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Conflict of interest declaration

N. Czeloth, B. Dälken, A. Engling, F. Osterroth, S. Aigner, A. Abufarag, A. Wartenberg-Demand, H. Koch and C. Uherek are employed by Biotest AG. C. Becker, H. Jonuleit, V. Daniel, W. E. Haefeli, A. Schwarz, J. Haas and B. Wildemann received research funding by Biotest AG.

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Selective activation of naturally occurring regulatory T-cells (T_{regs}) by the monoclonal antibody BT-061 as a novel therapeutic opportunity: Pre-clinical and early clinical results

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Background: Naturally occurring T_{regs} are essential for maintaining normal immune homeostasis in healthy individuals by down-regulating excessive immune responses. In patients with autoimmune diseases, reduced numbers, or functional impairment, of T_{regs} results in loss of this finely-tuned mechanism.

Objectives: Here we report on the mode of action and first clinical data of the humanized agonistic monoclonal antibody (mAb) BT-061, a selective activator of human T_{regs}.

Results: BT-061 binds to a unique epitope of the CD4 molecule leading to phosphorylation of the ZAP70 protein kinase associated with the T-cell receptor complex. This phosphorylation induces T_{reg} specific signalling events which result in activation of their suppressive functions. *In Vitro* we demonstrated that while freshly isolated and resting T_{regs} did not effectively inhibit proliferation of conventional T-cells, pre-treatment of T_{regs} with BT-061 leads to induction of their suppressive activity. We have shown that BT-061 treated T_{regs} are able to strongly suppress proliferation and cytokine secretion of CD4 and CD8 effector T-cells following allogeneic or antigen-specific activation. In contrast to reports of T_{reg} activation with anti-CD3 mAbs, we report that although BT-061 appears to similarly bind to T helper cells, BT-061 does not induce secretion of inflammatory cytokines or proliferation of conventional T-cells. Moreover, we were able to demonstrate *in vitro* that antigen-specific stimulation of human PBMC in the presence of BT-061 resulted in significant reductions of inflammatory cytokines such as IFN-gamma and a moderate increase of the anti-inflammatory cytokine TGF-beta, indicating a shift towards an immunosuppressive milieu. In the first-in-human clinical trial, BT-061 was well tolerated by healthy volunteers, and single doses of up to 60 mg i.v. or 180 mg s.c. could be administered without reaching dose limiting toxicities. The most frequently reported adverse events were mild and comprised headache and pharyngeal erythema. In contrast to other T_{reg} activating biologicals, pronounced cytokine releases were not detected. In addition, application of BT-061 did not cause depletion of CD4 T-cells.

Conclusion: Currently, BT-061 is being tested in Phase I and Phase II clinical trials in patients with rheumatoid arthritis and chronic plaque psoriasis to investigate the suitability of T_{reg} activation with BT-061 as a therapeutic concept. The unique and specific mode of action of BT-061 has been shown to have potential for the management of these autoimmune diseases where diminished activity of T_{regs} contributes to disease activity.

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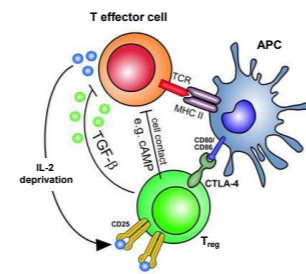
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BT-061 – Compound specifics

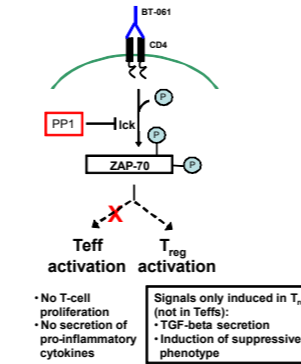
- Humanized monoclonal antibody (IgG1)
- Binds to a unique epitope of CD4 (low nanomolar affinity)
- Non-depleting (no ADCC or CDC)
- Binds to both T helper and regulatory T-cells
- Provides an activation signal to naturally occurring regulatory T-cells by binding to a unique epitope (not reported for other therapeutic CD4 antibodies)
- Specifically activates regulatory T-cells*

*naturally occurring T_{regs} (CD4⁺CD25^{hi}FoxP3⁺)

T_{reg} mediated suppression of T effector cells

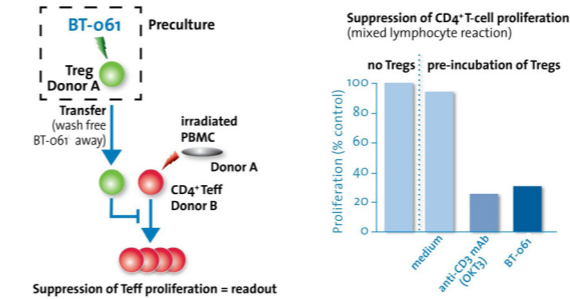


Selective activation of T_{regs} by BT-061



BT-061 binds to a unique epitope as compared to several other CD4 antibodies

BT-061 functionally activates regulatory T-cells



BT-061 activates regulatory T-cells without activation of T helper cells. The T_{reg} stimulating activity is a differentiating characteristic of BT-061 compared to all other anti-CD4 mAbs analyzed (12 tested)

