Innovative Pipeline

Sir Andrew Witty

3 November 2015
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Innovation is critical to maximising the potential of GSK in the current environment

Future R&D innovation + Broad portfolio offering

Global footprint + regulatory and quality competence

Pharmaceuticals Vaccines Consumer

>7 billion people

650m new babies by 2020

~1 billion 60+ year olds by 2020 (+20%)

>6 billion people outside US & Europe

Clear volume opportunity

But pricing environment uncertain

Innovation is critical to maximising the potential of GSK in the current environment
**R&D Strategy: Reliable fill & flow with greater novelty and improved return on investment**

<table>
<thead>
<tr>
<th>Accelerate Discovery output</th>
<th>Focus where science is innovative</th>
<th>Improve balance internal vs external</th>
<th>Reduce fixed cost and improve ROI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Now have 30 DPUs, of which two thirds are from the original 2009 set. Average 20% turnover every 3 year cycle</td>
<td>• Of the ~40 assets profiled today, 80% of new molecules, biologicals and vaccines are potentially 1st in class</td>
<td>• 60% of NMEs* in the clinic are home-grown, 40% partnered or in-licensed</td>
<td>• 20% faster study execution times*</td>
</tr>
<tr>
<td>• 65% of NMEs* in the clinic were either discovered or worked on by the DPUs</td>
<td>• Almost 50% of clinical stage NMEs* are biopharm, CGT, or oligos. i.e. non-traditional white pill</td>
<td>• &gt;1,500 collaborations inclusive of academic, public-private partnerships, biotech and pharma</td>
<td>• Pharma R&amp;D headcount reduced from 12,000 to 8,500 since 2008, reduced to 2 global pharma R&amp;D hubs</td>
</tr>
<tr>
<td>• Average of 60-65 publications annually in world class journals across pharma and vaccines</td>
<td>• Competitive advantage through epigenetics, cell &amp; gene technology, adjuvants, self amplifying RNA, inhaled technology, chimp adenovector</td>
<td></td>
<td>• Balance discovery and development (pharma split 38% Discovery; 62% Development)</td>
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<tr>
<td></td>
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<td></td>
<td>• Divested marketed oncology portfolio for $16bn</td>
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</table>

**To deliver multiple launches per year**

*NMEs: Phase I – III/submitted, per pipeline chart; † Pipeline = Phase I-III/submitted; ^ comparison vs peers based on CMR data.*
New product contribution increasing as generic exposure reduces

2008 - 2014
28 first approvals of new molecules, vaccines or significant combinations, generating £2.6 billion sales in 2014

2008 - 2014
~£6bn loss to generics + Avandia

2015 - 2020
11 new products* with at least £6bn expected sales, with 9 marketed products generating £1.3 billion in 2015 YTD

2015 - 2020
Avodart (Q4 2015), Advair†

2021 - 2025
~ 30 Phase II NME/PLE starts in 2016/17

2021 - 2025
~ 20 Phase III NME/PLE starts in 2016/17

Reduced generic exposure

* Includes key recent and near-term launches plus late-stage assets. Rx: Breo, Anoro, Incruse, Arnulty, Tanzeum, Nucala, Tivicay, Triumeq. Vx: Menveo, Bexsero, Shingrix.
† A number of assets in the portfolio will face generic competition in this time frame, the most significant of which is Advair. PLE = New formulations or combinations
New product growth more than offsets Advair decline

* New products defined as: Rx: Breo, Anoro, Incruse, Arnuity, Tanzeum, Tivicay, Triumeq. Vx: Menveo, Bexsero
^ Growth and decline in the respective quarters on a Sterling basis
### Assets profiled at R&D day by planned filing date

<table>
<thead>
<tr>
<th>2014 to 2017</th>
<th>2018 to 2020</th>
<th>2021 to 2025</th>
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</thead>
<tbody>
<tr>
<td><strong>7 NMEs &amp; 5 PLEs</strong></td>
<td><strong>11 NMEs &amp; 5 PLEs</strong></td>
<td><strong>21 NMEs &amp; 5 PLEs</strong></td>
</tr>
<tr>
<td><strong>Severe Asthma</strong></td>
<td><strong>HIV</strong> &amp; <strong>NNRTI</strong></td>
<td><strong>Severe Asthma</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>Nasal Polyps</td>
<td>Severe Asthma</td>
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<tr>
<td>sirukumab IL-6 mAb</td>
<td>Tarextumab TACE 2/3 mAb</td>
<td>Alpha V beta 6 integrin antagonist</td>
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<tr>
<td>Rheumatoid Arthritis</td>
<td>Pancreatic Cancer, SCLC</td>
<td>IPF</td>
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<tr>
<td>GSK2998552 + GSK2315689 SAP mAb + SAP depleter</td>
<td>GS-9852 + TTR production inhibitor</td>
<td>BET inhibitor</td>
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<tr>
<td>COPD</td>
<td>HES</td>
<td>Therapy Resistant RA</td>
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<tr>
<td>mepolizumab IL-5 mAb</td>
<td>GSK259762 BET inhibitor Solid Tumours, Haematological Malignancies</td>
<td>GSK252762</td>
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<tr>
<td>COPD</td>
<td>GSK2998728 TTR production inhibitor</td>
<td>RA, OA</td>
</tr>
<tr>
<td>mepolizumab IL-5 mAb</td>
<td>GSK2998728 TTR production inhibitor</td>
<td>COPD Vaccine</td>
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<tr>
<td>COPD</td>
<td>dapirodast Prolyl hydroxylase inhibitor</td>
<td>COPD</td>
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<tr>
<td>mepolizumab IL-5 mAb</td>
<td>Anemia of CKD</td>
<td>COPD Vaccine</td>
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<tr>
<td>COPD</td>
<td>Dolagrelavir + Iamivudine FDC Integrase inhibitor + NRTI HIV</td>
<td>COPD, Asthma</td>
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<tr>
<td>EGPA</td>
<td>Cabilagrelavir Long acting integrase inhibitor HIV, HIV PreP</td>
<td>Long acting IL-5 mAb (NBE)</td>
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<tr>
<td>GSK2696273 Ex-vivo stem CGT</td>
<td>GSK3174998 GSK40 agonist mAb Solid tumours, Haematological Malignancies</td>
<td>IL-5/13 bispecific antibody</td>
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<tr>
<td>Metachromatic Leukodystrophy</td>
<td>MenABCWY US filing Meningococcal A,B,C,W and Y disease prophylaxis</td>
<td>Sjogren’s Syndrome</td>
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<tr>
<td>fluticasone furoate-vilanterol + umecedinium ICS/LABA/LAMA COPD</td>
<td>GSK2878552 LSD1 inhibitor Acute Myeloid Leukaemia, SCLC</td>
<td>Sjogren’s Syndrome</td>
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<td>Wiscott-Aldrich Syndrome</td>
<td>GSK38111124 ND0 agonist mAb Solid tumours, Haematological Malignancies</td>
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<td>Amyloidosis depleter SAP</td>
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<td>Sjogren’s Syndrome</td>
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<td>SLE</td>
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<td></td>
<td>GSK2618960</td>
<td>Sjogren’s Syndrome</td>
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</tbody>
</table>

See www.gsk.com for full clinical pipeline

Subject to collaborator agreement
EU filing
Subject to USAN, INN approval pending
Planned to be filed post 2025
Focus on delivering innovative and sustainable presence in 6 key areas

- HIV / Infectious Diseases
- Respiratory
- Vaccines
- Immuno-Inflammation
- Oncology
- Rare Diseases
Focus for today: Innovation to deliver products of value

