Results of a Subgroup Analysis by Access to Biologics in a Phase IIb Study of Vobarilizumab in Patients with Moderate-to-Severe Rheumatoid Arthritis despite Treatment with Methotrexate

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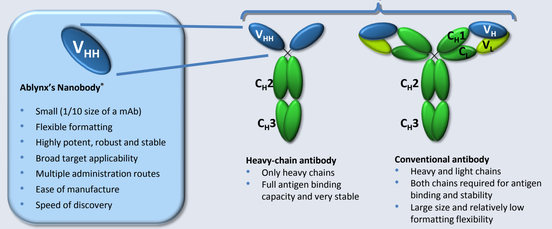
Background: vobarilizumab, an IL-6R targeting Nanobody

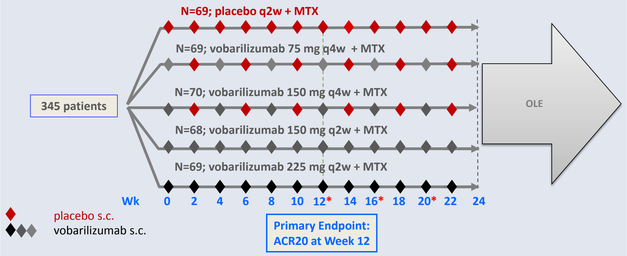
- **Ablynx's Nanobodies®**

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)

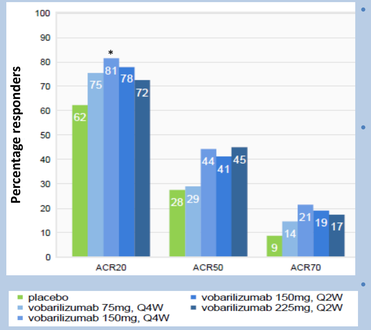
Study Design of the Phase IIb Clinical Trial



- 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: High Placebo Responses at Week 12



- At Week 12, 62%, 28%, and 9% of patients allocated to the placebo arm (N=69) achieved an ACR20, ACR50, and ACR70 response, respectively.
- As a consequence, statistical significance for the primary endpoint was not achieved, i.e. the proportion of patients achieving ACR20 response did not increase significantly by increasing dosing regimen.
- A post-hoc analysis of the proportion of patients achieving an ACR20 response was performed for patients in the subset of countries with and without widespread access to biologicals.

NRI: non-responder imputation

* nominal p<0.05 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

- In this **phase IIb** study of vobarilizumab an **unexpectedly high response to placebo** for ACR20 was observed. A **post-hoc subgroup analysis** was performed to better understand the results.

Methods

- The proportion of patients achieving an ACR response at Week 12 was calculated separately for the subset of **countries with widespread access to biologicals** and for the subset **without such access**.
- Countries **with widespread access** to biologicals: **Belgium, Czech Republic, Hungary, Spain, and US**.
- Countries **with limited access** to biologicals: **Bulgaria, Georgia, Macedonia, Mexico, Poland, Republic of Moldova, Romania, and Serbia**.

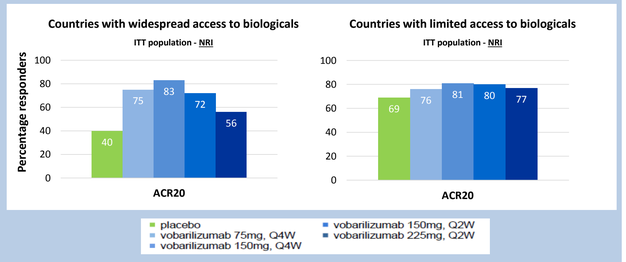
Baseline Disease Characteristics across Groups with/without Access to Biologicals

With Widespread Access to Biologicals Mean (SD)	placebo N=15	vobarilizumab 75mg, Q4W N=16	vobarilizumab 150mg, Q4W N=12	vobarilizumab 150mg, Q2W N=18	vobarilizumab 225mg, Q2W N=16
Duration of RA, years	6.4 (7.4)	6.4 (7.5)	10.1 (13.5)	12.2 (9.5)	7.7 (8.1)
TJC68	22.7 (12.7)	26.6 (10.7)	25.9 (17.8)	23.0 (14.8)	22.8 (14.9)
SJC66	15.6 (7.9)	16.4 (6.5)	18.9 (14.7)	15.7 (11.2)	16.1 (12.0)
CRP, mg/L	17.9 (22.3)	17.6 (20.4)	21.8 (29.8)	31.8 (23.1)	14.0 (14.7)
$DAS28_{CRP}$	5.8 (1.1)	5.8 (0.7)	6.0 (1.1)	5.9 (0.8)	5.4 (1.0)
HAQ-DI score	1.6 (0.6)	1.5 (0.6)	1.4 (0.6)	1.6 (0.5)	1.4 (0.8)
Limited Access to Biologicals Mean (SD)	**placebo N=54**	**vobarilizumab 75mg, Q4W N=53**	**vobarilizumab 150mg, Q4W N=58**	**vobarilizumab 150mg, Q2W N=50**	**vobarilizumab 225mg, Q2W N=53**
Duration of RA, years	7.7 (6.9)	7.6 (6.7)	8.7 (9.0)	7.4 (6.8)	8.1 (8.1)
TJC68	25.5 (12.7)	25.7 (13.0)	23.9 (11.1)	27.8 (13.4)	24.3 (13.1)
SJC66	17.4 (10.5)	16.3 (7.5)	14.3 (6.4)	18.5 (8.8)	15.2 (12.0)
CRP, mg/L	24.9 (27.1)	23.2 (23.5)	24.2 (25.7)	28.2 (46.7)	22.3 (23.4)
$DAS28_{CRP}$	6.0 (0.9)	6.1 (0.8)	5.8 (0.9)	6.3 (0.9)	5.9 (0.8)
HAQ-DI score	1.8 (0.5)	1.7 (0.7)	1.6 (0.6)	1.9 (0.7)	1.7 (0.7)

- Across subgroups, no obvious differences in the baseline disease characteristics were observed.

Post-hoc Analysis by Access to Biologicals

Proportions of Patients achieving ACR20 at Week 12 Depending on Access to Biologicals



- In the subset of countries with widespread access to biologicals, 40% (6/15) of patients in the placebo group achieved an ACR20 response.
- In the subset without such access a response of 69% (37/54) was observed.
- Responses in the vobarilizumab dosing arms were 75%, 83%, 72%, and 56%, and 76%, 81%, 80%, and 77% in the two subsets, respectively.

Conclusions

- This phase IIb study showed that in patients with active RA despite MTX, treatment with vobarilizumab (150mg q4w, 150mg q2w and 225mg q2w) had a positive impact on signs and symptoms and a acceptable safety profile.
- A striking placebo effect was observed for ACR20, driven by patients in the subset of countries without widespread access to biologicals. This may have been due to the protocol-specified discontinuation of non-responders and the fact that only patients who completed the study could enroll in a 2-year open-label extension study.