Biotest

From Nature for Life

Study 973 - EudraCT Number: 2008-007458-37

Synopsis

Title of study: A randomized, placebo-controlled, double-blind, multicentre, multiple dose, cohort study with escalating doses to evaluate the safety and efficacy of the humanized monoclonal antibody BT061 administered subcutaneously or intravenously as 8 repeated doses to patients with moderate to severe chronic plaque psoriasis.		
Study Number: 973		
Investigators and Study Centres: **Active:** 4 sites (Czech Republic) and 8 sites (Hungary)		
Publication (reference): ClinicalTrials.gov Identifier: NCT01072383 EU Clinical Trials Register: 2008-007458-37		
Studied period (years): (date of first enrolment) (date of last completed)	1 year and 3 months 15-FEB-2010 23-MAY-2011	**Clinical phase:** IIa
Objectives: Safety and efficacy assessments of multiple doses of BT061. Identification of the most effective intravenous (IV) and subcutaneous (SC) dose strength in comparison to placebo, and comparison of the efficacy of SC versus IV administration		
Methodology: Prospective, randomized, placebo-controlled, double-blind.		
Number of patients (planned and analyzed): Planned: In total, 48 patients in 6 cohorts with 8 patients per cohort receiving either the active Investigational Medicinal Product (IMP) (6 patients) or placebo (2 patients) resulting in a randomization ratio of 3:1 active IMP versus placebo. It was estimated that approximately 60 patients had to be screened to identify 48 patients eligible for randomization. Analyzed: A total of 66 patients were screened, of which 49 patients were randomized and analyzed. Enrolment target was reached with 8 patients per cohort, only the highest cohort receiving 100 mg SC included 9 patients.		
Diagnosis and main criteria for inclusion: Male and female patients, age ≥ 18 to ≤ 75 years, with moderate, moderate to severe or severe chronic plaque psoriasis diagnosed ≥ 12 months prior to Screening, with body surface area (BSA) involvement > 10% for more than 6 months, who signed and dated the written informed consent form (ICF).		
Test product, dose and mode of administration, batch number: BT061 (tregalizumab): SC or IV administration of BT061 at weekly intervals. SC doses administered in the anterior abdomen or upper thigh; IV doses given as a continuous infusion over 2 hours via an infusion pump after dilution with 0.9% sodium chloride solution up to a total volume of 50 mL.		

Total dose per application administered: 0.5 mg BT061 IV (Cohort 1); 2.0 mg BT061 IV (Cohort 2); 25 mg BT061 SC (Cohort 3); 50 mg BT061 SC (Cohort 4); 75 mg BT061 SC (Cohort 5) and 100 mg BT061 SC (Cohort 6). Cohorts 1 and 2, Cohorts 3 and 4, and Cohorts 5 and 6 treated simultaneously and treatment blinded within each group of 2 cohorts. Two out of 8 patients in each cohort received placebo. Recruitment into Cohorts 5 and 6 started only after Data and Safety Monitoring Board (DSMB) review of at least 31 patients from Cohorts 1 to 4 and after the corresponding approval to continue with the study. . Batch numbers: A061018A (12.5 mg), A061028A (25 mg), A061038A (50 mg), A061018B (12.5 mg), A061028B (25 mg), A061038B (50 mg), A061018C (12.5 mg), A061028C (25 mg) and A061038C (50 mg).
Duration of treatment: 8 weeks: A total of 8 SC injections or IV infusions at weekly intervals. Follow-up: 12 weeks.
Reference therapy, dose and mode of administration, batch number: Placebo: SC or IV administration at weekly intervals. Doses administered as per BT061. Total dose per application administered: 0.5 mg placebo IV (Cohort 1); 2.0 mg placebo IV (Cohort 2); 25 mg placebo SC (Cohort 3); 50 mg placebo SC (Cohort 4); 75 mg placebo SC (Cohort 5) and 100 mg placebo SC (Cohort 6). Batch numbers: A015018A, A015018B and A015018C.
Criteria for evaluation Efficacy: The primary endpoint was the response rate defined as the proportion of patients experiencing a 75% reduction in psoriasis using the psoriasis area and severity index (PASI) 75 at the End-of-Treatment visit (Visit 18, Week 9). The following secondary efficacy variables were analyzed: Number of responders (PASI90, PASI75 and PASI50); time course (PASI90, PASI75 and PASI50); time to response (PASI75); time to relapse (when the achieved maximal improvement from baseline is reduced by > 50%); Physician's Global Assessment (PGA); Itching Score; Dermatology Life Quality Index (DLQI) Questionnaire; number of patients either dropping out early because of lack of efficacy or showing a PASI improvement of less than 25% at the end of treatment visit and identification of biomarkers as potential surrogate parameters for efficacy. Safety: Lymphocyte subpopulations (CD45-lymphocytes, CD3+CD4+, CD3+CD8+, CD19+); cytokine profiles (interleukin [IL]-2, IL-6, tumor necrosis factor (TNF)-α and transforming growth factor [TGF]-β); vital signs; physical examination; safety laboratory parameters (hematology and clinical chemistry, endocrine profile), infections / serology; adverse events (AEs) and serious adverse events (SAEs); development of anti-drug antibody (ADA) response; autoantibodies (anti-nuclear antibody [ANA] and anti-double-stranded deoxyribonucleic acid [anti-dsDNA]); delayed-type hypersensitivity (DTH) response; assessment for diphtheria, tetanus, tuberculosis (TBC) antibody titres; Epstein-Barr virus (EBV)-reactivation, cytomegalovirus (CMV)-reactivation; monitoring of electrocardiogram (ECG); change in testicle size and premature withdrawals due to AEs. Pharmacokinetics (PK): Time dependency of BT061 plasma concentrations.
Statistical methods: Descriptive statistical methods for evaluation of efficacy and safety parameters were used (explorative study). In addition Fisher's exact test, odds ratios and

