrence in a subject or clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign [including an abnormal laboratory finding, for example], symptom, or disease temporally associated with the use of a medical product, whether or not considered related to the medical product.

An Adverse Drug Reaction [ADR] is defined as any untoward and unintended responses to an investigational medicinal product related to any dose administered

In accordance with the above definition, adverse events may include:

- Worsening [change in nature, severity or frequency] of conditions present at the onset of the study
- Condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study

An AE does not include:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion), the condition that leads to the procedure is an adverse event.
- Pre-existing diseases or conditions present or detected prior to start of the study drug administration that does not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and / or convenience admissions).

A Serious Adverse Event [SAE] is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening*
- Results in persistent or significant disabling / incapacity
- Requires in-patient hospitalization or prolongation of existing hospitalization[#]
- Occurrence of congenital anomaly or birth defect if relevant
- Other important medically significant events that may not result in death, be immediately life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the well-being of the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or

convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

*The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

#“Inpatient hospitalization” does not imply that the subject must have had an overnight stay in the hospital. If the subject was admitted to the hospital for less than a day for the purpose of treatment or observation, the definition of “Inpatient hospitalization” is met, **provided** the subject is admitted solely for treatment of the event and not admitted for any social reasons, ease of compliance, day care procedures, or for medical or hospital records (insurance reimbursement) purpose. Although, brief treatment in an outpatient clinic or Emergency department does not constitute “inpatient hospitalization”, depending on the intervention/treatment required for the event, it may satisfy the criteria of inpatient hospitalization to be reported as an SAE.

An Unexpected Adverse Drug Reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information [e.g., Prescribing Information]

Events previously unobserved or undocumented must be classified as unexpected on this basis, and not on the basis of what might be anticipated from the pharmacological properties of a medicinal product.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

b. Classification of Adverse Events

All adverse events will be classified, MedDRA coded (Version 17.0 or higher) and documented as per the grading system presented in NCI CTCAE v5.0.

In the course of the study, if adverse events are not covered in the NCI CTCAE v5.0 occur the Investigator will determine the severity of these adverse events as follows:

- Mild: Awareness of symptoms but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity
- Severe: Incapacitating with inability to work or carry out usual activity
- Life threatening
- Death related

The SAE will not be closed out if it is of changing severity during the course. It will be reported with changes in the severity as it upgrades in follow up reports such that each upgraded sequelae will not be recorded as a new SAE but continuation of same SAE and the serious and unexpected adverse

reactions will be reported to DCGI within the stipulated timeline. Only the highest grade of severity will be considered for analysis purpose.

c. Clarification in Reporting of Deaths

All subject deaths (regardless of relationship to study drug) should be reported for subjects while on the study protocol. This should be recorded on the end of study CRF page and the SAE form. If a subject dies after signing consent but before the first dose of the study drug, this will also be recorded in the CRF. Death is an outcome of an adverse event and not an adverse event in itself. All reports of subject death should include an adverse event term (other than “Death”) for the cause of the death. If an adverse event term is not provided, the treating physician will be queried to obtain the cause of death. Only in the rare occurrence that no verbatim description of an adverse event can be obtained from the investigative site, will “Death-Unknown cause” be used as the event term.

d. Causality of the adverse event:

The Investigator’s causality assessment should consider the potential etiologies for the observed adverse event. An adverse event may be related to the study drug, other concomitant medications, the underlying disease pathology, inter-current illness, a procedure performed in the course of the study, or another reason. Among the potential etiologies, the investigator should make a determination based on the most likely causal relationship. When a causality assessment is provided for a SAE, it is important to include a rationale for the assessment so that a better understanding of the reported event can be compiled. The rationale should be accompanied by all available supporting evidence, including relevant laboratory tests, histopathology evaluations and the results of other diagnostic procedures.

The Investigator will make a judgment considering whether or not, in his opinion, the adverse event was related to the drug according to the following classification.

The likelihood of the relationship of the adverse event to the study drug is to be recorded as follows.

