R&D Strategy and Pipeline Transformation

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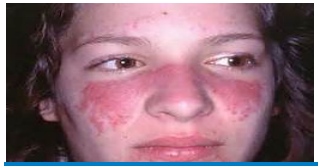
Shire

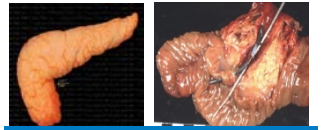
Through growth and transformation, patients at the very heart of our thinking

HEMOPHILIA



SLE

HUNTER



Pancreatic Cancer

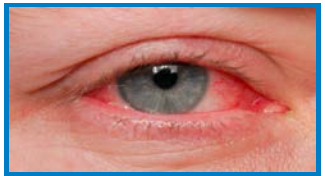
ALL

HAE

ADHD

MLD

Complications of Prematurity



CONJUNCTIVITIS

DRY EYE

adRP

Type 1 Gaucher Disease

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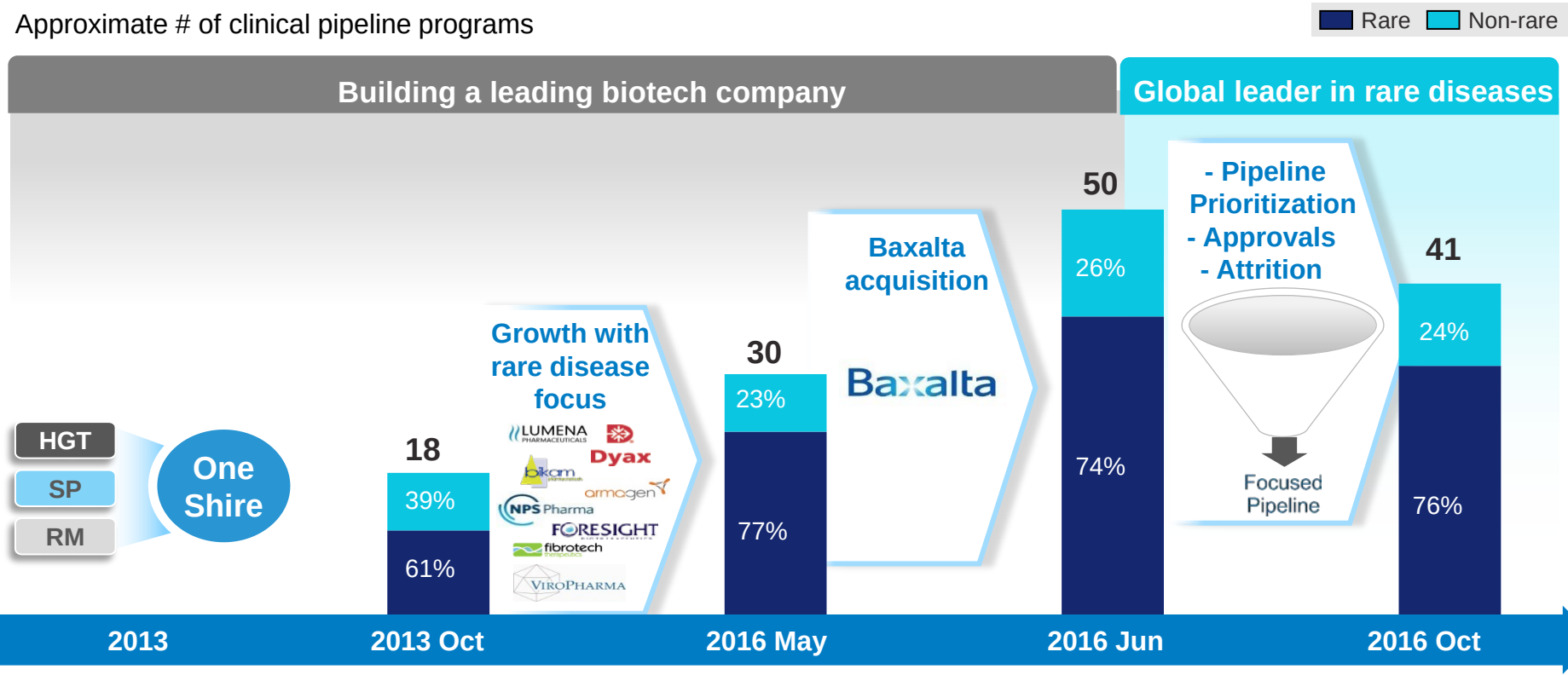
Over three years Shire has built an industry-leading rare disease pipeline

