Biotest
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Study 971 - EudraCT Number: 2008-001241-26

Synopsis

Name of Sponsor/Company: Biotest AG	
Title of study: A randomized, placebo-controlled, double-blind, dose escalation study to evaluate the efficacy, safety and tolerability of the study drug BT061 in patients with rheumatoid arthritis receiving concomitant methotrexate	
Study Number: 971	
Coordinating investigator: [redacted]	
Study center(s): Multicenter: Step 1 IV: Romania (10 centers), Hungary (5 centers), Bulgaria (4 centers) Step 2 SC: Russia (5 centers), Hungary (5 centers), Bulgaria (2 centers)	
Publication (reference): Not applicable	
Studied period (years): (date of first enrolment) 20-OCT-2008 (Step 1 IV) 02-FEB-2010 (Step 2 SC) (date of last completed) 18-SEP-2009 (Step 1 IV) 29-NOV-2010 (Step 2 SC)	**Clinical phase:** II
Objectives: To evaluate the efficacy, safety and tolerability of BT061 monoclonal antibody (mab) therapy in patients with rheumatoid arthritis (RA) receiving concomitant methotrexate (MTX).	
Methodology: Prospective, randomized, placebo-controlled, double-blind, parallel-group study; two independent study parts – Step 1 IV (3 treatment groups) and Step 2 SC (2 treatment groups).	
Number of patients (planned and analyzed): <u>Planned:</u> For Step 1 IV, a total of 70 patients were planned to be randomized into 3 groups in a ratio of 1:3:1, i.e., 14 patients each receiving either placebo or BT061 0.5 mg intravenous (IV) and 42 patients receiving BT061 2.0 mg IV. A planned interim analysis (results were not available to study personnel) on selected parameters was carried out after 40 patients. For Step 2 SC, a total of 40 patients were planned to be randomized into 2 groups in a ratio of 3:1, i.e., 30 patients receiving BT061 50 mg subcutaneous (SC) and 10 patients receiving placebo. Analogue to Step 1 IV an interim analysis was carried out when all patients (41) reached study Week 9. <u>Analyzed:</u> Step 1 IV: Screened: 143 patients Randomized: 73 patients; 67 females, 6 males (2 mg : 47, 0.5 mg: 13, placebo: 13) FAS/Safety: 73 patients (2 mg: 47, 0.5 mg: 13, placebo: 13) Per-protocol (PP): 60 patients; 54 females, 6 males (2 mg: 36, 0.5 mg: 12, placebo: 12) *Interim analysis on 40 randomized patients* Step 2 SC: Screened: 61 patients	

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Randomized: 42 patients (50 mg: 31, placebo: 11)
Full analysis set (FAS) / Safety set: 41 patients; 39 females, 2 males (50 mg: 30, placebo: 11)
PP set / Study completer set*: 33 / 31 patients (50 mg: 23 / 21, placebo: 10 / 10)
**All patients of the PP set who received complete course of study medication.*
Interim analysis of FAS / Safety population after completion of study Week 9

Diagnosis and main criteria for inclusion:
Male aged ≥ 18* - ≤ 75 years and female aged: ≥ 18 - ≤ 75 years with active RA (functional class II to III), body mass index (BMI) 18 to 30 kg/m^2 inclusive, and body weight 50 - 110 kg. Active RA defined as: ≥ 6 swollen joints on 66 joint count; ≥ 6 tender joints on 68 joint count; at least two of the following criteria: erythrocyte sedimentation rate (ESR) ≥ 28 mm/h, morning stiffness ≥ 45 min, and C-reactive protein (CRP) ≥ 20 mg/L.

**In Russian centers only males ≥ 50 years were included - as requested by the Russian regulatory authority- due to potential testicular safety concerns raised by the initial interpretation of nonclinical data in Rhesus monkey.*

In addition, patients had to have an inadequate previous response to at least one traditional disease modifying anti-rheumatic drug (DMARD), pre-enrolment stable MTX medication**, concomitant stable oral corticosteroids ≤ 10 mg (if any) and/or stable non-steroidal anti-inflammatory drugs (NSAIDs; if any), no previous CD4 mab or biological therapy, no concomitant DMARD except MTX or biological therapy, no serious local or systemic infection.

