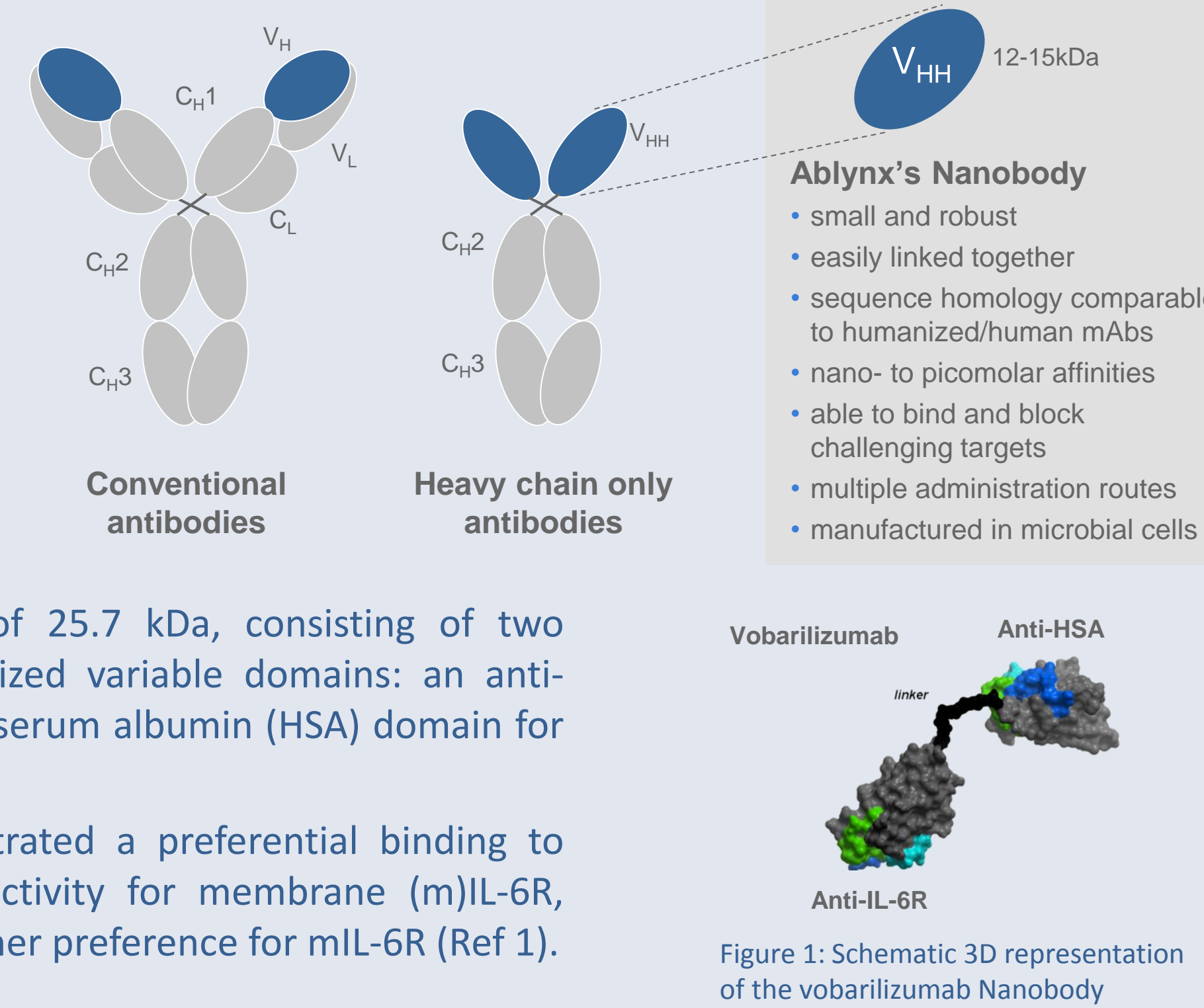


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Background: Vobarilizumab, an IL-6R targeting Nanobody

- 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).