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug [de-challenge] should be clinically plausible. The event must be definitive pharmacologically or as a logical phenomenon, using a satisfactory re-challenge procedure if necessary.

Probable /Likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal [de-challenge]. Re-challenge information is not required to fulfill this information.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug , but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Unrelated: Event or laboratory test abnormality – is clearly NOT related to the investigational agent(s)

e. Laboratory Abnormalities

Abnormal laboratory findings (e.g., biochemistry, hematology) or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) per se are not reported as AEs. However, abnormal findings that are deemed clinically significant must be recorded as AEs if they meet the definition of an adverse event (and recorded as an SAE if they meet the criteria of being serious) as described previously, as per the classifications accorded in NCI CTCAE v5.0 for laboratory AEs.

Clinically significant abnormal laboratory or other abnormal findings that are detected after study drug administration or that are present at baseline and worsen following the administration of study drug are included as AEs (and SAEs if serious). The Investigator should exercise his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom, or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant.

f. Documentation of Adverse Events

Any AE occurrence during the study must be documented in the subject's medical records in accordance with the Investigator's normal clinical practice and on the AE page of the CRF. SAEs that occur during the study must be documented in the subject's medical record, on the AE page of the CRF and on the SAE form of the CRF.

The Investigator should attempt to establish a diagnosis of the event based on the signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms. If a clinically significant abnormal laboratory finding or other abnormal assessment meets the definition of an AE, then the AE page of the CRF must be completed as appropriate. In addition, if the abnormal laboratory finding meets the criteria for being serious, the SAE form must also be completed. A diagnosis, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. As additional information becomes available and a diagnosis is achieved, the signs/symptoms or abnormal finding verbatim should be updated on the CRF.

If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded on the AE/SAE page. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with baseline values and copies of laboratory reports. The SAE form should be completed as thoroughly as possible. It is very important that the

Investigator provide an assessment of the causal relationship between the event and the study drug at the time of the initial report.

g. Follow-up of Adverse Events and Serious Adverse Events

Subjects will be monitored for adverse events/reactions to the study drug and/or study procedures during the study product administration. All AEs related to ALZUMAbTM and all SAEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject dies or is lost to follow-up. The investigator will administer appropriate treatment for the SAE resolution. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

h. SAE/SADRs reporting (Investigator's Responsibilities)

All study drug related SAEs (SADRs), occurring **after the patient signs the informed consent and until the one year follow-up period is over or until the patient has prematurely stopped participation in the study** must be reported to drug manufacturer (Biocon Ltd) within 24 hours of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SADRs must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. An SADR occurring at a different time interval should be reported separately as a new event.

Information about all SADRs is collected and recorded on the Serious Adverse Event Report Form. The Investigator must assess the relationship to drug and report all SADRs by completing the SAE Report Form in English, and send the completed, signed form within 24 hours to Biocon Ltd. The original SAE Report Form and the fax confirmation sheet must be kept with the documentation at the site. The investigator should notify all SADRs to Biocon through email. The telephone and fax number of the contact persons listed below for SADRs reporting can be used as alternate modes of communication.

The Investigator must **inform one of the responsible persons** of Biocon Ltd (Pharmacovigilance personnel listed below) **by telephone as soon as possible and not later than 24 hours** of the occurrence of an SADR.

Questions pertaining to a specific serious adverse drug reaction occurring in a patient should be directed to the contact persons listed in the protocol.

Follow-up information should be sent to Biocon Ltd PVD (where the original SAE Report Form was sent), using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event even if it occurs at a different time interval. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from surveillance participation. If there are SADR/SAEs, they should be intimated to all the other IRB/IEC through the sites. They should be intimated to the other sites within 14 calendar days of SAE/SADR occurrence and the sites will in turn inform the IRB/IEC within 24 hours of getting the information.