**By Amendment 7 (between Step 1 IV and Step 2 SC) the required stable dosing period was increased from 3 to 6 months and parenteral or oral MTX administration was changed to oral MTX administration only.

Test product, dose and mode of administration, batch number:
Investigational medicinal product (IMP): BT971 (active ingredient BT061 mab [CD4 mab])

Step 1 IV: The following were administered IV + oral or parenteral MTX

- 0.5 mg IV BT061 in 0.04 mL (n=14) / Biotest batch number: A061016
- 2.0 mg IV BT061 in 0.04 mL (n=42) / Biotest batch number: A061036

Mode: Study medication (0.04 mL) was diluted in 50 mL sodium chloride solution and infused over 2 hours IV. Administration was weekly for 8 weeks.

Step 2 SC: The following were administered SC + oral MTX

- 50 mg BT061 in 1.0 mL (n=30) / Biotest batch number: A061038

Each dose (1 mL) of BT601 SC 50 mg/mL was given undiluted once weekly as a single, SC, bolus injection in the anterior abdomen.

Duration of treatment: 8 weeks

Reference therapy, dose and mode of administration, batch number:
Step 1 IV: The following were administered IV + oral or parenteral MTX

- Placebo IV in 0.04 mL (n=14) / Biotest batch number: A015016

Mode: Study medication (0.04 mL) was diluted in 50 mL sodium chloride solution and infused over 2 hours IV. Administration was weekly for 8 weeks.
Step 2 SC: The following were administered SC + oral MTX

- Placebo in 1.0 mL (n=10) / Biotest batch number: A015018

Each dose (1 mL) of placebo (formulation buffer of BT061 mab) was given undiluted once weekly as a single, SC, bolus injection in the anterior abdomen.

Criteria for evaluation
Efficacy:
A composite clinical-response panel – the American College of Rheumatology (ACR) response criterion – assessing swollen and tender joint counts, acute phase response (i.e. ESR), patient's global assessment of disease activity and pain, physician's global assessment

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of disease activity, and Health Assessment Questionnaire (HAQ) – was used to assess efficacy.
Primary efficacy variable of this study was the ACR20 response after 8 weeks of treatment i.e. one week after conclusion of treatment (Week 9).

Secondary efficacy variables:

- ACR20 response at Weeks 6, 12, and 16
- ACR50 and ACR70 response at Weeks 6, 8 (Step 1 only), 9, 12, and 16
- Time course of ACR score components
- Time to ACR20, ACR50, and ACR70 response
- Duration of ACR20, ACR50, and ACR70 response (time from first occurrence of response to first occurrence of non-response)
- Disease Activity Score (DAS)28 response

Pharmacokinetics:

- Plasma concentration of BT061 mab

Safety:
Secondary Safety Variables:

- Treatment emergent adverse events (TEAEs)
- Premature withdrawals
- Physical examination
- Vital signs
- Electrocardiogram (ECG)
- Safety laboratory (hematology, blood chemistry, urine analysis)
- CRP
- Hormones levels in males (cortisol, FSH, LH, testosterone and ACTH)
- Lymphocyte subpopulations (CD19, CD3CD4, CD3CD8, CD4CD25FoxP3, CD45)
- Cytokine levels (IFN-γ, TNF-α, IL-2, IL-6, and TGF-β)
- Soluble CD4 (sCD4, Step 1 IV only)
- Anti-drug antibody (ADA) response
- HBV, HCV, HIV serology
- Epstein-Barr Virus (EBV) (serology and PCR)
- Diphtheria, tetanus
- Tuberculosis
- Auto-antibodies (ANA, anti-dsDNA, RF and anti-CCP) titers
- Testes size measurements for male patients (ultrasonography)

Statistical methods:
Apart from the primary efficacy analysis for Step 1 IV all analyses of variables were exploratory in nature using descriptive statistics.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:
Generally, if not stated otherwise, efficacy results are presented for the FAS.

Step 1 IV:
For the primary efficacy analysis, ACR20 response at Week 9, no relevant difference between the 3 treatment groups (0.5 mg, 2 mg and placebo) was detected. Also, in the secondary analyses, ACR20/50/70 and DAS28 over time, no clear benefits for the active treatment with

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0.5 or 2.0 mg compared to placebo were observed. Comparable results were observed for the PP analysis set.