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:

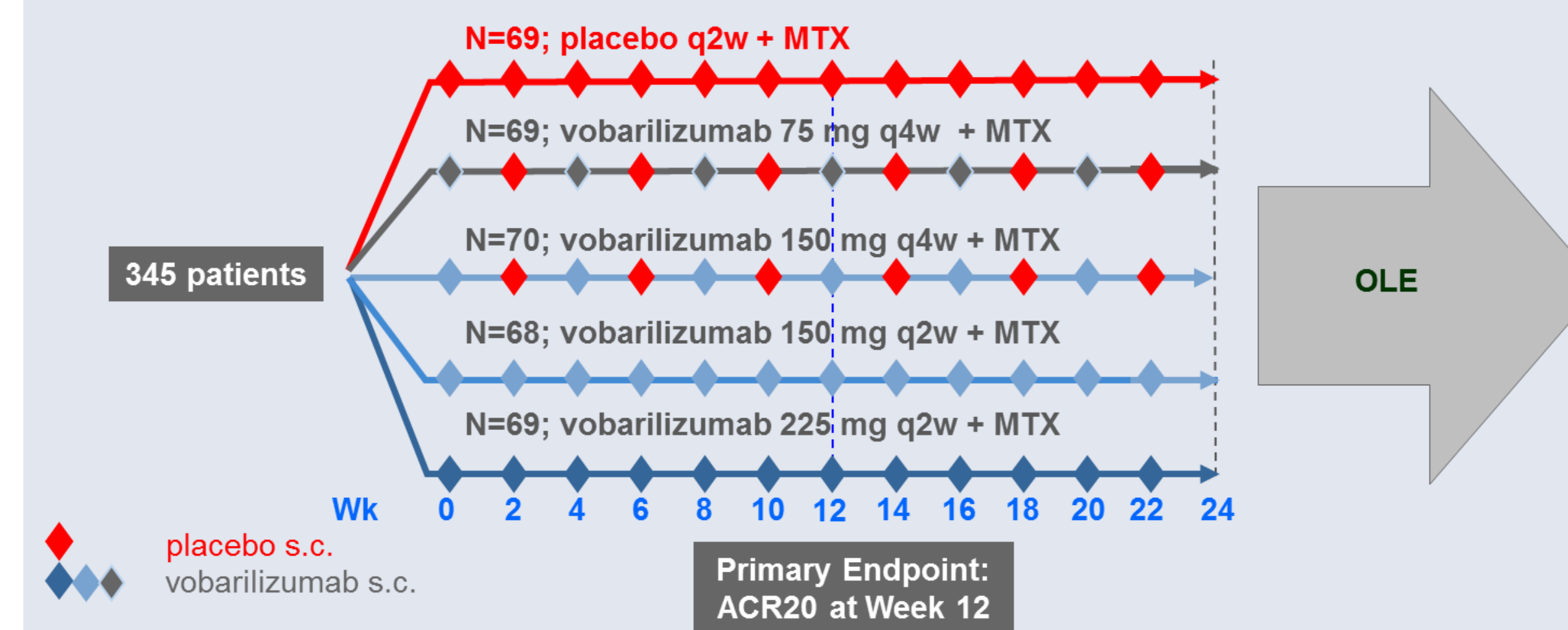
- **Total sIL-6R** is a valuable PD biomarker for anti-IL-6R targeting drugs, as demonstrated in the Phase 1/2a clinical trial with vobarilizumab and as previously reported for TCZ (ref 2).
 - An increase in circulating total sIL-6R levels reflects accumulation of sIL-6R/drug complex due to the longer 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:

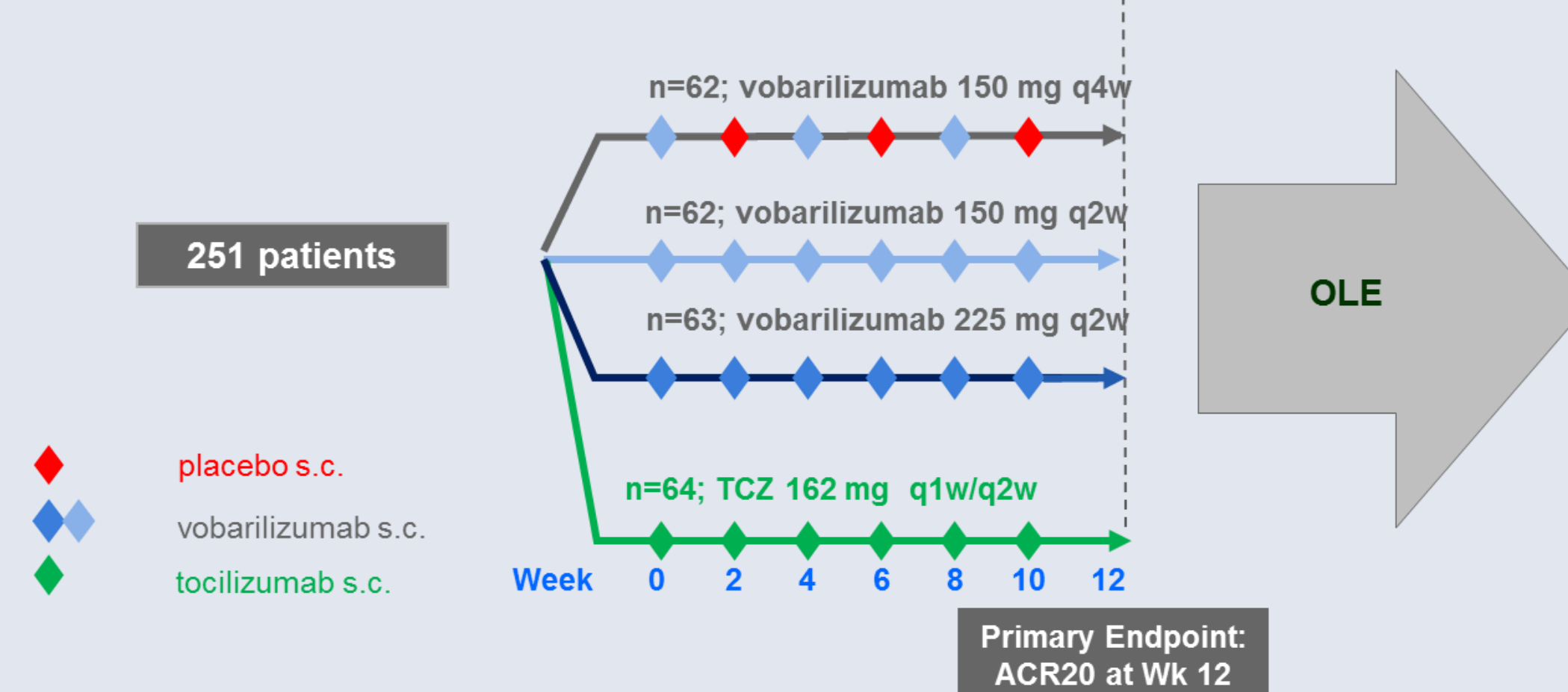
- Serum **Matrix Metalloproteinase-3 (MMP-3)** levels are elevated in RA patients and have been shown to correlate with radiographic progression (ref 3). It holds potential as a surrogate biomarker for imaging.
- **Chemokine (C-X-C motif) ligand 13 (CXCL13)** are elevated in RA patients and have been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

