

Selective activation of regulatory T cells (Tregs) by BT-061: Clinical data from a completed Phase IIa trial in rheumatoid arthritis (RA) and design of a multi-centre, double-blind, randomised, placebo-controlled, Phase IIb dose-finding trial

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Disclosure

This study was designed and sponsored by Biotest AG.

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Abstract

Background

Tregs are essential for maintaining normal immune homeostasis. In patients with autoimmune diseases reduced numbers or functional impairment of Tregs has been observed. BT-061, a humanized agonistic monoclonal antibody, binds to a unique epitope of CD4, induces Treg-specific signalling events and leads to their functional activation. Pre-clinical data using isolated Tregs and RA synovial fluid, indicate that BT-061 leads to suppression of CD4 and CD8 T effector cell proliferation, reduction of the expression of pro-inflammatory cytokines, and increase in the production of the anti-inflammatory cytokine TGF- β . BT-061 is currently under clinical investigation in rheumatoid arthritis and psoriasis.

Method

A Phase IIa trial in 96 RA patients non-responsive to DMARDs evaluated doses of 1.25 mg to 100 mg BT-061 SC and 0.5 mg to 25 mg BT-061 IV, versus placebo.

Results

The trial demonstrated that the best response was achieved with 50 mg BT-061 SC as monotherapy. This dose of BT-061 resulted in ACR20/50/70 responses of 67%/33%/17%, versus 14%/7%/0%, respectively, of patients in the placebo group after 6 weeks of therapy. Rapid improvements in tender (TJC) and swollen (SJC) joint counts were observed (TJC: mean reduction of 50.4% at Week 7, SJC: mean reduction of 62.5% at Week 7). Therapy with BT-061 was generally well tolerated.

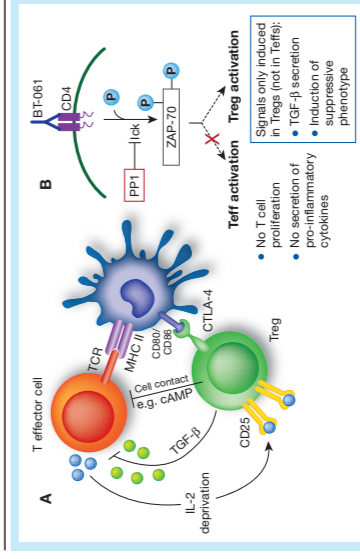
Conclusion

Based on these results, a placebo-controlled, Phase IIb trial, involving approximately 35 clinical centres across Europe has been initiated to evaluate clinical use of BT-061 in combination with methotrexate (MTX) in RA patients with an inadequate response to MTX. Placebo or 25, 50 or 75 mg of BT-061 SC will be given once-weekly, for 12 weeks. Initially 100 patients (25 per group) will be enrolled. After an interim analysis to identify the optimal dose of BT-061, an additional 76 patients will be randomised to this dose of BT-061 or placebo (38 per arm). The primary end point will be ACR20 response at week 13, with secondary endpoints including ACR50 and ACR70 responses, DAS28, health related quality of life, safety and pharmacokinetics. Enrolment into this study commenced in December 2010.

Background

Tregs modulate and balance the immune system. Once activated, they suppress T cells in an antigen-independent manner (Figure 1A). In patients with autoimmune diseases, reduced numbers or functional impairment of Tregs results in loss of this finely-tuned mechanism.

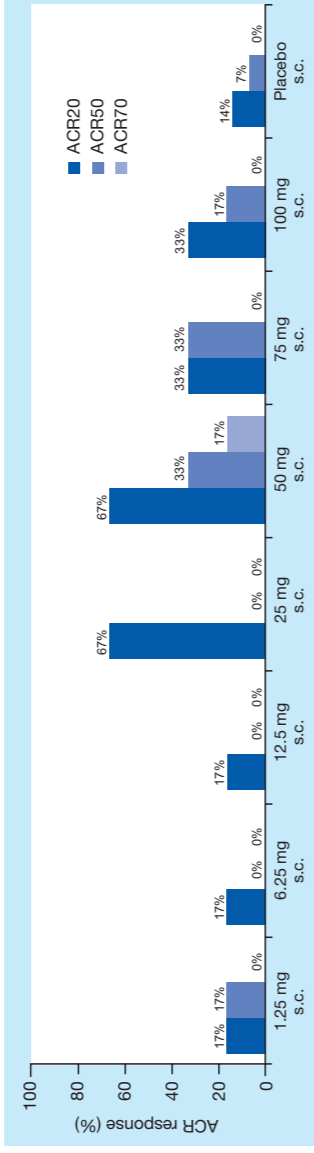
Figure 1: Effect of Tregs and mechanism of action of BT-061



