No. OP0228

Otilimab (GSK3196165) An Investigational Anti-GM-CSF Monoclonal Antibody, Improves Patient-Reported Outcomes in a Phase IIb Study of Patients With Rheumatoid Arthritis (RA)

Chris Buckley[1], Jesus A Simon Campos[2], Vyacheslav Zhdan[3], Brandon Becker[4], Deven Chauhan[5], Katherine Davy[6], Carol Hawkes[5], David Inman[6], Mark Layton[6], Jatin Patel[5], Didier Saurigny[6], Nina Mitchell[6], Russell Williamson[7] and Paul Peter Tak[8]

[1]University of Birmingham, Birmingham, UK; [2]Köhler & Milstein Research, Mérida, Mexico; [3]M.V. Sklifosovskyi Poltava Regional Clinical Hospital, Poltava, Ukraine; [4]GSK, Upper Providence, Pennsylvania, PA, USA; [5]GSK, Stockley Park, UK; [6]GSK, Stevenage, Hertfordshire, UK; [7]Formerly GSK, Stockley Park, Uxbridge, UK; [8]Formerly GSK, Stevenage, Hertfordshire, UK

The BAROQUE study (NCT02504671; study 201755) was funded by GlaxoSmithKline (GSK)

Presenter Disclosure Information

CB has received consulting fees or other remuneration from GSK

JASC and VZ report no conflicts of interest

BB, DC, CH, KD, DI, ML, DS and JP are employees and stockholders in GSK

NM, RW, and PPT were employees of GSK at the time of study conduct

Acknowledgments

Medical writing support was provided by Olga Conn, PhD, of Fishawack Indicia Ltd, UK, funded by GSK

Our thanks to the study participants and study site staff

Study Principal Investigators

Bulgaria *Goranov, Batalov, Oparanov, Stolilov*	**Canada** *Aggarwal*	**Czech Republic** *Blahova, Dokoupilova, Galatikova, Hejlova, Horvath*	**Estonia** *Ojassalu, Talli*	**Germany** *Neeck*	**Hungary** *Drescher, Szombati, Toth*
Mexico *Riso, Simon Campos, Xibille*	**Poland** *Jaworski, Jedrychowicz-Rosiak, Jeka, Kulig, Mastalerz, Racewicz, Wojciechowski*	**Russian Federation** *Ershova, Kropotina, Mikhaylova, Nikulenkova, Platonov, Repin, Shilkina, Yakushin*	**South Africa** *Ally, Louw, Reuter*	**Ukraine** *Gasanov, Grishyna, Kuzmina, Nadshkevych, Shevchuk, Stanislavchuk, Vasylets, Vyshnyvetskyy, Yatsyshyn, Zhdan*	**United Kingdom** *Buckley, Emery*

NCT02504671; this study (201755) was funded by GSK.

Background

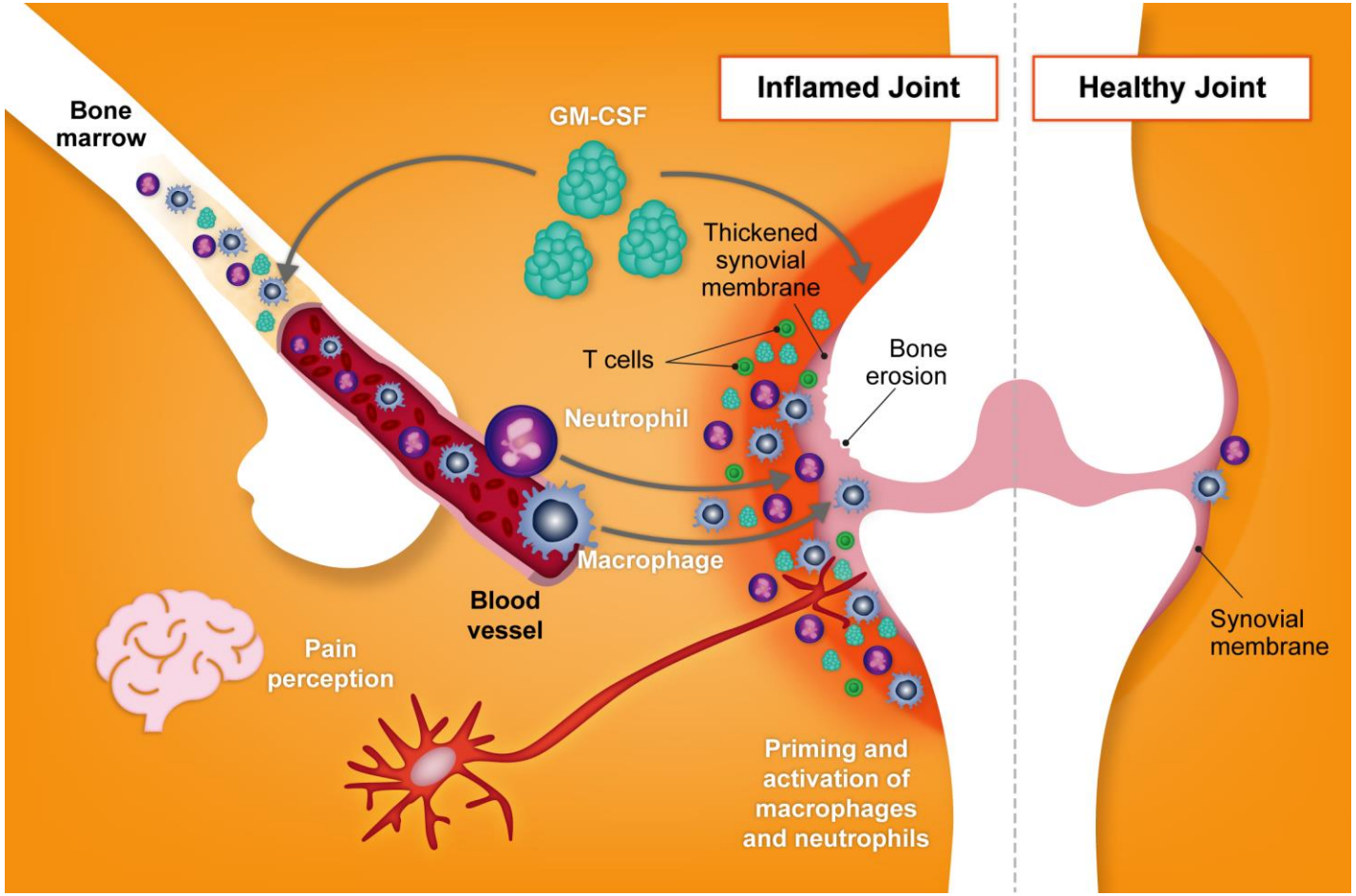
Otilimab is a human mAb that inhibits GM-CSF, a **key driver** in a broad range of immune-mediated conditions[1]