Approximate # of clinical pipeline programs



Sharp focus has lead to industry-leading rare disease pipeline

Focus and invest in areas of domain expertise

- Therapeutic area focus
- Rare Disease focus

Expand areas of domain expertise

- Targeted licensing and acquisition
- Expand into Ophthalmology
- Increase value of acquired assets (e.g., ViroPharma)

Innovation focused on the needs of patients

- Balance internal and external programs
- External partnerships

Operational excellence

- Clinical trial design, trial recruitment
- Engagement with regulatory authorities

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Pipeline transformation since 2013

Progression of in-house programs

- E.g. Vyvanse for BED, Intrathecal Programs
- 'One Shire' consolidated Shire business units

Vyvanse® (lisdexamfetamine dimesylate)
10 • 20 • 30 • 40 • 50 • 60 • 70 mg capsules

ONE INTEGRATED R&D ORG
ONE
Structure | Culture | Purpose

Access to external innovation

- Multiple partnerships with world leading technology providers

ethris ENABLING THERAPIES
ARMAGEN TECHNOLOGIES Biotechnology for the Brain
arGEN-X
SOPHYSA
Nimbus Discovery

Acquisition of external assets and companies

- Baxalta (Hematology, Immunology, Oncology)
- Dyax (HAE)
- Premacure (complications of prematurity)
- NPS (SBS and hypoparathyroidism)
- SARCode (Dry eye)
- ViroPharma (HAE)
- Lumena (cholestatic liver disease)

Baxalta
Dyax
NPS Pharma
SARCode bioscience
premacure
LUMENA PHARMACEUTICALS

Increase value of acquired assets*

- Investigation of potential new uses of Cinryze
- Eosinophilic esophagitis
- CMV infection

CINRYZE® C1 esterase inhibitor (human)
ViroPharma Incorporated

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* Subject to regulatory approval

Resulting pipeline is robust with rare disease indications at all stages of development

Research and Preclinical	Phase 1	Phase 2		Phase 3		Registration	Recent approvals
35+ programs • Internally developed and via partnership • Both rare disease and specialty conditions • Multiple modalities including NCEs, MAbs, proteins, and gene therapy	**SHP611** (MLD)	**Onivyde** (Pancreatic Cancer, 1st line)	**SHP620**[5] (CMV infection in transplant patients)	**SHP609** (Hunter IT) Ph 2/3	**Obizur** (CHAWI surgery)	**Natpar - EU** (Hypoparathyroidism)	**Cuvitru** (PID)
	SHP622 (Friedreich's Ataxia)	**Onivyde - Japan**[2] (Pancreatic Cancer, post gemcitabine)	**SHP625**[4] (PFIC)	**SHP621**[4] (EoE)	**Calaspargase Pegol** (ALL)	**Adynovate** (Hemophilia A)	**Xiidra** (Dry eye)
	SHP623[1] **(rC1-INH)** (NMO)	**SHP607**[3] (BPD and IVH)	**SHP625** (ALGS)	**SHP643**[4] (HAE Prophylaxis)	**10% Hyqvia+Kiovig** (CIDP)	**Intuniv - Japan** (ADHD)	**Onivyde - EU** (Pancreatic Cancer, Line 2)
	SHP631 (Hunter CNS)		**SHP626** (NASH)	**Firazyr - Japan** (Acute HAE) Ph 2/3	**Obizur** (CHAWI on demand)		
	SHP655[5] **(BAX930)** (hTTP)		**SHP640**[5] (Infectious Conjunctivitis)	**Cinryze - Japan** (HAE Prophylaxis)	**Alpha-1 Antitrypsin** (Acute GvHD)		
	SHP656 (BAX826) (Hemophilia A)		**SHP647**[5] (CD)	**Cinryze SC** (HAE Prophylaxis)	**SHP465**[6] (ADHD)		
			SHP647[5] (UC)	**Cinryze** (AMR)	**SHP555 - US** (Chronic Constipation)		
			SHP652 (SM101) (SLE)	**Gattex - Japan** (Adult SBS)	**Vyvanse - Japan** (ADHD) Ph2/3		
			SHP653 (imalumab) (mCRC)	**Vonvendi**[7] (VWD)			

