GSK’165: anti-GM-CSF antibody

A novel mechanism with potentially differentiated impact on pain in the treatment of Rheumatoid Arthritis

23 October 2018

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All expectations and targets regarding future performance should be read together with "Assumptions related to 2018 guidance and 2016-2020 outlook" on page 40 of our second quarter 2018 earnings release.

Agenda

GSK‘165: anti-GM-CSF antibody

Dr Hal Barron
Chief Scientific Officer and President R&D

Results of BAROQUE Phase 2 study

Dr Roy Fleischmann
Clinical Professor of Medicine at the University of Texas Southwestern Medical Center

RA market and commercial opportunity

Luke Miels
President, Global Pharmaceuticals

Q&A

Dr Mark Layton
Medicine Development Lead, GSK’165

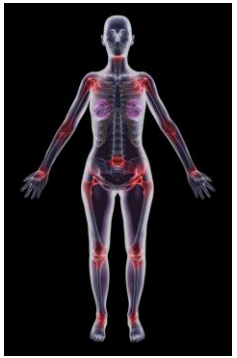
Presentation
20-25 mins

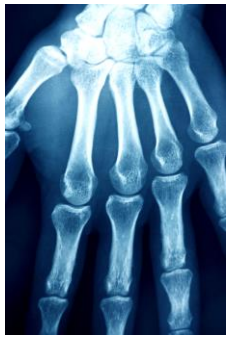
Q&A
20-25 mins

Rheumatoid Arthritis (RA): a chronic and debilitating inflammatory disease

Disease background

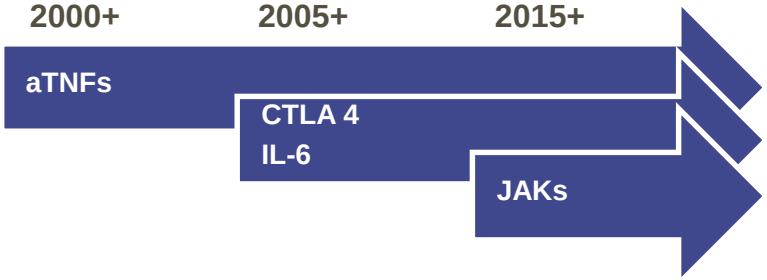
- RA is an autoimmune disease which causes inflammation in the joints and results in pain, swelling and stiffness
- Estimated prevalence[1,2]:
  - Global: 24.5 million (~1% of 18+ world population)
  - US: 2.7 million
  - EU5: 2.6 million
  - Japan: 0.8 million
- Incidence is three times higher in women than men with peak onset typically between the ages of 30 and 50 years[3]
- RA results in significant disability and increased mortality, largely due to accelerated cardiovascular disease





Sources: 1. GBD 2015 Disease and Injury Incidence and Prevalence, Collaborators. "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015". Lancet (2016). 388 (10053): 1545–1602. 2. https://www.tandfonline.com/mwginternal/de5fs23hu73ds/progress?id=RUnd3_7MFjCNX58ZhG28PwtiEQVsG2V8XpJB-0RdVLc,&dl;
3. https://www.arthritis.org/about-arthritis/types/rheumatoid-arthritis/what-is-rheumatoid-arthritis.php

Recent progress with new treatment options, but unmet need remains



New biologic therapies have improved treatment of RA, reducing symptoms and signs of the disease and reducing the progression of structural damage to joints in a subset of patients

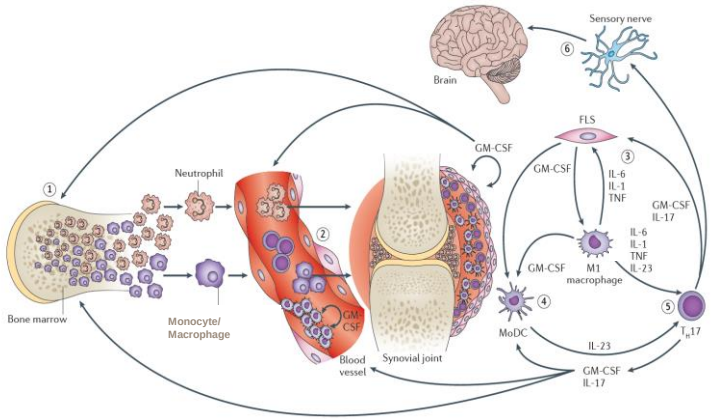
Substantial unmet need remains

- Most effective current therapies only achieve ~50% disease improvement in <50% of patients
- Even with multiple targeted therapies only 30% of patients achieve remission
- ~50% of patients do not achieve low disease activity criteria within 12 months of aTNF treatment and ~80% do not achieve Disease Activity Score 28 remission
- 45% of patients report daily pain and pain is the key driver in 25% of switches biological and oral therapies

Sources: Targeted treatments for rheumatoid arthritis, Novel treatment strategies in rheumatoid arthritis, Gerd R Burmester, Janet E Pope; Adelphi RA DSP 2016

GSK‘165 (aGM-CSF): potential for a disease modifying effect in rheumatoid arthritis (RA) with a unique impact on pain

The target	– GM-CSF is a pro-inflammatory cytokine that induces differentiation and proliferation of granulocytes and macrophages – One of the first cytokines detected in human synovial fluid from inflamed joints – Preclinical data suggests a broader range of actions than existing biologics (including a beneficial effect on pain)
The agent	– GSK’165 is a human antibody targeting anti-granulocyte macrophage colony-stimulating factor (aGM-CSF) – Administration will likely be weekly via a subcutaneous injection with a choice of autoinjector or prefilled syringe
Current status	– Encouraging Phase 2 results in RA presented at ACR October 2018 – Discussions with regulators planned to advance development rapidly in RA – Exploration of additional indications beyond RA