In pathological situations, **GM-CSF** is produced by multiple cell types **in response to immune activation**[1]

GM-CSF exacerbates monocyte/macrophage activation to produce cytokines, including IL-6, IL-1 and TNF, and induces and perpetuates inflammation, **which can cause severe tissue damage**[1-4]

In pathological situations, **GM-CSF** may be involved in the **pain response** as evidenced by inhibition of pain in pre-clinical models following inhibition/absence of **GM-CSF**[5-7]

GM-CSF levels are elevated in disease-relevant tissues of patients with RA[8,9]



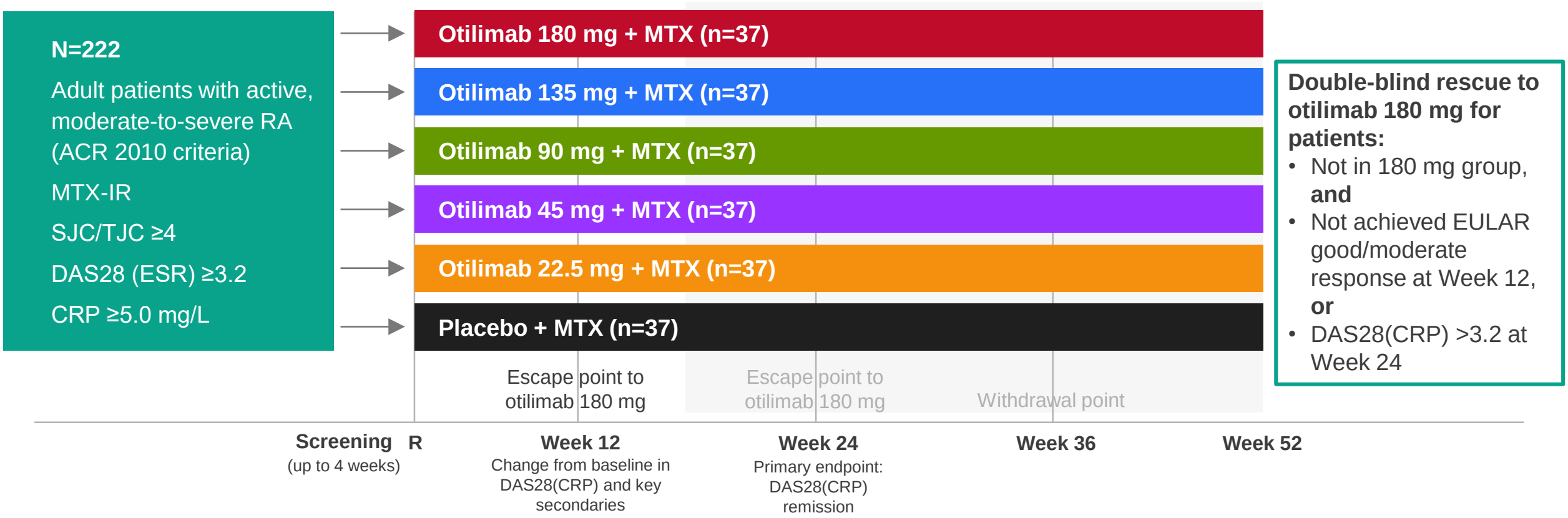
GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; mAb, monoclonal antibody; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

[1]Wicks IP, Roberts AW. *Nat Rev Rheumatol.* 2016; 12:37–48; [2]Budai MM, et al. *J Leukoc Biol.* 2017; 101:1335–47; [3]Fleetwood AJ, et al. *J Immunol.* 2007; 178:5245–52; [4]Hamilton JA, et al. *Nat Rev Drug Disc.* 2016; 16:53–70; [5]Achuthan A, et al. *J Clin Invest*. 2016; 126:3453–66; [6]Conaghan PG, et al. *Nat Rev Rheumatol*. 2019; [7]Cook et al. *JCI Insight.* 2018;3:e99249; [8]Avci AB, et al. *Clin Exp Rheumatol.* 2016, 34(4 Suppl 98):39–44; [9]Bell AL, et al. *Rheumatol Int.* 1995, 14:177–82.

Randomized, Phase IIb, Multicenter, Double-blind, Parallel-group, Placebo-controlled Study

Design employed novel features to support a 52-week study

Otilimab or placebo administered as 5-weekly SC injections, followed by bi-weekly injections



ACR, American College of Rheumatology; CRP, C-reactive protein; DAS28, Disease Activity Score for 28 different joints; ESR, erythrocyte sedimentation rate; IR, inadequate response; MTX, methotrexate; R, randomization; RA, rheumatoid arthritis; SC, subcutaneous; SJC, swollen joint count; TJC, tender joint count.

