Results of a Phase IIb Study of Vobarilizumab, an Anti-Interleukin 6 Receptor Nanobody®, in Patients with Moderate-to-Severe Rheumatoid Arthritis despite Treatment with Methotrexate

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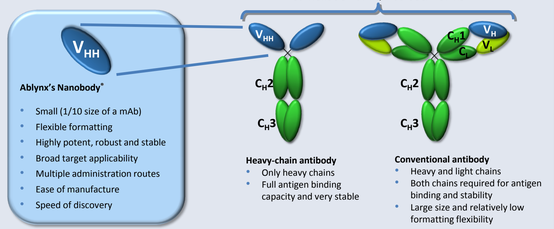
Background: vobarilizumab, an IL-6R targeting Nanobody

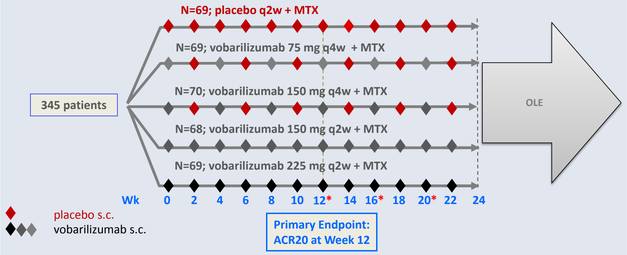
- **Ablynx's Nanobodies®**

Camelidae family has both forms



- **Vobarilizumab product description**
  - **monovalent interaction** eliminates IL-6R cross-linking
  - no induction of Antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity due to **lack of Fc**
  - **half-life extension** by binding to Human Serum Albumin (HSA)

Study Design of the Phase IIb Clinical Trial

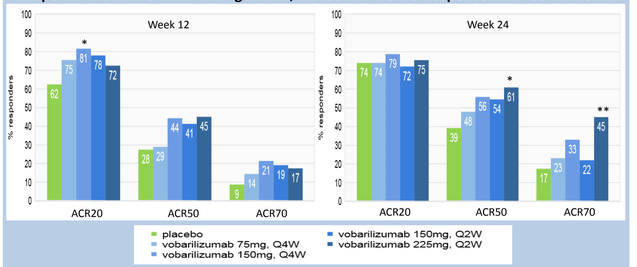


- A total of 345 patients were enrolled (placebo N=69, vobarilizumab 75mg q4w N=69, 150mg q4w N=70, 150mg q2w N=68, or 225mg q2w N=69)

* At Weeks 12, 16 or 20, patients with < 20% improvement in both TJC and SJC from baseline had to discontinue from the trial but remained blinded to study drug assignment

Efficacy Results: ACR Responses at Weeks 12 & 24

Proportions of Patients achieving ACR20, ACR50 and ACR70 Responses at Weeks 12 & 24



- At Week 12, statistical significance for the primary endpoint analysis was not achieved, i.e. the % achieving ACR20 responses did not increase significantly by increasing dosing regimen per Cochran-Armitage trend test (5% significance level).
- ACR50 and ACR70 responses of up to 45% and 21% were achieved (placebo 28% and 9%). Responses continued to increase through Week 24.

* nominal p<0.05 vs. placebo; ** nominal p<0.01 vs placebo

Safety

Safety through Week 24

Number of subjects (%) with treatment-emergent adverse events (TEAE)	placebo N=69	vobarilizumab 75mg, Q4W N=69	vobarilizumab 150mg, Q4W N= 70	vobarilizumab 150mg, Q2W N=68	vobarilizumab 225mg, Q2W N=69
Any TEAE	**36 (52.2%)**	**42 (60.9%)**	**44 (62.9%)**	**44 (64.7%)**	**44 (63.8%)**
- treatment-related	18 (26.1%)	26 (37.7%)	25 (35.7%)	26 (36.8%)	25 (36.2%)
- leading to study drug discontinuation	3 (4.3%)	4 (5.8%)	5 (7.1%)	5 (7.4%)	4 (5.8%)
Any serious TEAE	**4 (5.8%)**	**5 (7.2%)**	**4 (5.7%)**	**0**	**1 (1.4%)**
- treatment-related	2 (2.9%)	1 (1.4%)	3 (4.3%)	0	1 (1.4%)
- leading to death (not treatment-related)	0	1 (1.4%)	0	0	0

- Of all vobarilizumab treated patients, 3.6% experienced at least one SAE during the treatment period with no dose dependency (placebo 5.8%).
- One death, considered not related to study treatment, was reported.
- Grade 3 toxicities for liver enzymes (AST 0.7%, ALT 1.8%) and neutrophils (1.1%) were infrequent and independent of dose.