Source: Targeting GM-CSF in inflammatory diseases. Ian P. Wicks & Andrew W. Roberts. Nature Reviews Rheumatology volume 12, pages 37–48 (2016)

Strong rationale for moving forward

Strong preclinical data	– Wealth of preclinical data in multiple animal models, including evidence specific to pain[1]
Interesting biology	– GM-CSF upregulates CCL17 production in human monocytes and macrophages AND is required for GM-CSF dependent arthritic pain and disease[2]
Compelling clinical data	– **DAS 28 (CRP)** improvement in efficacy was statistically significant at Week 12 and Week 24 – Endpoint most relevant to patients met at 12 weeks: – **ACR 20:** % difference 40.5% (21.6, 59.5); Odds ratio 8.23 (2.41, 28.04) p<0.001 – **Swollen Joint Count 66:** -7.54 (-11.78, -3.30); p<0.001) – **Tender Joint Count 68:** -8.91 (-14.72, -3.10); p=0.003 – **Simple disease activity index (SDAI):** -16.86 (-24.39, -9.32); p<0.001 – **Clinical disease activity index (CDAI):** -16.63 (-23.97, -9.30); p<0.001

DAS28(CRP) <2.6 (remission) at 24 weeks was not statistically significant

Sources: 1. Avci et al, 2016; Wicks et al, 2016); Cook et al, 2001; Plater-Zyberk et al, 2007; Cook et al, 2012 & 2013; Achuthan et al, 2016; Cook et al, 2012, 2013 & 2018 ; Schweizerhof et al, 2009 ; Nicol et al, 2018
2. Achuthan et al, 2016; Cook et al, 2018; Lee et al, 2018

Key data demonstrating efficacy of GSK'165 aGM-CSF from the BAROQUE Phase 2 study

Presented at ACR 22 October 2018

Phase 2 study design

A randomised, multicentre, double-blind, parallel group, placebo controlled study with novel features to support a 52 week study

GSK3196165 or placebo administered as 5 weekly SC injections, followed by every other week injections

N=222

Adult patients with active, moderate to severe RA;

(ACR 2010 criteria);

MTX-IR;

SJC/TJC ≥ 4;

CRP ≥ 5.0mg/L

- GSK3196165 180mg + MTX (n=37)
- GSK3196165 135mg + MTX (n=37)
- GSK3196165 90mg + MTX (n=37)
- GSK3196165 45mg + MTX (n=37)
- GSK3196165 22.5mg + MTX (n=37)
- Placebo + MTX (n=37)

Escape point to GSK3196165 180 mg

Escape point to GSK3196165 180 mg

Withdrawal point

Screening (up to 4 weeks)

R

Week 12 Change from baseline in DAS28(CRP) and key secondaries

Week 24 Primary endpoint: DAS28(CRP) remission

Week 36

Week 52

ACR, American College of Rheumatology; DAS28(CRP), Disease Activity Score for 28 different joints with C-reactive protein value; IR, incomplete responder; MTX, methotrexate; R, randomization; SC, subcutaneous; SJC, swollen joint count; TJC, tender joint count.

Baseline patient demographic characteristics

Typical, established RA MTX-IR population; well balanced across treatment groups

	Placebo + MTX (n=37)	GSK3196165 + MTX				
		22.5mg (n=37)	45mg (n=37)	90mg (n=37)	135mg (n=37)	180mg (n=37)
Age (y), mean (SD)	50.0 (11.33)	48.4 (11.31)	52.8 (12.22)	52.7 (11.28)	47.1 (10.04)	52.3 (10.76)
Female, n (%)	28 (76)	30 (81)	33 (89)	27 (73)	33 (89)	29 (78)
RA diagnosis (mo), mean (SD)	73.8 (94.98)	75.3 (81.93)	61.3 (76.25)	73.1 (71.63)	82.3 (67.58)	85.9 (79.12)
ACPA positive, n (%)	28 (76)	24 (65)	24 (65)	23 (62)	28 (76)	30 (81)
RF positive, n (%)	28 (76)	26 (70)	27 (73)	21 (57)	22 (59)	30 (81)
MTX (mg/week), mean (SD)	15.27 (3.475)	15.84 (4.313)	16.55 (4.270)	15.34 (3.688)	15.90 (3.213)	16.10 (3.268)
Oral glucocorticoid use, n (%)	15 (41)	24 (65)	20 (54)	22 (59)	21 (57)	22 (59)
Oral glucocorticoid dose (prednisolone equivalent mg/day), mean (SD)	6.37 (2.108)	6.04 (2.918)	6.83 (2.597)	6.75 (3.020)	5.90 (3.231)	5.89 (2.737)

IR, incomplete responder; mo, months; MTX, methotrexate; RA, rheumatoid arthritis; SD, standard deviation; y, years.