Step 2 SC:
The primary efficacy analysis, ACR20 response at Week 9, revealed a higher ACR20 response for BT061 50 mg SC (33.3%) compared to placebo (18.2%), which is supported by secondary efficacy variables. At Week 9, ACR50 response was 23.3% versus 9.1% and ACR70 response 6.7% versus 0%. Treatment effects were more pronounced in the PP and study completer analysis sets. The ACR improvements were mainly driven by the single ACR components tender joints, swollen joints, physician's and patient's global assessment of disease activity, and patient's assessment of pain. DAS28 response supported the ACR response results.

For the 50 mg SC group first ACR20 and DAS28 responses (> 15% of patients) were observed after 2 weeks of treatment. The rate of responders increased during treatment. The response of the placebo group was always below the response of active treatment group over time.

STUDY DRUG CONCENTRATION AND IMMUNOGENECITY

Step 1 IV:
One week after dosing (first assessment), BT061 was not detected in any patient of the 0.5 mg group, even after repeated dosing. In 5 of 47 patients of the 2 mg group low levels of BT061 were detected in overall 6 samples during the study period; no BT061 was detected in the majority of samples (98.8%).
No ADAs were detected in any patients.

Step 2 SC:
6 hours after administration (first assessment; timing changed as compared to Step 1 IV), BT061 was detected at least once during the 8-week treatment in plasma in 10 of 30 patients following 50 mg BT061 SC and in 0 of 11 patients receiving placebo. No accumulation of BT061 after multiple dosing was observed.
ADAs with neutralizing activity were detected in one patient of the active treatment group (50 mg SC) 8 weeks after end of treatment at Week 16.

SAFETY RESULTS:
Safety data obtained from the IV and SC steps of the study generally demonstrated good tolerability and no serious safety concerns.

Step 1 IV:
Treatment emergent adverse events
Overall 122 TEAEs (according to Medical Dictionary for Regulatory Activities [MedDRA] coding process; 109 completed AE reporting forms) were reported in 40 of 73 (54.8%) patients in the safety population; thereof 26 of 47 (55.3 %) patients in the 2 mg IV group, 7 of 13 (53.8%) in the 0.5 mg IV group, and 7 of 13 (53.8%) patients in the placebo group. The majority of reported TEAEs (80.7%) were mild. One serious TEAE (pneumonia) of moderate intensity and assessed as not related occurred in the 2 mg IV group. By far most TEAEs – as coded by MedDRA - occurred in the MedDRA System Organ Class (SOC) Investigations (52 of 122 (42.6 %) TEAEs in 22 of 73 (30.1%) patients). Most commonly reported preferred terms within this SOC were 'T-lymphocyte count decreased' (7 TEAEs in 6 patients), and 'CD4 lymphocytes decreased' (5 TEAEs in 5 patients); none of these were reported for placebo treatment. However, no specific pattern of an effect of BT061 (as compared to placebo) on the course of CD4 lymphocytes (CD3CD4 counts) or other lymphocyte phenotypes was identified as the

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overall levels of CD4 lymphocytes were highly variable intra- and interindividually throughout all treatment groups including placebo. TEAEs led to treatment discontinuation in 5 patients of the 2 mg group and in no patients of the other two groups. 6 patients, all of the 2 mg group, were withdrawn from treatment. Thereof 3 patients withdrew due to TEAEs of low CD3CD4 (CD4 lymphocytes) count. Apart from TEAEs in the MedDRA SOC Infections and infestations the distribution of TEAEs across treatment groups was comparable. 5 of 47 patients of the 2 mg group, 3 of 13 patients of the 0.5 mg group, and 0 of 13 patients of the placebo group had uncomplicated unrelated self-limiting infections. Except of one moderate event all infectious TEAEs were mild.

Vital signs, physical examination, and ECG
No relevant findings during the study were observed by physical examination, vital signs, or ECG.

Testicular volume: In 4 patients treated with 2 mg IV pre- and post-dose data on testicular volume assessments over time is available; no effect of BT061 on testes size was identified.