Patrick Vallance
President, Pharmaceuticals R&D

Moncef Slaoui
Chairman of Vaccines
Patrick Vallance

President, Pharmaceuticals R&D
GSK R&D: what is important to us

Innovative science

• Average of 35 publications annually in worlds-class journals (Nature, Cell, Science)
• In 2014 and 2015 to date, GSK scientists listed as co-authors in more than 1,600 publications
• 80% of pre-clinical to Phase II assets have a novel mechanism of action
• Target sciences initiative with EBI/Sanger & Altius Institute in Seattle

Patient need

• 5 Breakthrough Designations since 2013
• 3 FDA Priority Reviews since 2010
• Focus on preventative and curative medicines
• Strong focus on patient input
• Quality of life study endpoints

Quality

GSK achieved highest number of FDA approvals, 2010-15

14

GlaxoSmithKline

Company 1

Company 2

Company 3

Company 4

• All first cycle approvals since 2012
• 10% faster in time to file approval than industry average
• Clinical study cycle times 20% faster than average
• Cost per patient visit 30% less than 2008
• Molecule quality focus

Partnership

Collaborations with academia, biotechs, pharmaceutical companies and regulators
Recruiting and developing the best scientists

We’re committed to ensuring GSK remains the best place to develop medicines
HIV / Infectious Diseases
Infectious disease burden continues to grow and present public health challenges

<table>
<thead>
<tr>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
<th>Acute complicated infectious diseases</th>
</tr>
</thead>
</table>
| • 36.9m living with HIV worldwide; 1.2m deaths & 2m new infections annually<sup>1</sup>  
• Resistance, adherence and addressing long-term toxicities remain areas of significant unmet medical need  
• The ultimate goal is remission and cure | • Globally, 240m people have Chronic Hepatitis B<sup>1</sup>  
• More than 780k people die each year  
• HBV evades immune system, with limited options for durable remission | • Globally, 130-150m people have Chronic Hepatitis C<sup>1</sup>  
• 350-500k people die each year  
• Need for a cure completed in a single visit | • Globally, ~3.5m annual deaths due to lower respiratory tract infections<sup>2</sup>  
• Increasing antimicrobial drug resistance (MDR)  
• Hospitalised infections & complications have direct costs >$35bn annually in US<sup>3</sup>  
• Pathophysiology & tissue damage suggest aberrant host immune responses as key driver |

<sup>1</sup> WHO 2015; <sup>2</sup> WHO 2014; <sup>3</sup> J Med Econ 2013
Infectious Diseases strategy: from innovative treatment regimens to the pursuit of cure

GSK Pipeline

- Innovative Treatment Regimens
- Long-acting Treatment
- Prevention
- Remission & Cure

HIV

HCV/HBV

Acute complicated infectious disease
Dolutegravir set to be at the heart of future treatment regimens

**Dolutegravir profile**

**Efficacy**
- Rapid and sustained viral load drop

**Barrier to Resistance**
- No resistance mutations selected in first line failures (one patient had E157Q/P mutation without decreased susceptibility to dolutegravir)
- Limited resistance mutation evolution in experienced patients on failure
- Distinct resistance profile compared to other INIs (RAL, EVG)

**Favorable PK Profile**
- Booster free
- No food requirement for adequate exposure

**Well tolerated**

**DTG/3TC: Planned launch H1 2019**
- 2-drug STR for HIV treatment in naïve and suppressed patients, QD
- Simplification - Potential benefit on tolerability and drug burden
- No food requirements

**DTG/RPV: Planned launch H1 2018**
- 2-drug STR for HIV treatment in suppressed patients, QD
- Simplification - Potential benefit on tolerability and drug burden
  (ViiV Healthcare - Janssen sponsored)

**Triumeq™ (abacavir/dolutegravir/lamivudine): Launched 2014**
- 3-drug STR for HIV treatment, QD
- Only currently available DTG containing Single Tablet Regimen (STR)

**Tivicay™ (dolutegravir): Launched 2013**
- For HIV treatment in combination with other ART, QD

ViiV Healthcare is a specialist joint venture solely dedicated to HIV, owned by GSK, Pfizer and Shionogi
PADDLE (Pilot Antiretroviral Design with Dolutegravir and Lamivudine): Investigator sponsored study design

- Investigator sponsored study
- 2 tablet treatment
- ARV naive patients
- 2 cohort study
- Open label single arm

Phase IV, pilot, open-label, single arm exploratory trial

<table>
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<tr>
<th>Patient #</th>
<th>Base line viral load</th>
<th>Week 8</th>
<th>Week 24</th>
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<tr>
<td>1</td>
<td>10.909</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
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<tr>
<td>2</td>
<td>10.233</td>
<td>&lt; 50</td>
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<td>3</td>
<td>151.669</td>
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</tr>
<tr>
<td>4</td>
<td>148.370</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
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<tr>
<td>5</td>
<td>20.544</td>
<td>&lt; 50</td>
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<td>6</td>
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<tr>
<td>20</td>
<td>7.368</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
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</table>

From week 8 onwards all patients VL was undetectable (pVL < 50 copies/mL)

Adapted from Cahn et al, EACS 2015, LBPS4/1
Cabotegravir: Long-acting antiretroviral

Long-acting

HIV Treatment

Mean concentration/time profile following single injection

THE LANCET Infectious Diseases
LATTE Week 96 Results

Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial

HIV Prevention

Mean concentration/time profile following single injection

1 Spreen et al, JAIDS 2014;67(5):481-486

PA-IC90

4 PA-IC90

100mg IM    100mg SC
200mg IM    200mg SC
400mg IM    400mg SC (split)
800mg IM (split)

0
0.1
1
10
100
Plasma CAB (g/mL)

0 4 8 12 16 20 24 28 32 36 40 44 48

Visit (week)

Proportion of patients with HIV-1 RNA concentration of less than 50 copies per mL by visit in the intention-to-treat exposed population

Error bars indicate 95% CI

Pre-clinical data

8/8 protected
cabotegravir LA
untreated

100% Protection in NHP Rectal Challenge

8/8 infected

p<0.0001

1 Margolis et al, Lancet Inf Dis 2015;15(10):1145-1155

3 Andrews et al, Science 2014;343(6175):1151-4
Cabotegravir long-acting clinical studies

Potential for better adherence

**HIV TREATMENT**

**CAB LA + RPV LA**

Planned launch: 2019/2020

**4Q2015 LATTE 2 results**

Key Phase III-enabling data: combination CAB LA + RPV LA as maintenance therapy (ViiV Healthcare - Janssen sponsored)

**Mid-2016 HIV Treatment Phase III start**

CAB LA + RPV LA switch studies (transition from oral therapy to long-acting)

**HIV PREVENTION**

**CAB LA monotherapy**

Planned launch: 2020+

**Mid-2016 PrEP Phase III start (men)**

CAB LA monotherapy vs. TDF/FTC (Truvada) in at-risk men who have sex with men/transgender women (Collaboration with third party being considered)

**End-2016 PrEP Phase III start (women)**

CAB LA monotherapy vs comparator in at-risk women (Collaboration with third party being considered)
Phase IIb trial examining long-acting (LA) cabotegravir (CAB) in combination with LA rilpivirine (RPV). 309 treatment naïve subjects initially treated with QD oral CAB 30mg + 2 NRTIs

Following virologic suppression 286 subjects qualified for entry into maintenance phase and were randomised 2:2:1 onto: 4 week injections with CAB LA + RPV LA (Q4W); 8 week injections with CAB LA + RPV LA (Q8W) or continuation of oral CAB + NRTIs

Through 32 weeks on 2-drug maintenance therapy with CAB LA and RPV LA, 95% (Q8W) and 94% (Q4W) of subjects were virologic successes (VL<50) compared to 91% of subjects continuing three drug oral CAB + NRTIs