95% Confidence Intervals (CIs) are presented to compare the PASI response for each IMP group against the respective combined placebo group.

Explorative evaluation of the time dependency of BT061 plasma concentrations.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

All patients (N=49, 100%) were included in the All Patients Treated Analysis Set, Full Analysis Set, PP Analysis Set and PK Analysis Set. The Full Analysis Set was used for all efficacy analyses.The PP Analysis Set was defined as all patients of the full analysis set without any major protocol violations. As there were no major violations recorded during the study, the PP Analysis Set is identical with the Full Analysis Set. A total of 40 patients were included in the Full Completers PP Set. This subpopulation was only to be used for the exploratory analyses of secondary efficacy endpoints.

SC Treatment

For the primary endpoint at Visit 18 (Week 9), the highest response rate for PASI75 was achieved for the 100 mg BT061 SC treatment group (3/7 patients; 42.9%) which was about twice that of the 75 mg BT061 SC treatment group (1/6 patients; 16.7%). No PASI75 response was achieved with 25 mg and 50 mg BT061 SC. In the placebo group, 1 of 8 patients (12.5%) achieved PASI75. For PASI50 the highest response was achieved in the 100 mg (5/7 patients; 71.4%) and 75 mg (3/6 patients; 50.0%) BT061 SC treatment groups. The PASI50 response rates of the 25 mg (2/6 patients; 33.3%) BT061 SC treatment groups were comparable to that of the placebo SC group (3/8 patients; 37.5%). No PASI50 response was achieved in the 50 mg BT061 SC treatment group. No patient reached PASI90 at Visit 18 (Week 9).

The mean PASI scores at Visit 18 (Week 9) were lower than the scores at Week -4 to -1 for all SC treatment groups. After an initial gradual decrease, the mean PASI scores remained stable until Visit 21 (Week 20). The 75 mg BT061 treatment group consistently had the lowest PASI scores at all time points.

The highest percentage of patients with a PGA improvement at Visit 18 (Week 9) was in the 75 mg and the 100 mg BT061 SC treatment groups (83.3% and 71.4%). In the placebo group 4/8 patients (50.0%) showed improvement and in the 25 mg BT061 treatment group 2/6 patients (33.3%). One (1) of 6 patients (16.7%) showed PGA worsening in the 25 mg dose group. At Visit 18 (Week 9), the 100 mg BT061 SC treatment group had the highest percentage of patients (5/7 patients; 71.4%) with an improvement in their itching score from baseline (Visit 2; Week 1). Similar improvements in the PGA and itching scores were also seen in the placebo SC group. The majority of the SC treatment groups (50 mg, 75 mg and 100 mg) showed a mean decrease in DLQI scores from baseline (Visit 2; Week 1) to Visit 18 (Week 9), with the largest mean decrease in the 100 mg BT061 SC treatment group.