BT-061

- Humanized monoclonal IgG1 antibody
- Binds to a unique epitope in the IgG like C2 type 1 domain of CD4 on T helper cells and Tregs
- Provides an activation signal to naturally occurring Tregs (Figure 1B); not known with other therapeutic CD4 antibodies (Czeloth *et al.*)
- Selectively activates Tregs but not normal T cells
- No evidence of ADCC or CDC and non-depleting

Figure 2: ACR 20/50/70 Responses (Day 43 ± 1)



Methods

- Biotest Study 962 was a randomised, placebo-controlled, Phase IIa trial
- 96 patients with RA who had a history of DMARD failure
- BT-061 SC (1.25–100 mg) or i.v. (0.5–25 mg) (n=6 per group) or matching placebo (n=2 per group) weekly for 6 weeks
- Primary end point: ACR 20 response after 6 weeks of treatment
- Secondary endpoints included ACR 50/70, DAS28 and EULAR criteria, safety, cytokine assessment, lymphocyte phenotyping.

Results

The most efficacious route of administration for BT-061 was found to be SC. Based on ACR responses (Figure 2) and improvements in tender (TJC) and swollen (SJC) joint counts, the most efficacious dose of BT-061 was identified to be 50 mg.

At the 50 mg dose, BT-061 induced rapid improvements in TJC and SJC, which in some cases was maintained beyond the dosing period (Figure 3)

Figure 3: Tender / Swollen Joint Scores

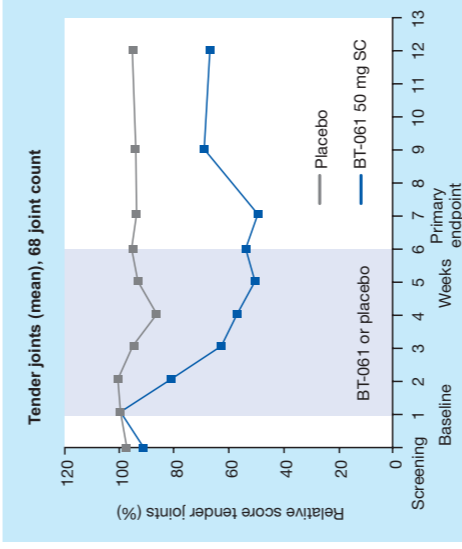


Figure 4: Study Design

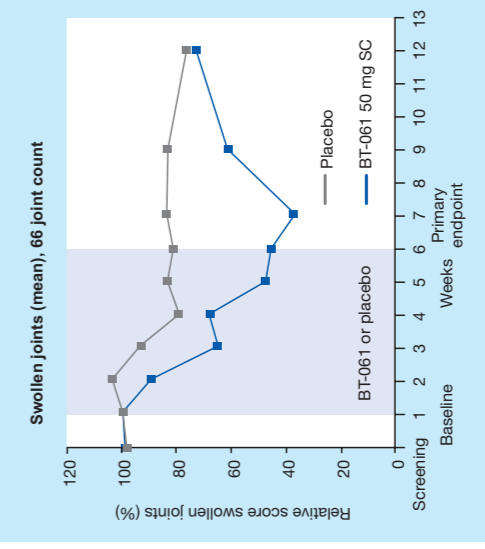


Table 1: Adverse events (SC doses)

	Placebo SC (n=14)	BT-061 SC
Patients with any AEs (%)	8 (57%)	25 mg (n=6) 3 (50%) 12.5 mg (n=6) 2 (33%) 6.25 mg (n=6) 6 (100%)
Patients with serious AEs	0	25 mg (n=6) 0 12.5 mg (n=6) 0 6.25 mg (n=6) 2 (33%)
Patients withdrawing due to AE	2 (14%)	25 mg (n=6) 0 12.5 mg (n=6) 0 6.25 mg (n=6) 0
		50 mg (n=6) 0 75 mg (n=6) 0 100 mg (n=6) 1 (17%)

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Safety

No depletion of CD4 cells was observed at any dose level. BT-061 was generally well tolerated; serious AEs were reported in 2 patients of 72 treated with BT-061 (both received 6.25 mg SC); and in 1 of 24 patients who received placebo (the patient was in the IV group). There were no serious infections and no deaths reported in the study.

Conclusion

- This is the first study of a CD4 antibody given via the SC route for the treatment of RA.
- In this trial, in patients with a history of DMARD failure, clinical effects of BT-061 given as monotherapy indicated 50 mg SC as the likely optimal dose.
- Induced activation of Tregs with BT-061 is a promising therapeutic strategy for the management of RA.

Study 979: Phase IIb Dose-Finding Study

Based on these findings a Phase IIb trial, Biotest Study 979, has been initiated (Figure 4).

Reference

Czeloth N, Dalken B, Engling A, *et al.* Selective activation of naturally occurring regulatory T cells (Tregs) by the monoclonal antibody BT-061 as a novel therapeutic opportunity: pre-clinical and early clinical results. Annual European Congress of Rheumatology, EULAR 2010. Abstract OP0138. Presented 18th June 2010.

Disclosure

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