Immuno-Inflammation
# Immuno-Inflammation areas of focus

*Immune modulation to alter disease course, induce and sustain remission*

## Rheumatoid Arthritis (RA)
- Circa 5.3m RA patients in G7 countries
- Aging demographics a major driver of market growth
- Highly debilitating; associated with higher mortality & progression to other serious conditions
- Significant medical needs for remission-inducing therapies & for patients resistant to current standard of care

## Osteoarthritis (OA)
- Circa 72m OA patients in G7 countries; largest proportion of musculoskeletal diseases
- Aging demographics a major driver of market growth
- Major opportunity for a disease-modifying therapy
- Immune modulation offers opportunity to move from only alleviating symptoms of “wear and tear”

## Systemic Lupus Erythematosis (SLE)
- Prevalence: 40 -100 out of 100,000; 9/10 sufferers are women in their 20s & 30s
- Chronic disease with poor QoL, involving musculoskeletal, haematological, cutaneous & renal systems
- Mortality rate 3x higher than the general population, and 10x higher in under 40
- Benlysta IV - 1st drug approved for SLE in 50 years (2011)

## Other immune-mediated diseases
- Mechanisms are relevant for mainstream diseases e.g. psoriasis, Crohn’s disease & ulcerative colitis
- Opportunities exist to treat less common disease e.g. primary Sjögren’s syndrome, systemic sclerosis & myasthenia gravis

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Immuno-Inflammation R&D strategy:
From symptomatic benefit to sustainable remission

GSK Pipeline

Targeted Biologicals
Targeted Small Molecules

Targeting Resistant Disease
Early Intervention & Remission Induction

macrophage
neutrophil
stromal cell
T cell
plasma cell
B cell
• Collaboration with Janssen Biologics (Ireland)
• Low frequency sc dosing potential (monthly)
• Targets the cytokine
• Efficacy demonstrated in Phase II; consistent safety profile across doses
• >3000 patients in studies to date
• Phase III interim read-out, full read out expected by year end 2015
• Indication expansion: Phase III in Giant Cell Arteritis started screening. Phase II in asthma start in 2016

sirukumab: rheumatoid arthritis

The anti-IL-6 class is the fastest growing of the biologicals in RA

Status: RA: Phase III
Indications: RA (lead), GCA, asthma
Planned Filing: RA 2016

12 wk data from Phase II study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ACR20 at wk 12</th>
<th>ACR50 at wk 12 (Primary EP)</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>30</td>
<td>3</td>
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<tr>
<td>50mg Q4W</td>
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<td>100mg Q2W</td>
<td>63</td>
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</tbody>
</table>

** p < 0.05

1 adapted from Smolen et al 2014 Ann Rheum Dis 73 (9)

24 w data from Japan monotherapy study

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<thead>
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<th>Treatment</th>
<th>ACR20</th>
<th>ACR50</th>
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<tr>
<td>50mg Q4W</td>
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<tr>
<td>100mg Q2W</td>
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ACR20 at wk 12
ACR50 at wk 12 (Primary EP)

2 ACR 2015 abstract #1672
Clinical improvement in RA is consistently associated with decreased macrophage infiltration

- Activated macrophages are abundantly expressed in early RA synovial tissue, representing the predominant cell type
- Reduction in macrophage infiltration correlates with improvement in disease activity scores\(^1,2\)
- Macrophage is a primary cause of tissue destruction and affects many other cell types
- GM-CSF is important in every step of macrophage production and infiltration in the tissues

GSK3196165 – aGM-CSF, targets key effector cells in RA

Aiming to induce remission in early rheumatoid arthritis

- In-licensed from MorphoSys AG
- Good magnitude of effect with fast onset of action and long duration post treatment
- Effect size appears similar or greater than anti-TNF
- Targeting the macrophage in early RA
- Potential for early use to induce remission
- BAROQUE (RA Phase IIb) ongoing. Initial clinical read-out 2016

% EULAR good/moderate response at 4 weeks: Rapid onset of action

Phase Ib/IIa study, N= 96

• The macrophage is a mediator of tissue destruction in OA
• aGM-CSF is effective in animal models of OA
• aGM-CSF rapidly reduces pain (through effect on nerves) in animal models of OA
• Hand OA presents unique clinical development path
• Phase II to start in 2016

GSK3196165: Potential for disease modification & analgesic activity in hand osteoarthritis (HOA)