Objectives and Methods

Objectives

- This **phase IIb** study of vobarilizumab was designed to assess the **efficacy** and **safety** of several dose regimens in adults with **moderate-to-severe RA despite methotrexate** (MTX) therapy.

Methods

- In this **24-week double-blind randomized controlled** global trial, patients were randomized 1:1:1:1:1 to receive subcutaneously administered placebo or one of 4 dose regimens of vobarilizumab in addition to MTX.
- **Early discontinuation** was mandatory for patients with **<20% improvement in both swollen and tender joint counts at Weeks 12, 16 or 20**.
- Patients who completed the study could enroll in a 2-year open-label extension study.
- The **primary endpoint** was the proportion achieving an **ACR20 response at Week 12**. Patients with missing ACR20 response were treated as non-responders. A Cochran-Armitage trend test was used to test the dose response of the primary endpoint.
- The **secondary endpoints** included assessments of **higher levels of ACR response** and **disease activity (DAS28$_{CRP}$).**
- **Adverse events** and routine **safety parameters** including laboratory assessments were recorded.

Baseline Demographics and Disease Activity – ITT Population

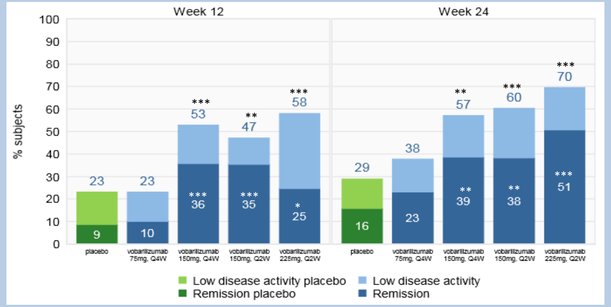
Mean (SD)	placebo N=69	vobarilizumab 75mg, Q4W N=69	vobarilizumab 150mg, Q4W N=70	vobarilizumab 150mg, Q2W N=68	vobarilizumab 225mg, Q2W N=69
Age, years	52.8 (11.9)	53.3 (10.4)	52.0 (13.2)	51.9 (11.9)	52.3 (13.4)
Females (%)	79.7	84.1	88.6	86.8	79.7
Duration of RA, years	7.4 (7.0)	7.3 (6.8)	8.9 (9.8)	8.6 (7.8)	8.0 (8.1)
TJC68	24.9 (12.7)	25.9 (12.3)	24.2 (12.3)	26.5 (13.8)	23.9 (13.4)
SJC66	17.0 (10.0)	16.3 (7.3)	15.1 (8.5)	17.8 (9.5)	15.4 (10.0)
CRP, mg/L	23.4 (26.1)	21.9 (22.8)	23.8 (26.2)	29.2 (42.1)	20.4 (21.9)
DAS28$_{CRP}$	6.0 (0.9)	6.0 (0.8)	5.8 (0.9)	6.2 (0.9)	5.8 (0.9)
HAQ-DI score	1.7 (0.5)	1.7 (0.7)	1.6 (0.6)	1.8 (0.7)	1.6 (0.7)
MTX dose, mg/week	15.9 (3.5)	17.4 (4.2)	17.3 (4.2)	16.2 (3.4)	17.3 (4.6)

- Demographics and baseline disease characteristics were similar across groups, with mean baseline DAS28$_{CRP}$ between 5.8 and 6.2, and were typical for patients with moderate-to-severe RA

ITT, intent-to-treat; TJC, tender joint count; SJC, swollen joint count; CRP, C-reactive protein; DAS28$_{CRP}$, disease activity score in 28 joints using CRP; HAQ-DI, health assessment questionnaire disability score for RA

Efficacy Results: DAS28$_{CRP}$ at Weeks 12 & 24

Proportions of Patients achieving Low Disease Activity and DAS28$_{CRP}$<2.6 at Weeks 12 & 24



- A sustained impact on disease activity was observed with up to 49% of patients achieving DAS28$_{CRP}$<2.6 at Week 24 (placebo 16%).

* nominal p<0.05 vs. placebo; ** nominal p<0.01 vs. placebo; *** nominal p<0.001 vs. placebo

Conclusions

- This phase IIb study showed that in patients with active RA despite receiving MTX, treatment with vobarilizumab (150mg q4w, 150mg q2w and 225mg q2w) had a positive impact on disease activity with an acceptable safety profile.
- A large placebo effect was observed and is under investigation.
- Overall, the results support the advancement of vobarilizumab into phase III of development.