CLINICAL STUDY REPORT

A 24-week phase IIb, randomized, double-blind, placebo-controlled, multicenter study to investigate the efficacy and safety of tregalizumab (BT061) in combination with methotrexate in the treatment of subjects with active rheumatoid arthritis who have had an inadequate response to methotrexate alone, followed by a 24-week extension phase: T cell REgulating Arthritis Trial 2b (TREAT 2b)

EudraCT / IND Number:	2013 000114 38
Study Number:	986
Clinical Phase:	IIb
Investigational Medicinal Product:	Tregalizumab
Indication Studied:	Rheumatoid arthritis
Date of Enrolment of First Subject:	28-OCT-2013
Date of Study Termination:	31-JUL-2015 (Extension Phase)
Date of Completion of Last Subject:	31-JUL-2015

Principal/Coordinating Investigator(s):	Ronald F van Vollenhoven, MD, PhD Academic Medical Center, Dept of Clinical Immunology & Rheumatology EULAR&FOCIS Center of Excellence Huispost F4-105, PO Box 22660, 1100 DD Amsterdam, The Netherlands Secretary: r.i.vanaalst@amc.uva.nl tel: +31 20 56 67 765
Sponsor:	Biotest AG Department of Corporate Clinical Research&Development Landsteinerstr. 5 63303 Dreieich Germany
Head of Corporate Clinical Research&Development:	Andrea Wartenberg-Demand, MD, PhD Telephone: +49 6103 801 497 Fax: +49 6103 801 341 Biotest AG (address see before)
Medical Manager Corporate Clinical Research&Development:	Xuefei Zhou, MBChB, PhD Telephone: +49 6103 801 1229 Fax: +49 6103 801 341 Biotest AG (address see before)

A 24-week phase IIb, randomized, double-blind, placebo-controlled, multicenter study to investigate the efficacy and safety of tregalizumab (BT061) in combination with methotrexate in the treatment of subjects with active rheumatoid arthritis who have had an inadequate response to methotrexate alone, followed by a 24-week extension phase:
T cell REgulating Arthritis Trial 2b (TREAT 2b)

SIGNATURES

By signing this report we certify that it provides a true and accurate record of the conduct of this study and its results.

17 May 2016
Date

Head of Corporate Clinical Research&Development
Andrea Wartenberg Demand, MD, PhD
Biotest AG

13 MAY 2016
Date

Statistician
Vanessa Steele, MSc
Quintiles UK Ltd

23 MAY 2016
Date

Coordinating Investigator
Ronald F van Vollenhoven, MD, PhD
Academic Medical Center, Dept of Clinical Immunology & Rheumatology EULAR&FOCIS Center of Excellence

2. SYNOPSIS

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use only)
Name of Finished Product: Tregalizumab		
Name of Active Substance: Tregalizumab		

Title of study: A 24 week phase IIb, randomized, double-blind, placebo-controlled, multicenter study to investigate the efficacy and safety of tregalizumab (BT061) in combination with methotrexate in the treatment of subjects with active rheumatoid arthritis who have had an inadequate response to methotrexate alone, followed by a 24-week extension phase: T cell REgulating Arthritis Trial 2b (TREAT 2b)

Study Number: 986

Investigators: 79 Investigators enrolled subjects in the study.

Study centers: A total of 84 study sites were opened and 79 centers in 14 countries enrolled subjects into the study: Bulgaria, Canada, Czech Republic, Estonia, Germany, Hungary, Lithuania, Mexico, Poland, Russia Federation, Serbia, Slovakia, Ukraine and the United States.

Publication (reference):

Studied period (years):	**Clinical phase:** IIb
(date of first enrolment) 28-OCT-2013	
(date of early terminated) 31-JUL-2015 (Extension Phase)	

Objectives: The main objectives of this study were to investigate the efficacy and safety of three different weekly subcutaneous (SC) BT061 doses administered for up to 48 weeks in subjects with active rheumatoid arthritis (RA) that are incompletely controlled on methotrexate (MTX) (MTX-inadequate responders [IR]).