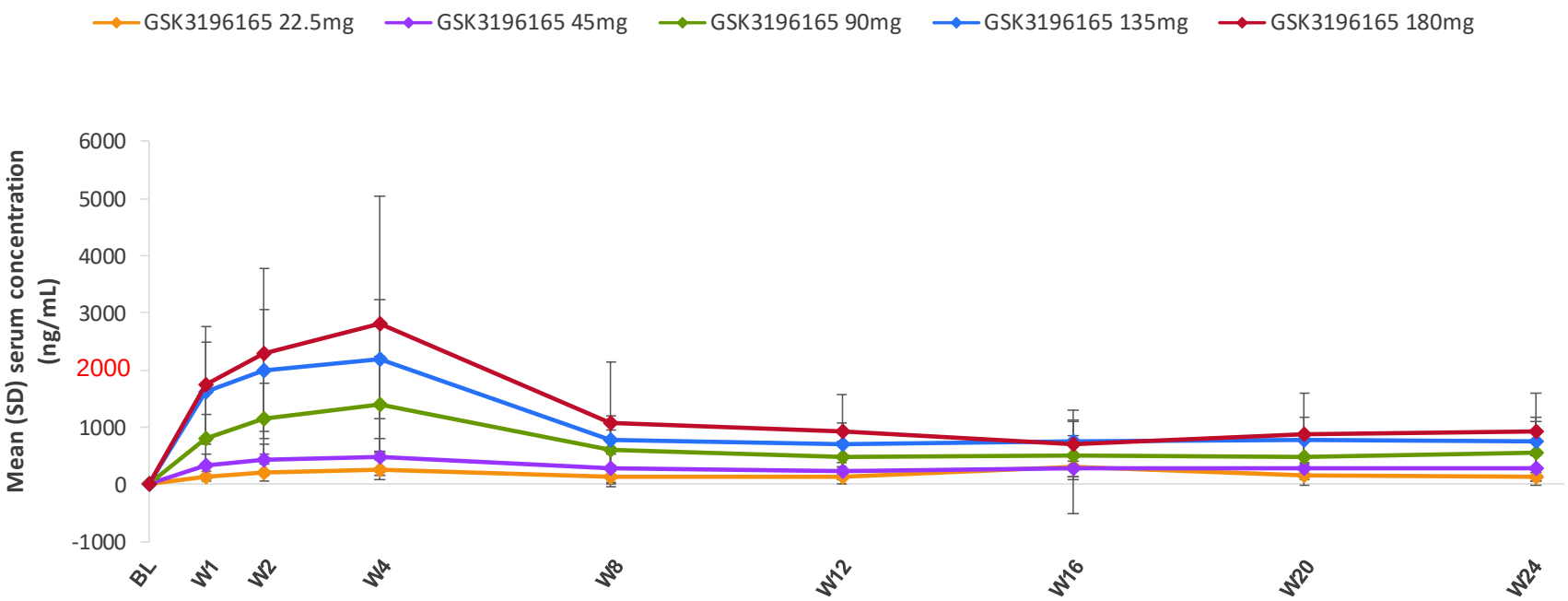
Baseline RA disease characteristics

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

	Placebo + MTX (n=37)	GSK3196165 + MTX				
		22.5mg (n=37)	45mg (n=37)	90mg (n=37)	135mg (n=37)	180mg (n=37)
DAS28(CRP), mean (SD)	6.2 (0.82)	6.4 (0.82)	6.1 (0.74)	6.2 (0.84)	6.3 (0.92)	6.0 (0.88)
SDAI (0–86), mean (SD)	47.4 (13.34)	48.0 (12.916)	45.2 (11.95)	46.5 (13.0)	48.2 (14.57)	44.4 (14.00)
CDAI (0–76), mean (SD)	45.7 (13.46)	45.2 (11.81)	42.8 (12.10)	44.5 (12.57)	45.3 (13.50)	42.5 (13.90)
TJC68, mean (SD)	28.5 (13.59)	27.9 (12.13)	26.1 (14.09)	28.8 (14.76)	30.1 (14.80)	25.3 (12.35)
SJC66, mean (SD)	18.5 (9.29)	17.7 (8.53)	17.2 (8.94)	18.3 (10.05)	18.9 (10.15)	18.9 (10.11)
Pain (100 mm VAS), mean (SD)	66.1 (16.68)	71.2 (15.84)	70.1 (17.27)	65.8 (20.38)	67.1 (19.27)	61.6 (20.62)
PtGA (100 mm VAS), mean (SD)	66.0 (15.64)	72.5 (14.21)	71.6 (14.90)	68.2 (17.59)	69.6 (16.96)	63.2 (16.64)
PhGA (100 mm VAS), mean (SD)	64.2 (11.88)	67.5 (10.27)	67.1 (15.86)	65.9 (18.58)	67.2 (15.37)	64.1 (5.72)
HAQ-DI, mean (SD)	1.77 (0.592)	1.72 (0.482)	1.88 (0.405)	1.73 (0.544)	1.80 (0.564)	1.63 (0.706)
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)

CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score 28-joint count; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high-sensitivity C-reactive protein; PhGA, Physician's Global Assessment of Arthritis; PtGA, Patient's Global Assessment of Arthritis Disease Activity; SDAI, Simplified Disease Activity Index; SJC66, swollen joint count for 66 different joints; TJC68, tender joint count for 68 different joints; VAS, visual analogue scale.