Status: Phase II start 2016
Indication: Hand OA
Planned Filing: 2021-2025
GSK2982772: RIP1 kinase inhibitor in the clinic

“a key regulator of inflammation, apoptosis and necroptosis, RIP1 is positioned at a strategic crossroads of multiple signalling nodes in the innate immune response”.1

- New class, oral therapeutic
- World leading internal team
- Anti-TNF effect with additional protection against effects of cell death
- GSK2982772 well tolerated at all doses with robust target inhibition achieved
- Exquisite kinase selectivity
- Multiple potential indications

**Kinome plot**

GSK2982772 -most selective ATP competitive kinase inhibitor to advance into man

**RIP1 kinase inhibition achieved in the clinic**

IC50=2 nM

**Blood levels (ng/mL)**

0.1 1 10 100 1000

0 50 100 150 200 250

**Molecular Cell**

“NF-κB-Independent Role of IKKα/IKKβ in Preventing RIPK1 Kinase-Dependent Apoptotic and Necroptotic Cell Death during TNF Signaling”

Authors: Yves Dondelinger, Sandrine Jouan-Lanhouet, Tatyana Divert, Emilie Theatre, John Berdin, Peter J. Cough, Piero Giansanti, Albert J.R. Heck, Emmanuel Dejardin, Peter Vandenabeele, Mathieu J.M. Bertrand


**Status:** Phase I
**Indications:** Rheumatoid arthritis, Psoriasis, Ulcerative Colitis
**Planned Filing:** 2021-2025
GSK2982772: studies in three indications to start in 2016

Key target, compelling target, compelling pre-clinical data

GSK2982772 blocks severe skin inflammation\(^1\)

Prevents against TNF induced shock\(^1\)

Inhibits TNF production in human gut from Crohn’s\(^2\)

Clinical Studies

- **rheumatoid arthritis**
- **ulcerative colitis**
- **psoriasis**

Three Phase II clinical studies to progress in parallel mid-2016

Plans in place to rapidly deliver clinical validation in 2017

Filing: 2021 - 2025

\(^1\)Berger et al. J Immunol. 2014;192:5476-80

\(^2\)GSK, data on file.
Benlysta™ (belimumab):
3rd consecutive positive pivotal study – new data

- Benlysta – the only medicine to treat systemic lupus erythematosus (SLE) to have succeeded in Phase III. Three other medicines have failed.
- Improvement in time to first severe flare (HR 0.5 p< 0.0003) – flare is the major driver of disease progression.
- Trend for reduction in corticosteroid use seen again (p=0.07). Further evaluation ongoing.
- Subcutaneous weekly medicine.
- 9 ongoing studies, including subgroups in SLE and other indications.

Status: IV approved 2011
Indication: SLE
Planned Filing: SC file Q4 2015/Q1 2016

Proportion of patients with SLE Responder Index (SRI) response at week 52

Placebo  belimumab-SC 200 mg

ACR 2015 - abstract #3218
Translating clinical experience into a new hypothesis: Phase II experimental study to start 2016

- After B-cell depletion with aCD20, BLyS levels increase
- BLyS drives persistence and re-population with auto-immune B-cells
- Benlysta suppresses BLyS
- Single patient case report suggests complete and persistent response in patient treated with aCD20 + Benlysta

CASE REPORT

- Severe, refractory Sjögren's syndrome, parotid B-cell lymphoma and cryoglobulinaemic vasculitis
- Failed several immunosuppressants, plasma exchange & surgical therapy as well as Benlysta alone and rituximab alone
- Dramatic response to combination including complete and persistent regression of lymphoma
Early Immuno-Inflammation clinical phase pipeline with multiple first in class assets

- Multiple first in class assets
- Eight key disease mechanisms
- Four biologicals
- Smart clinical development programmes to get early data read-outs

Potential first in class

* Biopharmaceutical
† Collaboration with third party
Anti-IL-7R antibody

“First in class” treatment for Sjögren’s syndrome

- IL-7R inhibition affects pathogenic T cell survival, reducing cytokine and auto-antibody production
- IL-7 promotes Sjögren’s-like syndrome in animal models
- Potential for disease modification by prevention of salivary and lacrimal gland destruction
- Phase I study in healthy volunteers completed - well tolerated

Status: Phase II start 2016
Planned Filing: 2021-2025

Ectopic lymphoid tissue and increased IL-7R+ cells in salivary glands of patients with Sjögren’s syndrome