Adverse events (AEs) leading to withdrawal were 5% (n=6) for Q4W, 2% (n=2) for Q8W, and 2% (n=1) for oral CAB + NRTIs. The most common AE was injection site pain (93% of injection recipients)

Detailed analyses just starting
Next wave cabotegravir long-acting combinations

Opportunities with broadly neutralising antibodies

- Cabotegravir long-acting
- Every 2 or 3 months

- Broadly neutralising antibodies (bnAbs)
- GSK and the National Institute of Allergy and Infectious Diseases/National Institutes of Health collaboration to be announced later this week

A pilot clinical combination study of VRC01 and cabotegravir is planned for 2016 start
**GSK & Regulus combination offers potential for a single administration treatment for HCV**

- **RG101 lowers viral load**
- **GSK2878175 lowers viral load**
- **Both molecules have potential for prolonged PK/PD activity**
- **Prolonged pan-genotype and anti-HCV activity**
- **Potential single administration option**
- **Clinical combination study starts 2016**

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**Single dose RG-101**

Prolonged VL declines in HCV patients

![Graph showing prolonged VL declines in HCV patients with RG101 at different dosages](EASL 2015. Van Der Ree et al. J. Hepatology. 2015;62: S261)

**Single dose GSK175-LA**

Potent anti-HCV activity (2 oral doses)

![Graph showing potent anti-HCV activity with GSK175-LA at different dosages](AASLD 2014. Gardner et al. Hepatology, 2014;60:1164A)

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**Potent anti-HCV activity**

- GSK: data on file
GSK & Isis collaboration targeting next generation of HBV medicines: functional cure

- Antisense approach taken to knock down immune suppressive antigens
- Entered collaboration with Isis Pharmaceuticals in 2010
  - GSK contributed target, Isis provided platform & discovery
- Lead compound GSK3228836
  - Phase II start planned 2016

Reduction of HBV antigen by anti-HBV ASO in mice

Note: GSK3228836 subject to exercise of option by GSK
Infectious Diseases strategy: from innovative treatment regimens to the pursuit of cure

HIV

HCV/HBV

Acute complicated infectious disease

GSK Pipeline

Innovative Treatment Regimens

Long-acting Treatment

Prevention

Remission & Cure
First in a new class of antibacterials: gepotidacin (GSK2140944) – a topoisomerase inhibitor

- Novel mechanism with bactericidal activity against MDR pathogens
- Promising safety & efficacy profiles in Phase II studies
- Effective against key resistant strains:
  - MDR MRSA, MDR E.coli & Drug resistant N.gonorrhoeae
- Potential to address multiple conventional & bio-threat indications
- Progressed via successful partnerships with BARDA & DTRA

Planned Filing: 2019 for resistant infections. Discussions with FDA on plague indication.

MDR: multi-drug resistant; DTRA: Defense Threat Reduction Agency (US DoD); BARDA: Biomedical Advanced Research & Development Authority (US HHS)
Infectious Diseases strategy: from innovative regimens to treatment and the pursuit of cure

- dolutegravir based regimens
- cabotegravir LA
- cabotegravir LA + rilpivirine LA
- Next generation agents and combinations

- HCV
- HBV

- gepotidacin
- tafenoquine
- i.v. danirixin

**GSK Pipeline**

**Innovative Treatment Regimens**
- HIV, HCV, HBV

**Long-acting Treatment**
- HIV, HCV, HBV

**Prevention**
- HIV

**Remission & Cure**
- HIV, HCV, HBV (Qura)
Respiratory
Respiratory diseases: still significant unmet need

**Asthma**
- Globally 242m people have asthma (32% increase since 1990)
- Gold-standard options delivered for mild/moderate asthma
- Major unmet medical need in severe asthma
  - 5-10% of asthma patients
  - 60% of cost burden
- Immune modulation offers potential for better disease control and even remission

**COPD**
- 329m people worldwide have COPD
- 3rd leading cause of death by 2030
- Longitudinal studies (e.g. ECLIPSE) helping to identify prognostic biomarkers (e.g. fibrinogen)
- Targeting underlying drivers of disease progression is key

**Lung Fibrosis & Acute Lung Injury**
- Each affects ~5m patients worldwide
- Idiopathic Pulmonary Fibrosis (IPF): median survival of just 2-5 years, 2 IPF products approved
- Urgent need to improve symptoms and delay disease progression
- Acute Lung Injury (ALI): hospital mortality rates of up to 50%
- Need to identify better clinical path for drug development
Asthma R&D strategy: from secondary prevention to primary disease modification

GSK Pipeline

- Targeted Biologicals
- Extended Duration Biologicals
- Once Daily Inhaled
- Remission-inducing

eosinophil
neutrophil
dendritic cell
Nucala™* (mepolizumab) demonstrates significant reduction in exacerbations

Nucala (subcutaneous anti-IL-5 mAb):

- Straightforward patient selection & biomarker
- 53% reduction in exacerbations
- 61% reduction in ER visits/hospitalisations
- Improvement in health status by 7 points (SGRQ)
- Significant reduction in daily oral corticosteroid dose while maintaining control seen in trials
- Dosing every 4 weeks, no weight adjustment required
- Well tolerated

Indication: Severe refractory eosinophilic asthma
Positive CHMP: 24 Sep 2015
PDUFA: 4 Nov 2015

*The name Nucala is not approved for use by the FDA or EMA.

Adapted from MENS study, Ortega et al. NEJM 2014; 371:1198-207
Nucala will be first in class with a strong profile

<table>
<thead>
<tr>
<th></th>
<th>Nucala</th>
<th>XOLAIR Novartis/Genentech</th>
<th>reslizumab Teva</th>
<th>benralizumab AstraZeneca</th>
<th>lebrikizumab Roche</th>
<th>tralokinumab AstraZeneca</th>
<th>dupilumab Sanofi/Regeneron</th>
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</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Submitted</td>
<td>Launched</td>
<td>Submitted</td>
<td>Ph III ongoing</td>
<td>Ph III ongoing</td>
<td>Ph III ongoing</td>
<td>Ph III ongoing</td>
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<tr>
<td>Mechanism</td>
<td>Anti-IL-5</td>
<td>Anti-IgE</td>
<td>Anti-IL-5</td>
<td>Anti-IL-5R</td>
<td>Anti-IL-13</td>
<td>Anti-IL-13</td>
<td>Anti-IL-4Ra</td>
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<tr>
<td>Delivery mechanism</td>
<td>SC</td>
<td>SC</td>
<td>IV</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>Efficacy data Ph III</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety data Ph III</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on published filing date plus average review times
Nucala* has potential in other indications

Anticipated file timelines

2014 to 2015

2016

2017

2018

2019

2020+

Asthma

Eosinophilic granulomatosis with polyangiitis (EGPA)

Hyper-eosinophilic syndrome (HES)

Nasal polyposis / Chronic rhinosinusitis

Atopic dermatitis

Evidence Generation

Evidence Generation

*COPD

Evidence Generation

*The name Nucala is not approved for use by the FDA or EMA and may not be approved for additional indications.
Two novel biologicals

Targeted approaches for uncontrolled asthma patients

sirukumab* (IL-6 mAb): Non-Th2 asthma

- Targets severe disease ineligible for Th2/eosinophilic directed mAbs (40% of severe asthma patients)
- IL-6: key inflammatory driver and genetic association of this pathway in asthma
- Expected to improve symptoms and exacerbations
- Phase II study start in 2016

Elevated IL-6 associated with eosinophilic-neutrophilic inflammation and decreased pulmonary function (FEV₁) in asthma patients