Baseline RA Disease Characteristics

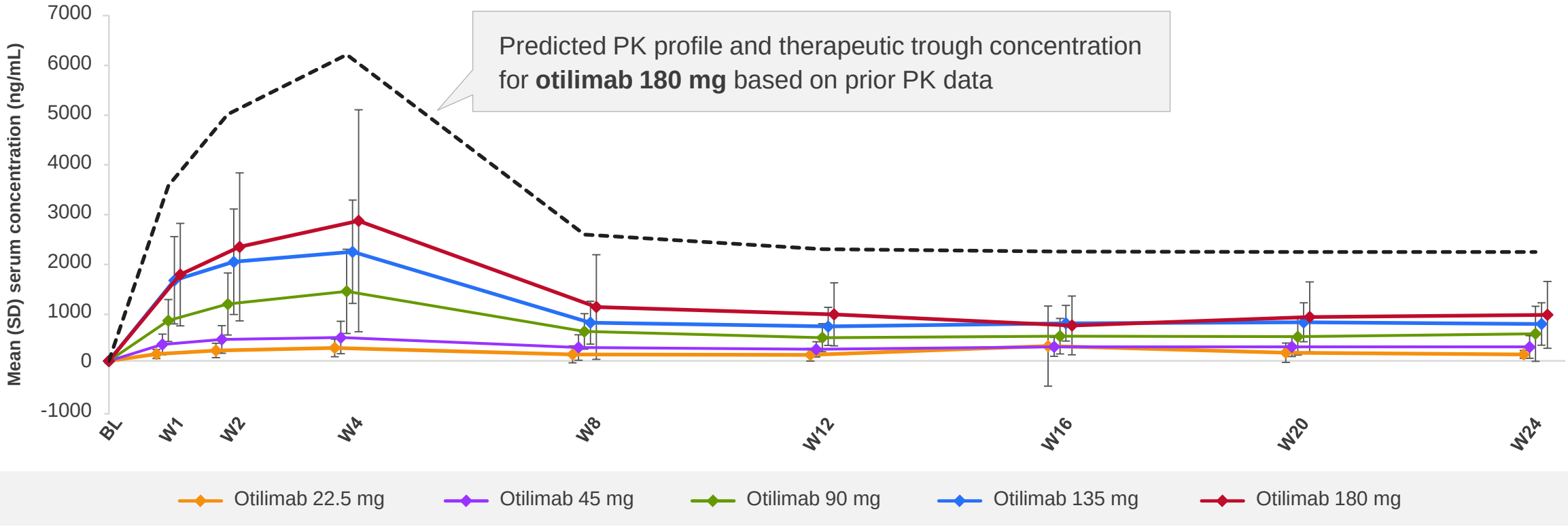
Well balanced, but with high DAS28(CRP), Pain, and HAQ-DI

	Placebo (n=37)	Otilimab 22.5 mg (n=37)	Otilimab 45 mg (n=37)	Otilimab 90 mg (n=37)	Otilimab 135 mg (n=37)	Otilimab 180 mg (n=37)
DAS28(CRP), mean (SD)	**6.2** (0.8)	**6.4** (0.8)	**6.1** (0.7)	**6.2** (0.8)	**6.3** (0.9)	**6.0** (0.9)
CDAI (0–76), mean (SD)	**45.7** (13.5)	**45.2** (11.8)	**42.8** (12.1)	**44.5** (12.6)	**45.3** (13.5)	**42.5** (13.9)
Pain (100 mm VAS), mean (SD)	**66.1** (16.7)	**71.2** (15.8)	**70.1** (17.3)	**65.8** (20.4)	**67.1** (19.3)	**61.6** (20.6)
FACIT-Fatigue, mean (SD)	**24.7** (8.6)	**25.9** (9.1)	**26.5** (9.2)	**25.1** (9.9)	**24.3** (9.6)	**27.6** (12.4)
PtGA (100 mm VAS), mean (SD)	**66.0** (15.6)	**72.5** (14.2)	**71.6** (14.9)	**68.2** (17.6)	**69.6** (17.0)	**63.2** (16.6)
SF-36 (Mental Score), mean (SD)	**42.5** (9.4)	**41.8** (9.9)	**42.3** (9.4)	**40.7** (10.4)	**41.4** (12.6)	**41.3** (13.1)
SF-36 (Physical Score), mean (SD)	**29.0** (5.6)	**28.6** (6.1)	**28.6** (7.0)	**30.2** (6.6)	**28.5** (7.0)	**31.8** (7.9)
HAQ-DI, mean (SD)	**1.77** (0.59)	**1.72** (0.48)	**1.87** (0.41)	**1.73** (0.54)	**1.80** (0.56)	**1.63** (0.71)
hsCRP (mg/mL), median (range)	**12.9** (2−66)	**19.5** (3−135)	**14.7** (1−158)	**13.7** (1−99)	**15.6** (1−261)	**12.7** (2−103)

Other baseline characteristics have been presented previously.
CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score 28-joint count; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C-reactive protein; PtGA, Patient's Global Assessment of Arthritis Disease Activity; RA, rheumatoid arthritis; SD, standard deviation; SF-36, 36-item short-form health survey; VAS, visual analogue scale.

Otilimab Trough Concentration

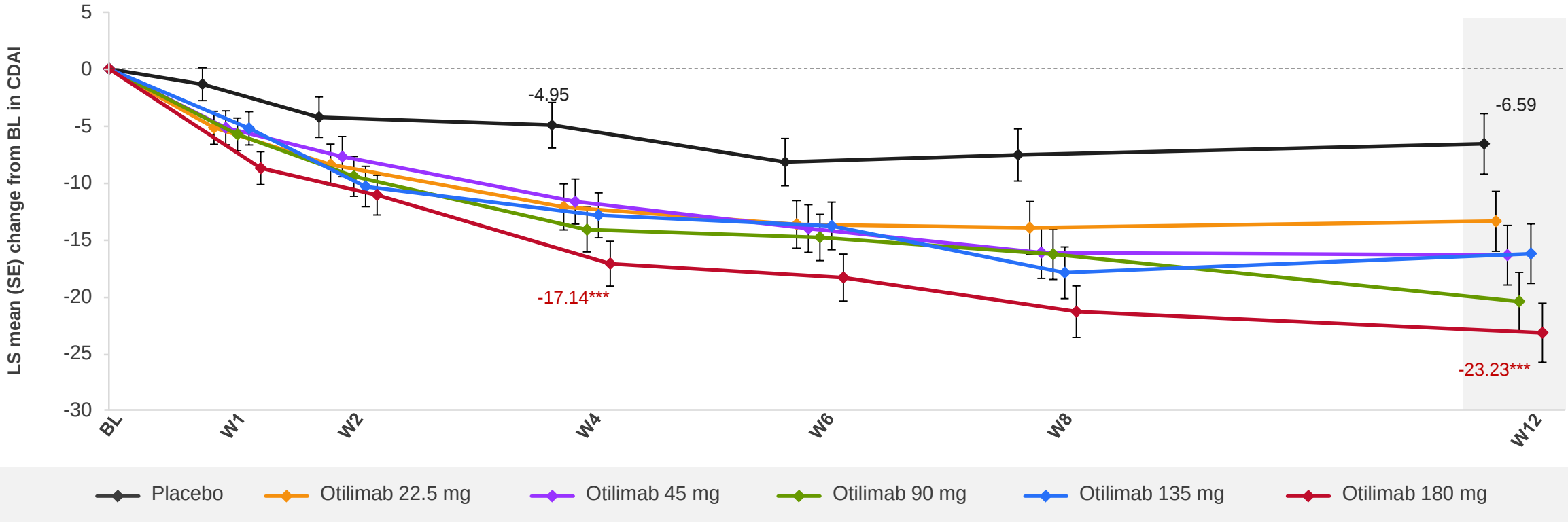
- **Observed PK for EOW dosing below target for GM-CSF inhibition**
- **Based on PK data, weekly dosing will be used for Phase III trials**