Further objectives included the assessment of the pharmacokinetics (PK) of BT061 and the pharmacodynamic assessment of cellular cluster of differentiation 4 (CD4) modulation and CD4 receptor occupancy, as well as optional analytical variables such as biomarkers or interleukin (IL)-22.

Methodology: This was a phase IIb, double-blind, randomized, placebo-controlled, multicenter, dose-ranging study to evaluate the efficacy and safety of three SC doses of BT061 in combination with MTX in subjects who had active RA and had an inadequate response to MTX alone (i.e., MTX-IR).

The study comprised a screening period (Days -28 to -7), a 24-week placebo-controlled Main Phase, an active treatment only 24-week Extension Phase, and a 4-week follow-up period.

The protocol planned the recruitment of 304 subjects into the study and by the end of the recruitment phase 321 subjects were randomized in a 1:1:1:1 ratio to one of the four treatment groups. Subjects with prior limited exposure to an anti-tumor necrosis factor (TNF) agent were balanced across treatment groups, and their number limited to no more than 20% of the total subject population. Subjects were also balanced with regard to the duration of MTX treatment (3-6 months, >6 months) and CRP level (≤ULN, >ULN).

All subjects were to have received MTX for ≥12 weeks, with an unchanged mode of administration and stable MTX dose for ≥8 weeks prior to baseline. In addition to this stable

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use only)
Name of Finished Product: Tregalizumab		
Name of Active Substance: Tregalizumab		

dose of MTX, subjects received blinded study treatment as follows:

- BT061 25 mg SC, once weekly (n=83)
- BT061 100 mg SC, once weekly (n=80)
- BT061 200 mg SC, once weekly (n=78)
- Placebo SC, once weekly (n=80)

At Week 12, all subjects who had a minimum improvement of at least 20% (from baseline) in their tender joint count (TJC) and swollen joint count (SJC) continued on the same treatment. Subjects who had not demonstrated an improvement of at least 20% of TJC and SJC were assessed as non-responders. Non-responders who received placebo were randomized to an active treatment dose in a blinded manner. Non-responders who received active treatment were rolled up to the next highest dose in a blinded manner, apart from those already on the highest dose. These subjects remained on the highest dose.

First 12 weeks of treatment (Week 0 to 11):		**Second 12 weeks of treatment (Week 12 to 23) for non-responders at Week 12:**
BT061 25 mg SC, once weekly	→	BT061 100 mg SC, once weekly
BT061 100 mg SC, once weekly	→	BT061 200 mg SC, once weekly
BT061 200 mg SC, once weekly	→	BT061 200 mg SC, once weekly
Placebo SC, once weekly	→	Randomized BT061 dose group (25, 100 or 200 mg SC once weekly

For subjects at sites in the United States (US) only: at Week 16, subjects who had not demonstrated an improvement of at least 20% of TJC and SJC were assessed as non-responders and were withdrawn from the study.

At Week 24, subjects who completed 24 weeks of treatment and fulfilled the Extension Phase inclusion criteria and did not meet any Extension Phase exclusion criteria entered an active treatment only 24-week Extension Phase of the study. Subjects on active treatment during the Main Phase of the study remained on the same dose of BT061; subjects who received placebo were randomized in a blinded manner to one of the three BT061 dose groups. The treatment blind was not broken for subjects entering the Extension Phase until after the database lock for the placebo-controlled Main Phase Week 24 analysis.

At each study visit during which subjects received investigational medicinal product (IMP), this was administered at the study site. Sufficient IMP was supplied at each visit for subjects to self-administer their weekly dose of IMP until the next study visit.

All subjects had a follow-up visit 4 weeks after the date of their last visit (Week 48) or early termination (ET) visit.