TSLP dAb: Inhaled biologic

- Thymic Stromal Lymphopoietin (TSLP): key cytokine in epithelial immune response in asthma
- Inhaled domain antibody (dAb) directly targets site of action and reduces systemic exposure to improve risk:benefit profile
- Clinical proof of concept demonstrated for anti-TSLP approach
- Phase I start in 2016

Target engagement after inhaled delivery of dAb: exemplar

Inhaled TNFR1 dAb reduced endotoxin (LPS) induced inflammation in healthy volunteers

IL-6

FEV₁

Lung neutrophils

Lung cytokines

* p<0.05 vs neutrophilic bronchitis and eosinophilic bronchitis groups
# p<0.05 vs eosinophilic bronchitis group

Chu, Allergy Asthma & Clinical Immunology.2015;11:14

* sirukumab is part of a GSK-Janssen Biologics (Ireland) collaboration

*p<0.05 t-test
n=18 subjects per group

Data on file (study TFR116236)
Nucala is at forefront of a diverse asthma biologic pipeline

<table>
<thead>
<tr>
<th></th>
<th>Nucala Anti-IL-5</th>
<th>sirukumab Anti-IL-6</th>
<th>Long acting Anti-IL-5 (NBE)</th>
<th>Anti-TSLP dAb</th>
<th>Anti-IL-5/13</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modality</strong></td>
<td>mAb</td>
<td>mAb</td>
<td>Extended pharmacology mAb</td>
<td>Inhaled dAb in Ellipta</td>
<td>Bispecific dAb-mAb extended pharmacology</td>
</tr>
<tr>
<td><strong>Delivery mechanism</strong></td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>Inhaled</td>
<td>SC</td>
</tr>
<tr>
<td><strong>Expected file</strong></td>
<td>2014</td>
<td>2021-25</td>
<td>2021-25</td>
<td>2021-25</td>
<td>2021-25</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Filed</td>
<td>Phase II start 2016</td>
<td>Phase I/II start 2017</td>
<td>Phase I start 2016</td>
<td>Preclinical</td>
</tr>
<tr>
<td><strong>Asthma segment</strong></td>
<td>Severe eosinophilic</td>
<td>Severe without elevated eosinophils</td>
<td>Moderate-severe eosinophilic</td>
<td>Moderate-severe eosinophilic and neutrophilic</td>
<td>Moderate-severe eosinophilic</td>
</tr>
<tr>
<td><strong>Reason to believe</strong></td>
<td>Clinical data and strong mechanism rationale</td>
<td>IL-6 is key driver of non-eosinophilic inflammation</td>
<td>Extended pharmacology allows six monthly dosing</td>
<td>Key cytokine in epithelial immune response; Inhaled - directly targets site of action</td>
<td>Additive efficacy of two complimentary mechanisms, in six monthly dosing</td>
</tr>
</tbody>
</table>
GSK2245035 intranasal TLR7 agonist

Demonstrates prolonged suppression of allergic response

- Activates immune pathways that suppress exaggerated Th2 response in asthma
- Allergen-independent immune modulation
- Clinical data demonstrate target engagement (IP-10) with no tachyphylaxis
- Protection from nasal allergen challenge up to 3 weeks after last dose
- Weekly treatment may induce remission from asthma
- Phase II asthma study 2016

Weekly dosing with intranasal GSK2245035 for 8 weeks in allergic rhinitis patients

- Increase in IP-10 levels 24 hours after last dose of 8 weekly treatments
- Total nasal symptom score (TNSS) reduced after 8 weekly treatments and maintained 3 weeks after last dose

**Status:** Phase IIa  
**Indication:** Asthma remission  
**Planned Filing:** 2021-2025
Asthma R&D strategy:
From secondary prevention to primary disease modification

GSK Pipeline

Targeted Biologicals
- Nucala
- sirukumab
- Anti-TSLP dAb
- Anti-IL-5/13

Extended Duration Biologicals
- Long-acting anti-IL-5
- Anti-IL-5/13

Once Daily Inhaled
- Relvar/Breo Ellipta™
- Arnuity Ellipta™
- Incruse Ellipta™
- Anti-TSLP dAb

Remission-inducing
- TLR7 agonist
COPD R&D strategy:
Targeting the fundamental drivers of disease

GSK Pipeline

Targeted Biologicals
Infection Driven Exacerbations
Once Daily Inhaled
Preserve Lung Function

eosinophil
neutrophil
epithelial cell
Closed Triple: once daily triple therapy in established Ellipta inhaler

- Collaboration with Theravance
- Open triple filed with FDA
- Phase IIIa lung function study fully recruited (FULFIL)
- EU Closed Triple filing: end 2016 (lung function)
- US Closed Triple filing: H1 2018 (exacerbations)
- Triple therapy already part of some clinical practice¹

¹Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2015

Eosinophil signature being evaluated prospectively in IMPACT study

Consistent improvement in lung function with UMEC plus ICS/LABA vs. ICS/LABA

- UMEC add on vs. ICS/LABA (Study 201314, ITT pop n=236)
- UMEC add on vs. Advair (Study 116136, ITT pop n=409)
- UMEC add on vs. Advair (Study 116135, ITT pop n=404)
- UMEC add on vs. Breo (Study 200109, ITT pop n=412)
- UMEC add on vs. Breo (Study 200110, ITT pop n=412)

Difference in trough FEV₁ 24 hours after last dose (mL, 95% CI)

Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2015

Current COPD meds

Follow-up

FF/UMEC/VI (n=4000)

FF/VI (n=4000)

UMEC/VI (n=2000)
GSK2269557, inhaled PI3Kδ inhibitor targets neutrophil-mediated lung damage in COPD

- PI3Kδ over-activation causes human rare disease activated PI3Kδ syndrome (APDS)
- APDS patients display severe recurrent COPD-like bacterial infections
- Inhaled delivery offers potential efficacy/safety advantage and opportunity for combination therapy
- Target engagement demonstrated in healthy smokers (PIP3)
- GSK2269557 on top of standard of care in COPD shows decreased markers of inflammation
- Currently testing in exacerbating COPD patients and Phase IIb studies to start 2016/17

Status: Phase IIa
Indication: COPD exacerbation
Planned Filing: 2021-2025

Activating mutations in PI3Kδ in APDS drive lung infections

Directionality of neutrophil migration is aberrant in COPD patients and corrected by PI3Kδ inhibition - *in vitro*

Angulo et al. Science 2013; 342: 866

Sapey et al. AJRCCM 2011;183:1176
Danirixin (GSK1325756): an oral CXCR2 antagonist

Demonstrates potential to reduce lung damage in COPD

- Blocks chemokine receptor on neutrophils and other cell types (CXCR2)
- Target engagement demonstrated with danirixin (neutrophil activation biomarker, CD11b)
- Competitor compounds produced clinical effects, but with reduction in blood neutrophils
- In the clinic, danirixin has efficacy at a dose not associated with reduced blood neutrophils
- COPD Phase IIb start 2016
- Influenza infection Phase IIa study ongoing

1Am J Respir Crit Care Med 2015;191:1001–1011

Real-time data demonstrate improvement of symptoms with danirixin in symptomatic COPD (frequent exacerbators)

Status: Phase IIa
Indication: Symptomatic COPD
Planned Filing: 2021-2025

GSK, data on file (study 200163)
COPD R&D strategy: pipeline
Targeting the fundamental drivers of disease

GSK Pipeline

Targeted Biologicals
- Nucala

Infection Driven Exacerbations
- PI3Kδ
- danirixin

Once Daily Inhaled
- Anoro™ Ellipta
- Relvar/Breo Ellipta
- Incruse Ellipta
- Closed Triple (Ellipta device)
- GSK961081 +FF
- PI3Kδ