If the SAE/SADRs is not previously documented in Package Insert (unexpected, new occurrence) a Biocon PVD personnel or designee may urgently require further information from the Investigator for Health Authority reporting. All SAE/SADRs will be reported to DCGI, and relevant IRB/IEC by the Investigator within 24 hours (first intimation) and due analysis within 14 days of first awareness of the event in required format as per the New Drugs and Clinical Trials 2019. The same guiding principle as described above for initial and follow up reports of SAE/SADRs will be followed for SAE/SADRs reporting to DCGI and IRB/IEC. Any report of the SAE/SADRs, after due analysis shall be forwarded by the sponsor to the DCGI, IRB/IEC where the trial has been conducted, within fourteen days of knowledge of occurrence of the serious adverse event as specified in Table 5 (as per the timeline for marketed products in New Drugs and Clinical Trials 2019).

All study drug related Serious Adverse Events should be reported by the Investigator to Biocon Pharmacovigilance department and email address given below:

Pharmacovigilance Department

Clinical Development & Medical affairs,
Biocon Biologics India Limited,
Biocon House, Semicon Park,
Bangalore 560 100: India

Email: DrugSafety@biocon.com

Fax +91 80 6775 5323

Toll Free No: 1800 102 9465

It should be sent within 24 hours of the occurrence of the event.

To ensure the patient safety each pregnancy in a patient occurring after the patient begins taking drug until the treatment is stopped should be reported to the above contact details of Biocon Pharmacovigilance within 24 hours of learning of its occurrence. The pregnancy should be followed to determine the outcome including the spontaneous or voluntary termination, details of birth, the presence of any birth defects, congenital abnormalities. Any patient in whom pregnancy occurs after signing of the informed consent form and before the patient is enrolled should be excluded from the surveillance.

The cases of pregnancy reported by female patients or female partners of male patients will be followed up till the outcome. Investigator should fill the Pregnancy Reporting Form and send to the above mentioned personnel. Pregnancy follow up should be recorded in the same form and should include an assessment of the possible relationship to ALZUMAbTM of any pregnancy outcome. The Investigator should arrange for the appropriate counseling of patients to discuss the implications of continuing or terminating pregnancy.

Pregnancies occurring during the post-treatment follow-up shall be reported and followed up if suspected to be unintended pregnancies related to ALZUMAbTM or are associated with abnormal outcome, birth defect or congenital anomaly related to ALZUMAbTM.

i. Infusion Reactions

During administration of ALZUMAb™ some patients may develop infusion reactions. Infusion reactions are most likely to occur during the first cycle of dosing and tend to decrease in severity and frequency upon subsequent infusions. Acute infusion-related reactions are expected with Itolizumab administration. Symptoms may include nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, wheezing, dyspnea, dizziness, headache, and hypertension. Acute infusion reactions should be treated using the standard of care; and physicians may need to delay dosing till the patient is stabilized.

ii Overdose Treatment:

Since the investigational products are directly administered by personnel involved in the study in controlled manner, overdose is unlikely to occur. However, in case of overdose, the management will be as per standard of care. In case there is overdose, the same should be informed to sponsor safety team on real time basis. Overdose with associated adverse events should be informed to sponsor safety team in line with AE/SAE reporting timelines (as applicable).

Appendix 4: Package Insert

For the use of Registered Dermatologist and Specialist Medical Practitioner

ALZUMAbTM

Itolizumab Injection

NAME OF THE MEDICINAL PRODUCT

ALZUMAbTM

COMPOSITION

Each vial contains 25 mg of Itolizumab. Itolizumab is a humanized recombinant anti-CD6 monoclonal antibody.

Each mL contains 5 mg of Itolizumab for intravenous use. For full list

of excipients, see Pharmaceutical Particulars. **PHARMACEUTICAL**

FORM

Solution for intravenous infusion

Colorless and transparent solution

PHARMACOLOGICAL PROPERTIES

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 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) signaling pathways, the secretion of pro-inflammatory cytokines (including tumor necrosis factor- α , interferon- γ and interleukin-6) and T-cell proliferation, even when co-stimulated with ALCAM.

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.