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use only)
Name of Finished Product: Tregalizumab	Volume:	
Name of Active Substance: Tregalizumab	Page:	

Number of subjects (planned and analyzed):

A total of 304 subjects were planned to be randomized (76 subjects per group). In total, 321 subjects were randomized (83, 80, and 78 in the BT061 25 mg, 100 mg and 200 mg groups, respectively and 80 in the placebo group). A total of 321 subjects were included in the Safety set (SS), 313 were included in the Full analysis set (FAS), and 183 subjects were included in the Per-protocol set (PPS).

Diagnosis and main criteria for inclusion:

Adult subjects of both genders with active RA that was incompletely controlled on MTX were eligible for inclusion in this clinical study. For inclusion in the study, subjects had RA with functional class I-III for ≥6 months.

The main inclusion criteria were:

- Subject demonstrated active RA according to the 1987 American College of Rheumatology (ACR) or 2010 ACR/European League against Rheumatism (EULAR) classification criteria for RA with functional class I–III for ≥6 months.
- Subject received oral or parenteral MTX treatment for ≥12 weeks (overall), with an unchanged mode of application and stable MTX dose of ≥15 mg per week (or ≥12.5 mg per week in case of MTX intolerance), but no more than the highest locally approved dose for RA, for ≥8 weeks prior to baseline. The dose of MTX was expected to remain stable throughout the study and could be adjusted only for safety reasons. If applicable, the dose of folic acid was to be unchanged for ≥8 weeks prior to baseline.
- Subject met the following two criteria at both screening and baseline:
    - At least 6 swollen joints at 28-joint assessment.
    - At least 6 tender joints at 28-joint assessment.
- Subject had a CD4 cell count of >400/µL at screening.
- Subject had an erythrocyte sedimentation rate (ESR) or CRP above the upper limit of normal (ULN) at screening. These tests could be repeated once during the screening period at the discretion of the investigator.
- Subject was receiving treatment with non-steroidal anti-inflammatory drugs (NSAIDs), stable for at least 2 weeks prior to baseline and during the study, if applicable
- Subject was ≥18 and ≤75 years of age, was willing and able to provide written informed consent, and was willing and able to self-administer SC injections or had a qualified person available to administer SC injections.

The main exclusion criteria were:

- Subject had previous exposure to any systemic biologic therapy (e.g., etanercept, adalimumab, rituximab, abatacept, tocilizumab), to Janus kinase (JAK) or spleen tyrosine kinase (SYK) inhibitors, or to BT061. Previous treatment with an anti-TNF agent was allowed only, if all of the following criteria applied:
    - treatment was stopped for reasons other than lack of efficacy or adverse

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use only)
Name of Finished Product: Tregalizumab		
Name of Active Substance: Tregalizumab		

events (AEs)

- o treatment was stopped at least 12 weeks or five half-lives of the compound prior to baseline (whichever was longer), and
- o the treatment period did not exceed 6 weeks.

- Subject received treatment with conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs) apart from MTX in the 12 weeks prior to baseline, and for DMARD leflunomide in the 24 weeks prior to baseline (except where specific leflunomide wash out procedures were completed, following applicable guidelines).
- Subject had an acute or clinically symptomatic Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infection.
- Subject had a serious local (e.g., abscess) or systemic (e.g., pneumonia, septicemia) infection or recurrent chronic infections in the 6 weeks prior to the screening visit (Visit V1) or during the screening period.
- Subjects with herpes labialis (of the mouth) were excluded if the disease was active at screening or during the screening phase. Subjects with onychomycosis were not excluded.
- Subject had any infection requiring antibiotic or antiviral therapy by any route of administration in the 2 weeks prior to baseline.
- Subject currently used or planned to use anti-retroviral therapy at any time during the study.

Test product, dose and mode of administration, batch number:
BT061, 25 mg, 100 mg, and 200 mg, administered via two SC injections once weekly.