Preserve Lung Function
- PI3Kδ
- danirixin
Drivers of our long-term leadership in asthma and COPD

- Excellence in inhaler / delivery technologies
- Targeted biological know-how
- Deep understanding of novel respiratory targets
- Understanding of patient phenotypes
- Expertise in trial design and delivery

Cell types:
- Neutrophil
- Eosinophil
- Epithelial cell
- Dendritic cell
Respiratory R&D beyond Asthma and COPD

Taking our respiratory know-how into new diseases

Platform for clinical development of IPF (GSK3008348)

- αvβ6 expression in IPF lung biopsies predicts mortality
- Small molecule inhaled αvβ6 inhibitor (deposition of Tc - labelled salbutamol in lungs of IPF patients supports inhaled approach)
- Displacement of αvβ6 PET ligand allows dose ranging in patients

An inhaled dAb platform for acute lung injury (GSK2862277)

- High sTNFR1 levels associated with high mortality
- dAb blocks TNFR1 signalling without impacting beneficial TNFR2 signalling
- Inhaled TNFR1 dAb reduced endotoxin (LPS) induced inflammation in healthy volunteers
- Now in Phase II study
PHI and Oxygen Sensing
Daprodustat\(^1\) (GSK1278863) low dose PHI for treatment of anaemia of CKD: New Phase IIb data

- Standard of care (rhEPO) limited by increased CV risk and IV/SQ administration
- PHI oral tablet to replace injectable rhEPO: low dose, convenient titration, potential for improved CV safety

Phase II summary (IIa and new IIb)
- Phase IIa data recently published\(^2\)
- Raises Hgb in dialysis and non-dialysis subjects, either naïve to or switching from rhEPO
- Low dose (most subjects \(\leq 10\) mg); Simple titration regimen
- Durable effect (up to 6 months in Phase IIb)
- Minimal elevation in EPO levels; No BP increase
- Safety profile consistent with CKD
- Phase III start 2016

\(^1\) USAN, INN approval pending
\(^2\) J Am Soc Nephrol Oct 22, 2015 (epub)
\(^3\) GSK, data on file (Study PHI113737)
Daprodustat: success factors for development

- Low dose
- No inhibition of collagen-4-hydroxylase
- Single Phase III CV outcomes studies for non-dialysis and dialysis

<table>
<thead>
<tr>
<th>Key success factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Large experience in CKD subjects</td>
<td>659 (up to 6 months)</td>
</tr>
<tr>
<td>Active comparator for CV safety assessment</td>
<td>Yes (rhEPO)</td>
</tr>
<tr>
<td>Low dose</td>
<td>≤ 10mg QD in most subjects</td>
</tr>
<tr>
<td>Flexible dose regimen: Non-Dialysis Dialysis</td>
<td>QD QD / TIW</td>
</tr>
<tr>
<td>Phase III designed for clear assessment of CV risk</td>
<td>Single CV outcome trials for ND and HD</td>
</tr>
<tr>
<td>Inhibition of collagen-4-hydroxylase (cardiac tox risk)</td>
<td>No</td>
</tr>
<tr>
<td>Concern for hepatotoxicity (e.g. exclusion of acetaminophen in phase III trials)</td>
<td>No</td>
</tr>
</tbody>
</table>
Diabetic Foot Ulcer
- Preclinical data demonstrate benefit of HIF induction in diabetic skin
- Topical daprodustat formulation in ongoing Phase Ib study
  - No systemic exposure and no Hgb elevation
  - Efficacy data on wound healing in 2016

Muscle Injury
- Novel muscle repair activity discovered in pre-clinical injury model
- Phase I: Reduction in muscle injury in healthy volunteers

Future potential expansion into other anaemia indications
- Myelodysplastic Syndrome (MDS)
- Peri-surgical anaemia (ortho, GI, CV)

![Graph showing muscle injury from repetitive arm motion in healthy volunteers and daprodustat reduces total CPK release over 72 hours](image)

**Daprodustat**

*Indication expansion to maximise value of HIF-activating mechanism*

*Figures and other data from GSK, data on file (Study PHI20084)*
Introducing our experts

GSK’s leading scientists in infectious disease, respiratory medicine and CV

John Pottage
Senior Vice President, Chief Scientific and Medical Officer for ViiV Healthcare

Zhi Hong
Senior Vice President, Head Infectious Diseases TAU

Dave Allen
Senior Vice President, Head Respiratory TAU

Edith Hessel
Vice President, Head Refractory Respiratory Inflammation DPU

Steve Pascoe
Vice President, Head Unit Physician Respiratory

John Lepore
Senior Vice President, Head Metabolic Pathways and Cardiovascular

Ruchira Glaser
Clinical Development Director, Metabolic Pathways and Cardiovascular
Moncef Slaoui
Chairman of Vaccines
R&D programmes to deliver near-term growth with significant future opportunities and novel immunisation platforms

**Near/mid term key R&D focus:**
- Shingrix™
- Meningitis
- Lifecycle management

**Longer term R&D Focus**
- RSV
- GBS

**A new vaccine concept**
- COPD

RSV=Respiratory Syncytial Virus; GBS=Group B Streptococcus; COPD=Chronic Obstructive Pulmonary Disease
Shingrix™ is not approved for use by the FDA or EMA
Existing zoster vaccine

One dose, live attenuated vaccine

Efficacy: 51% against shingles in ages 60+
- Inverse correlation between age at vaccination and protection
- Limited persistence of protection

Indication for ages 50+
US ACIP recommendation for ages 60+

Contraindicated in immunocompromised individuals

Estimated to have <25% coverage in US*

2014 reported sales of $868m (>600m in US)

*CDC: MMWR, February 2015; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6404a6.htm; Zostavax™ US PI
Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Zostavax data based on US PI.
Shingrix candidate vaccine developed to differentiate

Two doses, sub-unit (non-live) vaccine, novel adjuvant

Efficacy: 91% - 97% against shingles
- High efficacy across identified age groups
- Persistence over time

Targeting indication and recommendation in ages 50+

Data on immunocompromised individuals in 2017

Expect US, EU, Japan filings in 2H 2016

Expected to contribute ~1/3 of 2020 sales growth targets for GSK vaccines
Shingrix - Efficacy against shingles

Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Shingrix data based on ph III clinical trials.
Existing vaccine - Efficacy against shingles

Schmader et al. Clinical Infectious Diseases 2012;54(7):922–8;
Zostavax™ US PI
Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Zostavax data based on US PI.
Shingrix - Immune response across age segments

Frequency of gE-specific CD4+ T cells by age groups

Number of CD4+ T cells per million

- 50-59 yrs
- 60-69 yrs
- 70-79 yrs
- ≥ 80 yrs

saline  gE/saline  gE/AS01B

Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Shingrix data based on clinical trials.
Existing vaccine - Immune response across age segments

<table>
<thead>
<tr>
<th>Age Segment</th>
<th>Vaccine</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>60-64 yrs</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>65-69 yrs</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>70-74 yrs</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>75-79 yrs</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>&gt;79 yrs</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Zostavax data based on published data.
Shingrix - Efficacy against PHN

PHN: post herpetic neuralgia, a severe complication of zoster

ZOE-50 and ZOE-70 pooled analysis – unpublished data
Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Shingrix data based on ph III clinical trials.
Existing vaccine - Efficacy against PHN
PHN: post herpetic neuralgia, a severe complication of zoster

Efficacy against PHN - %

- 50-59 yrs
- 60-69 yrs
- 70+ yrs

Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Zostavax data based on published data.
Shingrix - Duration of protection against shingles