IV Treatment

An unexpectedly high placebo rate was observed in the IV dose groups. The primary endpoint at Visit 18 (Week 9), PASI75 was reached in the placebo IV group (1/4 patients; 25.0%) and the 0.5 mg BT061 IV (1/6 patients; 16.7%) treatment group. PASI50 was reached in the 0.5 mg BT061 IV treatment group (3/6 patients; 50.0%) and the placebo IV group (2/4 patients; 50.0%). No patient in the 2.0 mg BT061 IV treatment group reached PASI50. No patient reached PASI90 at Visit 18 (Week 9).

The mean PASI scores at Visit 18 (Week 9) were lower than the mean scores at Visit 1 (Week -4 to -1) for the 0.5 mg BT061 and placebo IV groups. These 2 treatment groups also showed a gradual decrease in their mean PASI scores from Visit 1 (Week -4 to -1) to Visit 20 (Week 16) and Visit 21 (Week 20) respectively.

The highest percentage of patients with a PGA improvement at Visit 18 (Week 9) was in the placebo group (all patients), whereas in the 0.5 mg and 0.2 mg BT061 IV treatment groups 4/6 patients (66.7% each) had improvements. No patient showed PGA worsening. At Visit 18 (Week 9), the 0.5 mg BT061 IV treatment group had the highest percentage of patient (all patients) with an improvement in itching score from baseline (Visit 2; Week 1) and 5/6 patients (83.3%) in the 2.0 mg IV treatment group. Improvements in the itching scores was also in the placebo IV group (3/4 patients; 75.0%). One (1) of 6 patients (16.7%) in the 2.0 mg IV BT061 treatment group had worsening of the itching score. A decrease in the DLQI scores was seen in all IV treatment groups from Visit 2 (Week 1) to Visit 18 (Week 9), with the largest mean decrease in the 0.5 mg BT061 IV treatment group.

Study Drug Plasma Concentration and Immunogenicity

BT061 Plasma Levels: Following 75 mg and 100 mg SC, median peak BT061 levels measured 4-4.5 hours post dose were between 24.5 and 188.1 ng/mL One week after dosing, plasma levels for the BT061 SC and IV treatment groups were around the LOQ and no accumulation after multiple dosing was observed in the SC treatment groups.

Immunogenicity: Two (2)/37 BT061 treated patients developed specific antibodies against BT061. One of the patients had antibodies with neutralizing capacity. Both patients were in the 100 mg SC treatment group and tested positive for anti-BT061 antibodies at the final follow-up visit (Visit 21; Week 20) only.

Pharmacodynamic Effects

For the SC treatment groups, there was a visible decrease of CD4 surface expression on CD4+ T cells (CD4 MFI) already at the first time point (4-4.5 hours post dose) after the first dose of IMP in the 25 mg, 50 mg, 75 mg and 100 mg groups in comparison to the placebo group. Generally, a dose-proportional effect was observed. CD4 MFI returned to baseline values after cessation of treatment, as measured at the last visit (Visit 21; Week 20).

For the IV treatment, there was no CD4 modulation observed in any of the IV treated groups.

No remarkable effect on cytokine levels (IL-2, IL-6, TNF-α and TGF-ß) were noticed, as well as no effect on average of the lymphocyte counts over the entire observation period.

The screening of a large panel of biomarkers identified few proteins which might have potential for prediction of response.

Although there were no significant differences at end of treatment in the active dose groups when compared to the pooled placebo group using Fisher's exact test, the efficacy results may suggest a dose response for the 75 mg and 100 mg BT061 SC treatment groups.

SAFETY RESULTS:

The IMP (BT061 and placebo) was well tolerated during the study.

TEAEs were experienced by 55.1% patients: 57 TEAEs in the SC treatment (68% of BT061 SC and 62.5% of placebo SC treated patients) and 8 TEAEs in the IV treatment (16.7% of BT061 IV and 75.0% of placebo IV treated patients). No fatal TEAEs were reported in the different treatment arms (SC, IV). Five serious, not study drug related TEAEs occurred in 4 patients; of which 2 TEAEs occurred in SC treated patients (50 mg SC and placebo SC)

and 3 TEAEs (2 patients) occurred in the IV placebo group. Two patients withdrew from the study due to non-serious TEAEs: 1 patient in the 25 mg BT061 SC and 1 patient in the 2.0 mg BT061 IV treatment group. The majority of TEAEs were mild (83.1%); 10.8% TEAEs were moderate and 6.0% TEAEs severe. A higher percentage of moderate/severe TEAEs were reported in the 25 mg and 50 mg BT061 SC treatment groups. In IV treated patients severe TEAEs have only been reported for the placebo group. Of all TEAEs reported, 75.9% were not study drug related. Study drug related TEAEs (24.1%) occurred only in SC treated patients. In 3 patients, TEAEs leading to dose interruption were reported in the SC treatent group but none in the IV treatment groups.

