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Assessment of dose-dependent effects of vobarilizumab, an anti-IL-6 receptor (IL-6R) Nanobody, on systemic biomarkers in patients with moderate-to-severe rheumatoid arthritis (RA): Results of two Phase 2b studies

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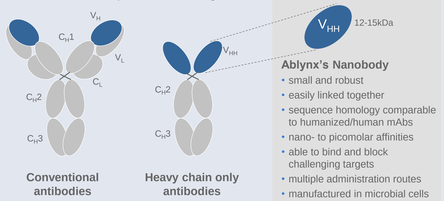
Background: Vobarilizumab, an IL-6R targeting Nanobody

- Camelid heavy-chain only antibodies are stable and fully functional
- Nanobodies represent the next generation of antibody-derived biologics



- Vobarilizumab is a Nanobody of 25.7 kDa, consisting of two humanized and sequence-optimized variable domains: an anti-IL6R domain and an anti-human serum albumin (HSA) domain for half-life extension.
- In vitro, Vobarilizumab demonstrated a preferential binding to soluble (s)IL-6R with a lesser activity for membrane (m)IL-6R, while Tocilizumab (TCZ) has a higher preference for mIL-6R (Ref 1).

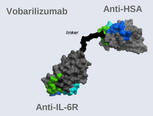


Figure 1: Schematic 3D representation of the vobarilizumab Nanobody

Clinical trial design of two Phase 2b studies

- ALX0061-C201 trial: Phase 2b combination study with methotrexate (MTX) in RA patients (NCT02309359)
  - Adults with moderate to severe RA despite MTX therapy
  - Randomized, double-blind, placebo-controlled 24 week dose ranging study in Europe, the USA and Latin America

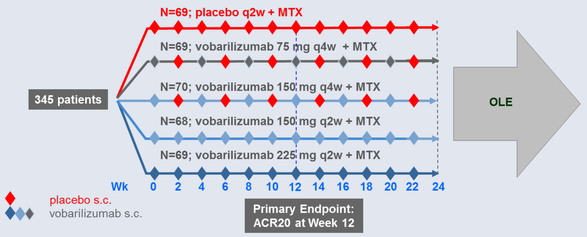


Figure 2: Study design of Phase 2b combination study with MTX in RA patients (ALX0061-C201 trial)

- ALX0061-C202 trial: Phase 2b monotherapy study in RA patients (NCT02287922)
  - Adults with moderate to severe RA who are intolerant to MTX or for whom continued MTX is inappropriate
  - 12 week study in Europe, the USA and Latin America
  - The open-label TCZ-arm enabled the collection of parallel descriptive information concerning the efficacy and safety of TCZ in the same clinical trial RA population.

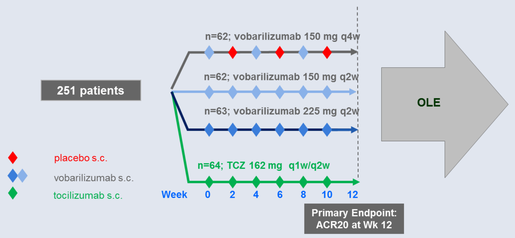


Figure 3: Study design of Phase 2b monotherapy study in RA patients (ALX0061-C202 trial)

- Main efficacy and safety results of both RA phase 2b studies with vobarilizumab when used in combination with MTX (ALX0061-C201) and as monotherapy (ALX0061-C202) were previously reported (ref 5 and 6).

Results: PD biomarkers

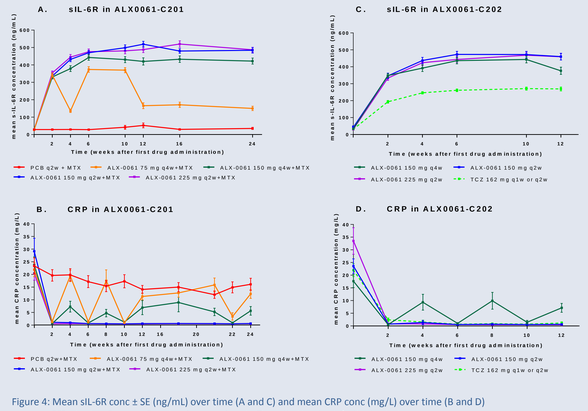


Figure 4: Mean sIL-6R conc ± SE (ng/mL) over time (A and C) and mean CRP conc (mg/L) over time (B and D)
PCB: placebo; q2w= every 2 weeks; q4w= every 4 weeks. The vertical bar stands for the standard error

- **Total sIL-6R**
  - In ALX0061-C201 and ALX0061-C202 studies, mean plasma total s-IL6R concentrations increased immediately from baseline following vobarilizumab or TCZ administration (Figure 4A and 4C).
  - After vobarilizumab/TCZ treatment discontinuation, a normalization of sIL-6R levels was observed at the follow-up visit 12 weeks after last drug administration (data not shown).
  - For vobarilizumab, a dose-dependency of the total sIL-6R biomarker response was observed in the C201 study.
- **CRP** was analyzed as inflammatory biomarker as well as a more distal PD biomarker.
  - In ALX0061-C201 and ALX0061-C202 studies, mean CRP concentrations decreased rapidly as of the first measurement at week 2 following administration of vobarilizumab and TCZ (Figure 4B and 4D).
  - Over the complete duration of both studies, mean CRP values remained suppressed for subjects in the two highest dosing regimens (150 mg q2w and 225 mg q2w).
  - For vobarilizumab, a clear dose-dependency of the CRP biomarker was observed.
- **Fibrinogen and ESR**
  - Similar dose-dependent biomarker response profiles as for CRP were obtained for acute phase proteins fibrinogen and ESR after vobarilizumab/TCZ treatment (data not shown).
  - For ESR, all vobarilizumab dose groups except for the 75 mg q4w dose were suppressed for the duration of the ALX0061-C201 trial (data not shown).