ZOE-50 statistical report – unpublished data
Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Shingrix data based on ph III clinical trials.
Existing vaccine - Duration of protection against shingles

Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Zostavax data based on published data.
Immune response persistency is a good predictor of duration of efficacy

Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Shingrix data based on clinical trials.
Shingrix: a potentially significant advance in vaccination to prevent shingles

High overall vaccine efficacy across identified age groups, including oldest persons

Persistence of vaccine efficacy up to 4 years across all ages

Six-year persistence of immune response, modeled to persist above baseline for at least 15 years (based on 6 year data)

Clinically acceptable reactogenicity

AS01 adjuvant = new platform for elderly vaccines

Annual capacity of ~25-30m doses by 2020

*Zostavax is a trademark of Merck & Co
Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Shingrix data based on clinical trials.
Meningococcal Meningitis
Meningococcal disease: evolving and unpredictable epidemiology – requires combination vaccine

~139 million annual global birth cohort
~4m US, ~5m EU, ~130m ROW

Changes in serogroup distribution in US over time

**Most advanced meningitis vaccines portfolio, including candidate pentavalent**

<table>
<thead>
<tr>
<th><strong>Menveo™</strong></th>
<th><strong>Bexsero™</strong></th>
<th><strong>MenABCWY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>− MenACWY tetravalent vaccine</td>
<td>− MenB vaccine</td>
<td>− Candidate pentavalent combination vaccine for adolescent in US</td>
</tr>
<tr>
<td>− Approved in US and EU (2010)</td>
<td>− Approved in US in 2015 (adolescents) and EU (2 months old and above)</td>
<td>− Most advanced in development</td>
</tr>
<tr>
<td>− ACIP recommendation for adolescents</td>
<td>− ACIP category B (permissive) recommendation</td>
<td>− Phase III start in 2017</td>
</tr>
<tr>
<td>− Approved in 64 countries</td>
<td>− Approved in 38 countries</td>
<td>− US filing expected in 2020</td>
</tr>
</tbody>
</table>

Meningitis portfolio expected to contribute ~1/3 of 2020 sales growth targets for GSK vaccines
Bexsero: multi-component antigen composition adds value, differentiation

Sources: Santolaya et al. Hum Vac & Imm 2013 http://goo.gl/8oWB4P; * Strain 4 GSK data on file. Post hoc assays on a subset
Competing vaccine for MenB

- 1 antigen composition with 2 variants
- 3 dose regimen

ClinTrial.gov, study NCT01299480 https://goo.gl/Eqbmph
Slide intentionally blank
MenABCWY Phase III starts in 2017

- US focused development
- 1 dose adolescent booster
- Phase III programme start in 2017
- Filing expected 2020 for adolescents previously immunised for MenACWY

% of subjects with hSBA titer ≥ threshold

<table>
<thead>
<tr>
<th>MenA</th>
<th>MenC</th>
<th>MenW</th>
<th>MenY</th>
<th>MenB</th>
</tr>
</thead>
<tbody>
<tr>
<td>93</td>
<td>99</td>
<td>100</td>
<td>97</td>
<td>100</td>
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<tr>
<td>100</td>
<td>99</td>
<td>64</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>

Post dose 2 immune response rate

MenACWY combination planned

MenABCWY

Bexsero

MenACWY (~80% penetration)

MenACWY (~29% penetration)

Bexsero or Other MenB

Other MenB

3-4 injections

11 years

17 years

Saez-Llorens X et al. Hum Vacc Imm 2015 http://goo.gl/PXXRs6; GSK data on file. CDC MMWR: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6429a3.htm#tab1
Meningitis portfolio presents significant opportunity

GSK has most advanced and comprehensive portfolio for meningitis vaccines

Bexsero demonstrated significant public health benefit, could drive further UMV recommendations

Combination approach is optimal option for prevention

Bexsero capacity ~25m doses in 2018
Respiratory Syncytial Virus (RSV)
Period of most severe RSV cases for young infants occurs from birth to 12 months

US Hospitalisations

Paramore, Pharmacoecnomics 22:274-285, 2004
Period of most severe RSV cases for young infants occurs from birth to 12 months

Period of greatest Risk for severe RSV disease

Maternal Vaccine

Paediatric Vaccine

Week of pregnancy

Age in months

Maternal IgG

Infant’s immune response

Paramore, Pharmacoeconomics 22:274-285, 2004
Candidate paediatric RSV vaccine, a novel approach

Genetically engineered recombinant CHAd155
Same vector used in ebola vaccine
Non-alum composition

Phase I
Healthy men
Sero+ infants 6-18 mos
Sero- infants 6-11 mos
Completed

Phase II
Sero- infants 2-12 mos
Proof of principle 2021
Planned

Phase III
Sero- infants 2 mos
Study start 2022
Planned
For RSV F protein, the correct antigen structure is critical

Pre-F absorbs out neutralising RSV antibodies more than 10x better than Post-F and induces potent antibody responses in humans

Graham B et al., Current Opinion in Immunology 35; 30-38, 2015
Stabilised Pre-F generated high titers by Day 7 and potent boost of PCA without adjuvant

GSK Pre-F

>20 fold PCA increase after single dose without adjuvant

GSK internal data, unpublished
Stabilised Pre-F generated high titers by Day 7 and potent boost of PCA without adjuvant

GSK Pre-F

Neutralising Ab Titer

Fold increase PCA

Day 0  Day 7  Day 30

Day 0  Day 7  Day 30

>20 fold PCA increase after single dose without adjuvant

Post-F

Neutralising Ab Titer

Fold increase PCA

Day 0  Day 7  Day 30

Day 0  Day 7  Day 30

>10 fold PCA increase requires 120 ug + adjuvant

Presentation by Novavax at World Vaccine Congress April 2015 (data on 120 ug/alum dose PCA)
Novel candidate RSV maternal vaccine approach

Phase I
- Healthy men

Phase IIa
- Non-pregnant women

Phase IIb
- Pregnant women
  - Dose selection
  - Proof of principle 2018

Phase III
- VE in infants of vaccinated women
  - Study start 2019

- Completed
- Ongoing
- Planned
Group B Streptococcus (GBS)
Maternal immunisation for GBS

The leading cause of pneumonia, meningitis and sepsis in neonates

1 in 2500 of babies develop GBS disease despite antibiotic prophylaxis of colonised mothers

No vaccine is available

Gibbs, Obstet Gynecol, 104;1062-1075, 2004
Maternal immunisation for GBS

The leading cause of pneumonia, meningitis and sepsis in neonates

1 in 2500 of babies develop GBS disease despite antibiotic prophylaxis of colonised mothers

No vaccine is available

Gibbs, Obstet Gynecol, 104;1062-1075, 2004
Large Phase II trivalent completed
Decision to expand composition to pentavalent
Validate correlate of protection with FDA
Clinical development plan to be agreed with FDA

Based on Capsular polysaccharide (CPS) from 5 dominant GBS serotypes conjugated to a protein carrier

Designed to help protect against >95% of globally prevalent serotypes

Phase II trivalent vaccine antibody data shows response at period of greatest risk

10^6 against serotypes 1a (µg/mL)

- Vaccinated mothers
- Infants of vaccinated mothers
- Unvaccinated mothers and their infants

Period of greatest risk disease for GBS

Le Doare, Vaccine 31(4) D7, 2013 ; GSK clinical data, unpublished
Maternal immunisation validated strategy to prevent diseases that afflict very young infants

Infants protected by maternal flu vaccination

GSK potential maternal immunisation vaccine portfolio

**Pertussis**

Winter K, MMWR 63:1122-1140, 2014

**Influenza**


**GBS**

Melin, Clin Microbiol Inf, 17:1294-1303, 2011

**RSV**

Paramore, Pharmacoeconomics 22:274-285, 2004
A new vaccine concept
Epi studies show association between lung infections & COPD exacerbations\(^1,2\)