Injection site reactions (mild, study drug related) were experienced by 3 patients in the SC group (one patient each in the 25 mg, 100 mg and placebo groups). Infections were reported in 40.0% BT061 SC treated patients compared to 12.5% placebo SC treated patients. The infections were non-serious, of mild/moderate severity, not study drug related and mostly associated to the respiratory tract. Neither TEAE related to infusion site reactions nor infections were reported in the IV treatment groups. The most common TEAEs in the IV treatment group were positive TBC tests without any symptoms of active TB infection occurring only in the placebo treatment group. It should be noted that due to the low patient numbers in each treatment group, the differences in the percentage and proportions may appear magnified.

There was no clear trend in any new abnormal physical examination findings developing during the course of the study. No consistent treatment effects of the IMP on testes volume were noted. There were individual patients who had decreases in testes volume; most of these patients were from one site. Overall, there was no notable influence of the IMP on the laboratory results.

CONCLUSION:

Administered weekly over 8 weeks, BT061 showed higher efficacy than placebo with 75 mg SC and 100 mg SC administration at the end of treatment. In the IV arm, a high placebo rate was observed. Both IV treatment groups were not superior to placebo in terms of efficacy at the end of treatment. The IMP (BT061 and placebo) was well tolerated in patients with moderate to severe chronic plaque psoriasis receiving IMP subcutaneously or intravenously.

Date of report: 16-DEC-2014

Name and the address of the consenting investigators pursuant to Section 4a of the Federal Data Protection Act

Multicenters in Europe:
Czech Republic (4 centers) and Hungary (8 centers) enrolled 49 subjects.

Overview of substantial protocol amendments

Amend-ment No.	Date	Sections concerned	Rationale
1	22-MAR-2010	Responsibilities and Signatures page, 4, 5, 11.1.1, 11.1.2.1, 12.3, 13.5.4, 15.3.9, 15.3.15, 15.7.2, 16.2.2, 16.2.6, 20.5, 20.6	- addition of details of an unblinded interim analysis - change to the selection of antigens used for the Delayed Type Hypersensitivity (DTH) test as tetanus toxoid is not available in the EU or US. Tetanus toxoid is to be replaced with Candida Albicans antigen. - explanation added to exclusion criterion 4 concerning the use of antihypertensives and removal of exclusion criterion 35 as superfluous - correction of typographical errors and minor inconsistencies, and clarification of some protocol sections.
5	14-SEP-2010	Responsibilities and Signatures page, 5, 11.1.1, 11.1.4, 16.2.6, 15.3.8, study Flowchart and 13.2., 20.1	- The recruitment in the study had been slower than expected, mainly due to higher rate of patients who failed screening and due to summer season that improves the condition of psoriatic patients. Currently 31 patients had been recruited in the study and no preliminary safety concerns had arisen. Waiting for the 32nd patient before conduct of the DSMB review would confer substantial delay not only to safety review of patients of cohorts 1-4 but also to recruiting the remaining cohorts and bringing in the final results of the whole study. Therefore a suggestion of bringing the DSMB review forward has been made. DSMB review should be possible already after at least 31 patients had reached visit 10. Safety of study subjects would not be compromised as the DSMB would be reviewing all available data from the 32nd patient, too, and could request data from the 32nd patient up to Visit 10 if necessary. Patient 32 would be recruited in Cohorts 3-4 and recruitment would be put on hold after the 32nd patient was randomised. The order of these steps would remain unaffected by the present amendment. The Synopsis, Dosage and mode of administration, 4th paragraph, would be amended to read: Cohorts 1 and 2, Cohorts 3 and 4, and Cohorts 5 and 6 will be treated simultaneously and treatment will be blinded within each group of 2 cohorts. Recruitment into Cohorts 5 and 6 will start only after DSMB review of at least 31 patients from Cohorts 1 to 4 and approval to continue with the study. Patients will be assigned to the respective cohort according to the randomization plan.

