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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



- 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





Infectious Diseases strategy: from innovative treatment regimens to the pursuit of cure







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

Approved

Investigational

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			
1 st cohort	2 nd cohort		
(n= 10)	(n= 10)		
DTG 50 mg QD	DTG 50 mg QD		
LMV 300 mg QD	LMV 300 mg QD		

Patient	Base line viral		
#	load	Week 8	Week 24
1	10.909	< 50	< 50
2	10.233	< 50	< 50
3	151.569	< 50	< 50
4	148.370	< 50	< 50
5	20.544	< 50	< 50
6	14.499	< 50	< 50
7	18.597	< 50	< 50
8	24.368	< 50	< 50
9	10.832	< 50	< 50
10	7.978	< 50	< 50
11	273.676	< 50	< 50
12	64.103	< 50	< 50
13	33.829	< 50	< 50
14	15.151	< 50	< 50
15	23.500	< 50	< 50
16	3.910	< 50	< 50
17	25.828	< 50	< 50
18	73.069	< 50	< 50
19	106.320	< 50	< 50
20	7.368	< 50	< 50

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

THE LANCET Infectious Diseases

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



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)

LATTE 2 - cabotegravir LA + rilpivirine LA for treatment of HIV

Headline data – path to Phase III

- Viiv gsk
- 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

Nano-formulation

- Every 2 or 3 months
 - Potential targets for neutralisation polymeric nanoparticles V1V2 Glycan: N332 Glycan supersite: polymer PG9. PG16 PGT121. PGT128 nanoemulsions PGT141-145 10-1074 CAP256-VRC26.25 PGDM1400 blend of SLN oil & solid lipid CD4 Binding site: solid lipid VRC01. PG04. NLC CH31, 3BNC117. Trimer (gp120/41): 12A12, VRC13, 8ANC195 VRC01-LS drug **PGT151** VRC07-523-LS. 35022 Z258-N6 ap41 MPER: nanocrystals 2FS. 4E10 10e8 100% drug Viral membrane Huang et al. Nature 2014;515(7525):138-42 A pilot clinical combination study of VRC01 and cabotegravir is planned for 2016 start

- 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



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



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





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







Respiratory

Respiratory diseases: still significant unmet need

COPD



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



- 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





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 MENSA study, Ortega et al. NEJM 2014; 371:1198-207

Nucala will be first in class with a strong profile



	Nucala	XOLAIR Novartis/ Genentech	reslizumab <i>Teva</i>	benralizumab <i>Astra</i> Zeneca	lebrikizumab <i>Roche</i>	tralokinumab <i>AstraZeneca</i>	dupilumab Sanofi/ Regeneron
Phase	Submitted	Launched	Submitted	Ph III ongoing	Ph III ongoing	Ph III ongoing	Ph III ongoing
Earliest launch assumption*	Q4 2015	Launched	Q4 2015/ Q1 2016	2017	2017	2019	2019
Mechanism	Anti-IL-5	Anti-IgE	Anti-IL-5	Anti-IL-5R	Anti-IL-13	Anti-IL-13	Anti-IL-4Rα
Delivery mechanism	SC	SC	IV	SC	SC	SC	SC
Efficacy data Ph III	~	~	√	Phase III ongoing			
Safety data Ph III	✓	~	\checkmark				

*Based on published filing date plus average review times

Nucala* has potential in other indications



Anticipated file timelines



*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 (FEV₄) in asthma patients



#p < 0.05 vs eosinophilic bronchitis aroup

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

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

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



Nucala is at forefront of a diverse asthma biologic pipeline



	Nucala Anti-IL-5	sirukumab Anti-IL-6	Long acting Anti-IL-5 (NBE)	Anti-TSLP dAb	Anti-IL-5/13
Modality	mAb	mAb	Extended pharmacology mAb	Inhaled dAb in Ellipta	Bispecific dAb-mAb extended pharmacology
Delivery mechanism	SC	SC	SC	Inhaled	SC
Expected file	2014	2021-25	2021-25	2021-25	2021-25
Status	Filed	Phase II start 2016	Phase I/II start 2017	Phase I start 2016	Preclinical
Asthma segment	Severe eosinophilic	Severe without elevated eosinophils	Moderate-severe eosinophilic	Moderate-severe eosinophilic and neutrophilic	Moderate-severe eosinophilic
Reason to believe	Clinical data and strong mechanism rationale	IL-6 is key driver of non- eosinophilic inflammation	Extended pharmacology allows six monthly dosing	Key cytokine in epithelial immune response; Inhaled - directly targets site of action	Additive efficacy of two complimentary mechanisms, in six monthly dosing 34

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

Status:	Phase IIa
Indication:	Asthma remission
Planned Filing:	2021-2025

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





Asthma R&D strategy:

From secondary prevention to primary disease modification





COPD R&D strategy:

Targeting the fundamental drivers of disease





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



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





GSK2269557, inhaled PI3K δ inhibitor targets neutrophilmediated 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 $\text{PI3K}\delta$ in APDS drive lung infections





Angulo et al. Science 2013; 342: 866

Directionality of neutrophil migration is aberrant in COPD patients and corrected by PI3Kō inhibition - *in vitro*



Healthy control CO Sapey et al. AJRCCM 2011;183:1176

COPD

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 neutrophils¹
- 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

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

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





COPD R&D strategy: pipeline

Targeting the fundamental drivers of disease





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



Respiratory R&D beyond Asthma and COPD

Taking our respiratory know-how into new diseases

Platform for clinical development of IPF (GSK3008348)

- $\alpha\nu\beta6$ expression in IPF lung biopsies predicts mortality
- Small molecule inhaled αvb6 inhibitor (deposition of Tc labelled salbutamol in lungs of IPF patients supports inhaled approach)
- Displacement of $\alpha vb6$ 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







mAb (grey, blue, red) vs. dAb (green)



PHI and Oxygen Sensing

Daprodustat¹ (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 published²
- Raises Hgb in dialysis and non-dialysis subjects, either naïve to or switching from rhEPO
- Low dose (most subjects ≤10mg); 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



daprodustat Phase IIb³:

Pre-dialysis subjects naive to rhEPO; target Hgb 10.0-11.5 g/dL (n=96)



¹ USAN, INN approval pending

² J Am Soc Nephrol Oct 22, 2015 (epub)

³GSK, 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

Key success factors	
Large experience in CKD subjects	659 (up to 6 months)
Active comparator for CV safety assessment	Yes (rhEPO)
Low dose	≤ 10mg QD in most subjects
Flexible dose regimen: Non-Dialysis Dialysis	QD QD / TIW
Phase III designed for clear assessment of CV risk	Single CV outcome trials for ND and HD
Inhibition of collagen-4-hydroxylase (cardiac tox risk)	No
Concern for hepatotoxicity (e.g. exclusion of acetaminophen in phase III trials)	No

Daprodustat



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)

Muscle injury from repetitive arm motion in healthy volunteers







GSK, data on file (Study PHI20084)

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Introducing our experts

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



Zhi Hong Senior Vice President. Head Infectious Diseases



John Pottage

Senior Vice President. Chief Scientific and Medical Officer for ViiV Healthcare



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Senior Vice President. Head Respiratory TAU



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