Laboratory results
No relevant effects on any of the safety laboratory parameters including thyroid hormones, cytokines, infectious and immunological laboratory markers, autoantibodies (ANA, anti-dsDNA), and hypophyseal / testicular hormones (assessed in males only) were identified. No laboratory signs for an increased infection rate were observed (EBV, CMV, HCV, HBV, HIV, diphtheria, tetanus).

Step 2 SC:
Treatment emergent adverse events
Overall 56 TEAEs were reported in 22 of 41 (53.7%) patients; 19 of 30 (63.3%) patients in the 50 mg SC group and 3 of 11 (27.3%) patients in the placebo group. The majority of TEAEs were mild (50 mg 75.5%, placebo 85.7%) or moderate in severity (50 mg 24.5%, placebo 14.3%); none was severe. Most of these TEAEs were assessed as possibly related to the study medication (50 mg 73.5%, placebo 85.7%). No SAEs occurred. The most commonly reported TEAEs were 'lymphocyte count' (23 TEAEs in 15 patients) followed by 'white blood cell count' (8 TEAEs in 8 patients) occurring more frequently with the 50 mg treatment group. Decreased CD3CD4 counts (CD4 lymphocytes) were recorded as TEAEs in 11 of 30 (36.7%) patients of the 50 mg group and in 2 of 11 (18.2%) of the placebo group. 9 patients were withdrawn prematurely; 7 due to TEAEs of low CD3CD4 or CD3 count (50 mg: 6 of 30, placebo: 1 of 11). However, as with Step 1 IV no specific pattern of an effect of BT061 (as compared to placebo) on the course of CD3CD4 counts or other lymphocyte phenotype counts was identified as the overall levels of CD3CD4 counts were highly variable intra- and interindividually including the placebo group.
There were no injection site reactions, no neoplasms, and no immune system disorders. No infection but one TEAE of oral herpes in the 50 mg group was observed.

Vital signs, physical examination, and ECG
No relevant findings during the study were observed by physical examination, vital signs, or ECG.
Testicular volume: In 1 patient treated with 50 mg SC pre- and post-dose data on testicular volume assessments over time is available; no effect of BT061 on testes size was identified.

Laboratory results

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No relevant effects on laboratory variables comprising hematology, clinical chemistry including CRP, thyroid hormones, urinary variables, autoantibodies, and hypophyseal / testicular hormones (2 males only) hinting towards a potential BT061 effect were identified during the study. No laboratory signs for an increased infection rate were observed. **CONCLUSION:** **Step 1 IV:** No relevant differences with regards to efficacy and safety between the 3 IV treatment groups receiving 2 mg, 0.5 mg, and placebo were detected. Few TEAEs attributed to the SOC Infections and infestations were reported in the active treatment groups but were all found to be mild (except of one moderate event) and self-limiting. Overall the treatment of 0.5 mg and 2 mg BT061 was considered to be well-tolerated and safe. **Step 2 SC:** 50 mg SC treatment showed higher proportions of ACR20, ACR50, ACR70, and DAS28 responses compared to placebo. TEAEs occurred in a higher number of patients in the 50 mg group and also the TEAE rate per patient was higher in the active treatment group, but all reported TEAEs were of mild to moderate severity and self-limiting. Overall, treatment responses of 50 mg BT061 SC were higher than placebo SC and treatment was considered to be well-tolerated and safe. **Date of Final Report (Version 1.1):** 28-FEB-2014

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

Multicenters in Europe:
Step 1 IV: Romania (10 centers), Hungary (5 centers), Bulgaria (4 centers) enrolled 73 subjects.
Step 2 SC: Russia (5 centers), Hungary (5 centers), Bulgaria (2 centers) enrolled 42 subjects.