Amend-ment No.	Date	Sections concerned	Rationale
			- In order to make Section 11.1.1, consistent with protocol synopsis, 4th paragraph of the section would be amended to read: Patients are to be recruited into cohorts sequentially and randomised to cohort within each group of 2 cohorts recruited and randomised to treatment within each cohort. Cohorts 1 and 2 will be recruited first, followed by Cohorts 3 and 4, and finally Cohorts 5 and 6. All patients within the 2 cohorts can be treated simultaneously. When at least 31 patients in Cohorts 1–4 have completed at least 4 treatment cycles and the testicle sonography after treatment 4 is performed (Visit 10), safety data will be reviewed by the DSMB. Cohorts 5 and 6 will not be recruited until the DSMB have confirmed there are no safety concerns. Refer to Figure 11-2 for a schematic diagram of the recruitment, randomisation and treatment of patients. - In order to make the Section 11.1.4 consistent with the synopsis, the section was amended to read: A DSMB will be established to monitor the riskbenefit and safety of the study. The DSMB will comprise 3 independent experts and cannot include any Investigator involved in this study, or personnel of the sponsor. There will be 2 meetings of the DSMB, a kickoff meeting at study start and a meeting during the study to evaluate safety data when at least 31 patients in Cohorts 1–4 have completed at least 4 treatment cycles and the testes sonography after treatment 4 (Visit 10). The DSMB will receive the following information for the DSMB review: • AEs; • Laboratory results (safety blood assessments, hormones, lymphocyte phenotyping); • Testicle sonography; • Details of all patient withdrawals (for any reason); • Details of any dose abruptions or treatment interruptions. All data will be blinded. However, unblinding can be requested by the DSMB if considered necessary for their medical judgement. The DSMB meeting should be held prior to completion of treatment cycle 8 of Cohorts 3 and 4 to avoid any unnecessary delays in recruitment of the remaining cohorts. All data

Amend-ment No.	Date	Sections concerned	Rationale
			collected from the 32nd patient up to date of the DSMB meeting will be provided to DSMB too. The DSMB can request data from the 32nd patient up to Visit 10 if necessary. Recruitment of Cohorts 5 and 6 must not be performed until after the DSMB meeting and approval to continue with the recruitment. Further details regarding the membership, roles and timing of DSMB meetings are provided in the DSMB charter. - For the same reasons as mentioned in section 2.1 it has been suggested that interim analysis is performed after 31 patients complete Visit 18. The suggestion has been discussed with a statistician who confirmed that it does not compromise statistical design of the study. All other aspects of interim analysis remain the same. Section 16.2.6. Interim analysis, the first paragraph will be amended to read: Export of preliminary data prior to database closure will occur to provide preliminary listings of efficacy data for information of Biotest about the progress of the trial. An unblinded interim analysis will be performed after 31 patients from Cohorts 1–4 have completed the End-of-Treatment Visit (Visit 18; Week 9). Two types of efficacy listings will be produced from the data of 31 study participants of cohorts 1–4 at this time. In both, the PASI development in the time window between baseline and Week 9 will be evaluated. - For an additional evaluation regarding data which are obtained anyway during the lymphocyte phenotyping, by the FACS (fluorescence-activated cell sorter) assay, Following wording was added to the protocol: 'FACS (fluorescence-activated cell sorter) assay will be performed during lymphocyte phenotyping, for an additional evaluation. FACS analysis will not have an impact on type, time, individual volume and overall volume of blood draws. No genetic testing is involved. This variable is the relative fluorescence intensity of C3CD4 T-cells, correlating with the relative abundance of CD4-molecules on the cell surface. Results are part of each stored FACS data set. It should be noted, however, that due to blinding reasons these data will only be transmitted after unblinding.'

Amend-ment No.	Date	Sections concerned	Rationale
			- The current protocol advises that Pre-Treatment Visit (Visit 2) and Interim visits (Visits 4, 6, 8, 10, 12, 14, and 16) are performed 2 days prior to Treatment visits (Visits 3, 5, 7, 9, 11, 13, 15, and 17). In reality Interim visits are performed for all study patients 3 days prior to Treatment Visits. However, the protocol allows a deviation of +/- 1 day from the visit window between Interim and Treatment visit. The protocol asks that blood samples are taken at Interim visits and the results must be available prior to each treatment. Patients' safety depends on the laboratory results. Due to the fact that all samples are analysed by central laboratory in Germany, the results are only known to sites in the afternoon of day 2 after interim visit, thus moving the Treatment visit for a day by using the deviation of +1 day as specified in the protocol. No change to protocol wording. - Due to change in local post code; the post code of ORION Clinical Services has been amended from SL1 3UE to SL1 3UA.

Interruption and early termination of the clinical trial

Not applicable.