Four “first in class” antibodies in the clinic: GSK3050002

**Anti-CCL20 antibody**
**Collaboration with Morphotek / Eisai**

“First in class” treatment for psoriatic arthritis
- Unique MOA - CCL20 inhibition blocks recruitment of pathogenic immune cells - single receptor
- Potential to perturb chronic inflammation & reduce disease activity – applicability in multiple diseases
- Inhibits CCR6+ T cells migration into inflamed tissue in humans *in vivo*

**Status:** Phase II start 2016
**Planned Filing:** 2021-2025

**Anti CCL20 prevents CCR6+ cells migration into inflamed blister in humans *in vivo***

<table>
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<tr>
<th>Mean change from baseline</th>
<th>placebo</th>
<th>0.1</th>
<th>0.5</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>20</th>
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<td>placebo (n=12)</td>
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<td>🎁</td>
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<td>🎁</td>
<td>🎁</td>
</tr>
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GSK, data on file. GSK3050002 in experimental medicine study (200784)
- Selective inhibition (CCR6 +ve cells only)
- Dose dependency
Cell depleting anti-LAG3 antibody
Collaboration with Prima BioMed

“First in class” treatment for T-cell driven II indications
- Unique MOA – a-LAG3 depletes recently activated, “pathogenic” T cells
- Potential for long term disease remission in multiple T cell-driven indications

Status: Phase I ongoing
Planned Filing: 2021-2025

Targeted depletion of LAG-3 T-cells with an antibody (A9H12) suppresses the immune reaction to the tuberculin antigen

Pre-dose
Post-dose

Depletion of LAG-3 T-cells at challenge site ...

..results in suppression in the skin reaction

"First in class" treatment for systemic sclerosis

- Systemic sclerosis patients have increased OSM serum levels and upregulated OSM and OSM-related genes in skin biopsies (data at ACR)
- Inhibition of OSM signalling is expected to reduce inflammation, vascular dysregulation and fibrosis

Status: Phase I ongoing
Planned Filing: 2021-2025
Four “first in class” antibodies in the clinic
All expected to progress to PhII in 2016

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>First in class Treatment</th>
<th>MOA &amp; Benefits</th>
<th>Status</th>
<th>Planned Filing</th>
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<tr>
<td>Anti-IL-7R antibody</td>
<td>Sjögren's syndrome</td>
<td>IL-7R inhibition affects pathogenic T cell survival, reducing cytokine and autoantibody production. IL-7 promotes Sjögren's syndrome in animal models. Potential for disease modification by prevention of salivary and lacrimal gland destruction. Phase I study in healthy volunteers completed - well tolerated.</td>
<td>Phase II start 2016</td>
<td>2021-2025</td>
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<tr>
<td>Anti-CCL20 antibody</td>
<td>Psoriatic arthritis</td>
<td>CCL20 inhibition blocks recruitment of pathogenic immune cells - single receptor. Potential to perturb chronic inflammation &amp; reduce disease activity - applicability in multiple diseases. Inhibits CCR6+ T cells migration into inflamed tissue in humans in vivo.</td>
<td>Phase II start 2016</td>
<td>2021-2025</td>
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<td>Cell depleting anti-LAG3 antibody</td>
<td>T-cell driven II indications</td>
<td>a-LAG3 depletes recently activated, “pathogenic” T cells. Potential for long term disease remission in multiple T cell-driven indications.</td>
<td>Phase I ongoing</td>
<td>2021-2025</td>
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<td>Anti-OSM antibody</td>
<td>Systemic sclerosis</td>
<td>Systemic sclerosis patients have increased OSM serum levels and upregulated OSM and OSM-related genes in skin biopsies (data at ACR). Inhibition of OSM signalling is expected to reduce inflammation, vascular dysregulation and fibrosis.</td>
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<td>2021-2025</td>
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**Anti-IL-7R antibody**
- **First in class** treatment for Sjögren's syndrome
- IL-7R inhibition affects pathogenic T cell survival, reducing cytokine and autoantibody production.
- IL-7 promotes Sjögren's syndrome in animal models.
- Potential for disease modification by prevention of salivary and lacrimal gland destruction.
- Phase I study in healthy volunteers completed - well tolerated.

**Anti-CCL20 antibody**
- **First in class** treatment for psoriatic arthritis.
- Unique MOA - CCL20 inhibition blocks recruitment of pathogenic immune cells - single receptor.
- Potential to perturb chronic inflammation & reduce disease activity – applicability in multiple diseases.
- Inhibits CCR6+ T cells migration into inflamed tissue in humans in vivo.