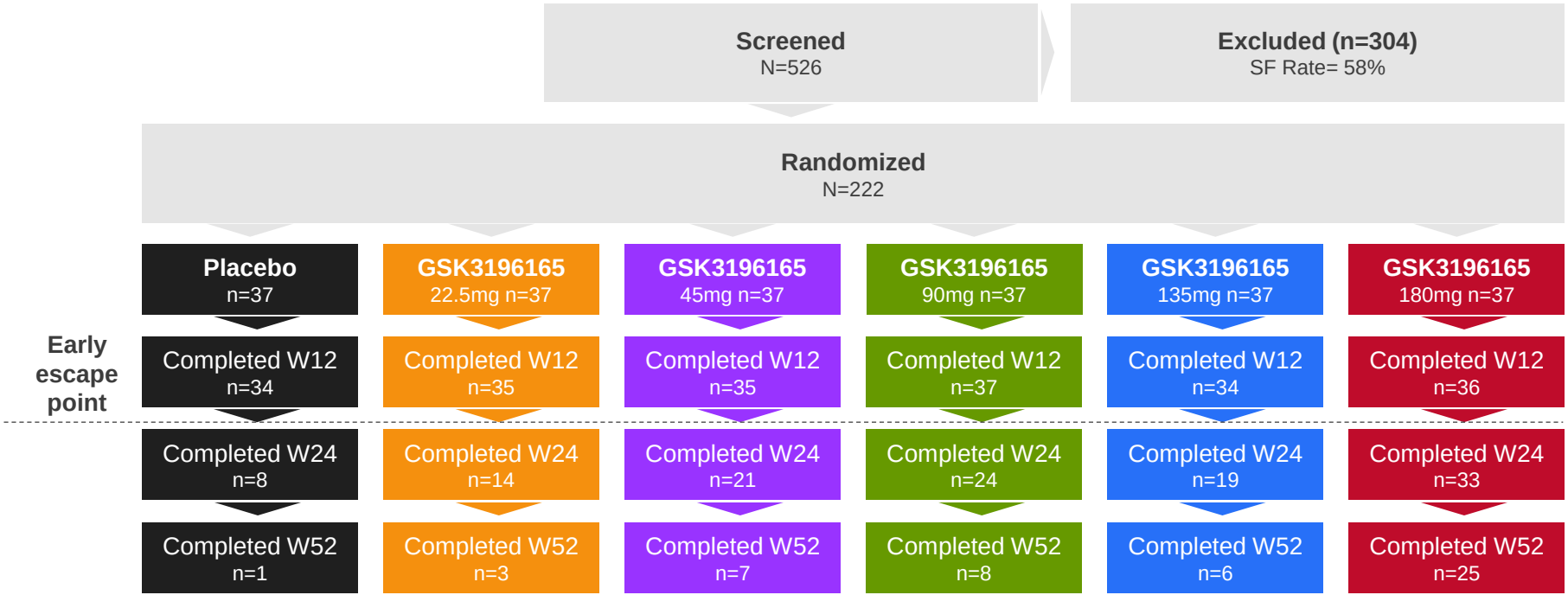
Rationale for weekly dosing going forward



BL, baseline; CI, confidence interval; D, day; EOW, every other week; GM-CSF, granulocyte-macrophage colony-stimulating factor; PK, pharmacokinetic; W, week

Patient disposition on randomised treatment

70% of placebo patients switched to GSK'165 180mg dose at Wk12 early escape point

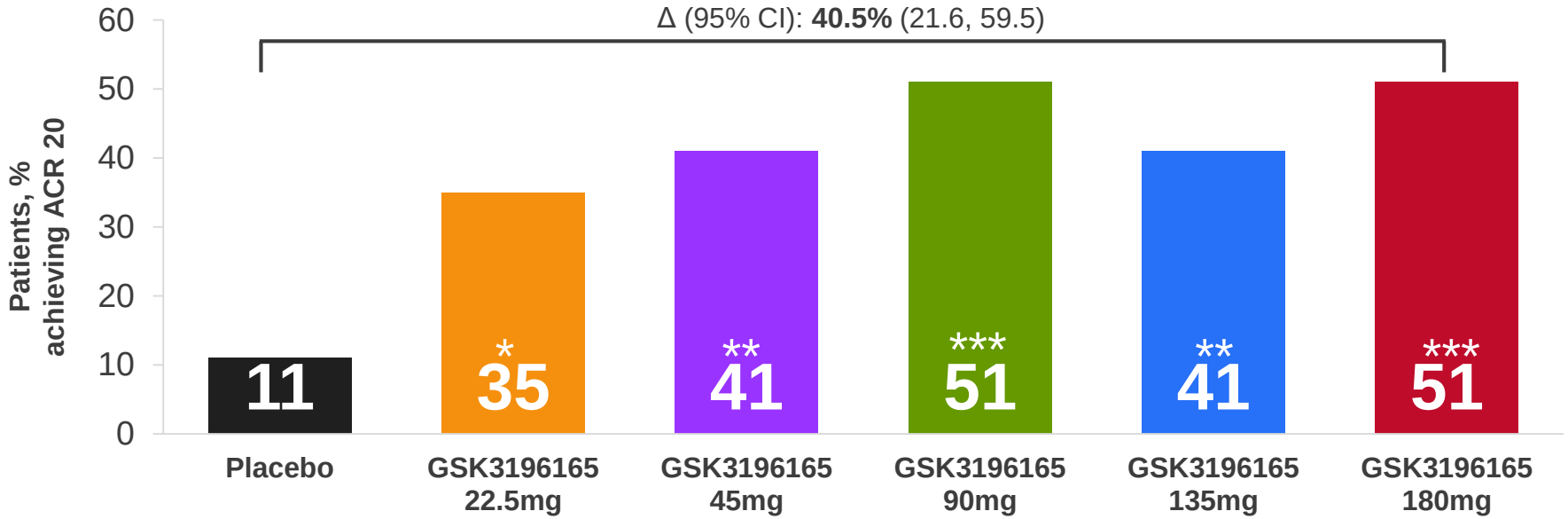


Escape criteria: EULAR Response (moderate/ good) at weeks 12 and 24 to 180mg dose

SF, screening failure; W, week.