BL, baseline; EOW, every other week; GM-CSF, granulocyte-macrophage colony-stimulating factor; PK, pharmacokinetic; SD, standard deviation; W, week.

Effect of Otilimab Treatment on CDAI

- **Large effect compared with existing targeted therapies**

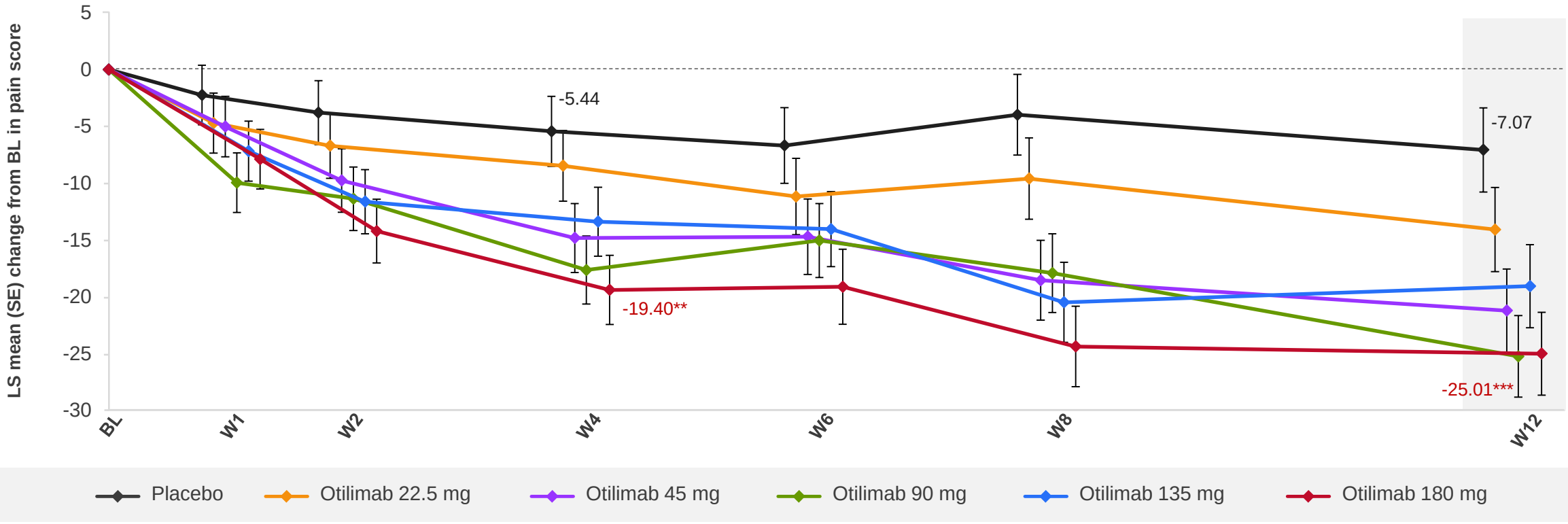


*p<0.05; **p<0.01; ***p<0.001 vs placebo
Repeated measures analysis adjusted for BL, treatment group, visit and treatment group by visit and BL by visit interactions.
Values on graph are LS mean change from BL at W4 and W12.
BL, baseline; CDAI, Clinical Disease Activity Index; LS, least squares; SE, standard error; W, week.

PATIENT-REPORTED OUTCOMES

Effect of Otilimab Treatment on Pain (VAS)

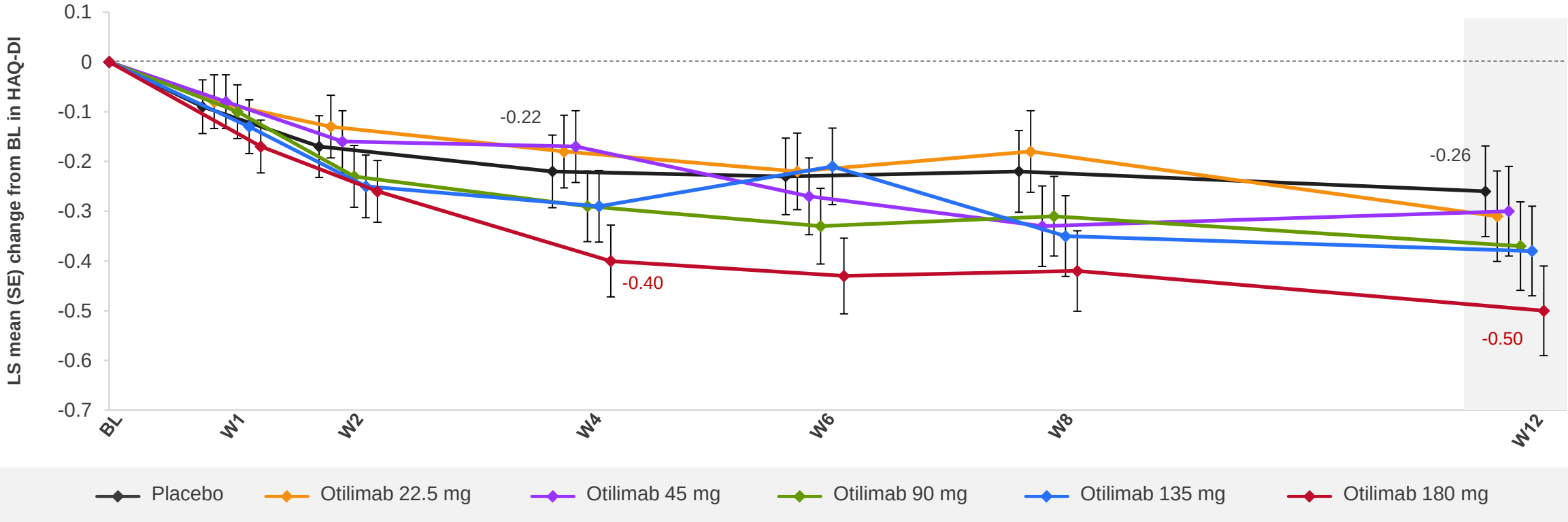
- **Rapid and substantial improvement in pain**