NTHi and Mcat: 2 lung pathogens potentially associated with 30-50% of COPD exacerbations\(^1,2\)

75% effective vaccine could eliminate 20-35% of exacerbations

3 antigen vaccine covering NTHi using AS01 adjuvant in Phase II POC trial

Key POC data in COPD patients = 2017

Phase III to be defined based on POC data

---

Data and planned filings support positive growth outlook

2016
- Q flu paediatric US filing
- Shingrix US, EU, Japan filings

2017
- MMR US filing

2018
- Shingrix immuno-compromised efficacy filing

2019
- US/UK Bexsero paediatric data
- MMR Japan filing

2020
- MenABCWY US filing
- Rotarix liquid US filing

2021-2025
- RSV maternal filings
- GBS maternal filings
- RSV paediatric filings
- COPD vaccine Phase III
R&D programmes to deliver near-term growth with significant future opportunities and novel immunisation platforms

1. Near/mid term key R&D focus:
   - Shingrix
   - Meningitis
   - Lifecycle management

2. Longer term R&D Focus
   - RSV
   - GBS

3. A new vaccine concept
   - COPD
Introducing the Vaccines panel

GSK’s leading scientists in vaccines

Alain Brecx
Vice President, Vaccine Development Lead - Zoster

Emmanuel Hanon
Senior Vice President, Head of Vaccines R&D

Giovanni Della Cioppa
Vice President, Head of Siena R&D Centre

Rip Ballou
Vice President, Head of Rockville R&D Centre
Immuno-Inflammation
### Immuno-Inflammation areas of focus

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

<table>
<thead>
<tr>
<th>Rheumatoid Arthritis (RA)</th>
<th>Osteoarthritis (OA)</th>
<th>Systemic Lupus Erythematosus (SLE)</th>
<th>Other immune-mediated diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Circa 5.3m RA patients in G7 countries¹</td>
<td>• Circa 72m OA patients in G7 countries; largest proportion of musculoskeletal diseases²,³</td>
<td>• Prevalence: 40 -100 out of 100,000 ⁴; 9/10 sufferers are women in their 20s &amp; 30s⁴</td>
<td>• Mechanisms are relevant for mainstream diseases e.g. psoriasis, Crohn's disease &amp; ulcerative colitis</td>
</tr>
<tr>
<td>• Aging demographics a major driver of market growth</td>
<td>• Aging demographics a major driver of market growth</td>
<td>• Chronic disease with poor QoL, involving musculoskeletal, haematological, cutaneous &amp; renal systems</td>
<td>• Opportunities exist to treat less common disease e.g. primary Sjögren's syndrome, systemic sclerosis &amp; myasthenia gravis</td>
</tr>
<tr>
<td>• Highly debilitating; associated with higher mortality &amp; progression to other serious conditions</td>
<td>• Major opportunity for a disease-modifying therapy</td>
<td>• Mortality rate 3x higher than the general population, and 10x higher in under 40⁵</td>
<td></td>
</tr>
<tr>
<td>• Significant medical needs for remission-inducing therapies &amp; for patients resistant to current standard of care</td>
<td>• Immune modulation offers opportunity to move from only alleviating symptoms of “wear and tear”</td>
<td>• Benlysta IV - 1st drug approved for SLE in 50 years (2011)</td>
<td></td>
</tr>
</tbody>
</table>

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
sirukumab: rheumatoid arthritis

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

- 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

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

12 wk data from Phase II study

ACR20 at wk 12
- Placebo: 30%
- 50mg Q4W: 57%
- 100mg Q2W: 63%

ACR50 at wk 12 (Primary EP)
- Placebo: 3%
- 50mg Q4W: 27%
- 100mg Q2W: 27%

** p < 0.05

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

24 w data from Japan monotherapy study

ACR20
- 50mg Q4W: 74%
- 100mg Q2W: 49%

ACR50
- 50mg Q4W: 82%
- 100mg Q2W: 64%

ACR70
- 50mg Q4W: 25%
- 100mg Q2W: 36%

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

GM-CSF plays a key role in activation of macrophages at the site of injury or inflammation

---

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


Status: Phase IIb
Indication: Rheumatoid Arthritis
Planned Filing: 2021-2025
GSK3196165: Potential for disease modification & analgesic activity in hand osteoarthritis (HOA)

- 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

**GM-CSF receptor expression on primary afferent nerve fibres in mouse tibial bone and periosteal nerves**


**Pain**


Statistical significance:
- * p<0.05
- ** p<0.01
- *** p<0.001
- control vs. anti-GM CSF
- # p<0.0001, control and anti-GM-CSF vs. t=0 readings

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

GSK3196165 in-licensed from MorphoSys AG
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”.

- 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**

**RIP1 kinase inhibition achieved in the clinic**

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

**Blood levels (ng/mL)**

<table>
<thead>
<tr>
<th>Blood levels (ng/mL)</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>100</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
</tr>
<tr>
<td>0.05</td>
<td>250</td>
<td>200</td>
<td>150</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>0.1</td>
<td>250</td>
<td>200</td>
<td>150</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>

**Kinase activity**

- IC50 = 2 nM

**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 Bertin, Peter J. Cough, Piero Giansanti, Albert J.R. Heck, Emmanuel Dejardin, Peter Vandenabeele, Mathieu J.M. Bertrand

---

GSK2982772: studies in three indications to start in 2016

Key target, compelling target, compelling pre-clinical data

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 Blocks severe skin inflammation
2 Prevents against TNF induced shock
3 Prevents against TNF induced shock
4 Inhibits TNF production in human gut from Crohn’s

---

2GSK, 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.

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

- Placebo
- belimumab-SC 200 mg

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

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

<table>
<thead>
<tr>
<th>Drug Code</th>
<th>Name</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK525762</td>
<td>(BET)</td>
<td></td>
</tr>
<tr>
<td>GSK2982772</td>
<td>(RIP1)</td>
<td></td>
</tr>
<tr>
<td>GSK3050002 * †</td>
<td>(aCCL20)</td>
<td></td>
</tr>
<tr>
<td>GSK2831781 * †</td>
<td>(aLAG3)</td>
<td></td>
</tr>
<tr>
<td>GSK2618960 *</td>
<td>(aIL7R)</td>
<td></td>
</tr>
<tr>
<td>GSK2330811 *</td>
<td>(aOSM)</td>
<td></td>
</tr>
<tr>
<td>GSK2646264</td>
<td>(Syk topical)</td>
<td></td>
</tr>
<tr>
<td>GSK3117391</td>
<td>(ESM -HDAC)</td>
<td></td>
</tr>
</tbody>
</table>

- 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


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

CCR6 pos T cells (%) in blister model

Mean change from baseline

placebo 0.1 0.5 1 5 10 20

mean ± SD
GSK3050002 (n=6)
placebo (n=12)

GSK, data on file. GSK3050002 in experimental medicine study (200784)

- Selective inhibition (CCR6 +ve cells only)
- Dose dependency
Four “first in class” antibodies in the clinic: GSK2831781

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

Depletion of LAG-3 T-cells at challenge site ...
..results in suppression in the skin reaction


Pre-dose

Post-dose

Erythema (mm)

