A Novel Individualised Treatment Approach in Open-Label Extension Study of Ozoralizumab (ATN-103) in Subjects with Rheumatoid Arthritis On a Background of Methotrexate

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Abstract

Background/Purpose:

Ozoralizumab (ATN-103), a novel TNF-α inhibitor, is a trivalent, bispecific Nanobody® that potently neutralizes TNF and binds to human serum albumin to increase its *in vivo* half-life.

Two singe ascending dose (SAD)/multiple ascending dose (MAD) studies in 313 patients (worldwide and Japan) with active RA on stable MTX background evaluated ozoralizumab's clinical activity and safety during 12 weeks of treatment. The 80 mg Q4W dosing regimen significantly improved disease activity measures compared with placebo. Patients completing the MAD trials were allowed to enroll in this 48-week open-label extension (OLE) study to evaluate the long-term safety and tolerability of ATN-103. An innovative dosing concept with individual dose escalation from 10 mg to max. 80 mg during first 12 weeks of treatment was tested in this OLE.

Methods:

Study start was defined as completion of 20-week follow-up visit in the MAD trials. Individualised dosing regimen was introduced with all patients starting on active treatment at 10 mg SC monthly. Subsequently, dose escalation to 30 mg and 80 mg monthly SC was dependent on patient's CDAI and safety. Primary objective was long-term safety and tolerability of ATN-103. Efficacy measures, as well as PK/PD, were included as exploratory endpoints.

Results:

266/313 patients (85%) enrolled in the OLE. Baseline mean age was 52 years, 80% female, DAS 6.11 and CDAI 42. Dropout rate was low with 13%, and 231/266 patients completed the study. 93% of patients reached individual final dose at or before week 12, 56% completed at 80 mg, 29% at 30 mg and 15% remained on the starting dose of 10 mg.

Safety: Treatment was well tolerated, most common AEs were infections (37.6%) with serious events in 3/100 patient-years.

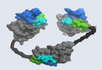
Efficacy: At study endpoint, ACR20, 50 and 70 scores were 84%, 63% and 32% respectively; 38% had DAS28_CRP <2.6; 132/230 patients (57%) had low or no disease activity; EULAR good/moderate response rate was 97%, with rapid and marked improvement of pain (47%) and morning stiffness (90%). 7/266 patients tested positive for neutralizing anti-drug antibodies (nADA) at any time during trial, all completed the study and 57% (4/7) had DAS28 <2.6. 0.75% of patients remained positive for nADA at end of study without effect on patient's safety or ability to achieve remission or improvement of disease activity.

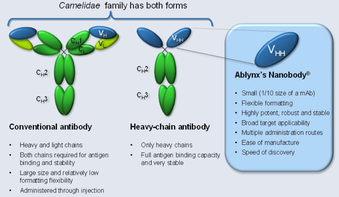
Conclusion:

The novel anti-TNF-α inhibitor ozoralizumab (ATN-103) enabled highly effective and well-tolerated individualised treatment. Specific molecular features of Nanobodies (small size, low immunogenic potential, manufacturability) contributed to the desired treatment outcome, with the majority of patients showing marked improvement in their disease activity and, moreover, once-induced remission could be maintained at doses less than 80 mg monthly. This treatment approach could prove beneficial to patients and minimize treatment costs.

Ozoralizumab (ATN-103)

- Novel, small biologic targeting TNF-α
  - Trivalent, bispecific Nanobody, 38 kD
  - Unique binding mode and no Fc
  - Albumin binding to extend half-life

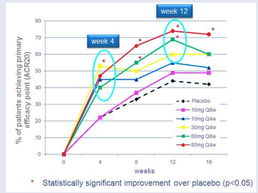




- A total of 346 patient-years of safety data is now available
  - So far, highly efficacious and excellent safety profile
  - Ozoralizumab at 80 mg Q4W met the primary endpoint (ACR20 at week 16) in Phase II POC, with significant improvements for other doses at various time points

MAD/POC study: top line results

- Double-blind, randomised MAD trial in 253 RA patients in EU, US and ROW
- 80 mg every 4 weeks (Q4W) achieved the primary efficacy endpoint for ACR20 at week 16: 72%
  - significant improvements in ACR50, EULAR, DAS28, tender joint count, swollen joint count, pain VAS, health VAS, physician and patient global assessments of disease activity at week 16
- No dose limiting toxicity or dose related AE and SAEs
- 2% subjects developed neutralizing anti-drug-antibodies (nADA)
  - no observed clinical effect of nADA



- 3 dose levels demonstrated significant improvements over placebo at any time: 30mg and 80mg Q4W, 80mg Q8W
- consistent improvement at week 8 and 12 with 80mg Q4W and 80mg Q8W
- week 16 significant improvement with 80mg Q4W –30mg Q4W and 80mg Q8W were equivalent