Overview of clinical trials with BT-061

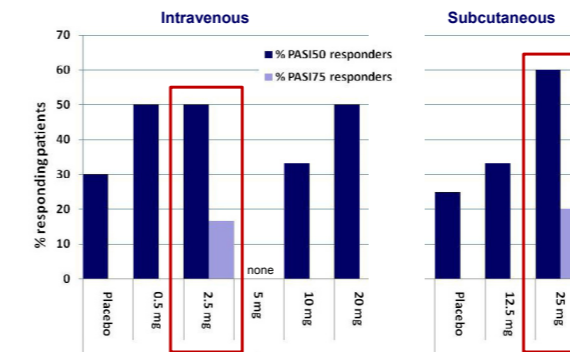
Study	Indication	Design	Dose	Subjects	Status
961	Healthy volunteers	Single dose	iv and sc: 3.5 µg–180 mg	57	Completed
967	Phase I/IIa: Psoriasis	Single dose, placebo controlled	sc: 12.5, 25 mg iv: 0.5–20 mg	55	Completed
973	Phase II: Psoriasis	Placebo controlled once weekly; 8 wks	sc: 4 groups iv: 0.5, 2 mg	48	Recruitment ongoing
962	Phase IIa: Rheumatoid Arthritis	Placebo controlled once weekly; 6 wks	sc: 1.25–100 mg iv: 2–25 mg	96	Recruitment completed
971	Phase II: Rheumatoid Arthritis	BT-061+ MTX placebo controlled once weekly; 8 wks	iv: 0.5, 2 mg sc: 50 mg	110	Recruitment ongoing

>250 subjects have been treated with BT-061 so far

Phase I/IIa single dose-escalation in Psoriasis

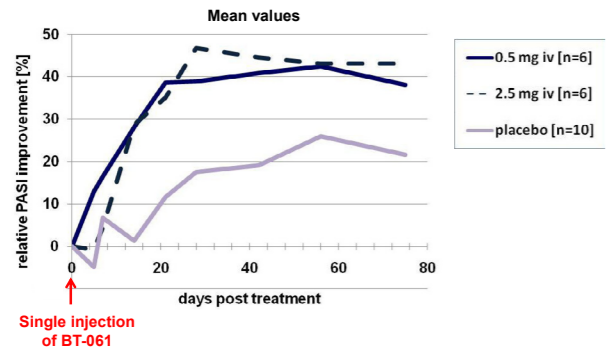
- **Design:** Single dose, placebo-controlled, 3:1 randomization
- **Study population:** 56 adult patients with moderate-to-severe chronic plaque psoriasis; PASI > 10; BSA > 10% for more than 6 months
- **Treatment:** iv: 5 groups: 0.5 mg, 2.5 mg, 5 mg, 10 mg, 20 mg
sc: 2 groups: 12.5 mg, 25 mg
- **Follow-up:** 75 days (amended to 90 days)
- **Endpoint:** Short-term efficacy: PASI 50, 75, 90
Physician's Global Assessment, Itching Score
Single dose pharmacokinetics: C_{max}, t_{max}, t_{1/2}, Cl, AUC

PASI 50 and PASI 75 responses after single dose



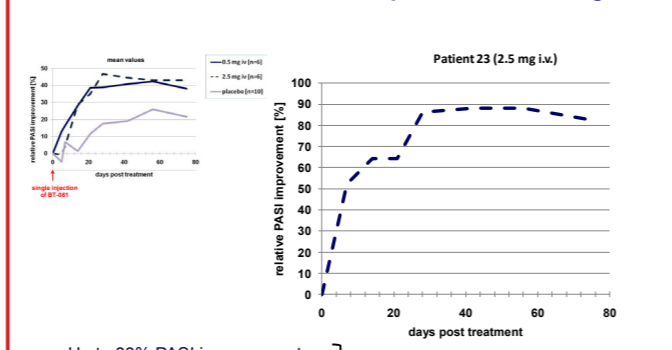
Next Phase II trial in Psoriasis commenced (study 973) to investigate efficacy after multiple applications and higher sc doses

Kinetics of relative PASI score improvement after single dose



Long lasting PASI improvement already observed after single application of very low doses of BT-061

Kinetics of relative PASI score improvement after single dose



- Up to 88% PASI improvement observed
- Long lasting effect of >75 d

BT-061: Summary clinical safety

- >250 subjects have been treated with BT-061 in clinical trials
- No interruption of infusion necessary due to AEs
- Headache was the most frequently reported AE (similar in active and placebo)
- Most AEs mild or moderate
- No evidence for increased risk of infections
- No clinically relevant changes in laboratory parameters
- No lymphocyte depletion observed
- Well tolerated and no evident safety concerns