Presentation # 1733

Early and Sustained Improvement In Pain and Physical Function As Measured By Visual Analog Scale and Short Form-36 Physical Component Summary Score In Rheumatoid Arthritis Patients Treated With Mavrilimumab, An Investigational Anti-GM-CSFR-Alpha Monoclonal Antibody, In a Phase 2a Study

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Disclosures

- Gerd-R. Burmester and Duncan Porter are consultants to MedImmune
- Didier Saurigny, David Close, Alex Godwood, and Ancilla W. Fernandes are employees of MedImmune. Yoojung Yang was an employee of MedImmune during the conduct of the study
- Tsutomu Takeuchi and Olga Barbarash are investigators on the EARTH study
- This study was sponsored by MedImmune Ltd

Impact of RA on Patient Quality of Life

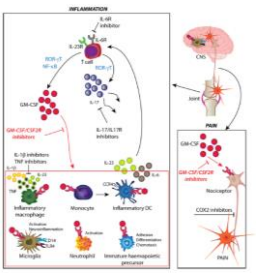
- The chronic and debilitating nature of RA negatively impacts upon patients' functional and overall health status, and reduces quality of life (QOL)[1–5]
  - Pain and fatigue associated with RA are debilitating symptoms for patients living with RA[4,5]
- Health-related QOL is significantly compromised among patients with RA[6,7] compared with the general population, and compared with other chronic diseases (eg lupus, fibromyalgia and osteoarthritis)
- There is a need for additional RA treatments that have a positive effect on pain and QOL, as well as on the day-to-day signs and symptoms of RA

1. Scott DL, Wolfe F, Huizinga TW. Lancet 2010;376(9746):1094–108
2. Russell AS. Pharmacoeconomics 2008;26(10):831–46
3. Michaud K, Wolfe F. Best Pract Res Clin Rheumatol 2007;21(5):885–906
4. Strand V, Singh JA. Am J Manag Care 2007;13(Suppl 9):S237–51
5. Strand V, Khanna D. Clin Exp Rheumatol 2010;28(Suppl 59):S32–40
6. Data on file. MedImmune. Study MI-CP219
7. Hammond G, Raju A, Parasuraman S, et al. Poster (82)–731. ACR Annual Meeting, Philadelphia, USA, 17–21 Oct 2009

Role of 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[1]
  - Inhibition of the GM-CSF pathway during inflammation (eg, RA joint inflammation) may inhibit differentiation, adhesion, chemotaxis and activation of multiple inflammatory and immune cells (eg, monocytes, macrophages, neutrophils, dendritic cells, etc)[2]
  - Inhibition of the GM-CSF pathway may reduce the production of other inflammatory cytokines, such as IL-1, TNF, IL-23 and IL-6[2]
- The GM-CSF pathway is being studied as a novel therapeutic target for inflammation and pain[2]

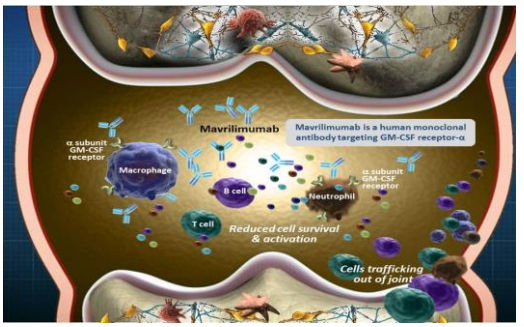
The effects of GM-CSF inhibition on inflammation and pain[2]



GM-CSF, Granulocyte-macrophage colony-stimulating factor

1. Cornish AL, Campbell IK, McKenzie BS, Chatfield S, Wicks IP. Nat Rev Rheumatol 2009;5(10):554–9
2. van Nieuwenhuijze A, Koenders M, Roeleveld D, Sleeman MA, van den Berg W, Wicks IP. Mol Immunol 2013;56(4):675–82

Mavrilimumab: A Human Monoclonal Antibody Targeting GM-CSF Receptor-α

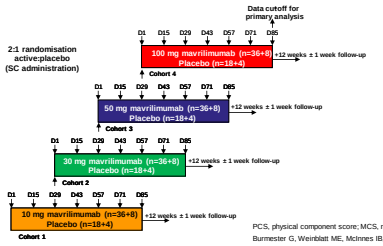


MedImmune data on file

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 (1987 ACR criteria); 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



Primary endpoint

- DAS28-CRP response (decrease >1.2 from baseline at Week 12)

Other endpoints

- DAS28-CRP remission
- ACR20 / 50 / 70
- HAQ-DI
- Pain VAS
- SF-36 PCS and MCS
- PK
- Safety / tolerability profile