OLE: study design

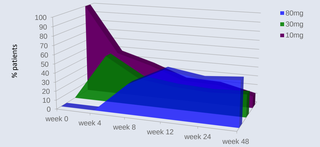
- All patients from Phase II double-blind studies were eligible to roll over into OLE study. 266/313 (85%) patients rolled over:
  - 211/253 (83%) from worldwide POC study
  - 55/60 (92%) from Japanese study
- Demographics

Characteristic	Mean / % (range)
Age	52 years (18-79 year)
Gender	Female 80%
Race	Caucasian 65%; Asian 25%; African American 8%
Weight & BMI	77.5 kg (37-152 kg) 28.9 kg/m2 (16.7 – 56.8 kg/m2)
Disease activity (DAS)	6.11 (3.85 – 8.50)
Disease activity (CDAI)	42 (18-76)

- Dosing: ozoralizumab 10, 30 or 80 mg Q4W for an additional 48 weeks
  - Initially, the starting dose was 10 mg Q4W for all subjects
  - At weeks 4, 8 and 12, subjects could have their dose increased to the next higher available dose level at the investigator's discretion and based on the RA disease activity score (CDAI)
  - The investigator could also decrease a dose if the subject could not tolerate the dose level. After the Week 12 visit, no dose adjustments based on individual subject response were allowed

Individualised dosing

- All patients started the individualised dosing regimen at 10 mg Q4W with dose adjustment based on CDAI
- Based on the safety and efficacy results of the MAD/POC study, dose increase to 30 mg Q4W or 80 mg Q4W was allowed beyond week 12 and regardless of CDAI
  - All patients had been started on the individualise dosing scheme prior to the protocol change



- 231/266 (87%) completed the 48 weeks dosing regimen
  - 129 patients (56%) completed at 80mg
  - 67 patients (29%) completed at 30mg
  - 35 patients (15%) completed at 10mg

Results: Safety

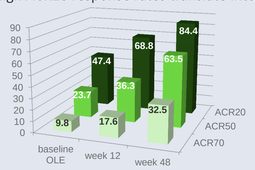
- Dosing: 93% of patients reached their individual final dose at or before week 12
- 87% completed the 48 weeks dosing regimen
  - 56% completed at 80 mg
  - 29% at 30 mg
  - 15% remained on the starting dose of 10 mg
- Treatment was well tolerated, with low incidence of SAEs
  - safety comparable with MAD/POC
  - adverse event rates within expectations and serious infections remain rare (i.e. 3 events in 100 patient-years)
  - dropout rate was low (13%); 231/266 patients completed the study

Adverse Events (treatment emergent)	ozoralizumab N=266 (% patients)
All adverse events	179 (67.3)
Infection	100 (37.6)
Laboratory changes	32 (12.0)
Allergic reaction	11 (4.1)
Rash	8 (3.0)

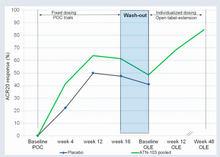
Serious Adverse Events (treatment emergent)	ozoralizumab N=266 (% patients)
All serious adverse events	33 (12.4)
SAE infection	6 (2.3)
SAE cardiac	7 (2.6)
SAE gastrointestinal	4 (1.5)
SAE neoplasm	4 (1.5)

Results: ACR20

- High ACR20 response rates translate into high ACR50 and ACR70



- Evolution of ACR20 response during MAD/POC, drug wash-out period and OLE (pooled data)

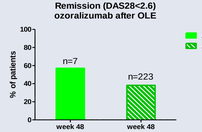


Results: Other clinical scores and nADA profile

- Other clinical scores also show very strong response at week 48

Efficacy Parameter	Change from Baseline (% patients)
DAS28 improvement	3.11 (51%)
DAS28 remission	38%
EULAR response (good + moderate)	97%
Pain improvement	47%
CDAI score improvement	76%
Morning Stiffness improvement	90%

- 2.6% (7/266) tested positive for neutralizing (n)ADA, of which 2 (0.75%) were persistent and 5 (1.9%) transient. All completed the trial
- The majority (4/7) achieved remission (DAS28 < 2.6).



Conclusion

- Ozoralizumab is a novel anti-TNF-α inhibitor and combines inherent Nanobody features (small size, stability, and low immunogenicity potential) with modular engineering (target specificity and potency, half life extension, tissue penetration)
- Ozoralizumab enabled highly effective and well-tolerated individualised treatment:
  - adverse event rates were within expectations and serious infections remained rare (i.e. 3 events in 100 patient-years)
  - 102/231 patients (44%) remained on doses <80 mg Q4W
  - high ACR20 rate (84%) at week 48, augmented by translation to high ACR50 and even ACR70 rates
  - 57% of patients reached low or no disease activity at end of study, including 38% of patients in DAS28 remission
  - low numbers of nADA: 0.75% of patients tested positive for nADA at end of study, without observed safety signals, or impact on efficacy parameters DAS28 remission and disease activity scores.
- Ozoralizumab delivered on safety and efficacy expectations and has the potential to demonstrate clinical benefit without clinically relevant immunogenicity, while minimizing treatment costs. This could lead to an important competitive and differentiated position in the future treatment of RA

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