**Cell depleting anti-LAG3 antibody**
- **First in class** treatment for T-cell driven II indications.
- Unique MOA – a-LAG3 depletes recently activated, “pathogenic” T cells.
- Potential for long term disease remission in multiple T cell-driven indications.

**Anti-OSM antibody**
- **First in class** treatment for systemic sclerosis.
- Systemic sclerosis patients have increased OSM serum levels and upregulated OSM and OSM-related genes in skin biopsies (data at ACR).
- Inhibition of OSM signalling is expected to reduce inflammation, vascular dysregulation and fibrosis.
Immuno-Inflammation R&D strategy:
From symptomatic benefit to sustainable remission

GSK Pipeline

Targeted Biologicals
- Benlysta
- sirukumab
- Anti-GM-CSF
- Anti-IL-7
- Anti-CCL20

Targeted Small Molecules
- RIP1
- I-BET

Targeting Resistant Disease
- RIP1
- I-BET
- Anti-IL-7
- Anti-CCL20
- Anti-OSM
- Anti-LAG3

Early Intervention & Remission Induction
- Anti-GM-CSF
- RIP1
- Anti-CCL20
- Anti-LAG3

macrophage
neutrophil
stromal cell
T cell
plasma cell
B cell
Oncology
Oncology R&D strategy

Focusing on 3 areas fundamental to oncology

Cancer Epigenetics

Immuno-Oncology

Cancer Stem Cells

GSK Pipeline

Long-Term Survival & Cures

Reprogram Cancer Cells

Stimulate Anti-Tumour Immunity

First in Class Medicines & Combination Therapy
GSK Epigenetics: an early commitment with a pipeline now at the forefront of industry

• World-leading science in epigenetics since 2008
• Team has published 9 papers in Nature & Cell
• World-leading academic collaborations
• Strategic collaborations with biotech
GSK525762: potential first in class BET inhibitor

Potential for broad activity

- GSK525762 blocks binding of BET family proteins (BRD2, 3 and 4) to transcriptional mediators changing gene expression including suppressing oncogene expression
- Potential use in many potential indications
- Broad activity in preclinical cell line models
- PoC opportunity in NUT midline carcinoma (NMC)
- Rare and rapidly lethal cancer caused by chromosomal translocation involving BET target (NUT gene and either BRD3, BRD4, or NSD3 (which binds BRD4) gene)

Preclinical data show activity of GSK525762 in many cancer types (gIC50 < 1 μM)

Status: Phase I
Indications: Solid Tumours, Heme Malignancies
Filing: 2018
GSK525762: early evidence of potential clinical benefit

Potential new treatment for rapidly lethal cancer

- Responses observed in NUT midline carcinoma
  - 6 patients treated at 60-100 mg QD with 4 Partial Responses

- Solid tumour studies underway across multiple tumour types;
  - 36 patients enrolled across CRC, NMC, CRPC, SCLC, BC & MM

- Haematological studies underway; partial responses seen in AML
  - 20 patients enrolled cross AML, NHL & MM

Chest CT of patient with NMC treated with GSK525762: ~90% reduction in tumour volume at week 16

GSK, data on file.
GSK525762: potential to treat and reset disease in rheumatoid arthritis: Extensive preclinical data package for BET inhibition

- GSK525762 interferes with stromal cells driving autonomous disease progression in RA
- Profound cytokine, chemokine and immunoglobulin inhibition in human macrophages\(^1\) and RA patient samples and biopsies
- Modulation of macrophage\(^1\), osteoclast\(^2\) and Th17 cell types
- Profound inhibition of disease in multiple RA preclinical models\(^2\)
- Rebalances gene expression in RA stromal cells (decreased cytokines, chemokines, metalloproteases, elevated protease inhibitors\(^3, 4\))


Status: Phase II start 2016
Indication: Therapy Resistant RA
Planned Filing: 2021-2025
GSK2879552 LSD1 inhibitor: Early signal of efficacy in SCLC

- Preclinical data give reason to believe
- Clinical studies ongoing in Small Cell Lung Cancer and Acute Myeloid Leukaemia
- Signal of significant progression-free survival for some patients