PCS, physical component score; MCS, mental component score

Burmester G, Weinblatt ME, McInnes IB, et al. Ann Rheum Dis 2013;72(9):1445–52

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

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EARTH Study Baseline Disease Characteristics

Baseline characteristics	Placebo (n=92)	Mavrilimumab 10 mg (n=48)	Mavrilimumab 30 mg (n=49)	Mavrilimumab 50 mg (n=48)	Mavrilimumab 100 mg (n=47)
DAS28-CRP*	5.4	5.2	5.4	5.1	5.3
Swollen joint count*	13.9	14.6	13.5	11.7	13.1
Tender joint count*	22.6	20.4	22.2	23.1	20.9
Patient pain (mm)*	61.0	59.2	59.1	56.4	55.8
Patient global disease activity (mm)*	61.3	59.7	60.8	58.0	57.3
Physician global disease activity (cm)*	6.2	5.4	6.1	6.0	5.6
SF-36 PCS	33.8	33.7	33.8	34.0	33.3
HAQ-DI*	1.4	1.3	1.3	1.4	1.5
CRP (mg/l)**	5.6	4.2	5.5	4.9	5.9
ESR (mm/hr)**	31.7	31.4	39.1	35.7	31.7

*Mean; **geometric mean

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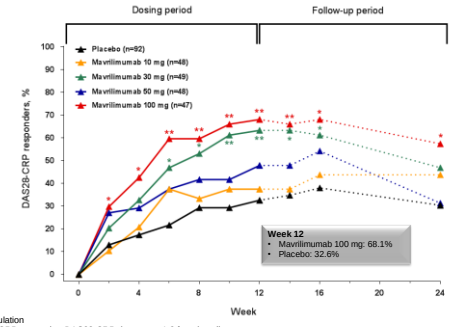
Intent-to-treat (ITT) population

DAS28-CRP Responders by Visit



ITT population
DAS28-CRP responder, DAS28-CRP decrease >1.2 from baseline
*p<0.05; **p<0.001, mavrilimumab vs. placebo

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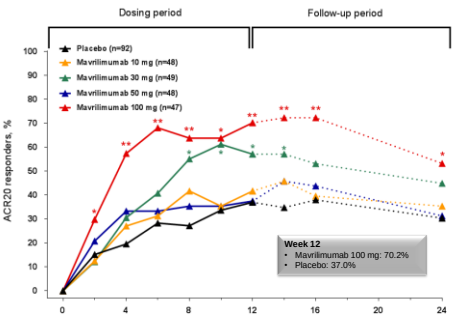
ACR20 Responders by Visit



ITT population
*p<0.05; **p<0.001, mavrilimumab vs. placebo

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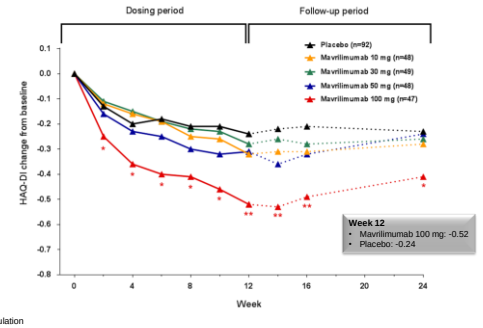
HAQ-DI Change from Baseline by Visit



ITT population
*p<0.05; **p<0.001, mavrilimumab vs. placebo

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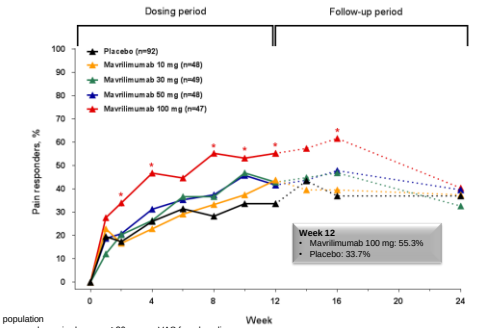
Pain VAS Responders by Visit



ITT population
Pain responder, pain decrease ≥20 mm on VAS from baseline
*p<0.05; **p<0.001, mavrilimumab vs. placebo

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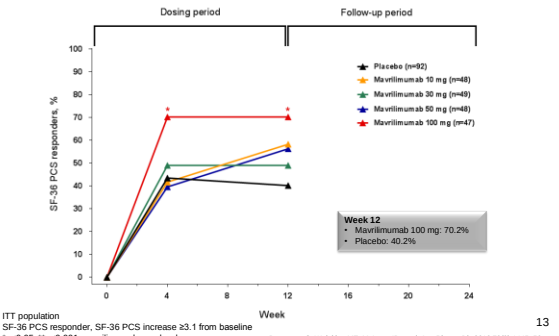
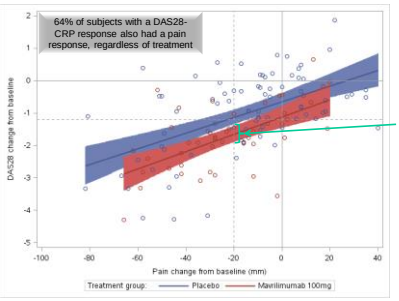
SF-36 PCS Responders by Visit