Overview of substantial protocol amendments

Amend-ment No.	Date	Sections concerned	Rationale
1	17-Jul-2008	4, 5, 11.5, 12.2, 13, 15.1.6, 15.1.7, 15.1.8, 15.1.9, 15.1.10, 15.1.20, 15.2, 16.2.4, 19, 20.7	- introduction the measurement Rheumatoid Arthritis (RF) as an additional laboratory parameter for auto-antibody - correction of a minimum safety level in lymphocyte counts for criteria for abruption of study treatment - correction of an error in the handling instruction for sample treatment prior to lymphocyte phenotyping - modification of lymphocyte subtyping - introducing new reference and list of laboratories and other services in Appendix 20.7
2	22-Aug-2008	10.1.4, 10.1.5,	- more clearly defining the dose escalation criteria between Step 1 (70 patients receiving 0.5 mg of BT061, 2.0 mg of BT061 or placebo in parallel) and Step 2 (40 patients receiving 10.0 mg of BT061 or placebo in parallel) - implementing a DSMB for the Study to decide independently about the possible dose escalation from Step 1 to Step 2
3	18-Nov-2008	Signature page, 4, 5, 6, 7, 8, 10.1.1, 10.1.3, 10.2, 11.1, 11.2, 12.2, 13, 14.1.1, 14.1.2, 15.1.3, 15.1.10, 16.1	- introduction of a new Coordinating Investigator - introduction of the measurement of anti-Cyclic Citrullinated Peptide antibodies in serum sample as an additional laboratory parameter - dosage correction for BT061 in administration Step 2: the overall dosage is corrected from 10 mg to 12.5 mg BT061 - withdrawal of the trial from Germany - clearance of clerical errors in the clinical study protocol.
4	11-FEB-2009	12.2, 13, 15.1, 15.1.21, 15.2	- detailed instructions for ultrasound diagnostics - defined rules for the used equipment, the qualification of the operator, and the measuring procedure of ultrasonography - introducing the principles used to achieve a maximum of reliability and validity comprise
5	31-JUL-2009	5, 12.2, 13, 15.1, 16.2.4, 17.2, 17.3, 20.1	- introducing an additional central laboratory to provide services for the study sites in Hungary and for some sites in the Western part of Romania due to logistic reasons - the center list was moved from the protocol text to an appendix. - Introducing an additional laboratory parameter C-reactive protein (CRP) - study duration was prolonged to April 2010.
6	13-AUG-2009	3.1, 4, 7, 8, 9.1.1, 9.2, 10.1.1, 10.1.2, 10.1.3, 10.2, 11.1, 14.1.1,	- revisions of the dosage and route of administration for BT061 for Step 2 -

Amend-ment No.	Date	Sections concerned	Rationale
		14.1.2, 16.1, 16.2.2	
7	26-NOV-2009	5, 8, 10.1.1, 11.2, 12, 13, 14.1.2, 15.1.5, 15.1.8, 16.1, 16.2, 16.2.2, 16.2.3, 17.2,	- introducing additional laboratory parameters IL-2 and IFN-γ as additional diagnostic indicators on the status of ongoing autoimmune reactions. - change of timing of determination of BT061 plasma levels - clear definition of the route of administration of Methotrexate (MTX) and duration of MTX-pretreatment-period. Revision of the dosage and route of administration for concomitant MTX for Step 2 - tightened conditions for rescue therapy for Step II of this study: use of corticosteroids and/or alternative NSAIDs would no longer be allowed. Instead, Paracetamol would be allowed as „rescue" medication for a defined period (not more than 1 gram per day, no longer than 3 consecutive days, not more than 10 days per month) in order to treat unacceptable pain conditions. - the statistical part was changed into a "proof of concept" evaluation which should investigate a beneficiary trend of a treatment with BT061. Therefore, the character of the second step was purely exploratory. - no direct data entry in CRF was allowed (exceptions: Health Assessment Questionnaire and Visual Analogue Scales). - other corrections
8	16-DEC-2009	Cover page, protocol synopsis, 11.2, 20.1,	- exclusion of males younger than 50 - administrative changes: as Step II was planned to include additional centers from Russian Federation, some administrative changes like an adapted list of the personnel was to be introduced.
9	28-JUL-2010	16.2.6,	- introducing an additional interim analysis regarding data on efficacy and immunological safety parameters for Step 2 of the protocol
10	05-APR-2011	5, 12.2, 13, 15.1.7, 15.2, 16.2.4, 17.2,	- to omit the measurement of soluble CD4 (sCD4).

Interruption and early termination of the clinical trial

Not applicable.