EFFICACY AND SAFETY OF THE BIASED MELANOCORTIN RECEPTOR AGONIST AP1189/RESOMELAGON IN COMBINATION WITH METHOTREXATE IN DMARD-NAÏVE RHEUMATOID ARTHRITIS PATIENTS: THE EXPAND TRIAL

ASGER R. BIHLET[1], PHILIP G. CONAGHAN[2], THOMAS BOESEN[3], METTE A. JENSEN[3], ALEJANDRO C. MONDRAGÓN[1], EMA E. PETERSEN[1], CATHRINE B. BAK[1], THOMAS E. N. JONASSEN[3].

[1]NBCD, SØBORG, DENMARK, [2]UNIVERSITY OF LEEDS & NIHR LEEDS BIOMEDICAL RESEARCH CENTRE, UNITED KINGDOM, [3]SYNACT PHARMA APS, HOLTE, DENMARK

Contact: Asger R. Bihlet
abi@nbcd.com

BACKGROUND & PURPOSE

AP1189/resomelagon is a novel, first-in-class, oral, biased melanocortin (MC)1 and MC3 receptor agonist in development for Rheumatoid Arthritis (RA) treatment. Through multiple actions including reduction in pro-inflammatory cells and cytokines and increased macrophage efferocytosis, it **induces inflammation resolution** in animal models (Figure 1). In a Phase 2a study in MTX-naïve RA patients, AP1189 100 mg+MTX showed a significant treatment effect compared to placebo+MTX treatment on ACR response and CDAI at week 4. **The purpose of the current randomized controlled trial was to evaluate 12 weeks treatment in MTX-naïve RA patients with high disease activity.**

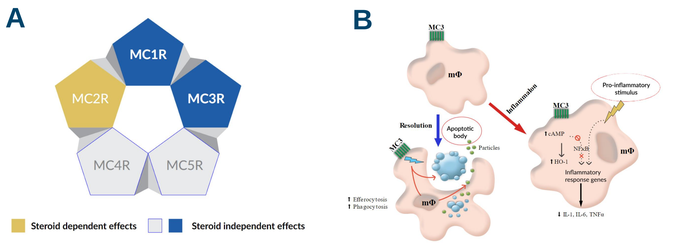


Figure 1: Overview of Melanocortin receptors (A) and the role of MC3 receptor in inflammation resolution (B)

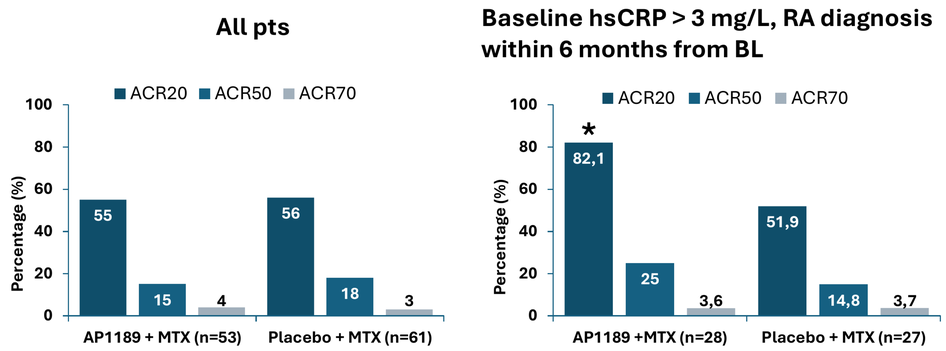
METHODS

The EXPAND trial was a **12-week, double-blind, placebo-controlled Phase 2b** clinical trial that enrolled **MTX-naïve patients presenting with CDAI > 22.** The **primary efficacy endpoint** was defined as the proportion of patients reaching **ACR20** at the completion of the 12-week treatment period. MTX therapy was initiated concurrently with AP1189/placebo. Participants were **randomized to receive either 100 mg AP1189 or matched placebo** tablets once daily **in addition to MTX**. Additional efficacy assessments included CDAI, DAS28-CRP and HAQ-DI. Glucocorticoid treatment was only permitted as rescue treatment after 4 weeks of study treatment. Dichotomous endpoints were analyzed using a CMH test adjusted for investigational site and other covariates.