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

Burmester G, Weinblatt ME, McInnes IB, et al. Ann Rheum Dis 2013;72(9):1445–52

Change in Pain is Strongly Related to Changes in DAS28

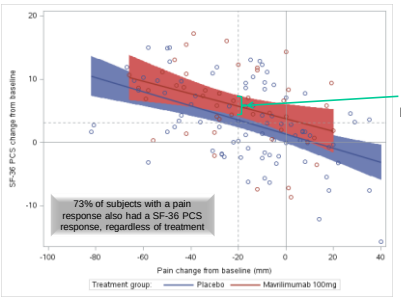


On average, a subject with a 20 mm improvement in pain had a 1.66 improvement in DAS28-CRP (95% CI: -1.91, -1.41)

The blue and red areas indicate the 95% CIs around each regression line

Linear regression used for statistical analysis:
DAS28 change from baseline = -0.64 + 0.02*change in pain (placebo)
DAS28 change from baseline = -1.13 + 0.03*change in pain (mavrilimumab)
P-value for regression line: <0.0001 for placebo and <0.0001 for mavrilimumab

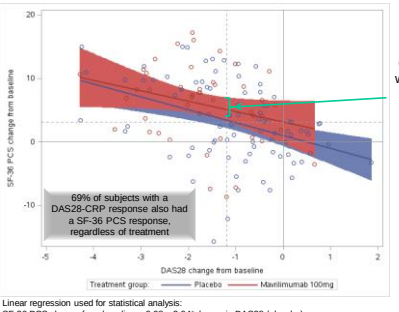
Strong Relationship Between Pain and SF-36 PCS



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

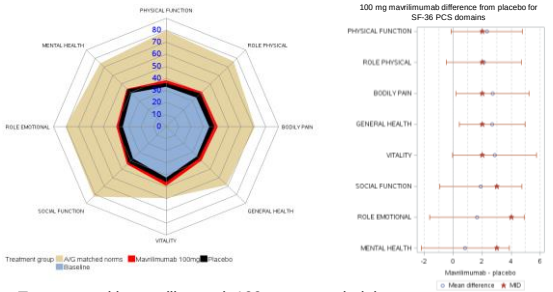
Change in DAS28 is Not Closely Related With Changes in SF-36 PCS



On average, a subject with a 1.2 improvement in DAS28-CRP had a 5.1 improvement in SF-36 PCS (95% CI: 3.1, 7.0)

Linear regression used for statistical analysis:
SF-36 PCS change from baseline = 0.98 – 2.04*change in DAS28 (placebo)
SF-36 PCS change from baseline = 3.09 – 1.64*change in DAS28 (mavrilimumab)
P-value for regression line: 0.0002 for placebo and 0.06 for mavrilimumab

Spidergram of SF-36 PCS Domains at Week 12



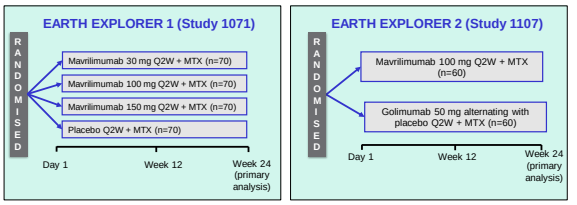
- Treatment with mavrilimumab 100 mg exceeded the Minimally Important Difference (MID) from placebo across 5 of 8 SF-36 PCS domains

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
  - NCT01706926 (CD-IA-CAM-3001-1071; EARTH EXPLORER 1)
  - NCT01715896 (CD-IA-CAM-3001-1107; EARTH EXPLORER 2)
- 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)



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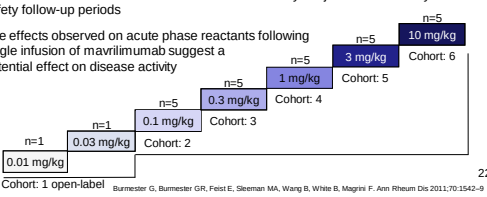
Daniela Yaneva	Elena Zonova			

Questions?

Mavrilimumab Phase 1 Study: Single Ascending Dose

- Double-blind, placebo-controlled, 5:1 randomisation mavrilimumab:placebo
- Single ascending IV doses once, with up to 24 weeks' follow-up
- 32 male and female subjects with adult onset RA ≥6 months

- 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



Burmester G, Burmester GR, Feist E, Sleeman MA, Wang B, White B, Magrini F. Ann Rheum Dis 2011;70:1542–9