Rare indication

Non-rare indication

Pipeline excludes: Oncaspar lyophilized, Alpha-1 prophylaxis, and Buccolam

(1) rC1-INH previously being developed as SHP623 for HAE prophy; After Ph1 completion will be developed for NMO; (2). Registrational study; (3). SHP607 originally developed for ROP

(4) Granted breakthrough designation by FDA; (5). Phase 3 ready study; (6). SHP465 received positive Ph3 data in April (child./Ado), June (Adults) 2016;

(7) Approved in US for on-demand in adults, in phase 3 for surgery, peds/prophylaxis Ph3 study to begin in 4Q16, and in EU is registration-ready for On-demand in adults

Note: Phase 2/3 programs shown as Phase 3

Innovation mindset matches rare disease terrain

- **Little understanding of the diseases** – very little information
- **No precedent** for clinical study design & endpoints
- **Regulatory path is untrodden**
- **Few and hard-to-find patients**, geographically dispersed for study and clinical trial enrollment
- Increased focus on **payers' perspective, real world evidence, value demonstration**
- **Intense need for education** of patients, caregivers and physicians
- Extremely high medical need – pressure for **early access**
- **Clinical trial transparency**

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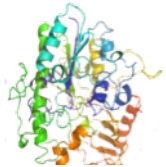
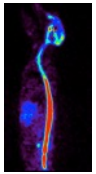
Serial innovation in areas of strategic focus:
Hunter Syndrome and HAE

Hunter Syndrome



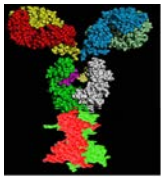
elaprase (idursulfase)

- Novel Enzyme Replacement Therapy (ERT)
- IV administration



Hunter IT program*

- Novel CNS delivery device for ERT
- Novel formulation
- Combination product



'Trojan Horse' program*

- Novel delivery approach for ERT
- IV delivery

HAE

CINRYZE (C1 esterase inhibitor (human)) firazyr (icatibant injection) KALBITOR ecallantide

- Ability to address both prophylactic and acute HAE needs
- Prophylaxis requires IV administration

SHP616* (CINRYZE) HAE Prophylaxis

- Novel delivery method
- Subcutaneous formulation to allow patient-administered prophylaxis

Dyax

- Novel antibody therapy
- Subcutaneous administration

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* Under investigation

Shire's approach to fostering a culture of innovation

Leaders role-modeling behaviors that support innovation	• Engagement of leaders with colleagues across organization
Set expectations around innovation and risk, support with resources	• Define risks and objectively manage to crisp go/no-go decision points • Balance risk across portfolio • Clear decision-making, minimize layers
Recognize innovation	• Clearly build into rewards and recognition
Acceptance that with risk comes some failures	• Remove fear of failure • Promote learning from failures
Drive innovation across organization, not just Research	• Clinical, Regulatory, Medical Affairs, Business Development, Finance, HR, Manufacturing, Commercial

Operational excellence in clinical development has been critical to our recent success

Critical Success Factors

- Innovative clinical trial design
- Frequent regulatory engagement
- Clinical Operations excellence
- Targeted recruitment strategy

Recent Example

Xiidra for Dry Eye Disease

- Before Xiidra, no agent approved for signs and symptoms of dry eye disease
- Xiidra clinical program was largest in dry eye disease (>2500 patients)
- Second Phase 3 symptom study (OPUS-3) complemented data from OPUS-2 and recruited with speed
- Early and frequent engagement with FDA
- Very high quality submission

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Making major progress while successfully integrating

Major Approvals & Launches

Approval of CUVITRU
for Primary Immune Deficiency in Europe and the US

FDA Approval of XIIDRA (Lifitegrast)
for Dry Eye Disease

EMA Approval of ONIVYDE for 2nd Line Metastatic Pancreatic Cancer

Approval of Vyvanse in Canada for BED in adults

Approval of Lialda in adults in Japan for UC

Launch of VONVENDI in adults in the US for vWD

Development Progress & Acquisitions

2 Breakthrough Therapy Designations
- SHP621, SHP625

1 Fast Track FDA Designation
- SHP626 for NASH

Completed Enrollment for Phase 3 Studies
- SHP609: Hunter Syndrome (IT Program)
- SHP643: HAE