Clinical studies

The efficacy and safety of ALZUMAbTM were assessed in 2 randomized, multicentric studies in patients 18 years of age and older with chronic, stable plaque psoriasis involving $\geq 10\%$ 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).

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. 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, or once in 4 weeks); or 1.6 mg/kg (once in 2 weeks or once in 4 weeks). Patients were treated for 8 weeks and were followed up for 24 weeks. Efficacy parameters of the study included PASI, Investigator’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 Weeks 8 and 12 is shown in Table 1. 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 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 1. 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: Investigator’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 weeks) and washout phases (if necessary, up to 8 weeks depending on current treatment):

Placebo controlled phase (12 weeks),

Crossover of Placebo and consolidation treatment phase (16 weeks) and, Randomized withdrawal phase (24 weeks).

In this study, 225 patients were treated as follows:

Week 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 weeks, followed by 1.6 mg/kg every 2 weeks for 8 weeks; (B) Itolizumab 1.6 mg/kg every 2 weeks for 12 weeks; or (C) placebo for 12 weeks.

Week 12-24 (double-blind): Patients from arms A and B continued to receive Itolizumab at the dose of 1.6 mg/kg every 4 weeks till week 24; and patients from arm C received Itolizumab at 1.6 mg/kg every 2 weeks till Week 24.

Week 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 weeks, and patients from arm A and B were re-randomized based on their PASI response:

Patients who achieved \geq PASI 75 were randomized (1:1) to receive either itolizumab 1.6 mg/kg every 12 weeks or placebo (double-blind) till Week 52;

Patients who achieved \geq PASI 50 but $<$ PASI 75 response received itolizumab 0.4 mg/kg every week for 4 weeks followed by 1.6 mg/kg every 4 weeks (open-label);

Patients failing to achieve PASI 50 were withdrawn from the study.

The last dosing visit (at Week 48) was followed by a 4-week treatment-free follow-up period. In the TREAT-PLAQ study, the primary endpoint was the proportion of patients achieving

\geq PASI 75 at Week 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 “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 2. In the primary analysis, at Week 12 both itolizumab treatment arms A and B demonstrated significant efficacy over arm C (placebo from Weeks 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 2. 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	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)	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%)
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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

Figure 1 represents the proportion of patients at each visit up to Week 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 weeks for arm A, where patients received a lower dose in the first

4 weeks compared to patients from arm B. After patients in arm C were crossed over to receive itolizumab at Week 12, they showed rapid improvement, and by Week 20 the proportion of patients achieving PASI 75 was similar in all arms.

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.

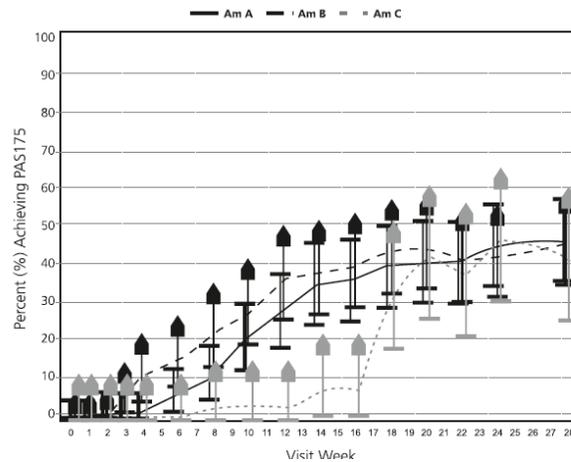


Figure 1. Proportion of Patients Achieving PASI 75 by study Arm and Visit in the TREAT- PLAQ Study. Bars represent exact 95% confidence intervals.

[Note: At Week 12, patients in arm C were crossed over to receive itolizumab 1.6 mg/kg every 2 weeks 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 3). 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.