Significantly higher response rates at Week 12 with GSK'165 versus placebo

ACR 20 at Week 12

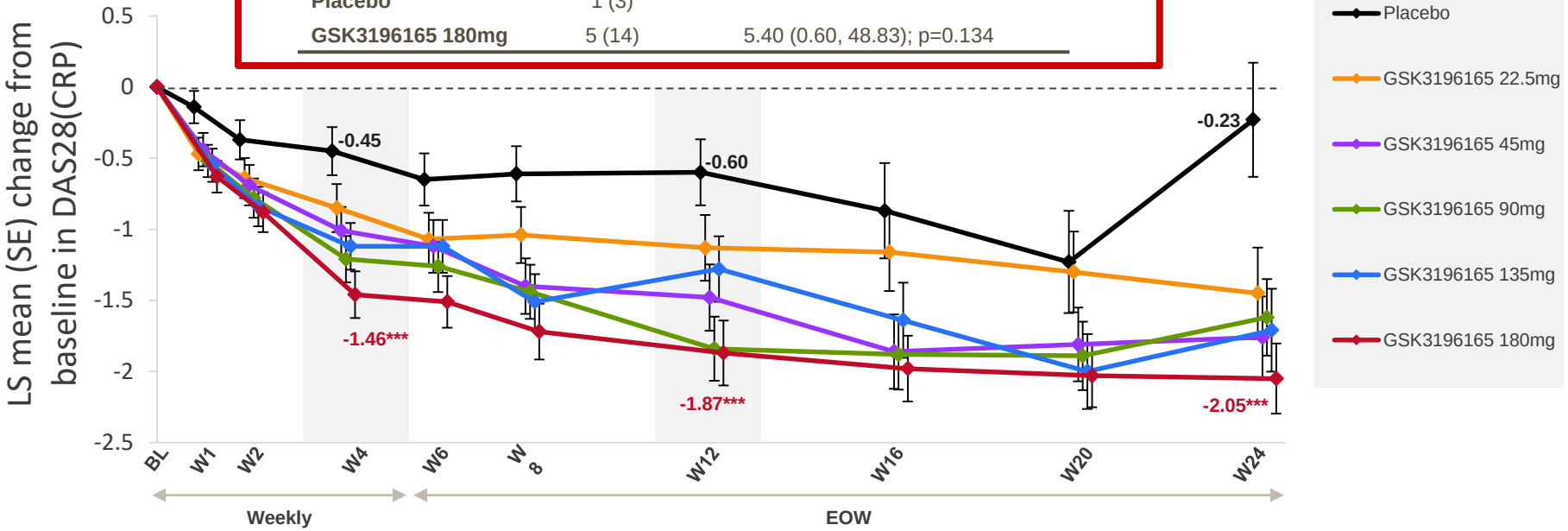


*P<0.05; **P<0.01; ***P<0.001 versus placebo. GSK3196165 versus placebo: OR (95% CI): 8.23 (2.41, 28.04); p<0.001. ACR, American College of Rheumatology; CI, confidence interval; OR, odds ratio.

Rapid onset of action during weekly dosing phase

Clinical Response: DAS28(CRP) and DAS28(CRP) <2.6

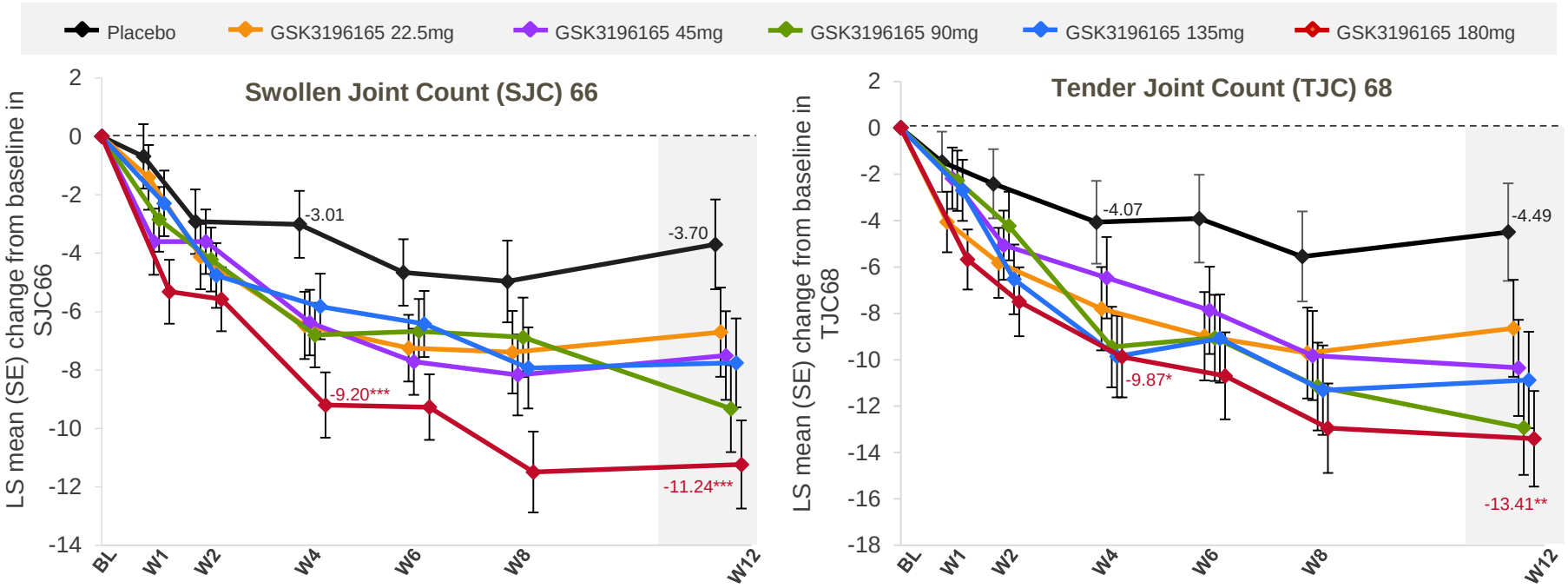
	DAS28(CRP) <2.6 (W24; primary endpoint)	
	N (%)	OR (95% CI); p-value
Placebo	1 (3)	
GSK3196165 180mg	5 (14)	5.40 (0.60, 48.83); p=0.134



Repeated measures analysis adjusted for DAS28(CRP) baseline score, treatment group, visit and treatment group by visit and baseline by visit interactions. Data post Week 24 were excluded due to quantity of missing data. Values on graph are LS mean change from BL at W4, W12 and W24. *P<0.05; **P<0.01; ***P<0.001 versus placebo. BL, baseline; CI, confidence interval; CRP, C-reactive protein; D, day; DAS28, disease activity score for 28 different joints; DAS28(CRP), DAS28 with CRP value; EOW, every other week; LS, least squares; SE, standard error; ITT, intent to treat; W, week.