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

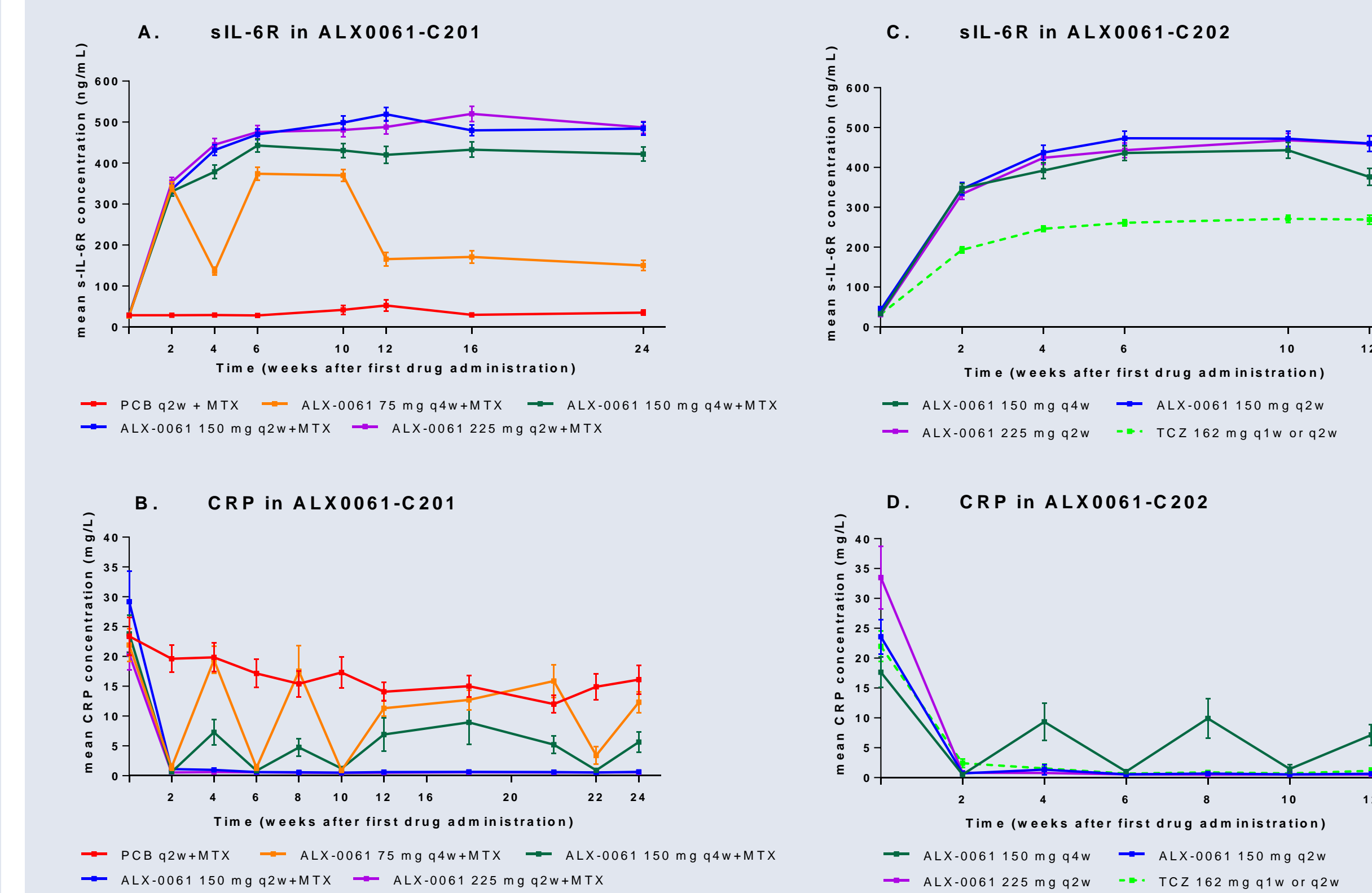


- ALX0061-C202 trial: Phase 2b monotherapy study in RA patients (NCT02287922)
 - Adults with moderate to severe RA who are intolerant to MTX or for whom continued MTX is inappropriate
 - 12 week study in Europe, the USA and Latin America
 - The open-label TCZ-arm enabled the collection of parallel descriptive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