Table 3. 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
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: Investigator’s global assessment

n=number of patients with response; N=total number of patients

¹A versus. C; ²B versus. C

Pharmacokinetic Properties

The pharmacokinetic (PK) data for itolizumab in psoriasis patients is based primarily on data from the phase 2 study (Study I). The PK parameters of itolizumab were determined over 8 weeks of treatment and 4 weeks of treatment-free follow-up. Itolizumab was administered at doses ranging from 0.4 to 1.6 mg/kg as intravenous (IV) infusion. An enzyme-linked immunosorbent assay (ELISA) method was used to measure itolizumab in serum samples.

A linear dose-dependent relationship was observed for various PK parameters after 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 weeks or once in 4 weeks) and 1.6 mg/kg (administered once in 2 weeks or once in 4 weeks) increased in proportion to dose (Table 4). Both AUC_{0-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 C_{min} . Volume of distribution and clearance increased marginally with decrease in 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 4. 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	8.01	20.98	569.69	4351.25
	Every 2 weeks	10.93	15.30	897.30	2750.49
0.8	Every week	19.95	29.75	1284.94	9663.53
	Every 2 weeks	20.03	29.19	1833.22	9205.22
1.6	Every 2 weeks	39.94	49.56	4103.77	14017.06
	Every 4 weeks	41.02	41.39	6682.89	10230.29

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

Preclinical Safety Data

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.

Chimpanzee and baboon 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 considered to be 16 mg/kg. 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 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.

CLINICAL PARTICULARS

Therapeutic Indications

ALZUMAb™ is indicated for the treatment of patients with active moderate to severe chronic plaque psoriasis who are candidates for systemic therapy.

Limitations of Use

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

Posology and Method of Administration

The recommended dose of ALZUMAb™ for the treatment of plaque psoriasis is 1.6 mg/kg given as IV infusion once every 2 weeks for 12 weeks, followed by 1.6 mg/kg every 4 weeks up to 24 weeks.

Prior to initiating ALZUMAb™ and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection [see Special Warnings and Precautions for Use and Contraindications].

ALZUMAb™ is intended for use under the guidance and supervision of a Investigator. The diluted infusion solution should be prepared by a trained medical professional using 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].

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.

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 2-8°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 over a period of not less than 120 minutes and using an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size of 1.2 µm or less).

Approximately 50 mL of diluted ALZUMAb™ solution should be administered during the first hour, followed by remaining solution (approximately 200 mL) in the next hour. The infusion period can be extended up to 8 hours for medical reasons.

The vials do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse [see Pharmaceutical Particulars].

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.

Contraindications

ALZUMAb™ should not be administered to patients having history of severe allergy or known hypersensitivity reaction to any component of ALZUMAb™ or any murine proteins. Additionally, ALZUMAb™ is contraindicated in patients with any active serious infection [see Special Warnings and Precautions for Use].

Special Warnings and Precautions for Use

Infusion-related reactions and hypersensitivity reactions

During administration of ALZUMAbTM some patients may develop acute infusion reactions. Symptoms may include nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, wheezing, dyspnea, 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. Infusion reactions reported during the TREAT-PLAQ study (Study II) were mild to moderate in severity, except in one patient who had delayed infusion reaction which was reported as serious adverse event (SAE). In the same patient, adjustment disorder anxiety also was reported as SAE [see Undesirable effects]. Acute infusion reactions should be treated using the standard of care; and Investigators may need to delay dosing till the patient is stabilized.

Infections

Investigators should exercise caution before and during ALZUMAbTM 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 infection during and after treatment with ALZUMAbTM, including patients who were evaluated negative for latent tuberculosis infection prior to initiating therapy. In case of new infection or reactivation of latent infection during the treatment, ALZUMAbTM treatment 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 weeks 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, ALZUMAbTM did not appear to increase rate of infections in patients compared to placebo, during the study.

ALZUMAbTM has not been studied in patients with active intercurrent infections, or a past history of serious infections such as HIV-AIDS or tuberculosis [see Contraindications]. ALZUMAbTM has not been studied in the patients having low absolute neutrophil or lymphocyte count (<1500 cell/ μ L). The effect of ALZUMAbTM 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 ALZUMAbTM administration, patients should be screened for active or latent tuberculosis infection using Mantoux test and or chest x-ray.