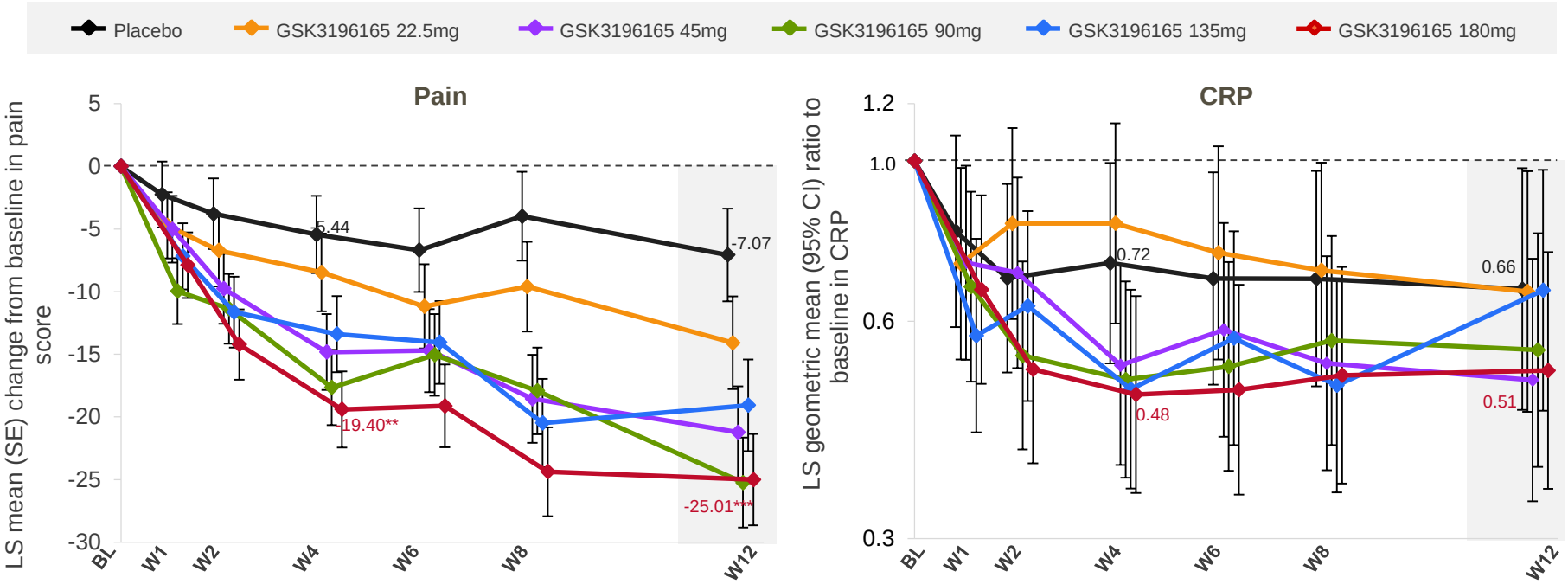
Rapid and substantial improvement in joint counts

Swollen Joint Count (SJC) 66 & Tender Joint Count (TJC) 68



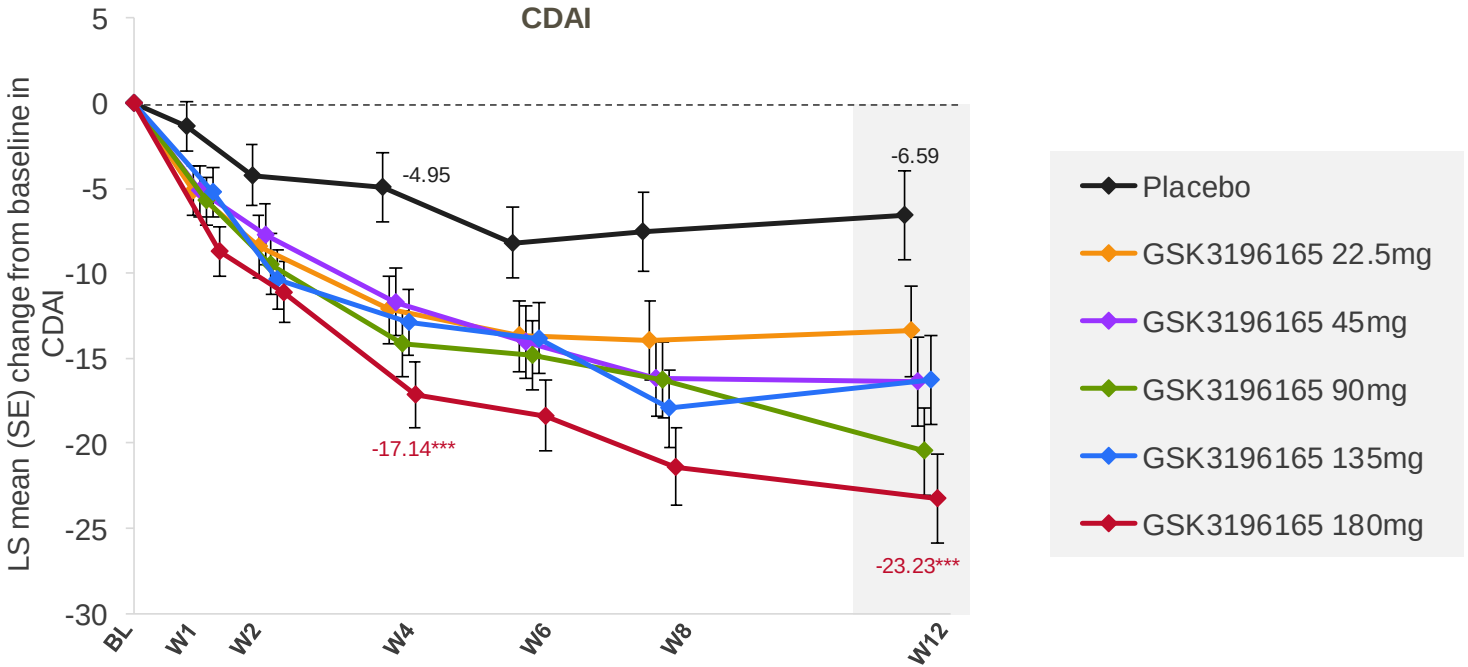
Repeated measures analysis adjusted for baseline, treatment group, visit and treatment group by visit and baseline by visit interactions. Values on graph are LS mean change from BL at W4 and W12.
*P<0.05; **P<0.01; ***P<0.001 versus placebo. BL, baseline; LS, least squares; SE, standard error; SJC66, swollen joint count for 66 different joints; TJC68, tender joint count for 68 different joints; W, week.

