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 Buckley¹, Jesus A Simon Campos², Vyacheslav Zhdan³, Brandon Becker⁴, Deven Chauhan⁵, Katherine Davy⁶, Carol Hawkes⁵, David Inman⁶, Mark Layton⁶, Jatin Patel⁵, Didier Saurigny⁶, Nina Mitchell⁶, Russell Williamson⁷ and Paul Peter Tak⁸

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

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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
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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, Jeku, Kulig, Mastalerz, Racewicz, Wojciechowski

Russian Federation
Ershova, Kropotina, Mikhailova, Nikulenkova, Platonov, Repin, Shilkina, Yakushin

South Africa
Ally, Louw, Reuter

Ukraine
Gasanov, Grishyna, Kuzmina, Nadshkevych, Shevchuk, Stanislavchuk, Vasylets, Vyshnyvetsky, 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\(^8\)\(^9\)

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

N=222
Adult patients with active, moderate-to-severe RA (ACR 2010 criteria)
MTX-IR
SJC/TJC ≥4
DAS28 (ESR) ≥3.2
CRP ≥5.0 mg/L

Otilimab 180 mg + MTX (n=37)
Otilimab 135 mg + MTX (n=37)
Otilimab 90 mg + MTX (n=37)
Otilimab 45 mg + MTX (n=37)
Otilimab 22.5 mg + MTX (n=37)
Placebo + MTX (n=37)

Screening (up to 4 weeks)
Week 12
Change from baseline in DAS28(CRP) and key secondaries
Week 24
Primary endpoint: DAS28(CRP) remission
Week 36
Week 52

Double-blind rescue to otilimab 180 mg for patients:
- Not in 180 mg group, and
- Not achieved EULAR good/moderate response at Week 12, or
- DAS28(CRP) >3.2 at Week 24

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

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

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

Predicted PK profile and therapeutic trough concentration for otilimab 180 mg based on prior PK data

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

LS mean (SE) change from BL in CDAI

*\( p<0.05 \); **\( p<0.01 \); ***\( p<0.001 \) 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

![](image)

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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

*Effect of Otilimab Treatment on HAQ-DI*

**Note:**
- MCID for HAQ-DI: -0.22. 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.

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

- Rapid improvement in patients perception of their RA disease activity

* * *
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

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

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

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

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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.