Batch numbers: 25 mg: (12.5 mg/ml) B061012 and B061013; 100 mg: (50 mg/ml) B061032, (25 mg/ml) B061022 and B061034, (75 mg/ml) B061042 ; 200 mg: (100 mg/ml) B061052B, B061062B, B061023, B061033, B061043

Duration of treatment:
The duration of treatment for the Main Phase of the study was 24 weeks. This was followed by an additional 24-week active treatment Extension Phase.

Reference therapy, dose and mode of administration, batch number:
Placebo to BT061 administered via two SC injections once weekly.

Batch number: B015012

Criteria for evaluation

Efficacy:
The primary efficacy variable is the proportion of subjects with an ACR20 response after 12 weeks of double blinded treatment with the study medication based on observed cases in

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use only)
Name of Finished Product: Tregalizumab		
Name of Active Substance: Tregalizumab		

the FAS. The ACR is a composite measurement tool reflecting the many aspects of RA and combining the different single components into one index. This composite measure is used to assess current disease activity, or change in disease activity.
The secondary efficacy variables are:

- Proportion of subjects with an ACR20 response at Week 24
- Proportion of subjects with an ACR50 response at Week 12 and at Week 24
- Proportion of subjects with an ACR70 response at Week 12 and at Week 24
- Proportion of subjects with a Disease Activity Score in 28 Joints (DAS28) <2.6 at Week 12 and at Week 24
- Proportion of subjects with low disease activity (DAS28 <3.2, Simplified Disease Activity Index (SDAI) ≤11, Clinical Disease Activity Index (CDAI) ≤10) at Week 12 and at Week 24
- ACRn score by visit
- DAS28 by visit
- DAS28 EULAR response by visit
- ACR and DAS28 score components by visit
    - TJC (68 joint count, including 28 joint count)
    - SJC (66 joint count, including 28 joint count)
    - CRP
    - ESR
    - Subject's Assessment of Pain (Visual Analog Scale [VAS])
    - Subject's Global Assessment of Disease Activity (VAS)
    - Physician Global Assessment of Disease Activity (VAS)
    - Health Assessment Questionnaire - Disability Index (HAQ DI)
- Morning stiffness, SDAI, CDAI Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT Fatigue), Short-form (36) Health Survey (SF 36), and Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI-RA) score components by visit
- Hybrid ACR score
- Proportion of subjects achieving critical difference defining valid criterion for clinical response as assessed by the DAS28 (DAS28DCRIT) at Week 12 and at Week 24
- Proportion of subjects achieving minimal clinically important difference (MCID) (Pain, HAQ DI, FACIT Fatigue) at Week 12 and at Week 24
- Proportion of subjects in remission according to the 2011 ACR/EULAR criteria at Week 12 and at Week 24.

Safety:
Safety and tolerability were assessed by adverse events (AEs), physical examination and vital signs, electrocardiogram, evaluation of chest X-ray, laboratory parameters, human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) status, Epstein Barr Virus (EBV) and cytomegalovirus (CMV) status, tetanus, tuberculosis (TB), and diphtheria status, CD4 (CD3CD4) Lymphocyte Count, auto-antibodies (anti-nuclear antibody [ANA], anti-double-strand DNA, Rheumatoid Factor [RF] and anti-citrullinated peptide antibody [ACPA]), and assessment of immunogenicity (specific anti-BT061 antibodies).

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use only)
Name of Finished Product: Tregalizumab	Volume:	
Name of Active Substance: Tregalizumab	Page:	

Pharmacokinetics and Pharmacodynamics :

Blood samples for the determination of BT061 plasma levels were taken prior to the administration of study drug at baseline, and at Week (W) 2/Visit (V) 4, W4/V5, W8/V7, W12/V8, W24/V10, W3/V122, W48 (end of Treatment [EoT]/ early termination ET), and at follow-up (post-EoT/post-ET).

Blood samples for the assessment of the pharmacodynamic endpoints (cellular CD4 expression and CD4 receptor occupancy, were collected at baseline, and at screening, Week (W) 2/Visit (V) 4, W4/V5, W8/V7, W12/V8, W24/V10, W3/V122, W48 (end of Treatment [EoT]/ early termination ET), and at follow-up (post-EoT/post-ET).

