This study was sponsored by MedImmune Ltd.

The GM-CSF Pathway and Macrophages in RA

- GM-CSF is a pro-inflammatory cytokine that plays a central role in RA through the activation, differentiation, and survival of macrophages and neutrophils.
- Inhibition of the GM-CSF pathway during inflammation (eg, RA and inflammation) may inhibit differentiation, adhesion, chemotaxis and activation of multiple inflammatory and immune cells (eg, monocytes, macrophages, neutrophils, dendritic cells, etc).
- The GM-CSF pathway is being studied as a novel therapeutic target for inflammation and pain.

Mavrilimumab Phase 2a Multicenter, Randomised, Double-blind, Placebo-controlled Study (EARTH; MI-CP219)

- 284 subjects (EU [n=233] & Japan [n=51]) with moderate-to-severely active RA
- Inclusion criteria: 18-80 years; RA ≥6 months; DAS28 ≥3.2 at screening and baseline; stable MTX ≥4 weeks prior to screening; RF+ and/or ACPA+
- Exclusion criteria: active or latent TB; clinically significant chronic or recurrent infection including hepatitis C or chronic active hepatitis B; previous treatment with ≥1 biologic therapy for RA that was discontinued for lack of efficacy.
Overview of Analysis

- Objective: to evaluate the relationship between RA disease activity, pain and physical function in subjects with moderate-to-severely active RA treated with mavrilimumab
  - RA disease activity: DAS28-CRP
  - Pain: self-reported VAS
  - Physical function: SF-36 PCS
- SF-36 is a 39-item questionnaire which measures QOL across eight domains including both physical and mental components
SF-36 PCS Responders by Visit

- Mavrilimumab 100 mg: 70.2%
- Placebo: 40.2%

ITT population
SF-36 PCS responder, SF-36 PCS increase ≥3.1 from baseline
*p<0.05, **p<0.001, mavrilimumab vs. placebo


Strong Relationship Between Pain and SF-36 PCS

- On average, a subject with a 20 mm improvement in pain had a 5.71 improvement in SF-36 PCS (95% CI: 4.04, 7.38)

Linear regression used for statistical analysis:
SF-36 PCS change from baseline = 1.29 – 0.11*change in pain (placebo)
SF-36 PCS change from baseline = 3.75 – 0.10*change in pain (mavrilimumab)

P-value for regression line: <0.001 for placebo and 0.008 for mavrilimumab

15 Spidergram of SF-36 PCS Domains at Week 12

- Treatment with mavrilimumab 100 mg exceeded the Minimally Important Difference (MID) from placebo across 5 of 8 SF-36 PCS domains

Conclusions

- In subjects with moderate-to-severely active RA, mavrilimumab (especially at 100 mg) produced rapid and clinically meaningful effects across a number of disease activity parameters and patient-reported outcomes, with no unexpected safety concerns (data not shown)
- Early and sustained improvements were observed in:
  - DAS28-CRP
  - Patient-assessed pain (VAS)
  - General physical health (SF-36 PCS)
- Little change was observed in mental component between mavrilimumab 100 mg and placebo at Week 12 (data not shown)
- These results support further investigation in Phase 2b in both DMARD-IR and TNF-IR subjects
Current Status of Mavrilimumab

- Two ongoing Phase 2b studies
  - NCT01712399 (CD-IA-CAM-3001-1109; EARTH EXPLORER 2)
  - NCT01706926 (CD-IA-CAM-3001-1107; EARTH EXPLORER 1)
- Open-label extension study for subjects who have participated in one of the qualifying development program studies (NCT01712399; CD-IA-CAM-3001-1109; EARTH Explorer X)

Mavrilimumab Phase 1 Study: Single Ascending Dose

- At single IV doses up to 10 mg/kg, mavrilimumab had an adequate safety and tolerability profile in subjects with mild-to-moderate RA
- PK analyses were consistent with an 'antigen sink' and a half-life of 8–15 days at 3 and 10 mg/kg doses, respectively
- Anti-mavrilimumab antibodies were not detected in any subject over the study and safety follow-up periods
- The effects observed on acute phase reactants following single infusion of mavrilimumab suggest a potential effect on disease activity

Acknowledgments

On behalf of the EARTH study team, the authors would like to thank the subjects and investigators who contributed to the study:

**Japanese investigators**

Makoto Asaka, Koichiro Kawabata, Tetsuya Komoda, Kazuaki Komori, Yukihiro Koyama, Kiyoshi Migita, Hisaaki Miyahara, Toshiaki Miyamoto, Eiichi Suematsu, Kazunori Sugimoto, Tsutomu Takeuchi, Yoshiya Tanaka, Shigeto Touma, Yukitaka Ueki, Yukitomo Urata, Kanjiro Yamanaka

**European investigators**


**Questions?**

- On behalf of the EARTH study team, the authors would like to thank the subjects and investigators who contributed to the study.