*p<0.05; **p<0.01; ***p<0.001 vs placebo.
Repeated measures analysis adjusted for BL, treatment group, visit and treatment group by visit and BL by visit interactions.
Values on graph are LS mean change from BL at W4 and W12.
BL, baseline; LS, least squares; SE, standard error; VAS, visual analogue scale; W, week.

Effect of Otilimab Treatment on HAQ-DI

- **MCID vs placebo was observed at Week 12 with otilimab 180 mg**

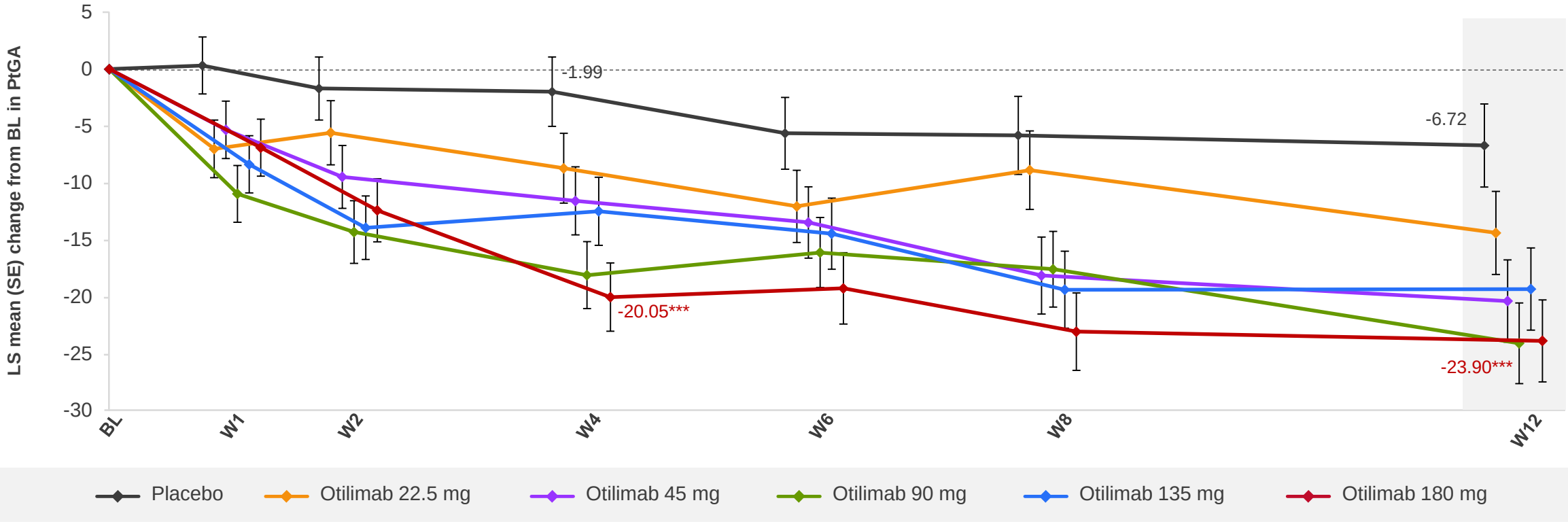


*p<0.05; **p<0.01; ***p<0.001 vs placebo.
MCID for HAQ-DI: -0.22[1]. Values on graph are LS mean change from BL at W4 and W12.
BL, baseline; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; MCID, minimal clinically important difference; SE, standard error; W, week.

[1]Strand V, et al. *J Rheumatol*. 2005; 32:590–601.

Effect of Otilimab on Patient's Global Assessment of Arthritis Disease Activity

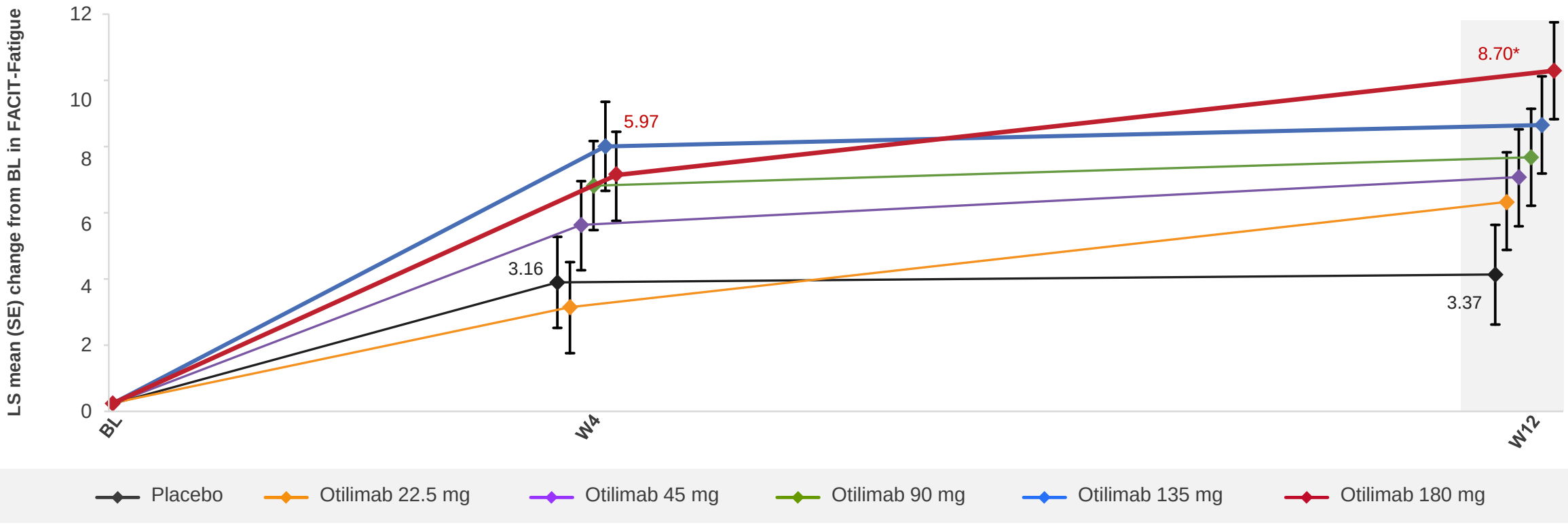
- **Rapid improvement in patients perception of their RA disease activity**