A	AP1189 (N=63)	Placebo (N=64)
Baseline Age (years) Mean (SD)	58.0(11.6)	55.0(12.3)
Sex, [n (%)] Female	54(85.7)	56(87.5)
Baseline BMI (kg/m²) Mean (SD)	28.0(5.8)	26.2(4.4)
Baseline CDAI Score Mean (SD)	42.04(12.11)	40.31(10.14)
Baseline DAS28 (CRP) Mean (SD)	4.89(0.66)	4.68(0.60)

B	AP1189 (N=28)	Placebo (N=27)
Baseline Age (years) Mean (SD)	56.7(12.3)	56.9(12.5)
Sex, [n (%)] Female	24(85.7)	23(85.2)
Baseline BMI (kg/m²) Mean (SD)	28.1(5.73)	26.2(5.1)
Baseline CDAI Score Mean (SD)	44.37(12.41)	37.97(8.48)
Baseline DAS28 (CRP) Mean (SD)	6.07(0.72)	5.67(0.56)

Table 1: Main baseline demographics of the (ITT) population (A) and subgroup with newly diagnosed RA and active inflammation



*: p<0.023 vs placebo (Fischer exact test)

Figure 2: Overview of ACR response in the ITT and subgroup with newly diagnosed RA and active inflammation

System Organ Class Preferred Term	AP1189 (N=63) Subject[a] n (%)	AP1189 (N=63) Events n	Placebo (N=64) Subject[a] n (%)	Placebo (N=64) Events n
Any Treatment-Emergent Adverse Event				
Overall	28(44.4)	46	27(42.2)	44
Gastrointestinal disorders				
Abdominal pain upper	4(6.3)	4	2(3.1)	2
Nausea	4(6.3)	4	2(3.1)	2
Vomiting	4(6.3)	7	0	0
Infections and infestations				
Upper respiratory tract infection	4(6.3)	4	4(6.3)	6
Investigations				
Hepatic enzyme increased	2(3.2)	2	3(4.7)	4
Alanine aminotransferase increased	1(1.6)	1	2(3.1)	2
Blood and lymphatic system disorders				
Anaemia	2(3.2)	2	1(1.6)	1

Table 2: Overview of Treatment-Emergent Adverse Events reported with a frequency of at least 3 % in any treatment group

METHODS - CONTINUED

Changes from baseline in secondary efficacy endpoints will be analyzed using a mixed model repeated measures (MMRM) with fixed effects treatment, visit (Week 2 through Week 12), and treatment-by-visit interaction and covariates investigational site and other covariates. **A post hoc analysis was performed in patients who were newly diagnosed (RA diagnosis within 6 months of baseline) and who had elevated hsCRP.**

RESULTS

Of **127 randomized patients**, 114 completed the study. Baseline characteristics are shown in Table 1. **Fifty-four percent** of the patients had **hsCRP>3 mg/L,** and 22% of patients had > 6 months between RA diagnosis and initiation of study treatments. In the **primary endpoint** analysis as shown in Figure 1, there was **no difference** between AP1189+MTX and placebo+MTX treatment; similarly, there were no significant differences in the secondary efficacy outcomes. **Adverse events (AEs) were equally distributed between the groups, as shown in Table 2 with no signs of liver- or other abnormalities.** Three subjects on AP1189 discontinued treatment due to upper GI AEs. **A post hoc analysis** in newly diagnosed patients with elevated hsCRP identified **a consistently improved treatment response** to AP1189 (n=28) relative to placebo (n=27) treatment - patients achieving **ACR20: AP1189+MTX 82% vs placebo+MTX 52%;** mean±SD reduction in DAS28-CRP: AP1189+MTX 1.9±1.2 vs placebo+MTX 1.2±1.1; CDAI: AP1189+MTX 24.6±14.2 vs placebo+MTX 14.7±12.3; and HAQ-DI: AP1189+MTX 0.7±0.7 vs placebo+MTX 0.3±0.7.

CONCLUSION

While there was no observed difference between AP1189 in combination with MTX and placebo+MTX in the study cohort as a whole, post hoc analyses in newly diagnosed RA patients with high disease activity including elevated hsCRP, together with safety data, suggest that AP1189 could be a promising treatment option in this patient group.

Financial Disclosures: The trial was sponsored by Synact Pharma. ARB, EEP: Full-time employee and shareholder of NBCD A/S. CBB, ACM: Full-time employee of NBCD A/S. MAJ: Employee of Synact Pharma. TB, TENJ: Full-time employee and shareholder of Synact Pharma. PGC: Speaker, consultant for: Eli Lilly, Eupraxia, Formation Bio, Galapagos, Genascence, GSK, Grunenthal, Janssen, Kolon TissueGene, Levicept, Medipost, Moebius, Novartis, Pacira, Sandoz, Stryker & Takeda