Completion of Phase 2 study
- SHP607: complications of prematurity

Acquisition
- SHP647 integrin antagonist for IBD

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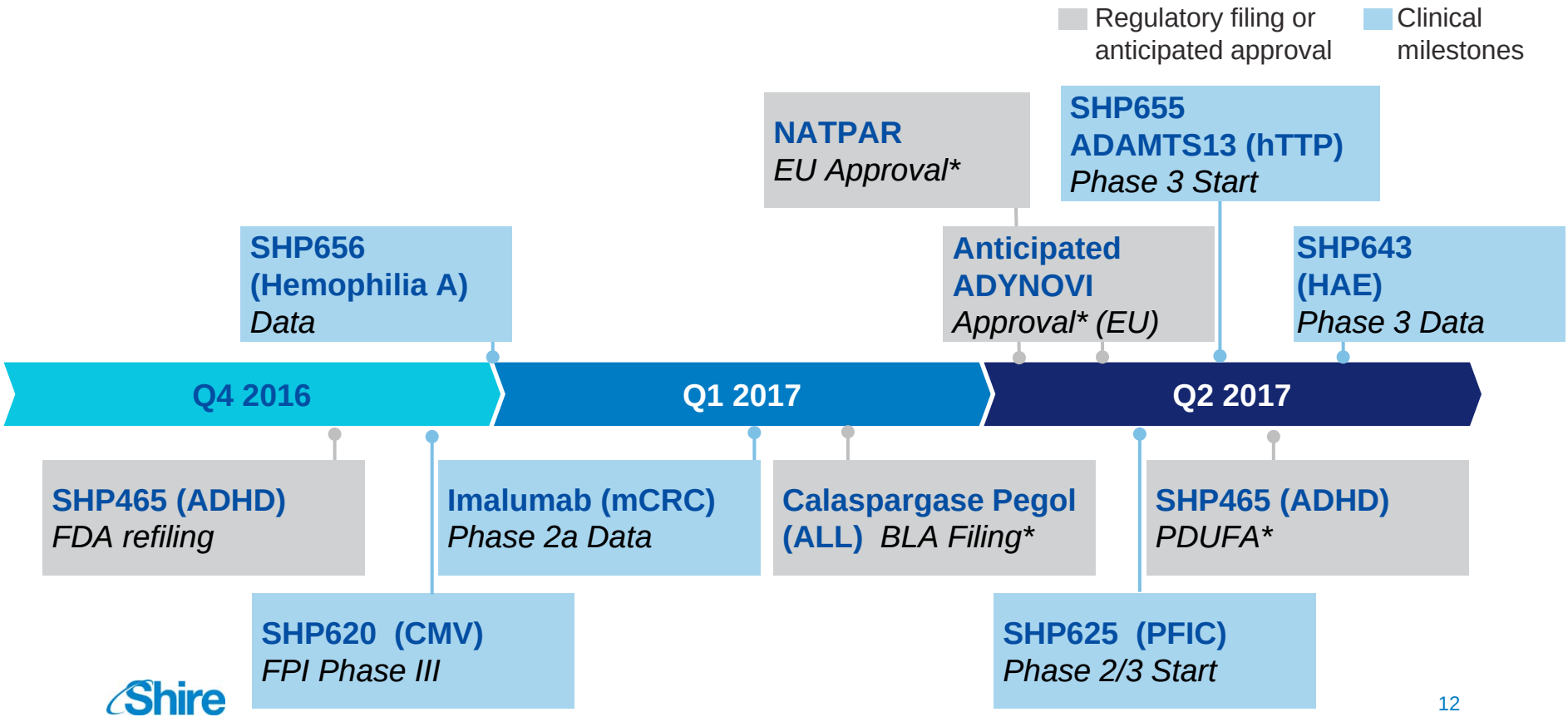
Looking forward – Anticipated near-term milestones



* Subject to regulatory approval

Afternoon session: Six late-stage programs

Rare Disease Leadership

Gastroenterology
SHP621 – (Eosinophilic Esophagitis)

Transplant Medicine
SHP620 – (CMV Infections)

Neonatology
SHP607 – (Complications of Prematurity)

Genetic Diseases
SHP643 – (Hereditary Angioedema)

Specialty Condition Leadership

Gastroenterology
SHP647 – (Inflammatory Bowel Disease)

Neuroscience
SHP465 – (ADHD)

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