*p<0.05; **p<0.01; ***p<0.001 vs placebo.
Repeated measures analysis adjusted for BL, treatment group, visit and treatment group by visit and BL by visit interactions.
Values on graph are LS mean change from BL at W4 and W12.
BL, baseline; LS, least squares; PtGA, Patient's Global Assessment of Arthritis Disease Activity; SE, standard error; VAS, visual analogue scale; W, week.

Effect of Otilimab on FACIT-Fatigue

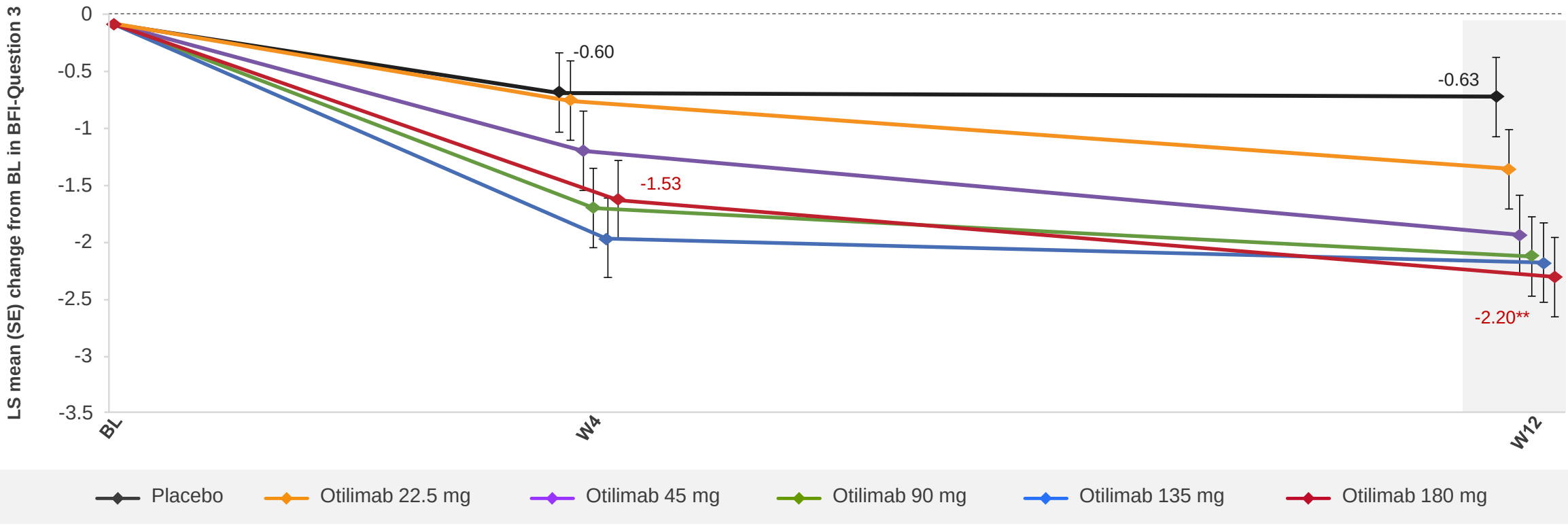
- **Early and substantial improvement in fatigue symptoms**



Higher scores indicate better quality of life. *p<0.05; **p<0.01; ***p<0.001 vs placebo.
Repeated measures analysis adjusted for BL, treatment group, visit and treatment group by visit and BL by visit interactions.
Values on graph are LS mean change from BL at W4 and W12.
BL, baseline; FACIT, Functional Assessment of Chronic Illness Therapy; LS, least squares; SE, standard error; W, week.