Use with other biologics

ALZUMAbTM has not been studied in combination with other biological agents approved for the treatment of plaque psoriasis. ALZUMAbTM should not be used with such agents because of the possibility of increased immunosuppression and increased risk of infection.

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 ALZUMAbTM therapy. Based on its mechanism of action, ALZUMAbTM may blunt the effectiveness of some immunizations. It is recommended that live/attenuated vaccines not be given concurrently with ALZUMAbTM. The patient's vaccination record and the need for immunization prior to receiving ALZUMAbTM should be carefully investigated. The interval between vaccination and initiation of ALZUMAbTM 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 ALZUMAbTM during pregnancy, since ALZUMAbTM may cross the placenta.

Malignancies

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

Drug Interactions

Drug interaction studies have not been performed with ALZUMAB™.

Pregnancy and Lactation

Use in 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 Preclinical Safety Data].

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, taking into account the importance of the drug to the mother.

Undesirable Effects

Clinical trial experience

Safety data of ALZUMAB™ has been derived from 2 randomized, multicentre studies in patients with chronic plaque psoriasis. 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 weeks).

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 weeks) 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 5).

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.

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 5). 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].

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

Preferred Term	Arm A	Arm B	Arm C	Total
	n (%)	n (%)	n (%)	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)

n=patients with adverse effect; N=total number of patients

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 6). In general, itolizumab did not appear to increase the rate of infections as compared to placebo. During the placebo-controlled period, (Weeks 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 weeks and 19 (8.5%) patients in Weeks 13 to 52 (5 patients had an infection in both periods).

Table 6. Incidence of Infections in TREAT-PLAQ Surveillance.

Study Period	Number of Patients (%)			Total
	Arm to Which Patient was Initially Randomized			
	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 weeks 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 Weeks 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 hematology 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.

Serious adverse events and deaths

During the TREAT-PLAQ study, 5 SAEs were reported in 4 (1.8%) patients (all on itolizumab) during the placebo controlled phase. Four of the 5 SAEs occurred within the first 12 weeks and 1 SAE occurred during the randomized withdrawal phase (after Week 28). The events were dermatitis exfoliative, erythrodermic psoriasis, arthritis, infusion-related reaction and adjustment disorder with anxiety. Two of the 5 SAEs (dermatitis exfoliative and erythrodermic psoriasis) were determined to be unlikely related to the study drug. Remaining 3 SAEs were determined to be possibly or certainly related. Of three SAEs, 2 (infusion-related reaction and adjustment disorder anxiety) were reported in the same patient. The third SAE was classified as septic arthritis. It was reported 8 months after the start of itolizumab treatment (6 months treatment followed by single dose of placebo). The event occurred 3 months after the last dose of itolizumab and was deemed related to the study drug by the investigator. However, bacterial culture and AFB culture of synovial fluid were negative.

No deaths were reported during the course of the study.

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.

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, rhinorrhea.

Skin and subcutaneous tissue disorders: psoriasis, keloid scar, dermatitis exfoliative, pruritis, erythrodermic psoriasis.

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 patient was normal. In case of 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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Monobasic sodium phosphate, dibasic sodium phosphate (anhydrous equivalent), sodium chloride, polysorbate 80 and water for injection. ALZUMAbTM contains no antibacterial preservatives. **Incompatibilities:** In the absence of compatibility studies, ALZUMAbTM must not be mixed with other medicinal products.

Shelf Life: 36 months

Storage and Precautions

Store at a temperature between 2°C and 8°C. KEEP OUT OF REACH OF CHILDREN.

Nature and Contents of Container

Pack size: 25 mg/5 mL

ALZUMAbTM 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).

Special Precautions for Disposal and Handling

Do not administer as IV push or bolus.

Prior to infusion, fully diluted ALZUMAbTM 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 accidentally frozen, or there has been refrigerator failure. Any unused product or waste material should be disposed of in accordance with local requirements.

MANUFACTURED BY

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