**MLL-AF9 mouse derived leukemia cells treated for 6 days in vitro**

**Untreated**  
**10 nM GSK552**

**Plot of duration of treatment (days) with Tumour Response (RECIST 1.1 criteria) SCLC**

**Status:** Phase I  
**Indications:** AML, SCLC  
**Planned Filing:** 2020

Best confirmed response – PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, NE: Not Evaluable  
Triangles indicate ongoing subjects

GSK, data on file.
Immuno-Oncology: NY-ESO T-Cell Therapy

- TCR T-cell therapy
- 50% ORR seen in sarcoma
- Ongoing studies in ovarian and other solid tumours and haematological malignancies
- Planned studies in combination with checkpoint modulators
- Collaboration with Adaptimmune

**Status:** Phase I/II  
**Indications:** NY-ESO-1 positive Cancers: Sarcoma, Myeloma, NSCLC, Melanoma, Ovarian Cancer  
**Filing strategy to be agreed with Adaptimmune**

*Note: GSK3377794 subject to exercise of option by GSK*
• GSK3174998 is one of four humanised OX-40s in clinic
• Dual mechanism: enhancing effector T-cell and suppressing T-regs
• Phase I Study started in eight cancers
• Combination with Merck PD1 in 2016
• Combination with GSK TLR4 in 2017
• Collaboration with MD Anderson

Status: Phase I
Indications: Solid tumours, Heme Malignancies
Planned Filing: 2020
**Universal mechanism across multiple cancers**

**Patient selection biomarker**

**Enhances T-cells associated with survival**

**Use after CTLA-4 and PD-1 in unresponsive or refractory patients**

**Possible anchor for use in combinations**

**Collaboration with INSERM**

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**Status:** Phase I start Q1 2016  
**Indications:** Solid tumours, Heme Malignancies  
**Planned Filing:** 2020

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DiGiacomo, Clin Immunol Immunother 2013
Cancer Stem Cells: tarextumab (anti-Notch 2/3)

- Inhibition of Notch 2/3 Receptors in cancer stem cells
- Phase Ib: Overall response rate of 38%
- Ongoing randomised Phase II studies in pancreatic cancer and SCLC
- Phase II read-out 2016
- Collaboration with OncoMed

**ALPINE (Phase Ib) Pancreatic Cancer:**
gemcitabine/Abraxane* + tarextumab
Dose range: TRXT from 5 to 15mg/kg Q2W

11 of 29 PR (38%) in Nab-P+Gem Cohorts

**Attractive signal over 23% ORR of Gem/Abraxane SOC in hard-to-treat cancer**

O’Reilly et al. 2015 Gastrointestinal Cancer Symposium

Note: tarextumab subject to exercise of option by GSK
*Abraxane is a trademark of Abraxis Bioscience LLC

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Status: Phase II
Indications: Pancreatic cancer and Small Cell Lung Cancer
Planned Filing: 2020
Oncology R&D strategy

Focusing on 3 areas fundamental to oncology

Cancer Epigenetics
- BET inhibitor (GSK525762)
- LSD-1 inhibitor (GSK2879552)
- EZH2 inhibitor (GSK2816126)

Immuno-Oncology
- NY-ESO-1 TCR-T
- OX40 agonist (GSK3174998)
- ICOS agonist
- TLR4 agonist

Cancer Stem Cells
- Notch2/3 (tarexumab)
- Notch1 (brontictuzumab)

Long-Term Survival & Cures
- Epigenetics
- Immuno-oncology
- Stem cells

Reprogram Cancer Cells
- Epigenetics

Stimulate Anti-tumour Immunity
- Immuno-oncology

First in Class Medicines & Combination Therapy
- Epigenetics
- Immuno-oncology
- Stem cells
Oncology – Pipeline snapshot

**Mechanism**
- BET inhibitor (GSK525762)
- LSD-1 inhibitor (GSK2879552)
- EZH2 inhibitor (GSK2816126)
- PRMT5 inhibitor (GSK3326595)
- Novel small molecule targets (X6)
- NY-ESO-1 TCR-T
- OX40 agonist (GSK3174998)
- ICOS agonist (GSK3359609)
- TLR4 agonist (GSK1795091)
- CAR-T and TCR-T targets (x6)
- Novel small molecule targets (x2)
- ImmTacs (x4)
- mAb-dAbs and dual-specific Abs (x5)

**Pre-clinical**
- Solid tumours, Heme Malignancies
- AML, SCLC
- Solid tumours, Heme Malignancies
- Solid tumours, Lymphoma
- Sarcoma, Multiple Myeloma, NSCLC, Ovarian, Melanoma
- Solid tumours, Heme Malignancies