Effect of Otilimab on Brief Fatigue Inventory – Question 3

- **Consistent improvements as shown by independent fatigue measures**

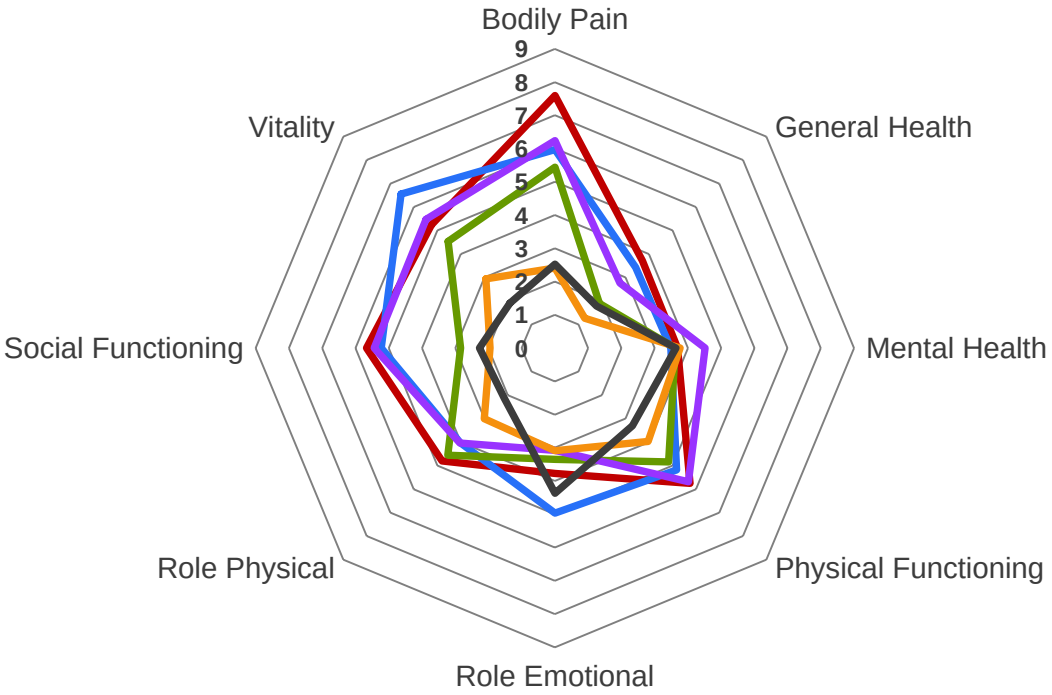


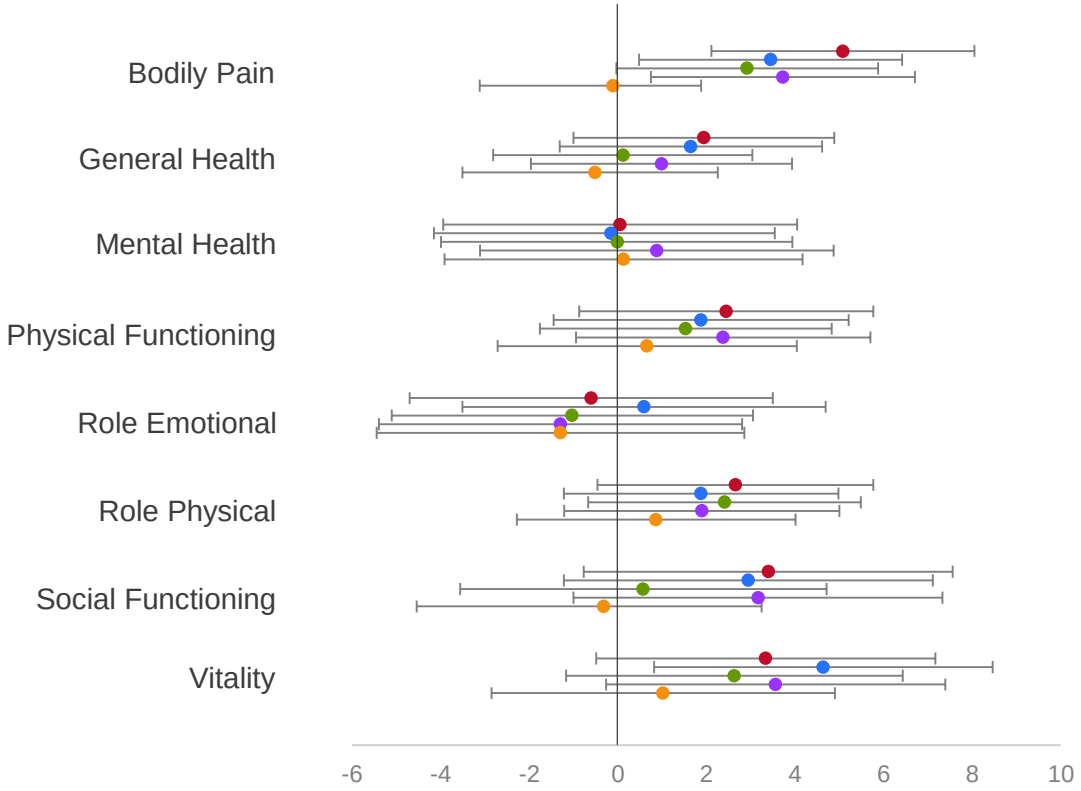
*p<0.05; **p<0.01 vs placebo.
Repeated measures analysis adjusted for BL, treatment group, visit and treatment group by visit and BL by visit interactions.
Values on graph are LS mean change from BL at W4 and W12.
BFI, Brief Fatigue Inventory; BL, baseline; LS, least squares, SE, standard error; W, week.

Effect of Otilimab on SF-36 at Week 4

Placebo | Otilimab 22.5 mg | Otilimab 45 mg | Otilimab 90 mg | Otilimab 135 mg | Otilimab 180 mg

LS mean change from baseline





Difference from placebo (95% CI)

Bodily Pain LS mean (SE) change from baseline

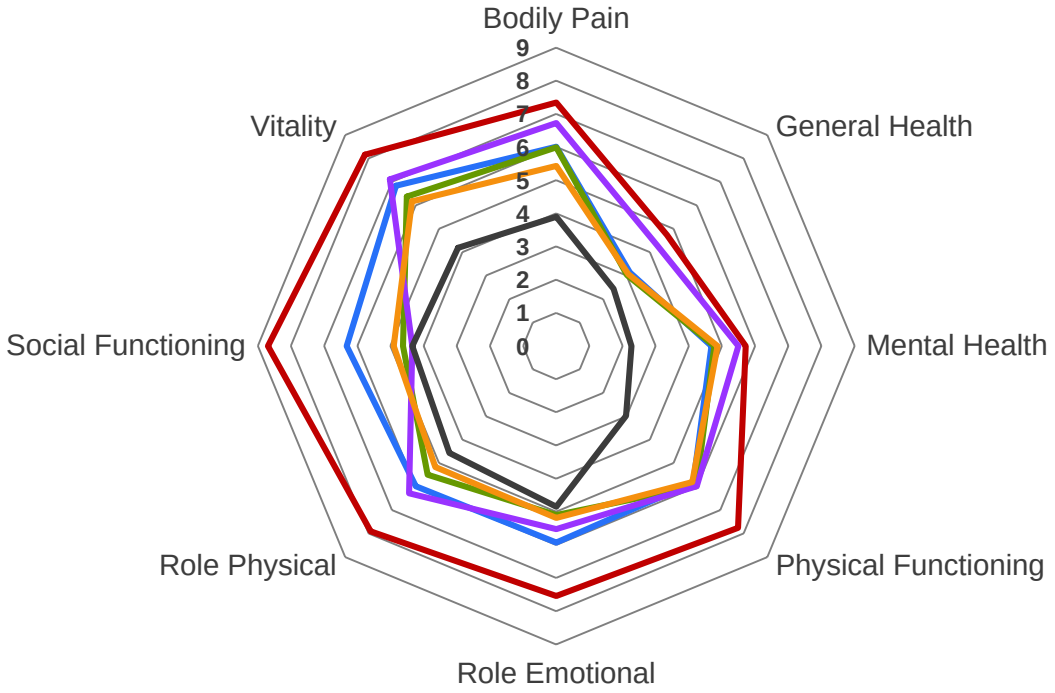
Placebo	Otilimab				
	22.5 mg	45 mg	90 mg	135 mg	180 mg
2.52 (1.07)	2.41 (1.07)	6.24 (1.04)	5.44 (1.03)	5.97 (1.05)	7.60 (1.05)

CI, confidence interval; LS, least squares; SE, standard error; SF-36, 36-item short form health survey.