Statistical methods:

Summaries of the data were produced using graphs and standard summary statistics. Baseline assessment for each parameter was the last assessment before first intake of IMP.

Discrete variables were summarized using count and percentages and were compared between the active and placebo groups using a stratified Chi-square test (Cochran Mantel-Haenszel [CMH]) with stratification for C-reactive protein (CRP) ≤upper limit of normal (ULN) or >ULN. If removal of the stratification factor still resulted in expected counts less than 5, in ≥25% of the cells then Fisher's exact test was used. This was done for observed cases and last observation carried forward (LOCF) and non-responder imputation (NRI) imputed values.

Continuous efficacy variables were summarized by summary descriptive statistics (number of subjects, mean, 95% confidence interval, standard deviation, first quartile, median, third quartile, minimum, maximum) at Week 12. Change from baseline at Week 12 and 24 in the continuous variables was compared between an active and placebo group using an analysis of covariance (ANCOVA) method with treatment and the stratification factor CRP level (≤ULN, >ULN) and the baseline value as a covariate. This was done for both observed and last observation carried forward (LOCF) imputed values.

No adjustments were made for multiple testing.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The Week 12 data showed that the proportions of subjects achieving an ACR20 response at Week 12 were only numerically, but not statistically significantly, greater in the BT061 groups compared with placebo. Therefore, the study failed to achieve the primary endpoint and did not demonstrate any statistically significant reductions in the signs and symptoms of RA, in comparison with placebo, for any of the BT061 doses when added to stable doses of MTX.

- The percentage of subjects achieving an ACR20 response at Week 12 was higher in the BT061 25 mg (42.3%) 100 mg (47.0%) and 200 mg groups (44.3%) than in the placebo group (35.2%). The results do not suggest any evidence of a dose response relationship.

- Compared with subjects receiving placebo, the difference in the proportions (CI) of

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use only)
Name of Finished Product: Tregalizumab	Volume:	
Name of Active Substance: Tregalizumab	Page:	

subjects with an ACR20 response at Week 12 was 1.20 (0.79, 1.82) for subjects receiving BT061 25 mg, 1.33 (0.89, 2.00) for subjects receiving BT061 100 mg and 1.26 (0.83, 1.90) for subjects receiving BT061 200 mg. None of these differences were statistically significant.

The Week 24 and Week 48 data for the following secondary efficacy variables have been analyzed according to the treatment groups that subjects were originally randomized to. Hence comparisons with placebo are only meaningful for time points up to Week 12. At Week 12, placebo non-responders were randomly assigned to an active BT061 treatment arm. Whereas non-responders on BT061 25 mg and 100 mg treatment groups were rolled over to the next higher dose of BT061. The actual treatments compositions for each treatment arm are presented in the table below:

		Placebo	**BT061 25 mg**	**BT061 100 mg**	**BT061 200 mg**	**Total**
		N	N	N	N	N
Main Phase 1	Placebo	80	0	0	0	80
	BT061 25 mg	0	83	0	0	83
	BT061 100 mg	0	0	80	0	80
	BT061 200 mg	0	0	0	78	78
	Total	80	83	80	78	321
Main Phase 2	Placebo	44	0	0	0	44
	BT061 25 mg	11	53	0	0	64
	BT061 100 mg	8	18	49	0	75
	BT061 200 mg	9	0	20	69	98
	Total	72	71	69	69	281
Extension Phase	BT061 25 mg	17	37	0	0	54
	BT061 100 mg	14	8	34	0	56
	BT061 200 mg	21	0	8	39	68
	Total	52	45	42	39	178

Source: tnum_phase.sas (used dataset: ADDA.SAS7BDAT)

- Compared to subjects randomized to placebo at Week 0, no statistically significant efficacy advantages were noted for the secondary endpoints in any treatment group:
    - All BT061 treatment groups showed a numerically higher ACR20 response rate (proportion of subjects) than placebo at Week 24. The response rates were between 55.4% and 59% with BT061 and 53.8% with placebo. After Week 24 all subjects receiving placebo have been rolled over to active treatment, therefore there was no placebo control arm in the Extension Phase (Week 24 to Week 48). Compared to the data of Week 24, the ACR20 response with BT061

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use only)
Name of Finished Product: Tregalizumab	Volume:	
Name of Active Substance: Tregalizumab	Page:	

increased to 66.7% with BT061 25 mg, 73.1% with BT061 100 mg and 81.0% with 200 mg at Week 48.