**Phase I**
- Pancreatic, SCLC
- Solid tumours, Heme Malignancies
- Multiple Myeloma
- Mesothelioma, NSCLC

**Phase II**
- Other targeted therapies

† Collaboration with a third party.
### Assets profiled at R&D day by planned filing date

See [www.gsk.com](http://www.gsk.com) for full clinical pipeline

<table>
<thead>
<tr>
<th>6 NMEs &amp; 5 PLEs</th>
<th>10 NMEs &amp; 5 PLEs</th>
<th>17 NMEs &amp; 5 PLEs</th>
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<tr>
<td><strong>2014 to 2017</strong></td>
<td><strong>2018 to 2020</strong></td>
<td><strong>2021 to 2025</strong></td>
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<td><strong>Nucala</strong> (mepolizumab) IL-5 mAb</td>
<td>mepolizumab IL-5 mAb</td>
<td>sirukumab IL-6 mAb</td>
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<td>Nasal Polyposis</td>
<td>Severe Asthma</td>
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<td>Ixekizumab*</td>
<td>GSK3008348 Alpha V beta 8 integrin antagonist</td>
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† Subject to exercise of option
* Subject to collaborator agreement
‡ EU filing
* USAN, INN approval pending

<table>
<thead>
<tr>
<th><strong>125</strong></th>
<th><strong>6 NMEs &amp; 5 PLEs</strong></th>
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<th><strong>17 NMEs &amp; 5 PLEs</strong></th>
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Rare Diseases

Amyloidosis and Cell and Gene Therapy
Amyloidosis: a complex protein deposition disease process with ~50% mortality at 3 years

- AL amyloidosis – monoclonal immunoglobulin light chains (plasma cell dyscrasia) (~70% of all cases)
- ATTR amyloidosis – hereditary disease caused by variant transthyretin (TTR) protein
  – acquired disease caused by wild type TTR (senile amyloidosis)
- AA amyloidosis – complication of chronic inflammation or infection
- Implication in other disease states. Growing recognition of its importance

Accumulation of amyloid deposits damages vital organs causing disease

Peripheral / visceral nerves: TTR
Kidney: AA, AL, TTR
Heart: AL, TTR
Liver: AL, AA
Two fundamental approaches to treatment: prevent amyloid formation and remove amyloid deposits

“Gene silencing” by antisense oligonucleotide

- Knockdown of TTR gene prevents production of mutant and wild type TTR protein
- Prevents formation of amyloid deposits in vital organs
- GSK2998728 in collaboration with Isis Pharmaceuticals

Removal of amyloid deposits by macrophage-mediated clearance

- Serum amyloid P component (SAP) in blood and all amyloid deposits
- SAP removed from plasma by GSK SAP depleter but still decorates deposits in organs
- Anti-SAP mAb can then target SAP in amyloid deposits
- Antibody binding triggers amyloid clearance by macrophages
- Organ function is restored
GSK2998728 RNA targeted transthyretin (TTR) knockdown

~80% TTR knockdown

Mean change - Time profile following 3 loading doses week 1, then 1 weekly dose (n=65; healthy volunteers)

TTR reductions observed in Phase III FAP open label extension

Mean max TTR reduction = 76%
Max TTR reduction = 92%

Status: Phase III
Indication: Familial amyloid polyneuropathy (FAP);
Familial and wild-type amyloid cardiomyopathy (TTR CM)
Filing: 2017 (FAP), 2020 (TTR CM)

GSK: data on file
Note: GSK2998728 is a collaboration with Isis Pharmaceuticals and subject to exercise of option by GSK
CPHPC + Anti-SAP mAb for systemic amyloidosis

- Directly targets amyloid deposits that cause disease
- Proof of concept in systemic amyloidosis
  - Regression of amyloid in liver, kidney, spleen, etc
- Potential for accelerated approval
- US breakthrough status application planned
- Use in cardiac AL and ATTR amyloidosis
- Example of academic partnership model
- Collaboration with Pentraxin

Liver ECV (median normal 29%)

Before anti-SAP: 36.0
Day 42 after anti-SAP: 29.0

Liver Stiffness (median normal 5.3 kPa)