Objectives and biomarker selection

Objectives

- Investigation of the effect of vobarilizumab on systemic biomarkers in two rheumatoid arthritis (RA) phase 2b studies, using validated assays.
- All biomarkers were analyzed at baseline and over time in serum or plasma.

Biomarker selection

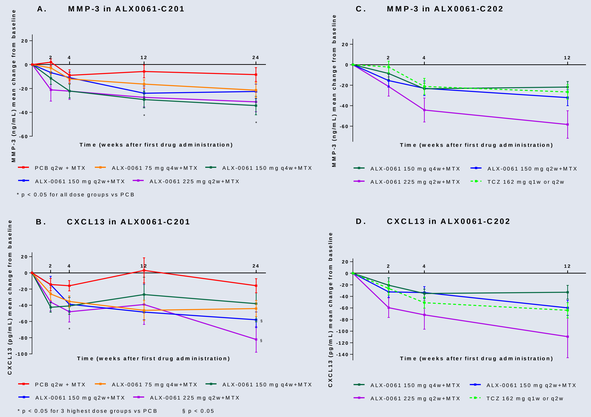
Both proximal and distal **pharmacodynamic (PD)** biomarkers were evaluated:

- **Total sIL-6R** is a valuable PD biomarker for anti-IL-6R targeting drugs, as demonstrated in the Phase 1/2a clinical trial with vobarilizumab and as previously reported for TCZ (ref 2).
  - An increase in circulating total sIL-6R levels reflects accumulation of sIL-6R/drug complex due to the longer half-life of the anti-IL-6R drug.
- The acute phase proteins **CRP, fibrinogen and ESR** were evaluated as inflammatory biomarkers as well as a more distal PD biomarkers.
  - As the IL-6/IL-6R pathway directly controls acute phase response, a decrease in these biomarkers can be expected after vobarilizumab or TCZ treatment.

The following biomarkers were selected as **efficacy** biomarkers:

- Serum **Matrix Metalloproteinase-3 (MMP-3)** levels are elevated in RA patients and have been shown to correlate with radiographic progression (ref 3). It holds potential as a surrogate biomarker for imaging.
- **Chemokine (C-X-C motif) ligand 13 (CXCL13)** are elevated in RA patients and have been shown to correlate with disease activity (and components) and joint erosion (Ref 4).

Results: Efficacy biomarkers



* p < 0.05 for all dose groups vs PCB
§ p < 0.05

- **Serum MMP-3** was studied as a cartilage degradation biomarker
  - Mean MMP-3 concentrations decreased in all treatment groups compared to baseline levels (Figure 5A and 5C).
  - Mean MMP-3 concentrations were significantly suppressed by vobarilizumab at week 12 and week 24 over all treatment groups, compared to the placebo group (Figure 5A).
  - For TCZ, a similar profile was observed as for vobarilizumab, with decreased MMP-3 levels over time, compared to baseline (Figure 5C).
- **Serum CXCL13** was studied as joint inflammation biomarker
  - Mean CXCL13 concentrations decreased in all treatment groups compared to baseline levels (Figure 5B and 5D).
  - Mean CXCL13 concentrations were suppressed by vobarilizumab over all treatment groups, compared to the placebo group (Figure 5B). Statistical significance was achieved for the highest dose groups at week 4 and week 24.
  - For TCZ, a similar profile was observed as for vobarilizumab, with decreased CXCL13 levels over time, compared to baseline (Figure 5D).

Figure 5: Mean change from BL of MMP-3 conc ± SE (ng/ml) over time (A and C) and mean change from BL of CXCL13 conc (pg/ml) over time (B and D)
PCB: placebo; q2w= every 2 weeks; q4w= every 4 weeks. The vertical bar stands for the standard error. Statistical significance of differences between treatment group and PCB was determined by ANCOVA analysis. Nominal p values are listed.

References

1. Van Roy M. et al., ACR/ARHP annual meeting, 2014 (Abstract number: 1498)
2. Nishimoto N. et al. Blood 2008
3. Ma et al. Arthritis Research and Therapy 2015
4. Rioja et al. Arthritis and Rheumatism 2008
5. Dörner T. et al, Eular 2017 (Abstract number: OP0098)
6. Dörner T. et al, Eular 2017 (Abstract number: FRI0239)

Conclusion

- **Dose-dependent modulation of proximal and distal PD biomarkers (total sIL-6R, CRP, fibrinogen and ESR) by vobarilizumab was demonstrated.**
- **The effects on cartilage degradation and joint inflammation biomarkers further support the disease modifying potential of vobarilizumab in RA.**
- **As serum MMP-3 levels tend to correlate with radiographic progression in RA patients (ref 3), the current results support further study of this biomarker as a potential surrogate biomarker for imaging.**