Rapid and substantial improvement in pain, CRP reduced but not suppressed



Repeated measures analysis adjusted for baseline, treatment group, visit and treatment group by visit and baseline by visit interactions. Values on graph are LS mean change from BL (pain score) or LS mean ratio to BL (CRP) at W4 and W12. *P<0.05; **P<0.01; ***P<0.001 versus placebo. BL, baseline; CI, confidence interval; CRP, C-reactive protein; LS, least squares; SE, standard error; W, week.

Marked clinical response on Clinical Disease Activity Index (CDAI)



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

Totality of data supports further studies

Benefits across multiple endpoints, notably in pain and swollen and tender joint counts

	Placebo + MTX (n=37)	GSK3196165 180 mg + MTX (n=37)	
Clinical endpoint at Week 12	**LS mean change from baseline (SE)**		**Difference from placebo (95% CI); p-value**
DAS 28(CRP)	**-0.60** (0.23)	**-1.87** (0.23)	**-1.27** (-1.91, -0.63); **p<0.001**
CDAI	**-6.59** (2.66)	**-23.23** (2.60)	**-16.63** (-23.97, -9.30); **p<0.001**
Pain	**-7.07** (3.71)	**-25.01** (3.65)	**-17.94** (-28.18, -7.70); **p<0.001**
HAQ-DI	**-0.26** (0.09)	**-0.50** (0.09)	**-0.24** (-0.49, 0.01); **p=0.059**
Patient's Global Assessment of Arthritis	**-6.72** (3.66)	**-23.9** (3.61)	**-17.18** (-27.27, -7.10); **p<0.001**
SJC66	**-3.70** (1.54)	**-11.24** (1.51)	**-7.54** (-11.78, -3.30); **p<0.001**
TJC68	**-4.49** (2.10)	**-13.41** (2.07)	**-8.91** (-14.72, -3.10); **p=0.003**
	Responders, n (%)		
ACR20	4 (**11**)	19 (**51**)	**40.5%** (21.6, 59.5); **p<0.001**
ACR50	3 (**8**)	8 (**22**)	**13.5%** (-2.4, 29.4); **p=0.134**
Good/moderate EULAR	8 (**22**)	28 (**76**)	**54.1%** (34.9, 73.2); **p<0.001**

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CI, confidence interval; DAS28(CRP), Disease Activity Score for 28 different joints with C-reactive protein value; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire - Disability Index; LS, least squares; SE, standard error; SJC66, swollen joint count for 66 different joints; TJC68, tender joint count for 68 different joints.

Overall AE profile unremarkable: majority were of mild or moderate intensity

Pre-rescue

Pre-rescue, n (%)	Placebo + MTX (n=37)	GSK3196165 + MTX 22.5mg (n=37)	GSK3196165 + MTX 45mg (n=37)	GSK3196165 + MTX 90mg (n=37)	GSK3196165 + MTX 135mg (n=37)	GSK3196165 + MTX 180mg (n=37)
Any AES	18 (49)	19 (51)	24 (65)	22 (59)	19 (51)	24 (65)
SAEs	0 (0)	2 (5)	1 (3)	2 (5)	1 (3)	0 (0)
Treatment-related AEs	2 (5)	9 (24)	6 (16)	6 (16)	5 (14)	9 (24)
Withdrawal due to AEs	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	2 (5)
Total exposure, patient-years	11.6	14.4	18.3	19.5	16.8	32.0

Post-rescue

Post rescue, n (%)	Placebo + MTX (n=33)	GSK3196165 + MTX 22.5mg (n=30)	GSK3196165 + MTX 45mg (n=27)	GSK3196165 + MTX 90mg (n=25)	GSK3196165 + MTX 135mg (n=28)
Any AEs	22 (67)	16 (53)	11 (41)	10 (40)	17 (61)
SAEs	1 (3)	0 (0)	0 (0)	0 (0)	1 (4)
Treatment-related AEs	5 (15)	6 (20)	4 (15)	0 (0)	6 (21)
Withdrawal due to AEs	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)
Total exposure, patient-years	19.6	16.0	15.2	13.9	14.6