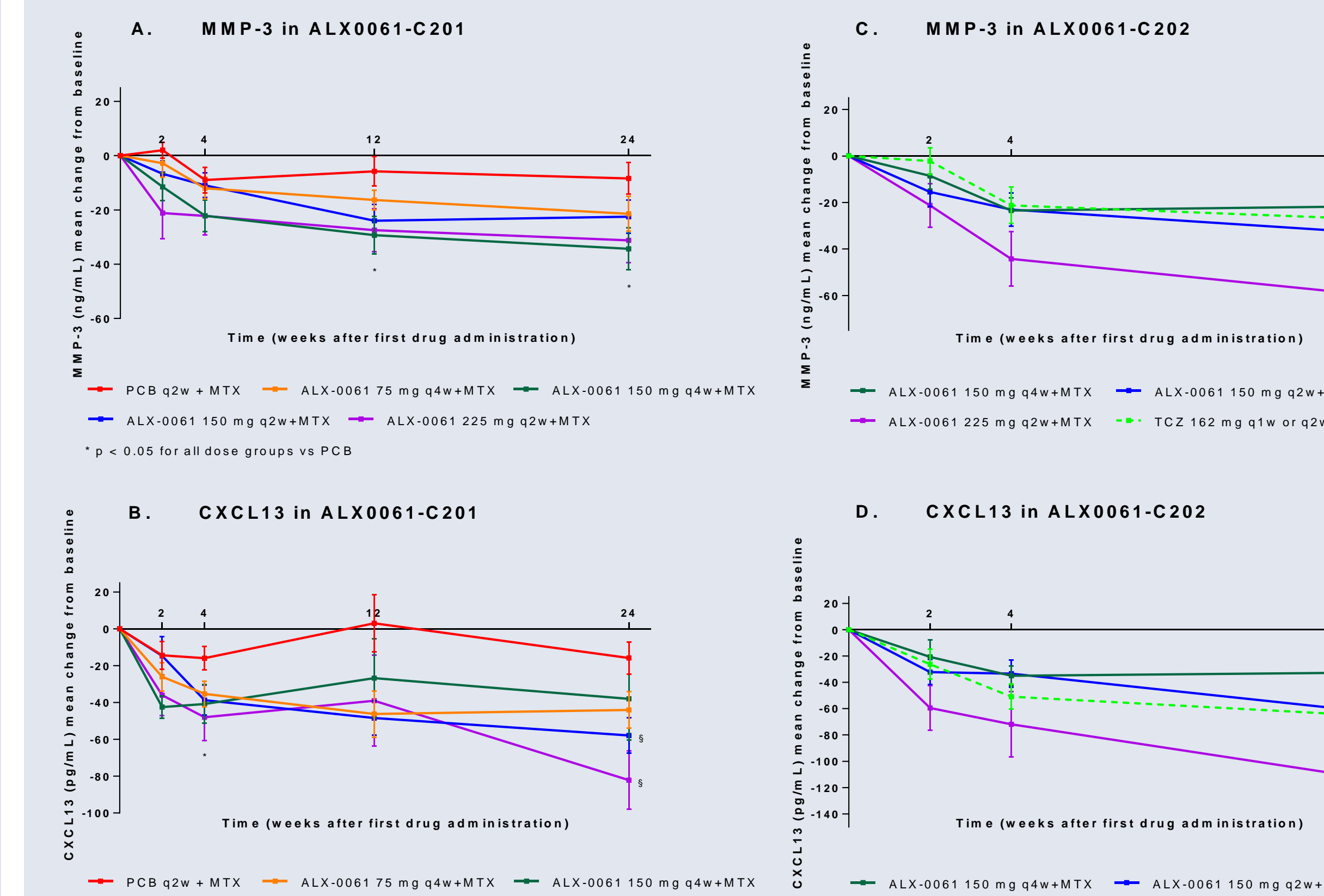
- Main efficacy and safety results of both RA phase 2b studies with vobarilizumab when used in combination with MTX (ALX0061-C201) and as monotherapy (ALX0061-C202) were previously reported (ref 5 and 6).

Results: PD biomarkers



- **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).

Results: Efficacy biomarkers



- **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 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 for vobarilizumab, with decreased CXCL13 levels over time, compared to baseline (Figure 5D).

References

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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.**