0.0 2.5 5.0 7.5 10.0 12.5 15.0

Days

0 2 4 6 8

2000 UI PPD

40 UI PPD

ch A9H12
0.1 mg/Kg

3 weeks

IDR 1

IDR 2

0 2 4 6 8 days

0.1 mg/Kg

2000 UI PPD

40 UI PPD

ch A9H12

3 weeks

IDR 1

IDR 2
Four “first in class” antibodies in the clinic: GSK2330811

**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

Status: Phase I ongoing
Planned Filing: 2021-2025

**OSM expression in skin biopsy**

![Graph showing OSM expression in skin biopsy](image)

- Healthy controls
- Diffuse cutaneous systemic sclerosis

**ACR 2015, abstract #1914**

- **P=0.0021**
Four “first in class” antibodies in the clinic

All expected to progress to PhII in 2016

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Status</th>
<th>Planned Filing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-IL-7R antibody</td>
<td>Phase II start 2016</td>
<td>2021-2025</td>
</tr>
<tr>
<td>Anti-CCL20 antibody</td>
<td>Phase II start 2016</td>
<td>2021-2025</td>
</tr>
<tr>
<td>Cell depleting anti-LAG3 antibody</td>
<td>Phase I ongoing</td>
<td>2021-2025</td>
</tr>
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**Immuno-Inflammation R&D strategy:**
*From symptomatic benefit to sustainable remission*

### GSK Pipeline

<table>
<thead>
<tr>
<th>Targeted Biologicals</th>
<th>Targeted Small Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Benlysta</td>
<td>• RIP1</td>
</tr>
<tr>
<td>• sirukumab</td>
<td>• I-BET</td>
</tr>
<tr>
<td>• Anti-GM-CSF</td>
<td></td>
</tr>
<tr>
<td>• Anti-IL-7</td>
<td></td>
</tr>
<tr>
<td>• Anti-CCL20</td>
<td></td>
</tr>
<tr>
<td>• Anti-LAG3</td>
<td></td>
</tr>
<tr>
<td>• Anti-OSM</td>
<td></td>
</tr>
</tbody>
</table>

### Targeting Resistant Disease

- RIP1
- I-BET
- Anti-IL-7
- Anti-CCL20
- Anti-LAG3
- Anti-OSM

### Early Intervention & Remission Induction

- Anti-GM-CSF
- RIP1
- Anti-CCL20
- Anti-LAG3
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 across AML, NHL & MM

GSK525762 active in NMC, a very difficult to treat cancer

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\(^3, 4\))


**I-BET resets disease in rat collagen-induced arthritis**

**I-BET inhibition of RA stromal cell activation – gene expression profile**

Status: Phase II start 2016
Indication: Therapy Resistant RA
Planned Filing: 2021-2025
Preclinical data give reason to believe that GSK2879552, an LSD1 inhibitor, may have significant progression-free survival benefits for some patients with Small Cell Lung Cancer and Acute Myeloid Leukaemia.

Clinical studies are ongoing in Small Cell Lung Cancer and Acute Myeloid Leukaemia.

There is an early signal of efficacy in Small Cell Lung Cancer (SCLC) with GSK2879552.

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

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

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

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

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

GSK, data on file.
• 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  

Survival in animal model (CT26)  
OX-40 + PD-1

Survival in animal model (CT26)  
OX-40 + TLR-4

GSK, data on file.
Immuno-Oncology: GSK3359609 first-in-class ICOS agonist antibody

- 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

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

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 (tarextumab)
- 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

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>BET inhibitor (GSK525762)</td>
<td>Solid tumours, Heme Malignancies</td>
<td>AML, SCLC</td>
<td></td>
</tr>
<tr>
<td>LSD-1 inhibitor (GSK2879552)</td>
<td></td>
<td>Solid tumours, Heme Malignancies</td>
<td></td>
</tr>
<tr>
<td>EZH2 inhibitor (GSK2816126)</td>
<td></td>
<td>Solid tumours, Lymphoma</td>
<td></td>
</tr>
<tr>
<td>PRMT5 inhibitor (GSK3326595) †</td>
<td></td>
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<tr>
<td>Novel small molecule targets (X6)</td>
<td></td>
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<tr>
<td>NY-ESO-1 TCR-T †</td>
<td>Sarcoma, Multiple Myeloma, NSCLC, Ovarian, Melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OX40 agonist (GSK3174998) †</td>
<td>Solid tumours, Heme Malignancies</td>
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<td>ICOS agonist (GSK3359609) †</td>
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<td>TLR4 agonist (GSK1795091)</td>
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<td>CAR-T and TCR-T targets (x6)</td>
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<td>Novel small molecule targets (x2)</td>
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<td>ImmTacs (x4) †</td>
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<td>mAb-dAbs and dual-specific Abs (x5)</td>
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<td>Notch2/3 (tarextumab) †</td>
<td>Pancreatic, SCLC</td>
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<tr>
<td>Notch1 (brontictuzumab) †</td>
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<td>BCMA ADC (GSK2857916)</td>
<td>Multiple Myeloma</td>
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<tr>
<td>FGF Ligand Trap (GSK3052230) †</td>
<td>Mesothelioma, NSCLC</td>
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</tbody>
</table>

† 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

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<td><strong>Therapy Resistant RA</strong></td>
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<td>dapanustat* Prolyl hydroxylase inhibitor</td>
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<td>HES</td>
<td>FAP</td>
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<td><strong>EGPA</strong></td>
<td><strong>HIV</strong></td>
<td><strong>RA, OA</strong></td>
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<td>Temple syndrome</td>
<td>dolotegravir + lamivudine FDC Integrase inhibitor+NRTI HIV</td>
<td>GSK3008348 Alpha V beta 8 integrin antagonist IFP</td>
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<td>PNTA-vilanterol +umeclidinium ICS/LABA/LAMA COPD</td>
<td>GSK3174998 CX40 agonist mAb Solid tumours, Haematological Malignancies</td>
<td>GSK2330811 OSM mAb</td>
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<td><strong>SLE</strong></td>
<td><strong>HIV</strong></td>
<td><strong>Beta Thalassemia</strong></td>
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<td>Benlysta Subcutaneous BlyS mAb</td>
<td>GSK327794 NY-ESO-1 TCR Sarcomas, Mult. Myel., Melanoma Ovarian, NSCLC</td>
<td>GSK2696277† Ex-vivo stem CGT</td>
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<td><strong>Giant Cell Arteritis</strong></td>
<td><strong>Bacterial Inf.</strong></td>
<td><strong>Wound Healing</strong></td>
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<tr>
<td>Sirukumab IL-6 mAb</td>
<td>GSK377784† Type 2 topoisomerase inhibitor</td>
<td>dapanustat* Prolyl hydroxylase inhibitor (topical)</td>
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<td><strong>Other</strong></td>
<td><strong>Respiratory</strong></td>
<td><strong>Severe Atopic Dermatitis</strong></td>
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<td>TEMSC</td>
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<td><strong>Rare Diseases</strong></td>
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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

Ackermann et al. International Symposium on Amyloidosis. 2012, poster #0P73
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

Reason to believe – amyloid imaging

Before anti-SAP

Day 42 after anti-SAP

Liver ECV (median normal 29%)
36.0
29.0

Liver Stiffness (median normal 5.3 kPa)
5.7
2.8

% of tracer in liver
61.1
17.4

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

Increased T cell count

Reduced infections

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

Cicalese 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 *a*
- Metachromatic Leukodystrophy *a*
- Wiskott-Aldrich Syndrome *a*
- Beta thalassemia *b*
- MPS1 *b*
- Chronic Granulomatous disease *b*
- Globoid Cell Leukodystrophy *b*

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

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

---

*Licensed from Telethon and Ospedale San Raffaele
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
See www.gsk.com for full clinical pipeline

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**HIV / Infectious Diseases**

**Immuo-Inflammation**

**Oncology**

**Rare Diseases**

**Other**

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