- The proportion of ACR50 responders at Week 12 was 12.7% with BT061 25 mg, 9.1% at 100 mg and 12.9% at 200 mg, compared with 9.9% in the placebo group. At Week 24 the proportion of ACR50 responders was between 19.6% and 21.3% in the BT061 groups compared to 20% in subjects randomized to placebo at Week 0. At Week 48 the proportion of ACR50 responders increased considerably to 52.4% in BT061 200 mg and also increased slightly to 30% with BT061 25 mg and 34.6% at 100 mg.

- The proportion of ACR70 responders at Week 12 was 2.8% with BT061 25 mg, 1.5% at 100 mg and 4.3% at 200 mg, compared with 1.4% in the placebo group. At Week 24 the proportion of ACR70 responders varied between 1.8% and 9.8% in the BT061 groups compared to 3.1% in subjects randomized to placebo at Week 0. At Week 48 the proportion of ACR70 responders in the BT061 200 mg group increased considerably to 23.8%, while the proportion in the BT061 25 mg and 100 mg groups remained stable with 3.3% and 7.7%.

- BT061 25 mg, 100 mg and 200 mg treatment groups were associated with generally similar improvements in other efficacy measures at Weeks 12, 24 and 48, including DAS28, EULAR good/moderate response, swollen and tender joint counts, CDAI and SDAI, FACIT and low disease activity and remission rates. However, comparable improvements were seen with placebo at Week 12 and 24.

- Mean ESR levels, subject's assessment of pain and disease activity and physician's global assessment of disease activity were slightly reduced in the BT061 treatment and placebo groups at Weeks 12 and 24. The reduction remained stable until Week 48.

- No consistent or clinically meaningful changes in SF-36 quality of life scales or other subject reported outcomes were demonstrated in the 48 week period covered by this study.

In general the improvements in all parameters seen at Week 24 were maintained until the end of the Extension Phase in each of the randomized treatment groups and some of them (ACR 50, ACR 70) increased considerably in the BT061 200 mg group at Week 48.

The Extension Phase of the study was terminated early on the 31 July 2015 due to lack of clinical efficacy.

PHARMOCOKINETICS AND PHARMACODYNAMICS RESULTS:

Pharmacokinetic data during the treatment period corresponded to trough levels measured at planned visits 7 days after last dosing. As expected, data were highly variable between

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use only)
Name of Finished Product: Tregalizumab	Volume:	
Name of Active Substance: Tregalizumab	Page:	

individuals within the same dose group. Plasma BT061 levels were mostly undetectable for the 25 mg dose group, and 100 mg dose group. Median plasma levels in the 200 mg dose group also showed a high degree of variability, ranging from 60.35 to 919.5 ng/mL across visits. At follow-up, plasma BT061 levels were generally undetectable, even in the 200 mg group

Pharmacodynamic response, represented by CD4 cell surface expression was consistent with findings in previous studies. The results showed a dose-dependent biological effect of BT061.