Before anti-SAP: 5.7
Day 42 after anti-SAP: 2.8

% of tracer in liver

Before anti-SAP: 61.1
Day 42 after anti-SAP: 17.4

Reason to believe – amyloid imaging

Therapeutic clearance of amyloid by antibodies to serum amyloid P component

Amyloidosis: a comprehensive R&D approach

- Similar prevalence to Pulmonary Arterial Hypertension
  - Approximately 30,000 cases but currently under-diagnosed
- Fundamental mechanism in diverse but medically important disease states
- GSK approaches address both removal of existing deposits and prevention of accumulation
- World class expertise – ability to maximise the opportunity from our leadership position
  - Oral SAP depleter/ anti fibril approaches

GSK’s dual approach to amyloidosis

1. “Gene silencing” by antisense oligonucleotide
   - TTR to prevent formation of amyloid deposits in vital organs
2. Removal of amyloid deposits by macrophage-mediated clearance
   - Anti-SAP mAb to target SAP in amyloid deposits
GSK2696273 for adenosine deaminase severe combined immunodeficiency: 100% survival at median 7 year follow up

Severe Combined Immuno-Deficiency (SCID)
- Fatal
- Life-threatening opportunistic infections

Status: Filed in Europe
Indication: ADA SCID
Planned Filing: US filing 2017

GSK2696273 is a collaboration with Telethon and Ospedale San Raffaele

Cicalesse et al. ESID 2015, poster #0779.
Gene therapy works in different monogenic diseases
Innovative collaboration with Telethon and Ospedale San Raffaele

- World first *ex vivo* autologous stem cell gene therapy filed
- Filing strategy agreed for 2 more
- Beta thalassaemia study started
- Building GSK platform capability in cell and gene therapy. New alliances and internal platform build
- Cell gene therapy approaches in oncology and potentially other areas. IP estate and know-how accumulating

### Pipeline of products

- **ADA SCID**
- **Metachromatic Leukodystrophy**
- **Wiskott-Aldrich Syndrome**
- **Beta thalassemia**
- **MPS1**
- **Chronic Granulomatous disease**
- **Globoid Cell Leukodystrophy**

#### Wiskott-Aldrich Syndrome (WAS)
- Thrombocytopenia
- Infections
- Autoimmune disease
- Lymphoma

#### Metachromatic Leukodystrophy (MLD)
- Fatal
- Rapid loss in cognitive & motor function, followed by death

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*a* Licensed from Telethon and Ospedale San Raffaele

*b* GSK holds an option to license programme from Telethon and Ospedale San Raffaele
Cell Gene Therapy clinical effect in MLD

Motor function by GMFM in LI patients

Biffi et al. ESCGT 2015 presentation
Introducing our experts

GSK’s leading scientists in immuno-inflammation, cancer research, amyloidosis and CGT

Paul-Peter Tak
Senior Vice President, Head Immuno-Inflammation (II) TAU

Ravi Rao
Vice President, Medicines Development Leader & Head Unit Physician II

John Bertin
Vice President, Head Pattern Recognition Receptor DPU

Axel Hoos
Vice President, Head of Immuno-Oncology

Chris Carpenter
Vice President, Head Cancer Epigenetics DPU

Duncan Richards
Vice President, Head Academic DPU

Sven Kili
Vice President, Development Head for Gene Therapy
### Assets profiled at R&D day by planned filing date