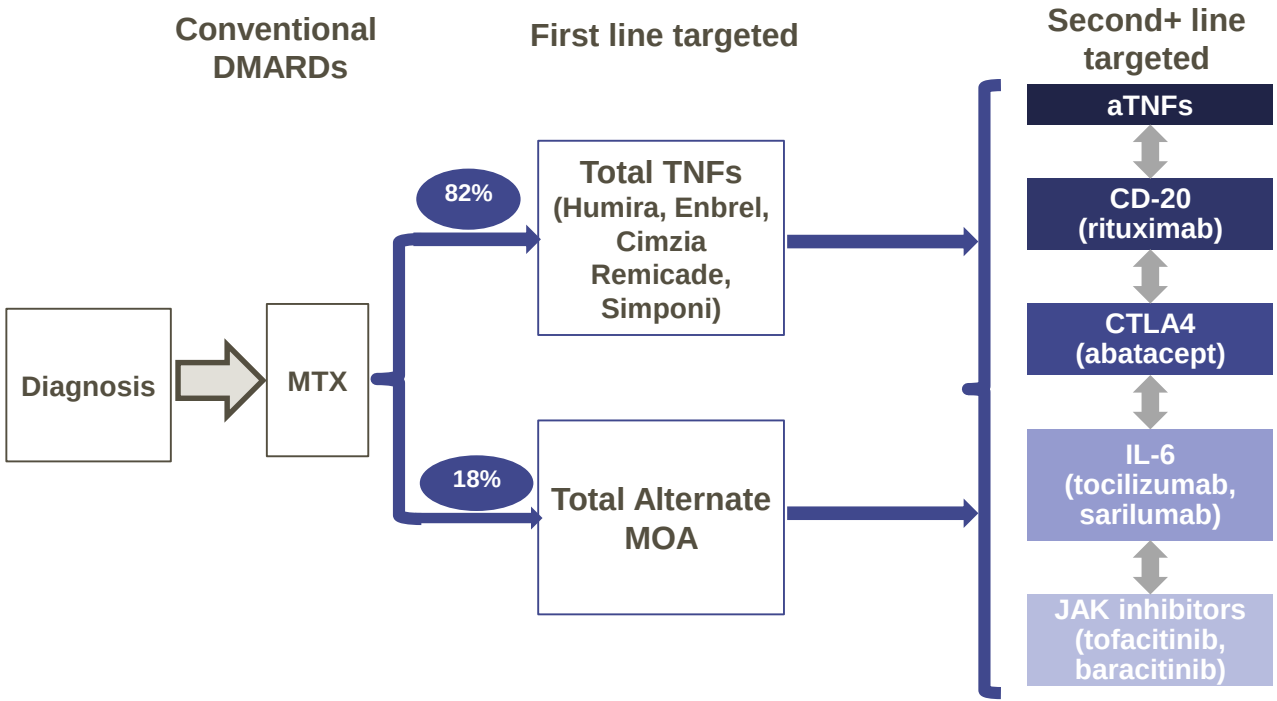
There were no deaths, malignancy or venous thromboembolism during the trial

AE, adverse event; AESI, AE of special interest; SAE, serious AE.

RA market and commercial opportunity

Luke Miels, President, Global Pharmaceuticals

Evolving treatment paradigm provides opportunity for new mechanisms of action



Source: Adelphi RA (DSP) – Data captured till December 2016

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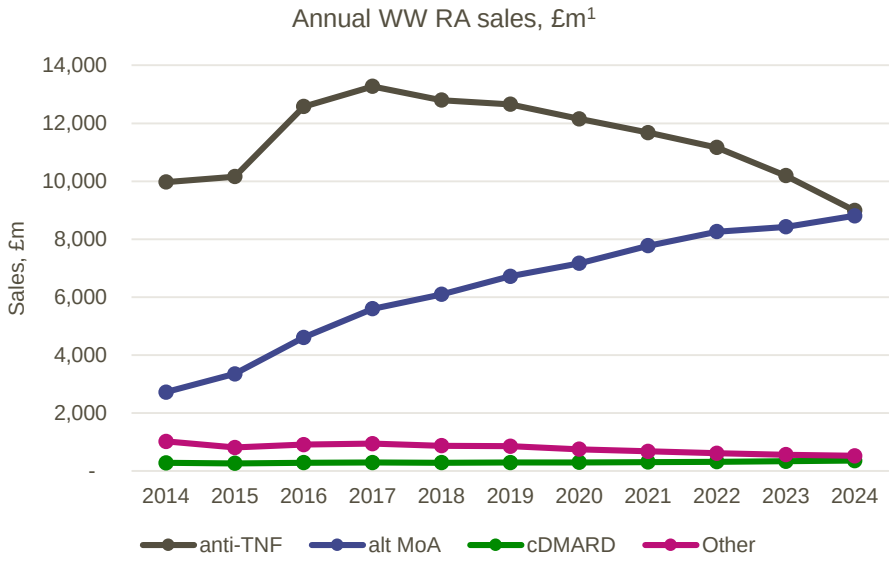
RA market growth to be driven by new mechanisms

RA market decline due to biosimilars; value opportunity for new MOA's



Opportunity for alternative mechanisms of action

Importance of demonstrating differentiated efficacy

Note: "Other" includes COX inhibitor, GCR agonist, MC2 agonist etc.

Source: 1. EvaluatePharma RA report (data exported on Oct 16, 2018)

Strong rationale for moving forward

Data supports further development	– Exciting asset with a novel mechanism of action which has shown compelling data across traditional endpoints for RA supporting further and accelerated clinical development
Next steps	– Plans for discussions with regulators with a view to rapidly advancing development
Life cycle management	– Explore potential efficacy of GSK’165 in additional indications

Q&A