- Compared with placebo a noticeable modulation of CD4 expression on T cells occurred with all three doses of BT061.
- The reduced level of CD4 expression measured between Week 2 and Week 12 was relatively constant suggesting, an expected, rapid effect of BT061 without remarkable accumulation (increase of effect) after multiple dosing. The degree of CD4 expression per dose group remained in the same range between Week 12, 24 and 48.
- A dose-dependent modulation of CD4 expression to 80.24% of baseline level after treatment with 25 mg, 66.32% with BT061 100 mg and 44.60% with BT061 200 mg was observed, compared with approximately 100% in the placebo group (at Week 12).
- No remarkable differences were observed when stratifying subjects according to their clinical response suggesting a probable dissociation between this biological effect and the clinical outcome.
- Although a clear dose-biomarker response was apparent based on mean values, notable between-subject variability was observed for these variables.
- At a cellular level, the CD4 counts in blood fluctuate around the value measured at Baseline. On average, highest change was seen in the 200 mg dose group with a reduction of 22.5% at Week 12. Overall, changes and shift below the threshold of 400 cells/µL were limited, but nevertheless showed a trend towards increased incidence at the 200 mg dose.

SAFETY RESULTS:

BT061 injections were well tolerated in this study. Most of the TEAEs were mild to moderate in intensity with only a few subjects (3.9%) experiencing severe TEAEs.

During the Main Phase of the study, 129/241 subjects (53.5%) who only received active BT061 (and no placebo) reported at least one TEAE and the incidence was similar in subjects initially randomized to placebo (46.3%). The incidence of TEAEs during the Extension Phase was 39.3% (70/178 subjects). There was no evidence to suggest that the incidence of TEAEs increased with increasing dose of BT061.

Over the study as a whole (Main and Extension Phases combined) 169/305 subjects (55.4%) who received active BT061 experienced at least one TEAE with no marked differences in

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use only)
Name of Finished Product: Tregalizumab		
Name of Active Substance: Tregalizumab		

incidence between the three doses of BT061. The overall incidence of TEAEs assessed as related to BT061 was 21.0%. The reporting rate was slightly higher in subjects starting treatment with BT061 200 mg (45.1 events per 100 subject-years) than in those starting treatment with BT061 25 mg or 100 mg (34.5 and 30.4 events per 100 subject-years, respectively).

The TEAEs that occurred during the Main Phase of the study were predominantly cases of pyrexia, upper respiratory tract infection, injection site bruising and nausea (Main Phase 1) or AST increased (Main Phase 2). These events occurred with a similar incidence in the placebo and BT061 groups.

Mild to moderate, treatment-related skin and subcutaneous tissue disorders were reported with a very low incidence (3.6%) under active BT061 treatment.

The incidence of treatment-related TEAEs during the active BT061 treatment period as a whole was approximately 20%; most frequently reported were CD4 lymphocytes decreased (1.6% all BT061 groups) and nasopharyngitis (1.3%).

Overall, the incidence of treatment emergent SAEs was low (6.3 events per 100 subject-years) under active treatment with BT061 during the Main and Extension Phases combined. The reporting rate was slightly higher with BT061 200 mg (12.1 events per 100 subject-years) than with BT061 25 mg or 100 mg (4.9 and 1.8 events per 100 subject-years, respectively).

In total, twelve subjects reported 17 SAEs during the Main and Extension Phases combined (one subject randomized to placebo group, three randomized to BT061 25 mg, one randomized to BT061 100 mg and seven randomized to BT061 200 mg). Nine subjects reported 13 SAEs during the Main Phase and three subjects reported four SAEs during the Extension Phase of the study.

Only two subjects reported SAEs that were assessed by the investigator as related to study treatment. In both cases the SAEs (generalized tonic/clonic seizures and lichen planus) were reported during Main Phase 2 in subjects treated with BT061 200 mg.

There were three fatal SAEs reported, one in each BT061 treatment group. None of the deaths was assessed as related to study treatment.

The reporting rate of TEAEs leading to discontinuation of BT061 during the study as a whole was 16.1 events per 100 subject-years. The reporting rate was slightly higher with BT061 200 mg (20.8 events per 100 subject-years) than with BT061 25 mg or 100 mg (13.2 and 14.3 events per 100 subject-years, respectively.