Effect of Otilimab on SF-36 at Week 12

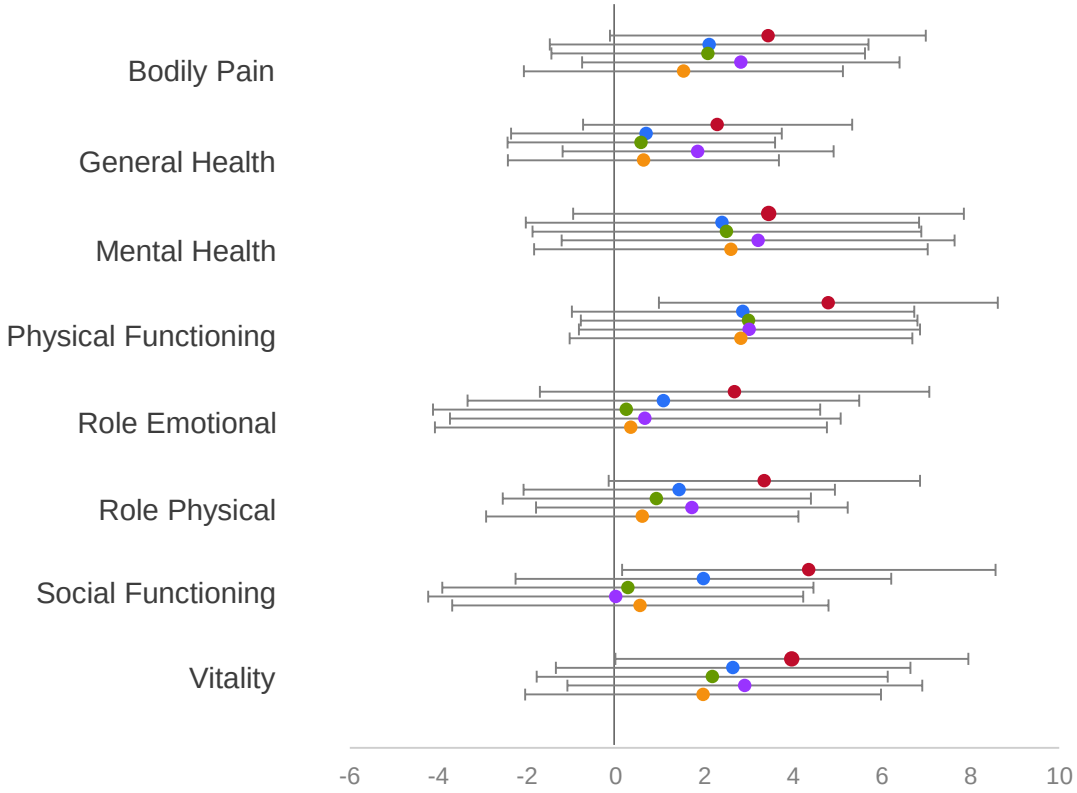
Placebo | Otilimab 22.5 mg | Otilimab 45 mg | Otilimab 90 mg | Otilimab 135 mg | Otilimab 180 mg

LS mean change from baseline



Bodily Pain LS mean (SE) change from baseline

Placebo	Otilimab 22.5 mg	Otilimab 45 mg	Otilimab 90 mg	Otilimab 135 mg	Otilimab 180 mg
3.90 (1.29)	5.43 (1.28)	6.72 (1.27)	5.99 (1.24)	6.01 (1.28)	7.34 (1.26)



Difference from placebo (95% CI)

CI, confidence interval; LS, least squares; SE, standard error; SF-36, 36-item short form health survey.

Conclusions

In subjects with moderate-to-severe active RA, otilimab (especially at 180 mg dose) produced rapid and clinically meaningful effects across a number of disease activity parameters and patient-relevant outcomes, with no unexpected safety concerns (data not shown)

Early (from Week 4), consistent and sustained (up to Week 12) improvements across the range of PRO measures:

- Patient-assessed pain (VAS)
- Patient Global Assessment (VAS)
- HRQoL as demonstrated by data in general physical health (SF-36, PCS) and fatigue (FACIT-F, BFI)
- CDAI and HAQ-DI

These results shed a new light on the potential role of GM-CSF in pain, and support further investigation in Phase III in MTX-IR, csDMARD-IR, biologic-IR, and JAK-IR patients

BFI, Brief Fatigue Inventory; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; GM-CSF, granulocyte-macrophage colony-stimulating factor; HAQ-DI, Health Assessment Questionnaire-Disability Index; HRQoL, health-related quality of life; IR, inadequate response; JAK, Janus kinase; MTX, methotrexate; PCS, physical component summary; PRO, patient-reported outcomes; RA, rheumatoid arthritis; SF-36, 36-item short form health survey; VAS, visual analogue scale.

Current Otilimab Status: Phase III contRAst Programme

contRAst
INVESTIGATING A NEW DRUG FOR RA

Two ongoing global Phase III studies

- contRAst 1 in MTX-IR
- contRAst 2 in DMARD-IR

Two planned global Phase III studies for later in 2019

- contRAst 3 in bDMARD/JAK-IR
- contRAst X: long-term extension for patients from contRAst 1, 2, and 3

Contrast 1, EudraCT 2019-000797-39, NCT03980483; contrast 2, EudraCT 2019-000867-26, NCT03970837; contrast 3, EudraCT 2019-000868-18
bDMARD, biological disease-modifying antirheumatic drug; IR, inadequate response; JAK, Janus kinase; MTX, methotrexate.