See [www.gsk.com](http://www.gsk.com) for full clinical pipeline

<table>
<thead>
<tr>
<th>Year to Year</th>
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<tr>
<td><strong>6 NMEs &amp; 5 PLEs</strong></td>
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<tr>
<td>Nucala (mepolizumab) IL-5 mAb</td>
<td>sirukumab IL-6 mAb</td>
<td>sirukumab IL-6 mAb</td>
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<tr>
<td>Severe Asthma</td>
<td>Respiratory</td>
<td>Respiratory</td>
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<tr>
<td>mepolizumab IL-5 mAb</td>
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<tr>
<td>COPD</td>
<td>Nasal Polyposis</td>
<td>COPD</td>
<td>Asthma, Others</td>
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<tr>
<td>mepolizumab IL-5 mAb</td>
<td>HES</td>
<td>COPD, Asthma</td>
<td>Acute Lung Injury</td>
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<tr>
<td>EGPA</td>
<td>mepolizumab IL-5 mAb</td>
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<tr>
<td>fluticasone furoate+vilanterol+umeclidinium ICS/LABA/LAMA COPD</td>
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<tr>
<td>dolutegravir + rilpivirine Integrase inhibitor + NNRTI HIV</td>
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<tr>
<td>Benlysta Subcutaneous BlyS mAb</td>
<td>Belimumab</td>
<td>belimumab + CD20 BlyS+CD20</td>
<td>belimumab + CD20 BlyS+CD20</td>
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<tr>
<td>SLE</td>
<td>Sirukumab IL-6 mAb</td>
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| **10 NMEs & 5 PLEs** | | | |
| mepolizumab IL-5 mAb | mepolizumab IL-5 mAb | sirukumab IL-6 mAb | mepolizumab IL-5 mAb |
| Nasal Polyposis | Iarexumab*  Notch 2-3 mAb | sirukumab IL-6 mAb | sirukumab IL-6 mAb |
| Pancreatic Cancer, SCLC | Pancreatic Cancer, SCLC | Pancreatic Cancer, SCLC | Pancreatic Cancer, SCLC |
| GSK2298852+ GSK2215698 SAP mAb + SAP depleter Amyloidosis | GSK2998728 TTR production inhibitor TTR Cardiomyopathy | Sirukumab IL-6 mAb | Severe Atopic Dermatitis |
| Dolutegravir + lamivudine FDC Integrase inhibitor+NRTI HIV | Diprodustat* Prolyl hydroxylase inhibitor Anemia of CKD | Dolutegravir IL-13 bispecific antibody | Dolutegravir IL-13 bispecific antibody |
| Metachromatic Leukodystrophy | | | |
| fluticasone furoate+vilanterol+umeclidinium ICS/LABA/LAMA COPD | | | |
| Dolutegravir | | | |
| Cibotegravir Long acting integrase inhibitor HIV, HIV PreP | | | |
| GSK2987872* TTR production inhibitor | | | |
| FAP | | | |

| **17 NMEs & 5 PLEs** | | | |
| sirukumab IL-6 mAb | sirukumab IL-6 mAb | sirukumab IL-6 mAb | sirukumab IL-6 mAb |
| Severe Asthma | Severe Asthma | Severe Asthma | Severe Asthma |
| danirixin CXCR2 antagonist | Long acting IL-5 mAb (NBE) | Long acting IL-5 mAb (NBE) | Long acting IL-5 mAb (NBE) |
| COPD | COPD | COPD | COPD |
| mepolizumab IL-5 mAb | HES | mepolizumab IL-5 mAb | mepolizumab IL-5 mAb |
| darapladust Prolyl hydroxylase inhibitor Anemia of CKD | mepolizumab IL-5 mAb | mepolizumab IL-5 mAb | mepolizumab IL-5 mAb |
| GSK3269557 P3 kinase delta inhibitor | GSK2618960 IL-7 receptor mAb Sjogren’s Syndrome | GSK2862277 TNFRI dAb | GSK2862277 TNFRI dAb |
| GSK2877952 LSD1 inhibitor Acute Myeloid Leukemia, SCLC | GSK2878175 NS5B inhibitor HCV | GSK2696275 Ex-vivo stem CGT Beta Thalassemia | GSK2696275 Ex-vivo stem CGT Beta Thalassemia |
| GSK3174998 CX40 agonist mAb Solid tumours, Haematological Malignancies | GSK3228836† Antisense oligonucleotide | GSK2696273 Ex-vivo stem CGT ADA-SCID | GSK2696273 Ex-vivo stem CGT ADA-SCID |
| GSK377794* NY-ESO-1 TCR Sarcomas, Mult. Myel. Melanoma | GSK328836† Antisense oligonucleotide | GSK2696274 Ex-vivo stem CGT ADA-SCID | GSK2696274 Ex-vivo stem CGT ADA-SCID |
| Bacterial Inf. | GSK2879552† TTR production inhibitor TTR Cardiomyopathy | GSK2831781 LAG-3 mAb | GSK2831781 LAG-3 mAb |
| GSK2987872* TTR production inhibitor | | | |
| GSK2245035 TLR7 agonist | GSK2882772 RIP1 kinase inhibitor Psoriasis, RA, UC | GSK2495035 TLR7 agonist | GSK2495035 TLR7 agonist |
| GSK2269557 PI3 kinase delta inhibitor | GSK2878175 NS5B inhibitor HCV | | |
| GSK2269557 PI3 kinase delta inhibitor | | | |
| | | | |
| | | | |

| Subject to exercise of option | Subject to collaborator agreement | EU filing | USAN, INN approval pending |
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