A total of 25 subjects were withdrawn from the study as a result of TEAEs, SAEs and/or AESIs during the Main Phase 1 and 2. In 12 of the 25 subjects the events leading to withdrawal were assessed as related to treatment with BT061. These events included two cases each of herpes zoster, ALT and/or AST increased, CD4 counts decreased and single cases of CMV positive, upper respiratory tract infection, genital herpes, spinal pain, tonic/clonic generalized

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use only)
Name of Finished Product: Tregalizumab		
Name of Active Substance: Tregalizumab		

seizures and lichen planus.

An additional six subjects discontinued the Extension Phase of the study due to nine TEAEs. Six of the nine TEAEs resulting in withdrawal from the Extension Phase of the study were assessed as being related to treatment with BT061 (CD4 lymphocytes decreased [three cases], worsening acne, syncope and allergic dermatitis [each one case]).

There was no evidence of an increased incidence of AESIs associated with Infections, Injection Site Reactions, Viral Reactivations, Malignancy or Cardiac Events relative to that seen with placebo. No cases of tuberculosis or other opportunistic infection occurred during the study and two subjects with serious infections required intravenous antibiotics for infections classified as AESIs. Over the study as a whole the reporting rate for Investigations was higher with BT061 200 mg (32.9 events per 100 subject-years) than with BT061 25 mg or 100 mg (18.1 and 19.7 events per 100 subject-years, respectively).

None of the subjects with abnormal EBV and CMV serology results, at least once throughout the whole study, had symptoms suggestive of clinical infection (e.g. enlarged lymph nodes, high fever, fatigue or other flu-like symptoms). There was no evidence of an increased risk of viral infection at the doses of BT061 administered in this study.

There were no clinically significant or treatment-related changes in hematology, clinical biochemistry, coagulation factors or urinalysis findings during the study. None of the mean changes from baseline were considered to be clinically relevant.

There was no clinically significant reduction in mean CD4 T cells counts after BT061 treatment. Subjects with decreased CD4 lymphocytes were withdrawn from study treatment according to the protocol.

There were no clinically significant or treatment-related changes in vital signs and ECG parameters during the study.

CONCLUSIONS:

The study did not demonstrate statistically significant differences in any of the efficacy parameters between BT061 (25 mg, 100 mg or 200 mg) and placebo when administered in combination with methotrexate for up to 24 weeks in subjects with active RA unresponsive to MTX. While the proportion of subjects with an ACR20 response at Week 12 was only numerically, but not statistically significantly, greater in the subjects receiving BT061 (25 mg, 100 mg or 200 mg) than in those receiving placebo, the primary efficacy endpoint, the ACR20 response at Week 12, was therefore not achieved. All BT061 treatment groups showed numerically greater ACR20 response (proportion of subjects) at Week 24 and better reduction in tender joint counts compared with placebo at Week 12 and 24, even though one part of the placebo subjects only received BT061 active treatment after Week 12. The changes in efficacy parameters seen at Week 12 and 24 were generally maintained and some of them (ACR 50, ACR 70) increased considerably in the BT061 200 mg group at Week 48.

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use only)
Name of Finished Product: Tregalizumab		
Name of Active Substance: Tregalizumab		

The study supported the expected pharmacodynamic activity of BT061 and dose-dependent biological effect. No correlation was seen between intensity of PD response and ACR20 response. Treatment was well tolerated when administered for up to 48 weeks, with no unexpected safety findings. From the analysis there was no conclusive evidence on a dose effect. If at all the 200 mg dose showed a slight increased risk of experiencing TEAEs, in any case without being considered of clinical relevance compared to the other doses. Due to the lack of efficacy the long term phase of the study was terminated early.

Name of Sponsor/Company: Biotest AG	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use only)
Name of Finished Product: Tregalizumab		
Name of Active Substance: Tregalizumab		

I hereby confirm, that the data in the results report were collected properly and are correct.

Date of report:

02 June 2016
Date

Head of Corporate Clinical Research&Development
Dr. Andrea Wartenberg-Demand, MD, PhD