Shire R&D Day

New York City, USA

December 10th, 2014

Our purpose
We enable people with life-altering conditions to lead better lives.

Shire

Shire R&D Day

Jeff Poulton, Head of Investor Relations

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The “SAFE HARBOR” Statement Under the Private Securities Litigation Reform Act of 1995

Statements included in this announcement that are not historical facts are forward-looking statements. Forward-looking statements can be identified by words such as “aspiration”, “will”, “expect”, “forecast”, “aspiration”, “potential”, “estimates”, “may”, “anticipate”, “target”, “project” or similar expressions suitable for identifying information that refers to future events. Forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire’s results could be materially adversely affected. The risks and uncertainties include, but are not limited to, that:

- Shire’s products may not be a commercial success;
- revenues from ADDERALL XR are subject to generic erosion and revenues from INTUNIV will become subject to generic competition starting in December 2014;
- the failure to obtain and maintain reimbursement, or an adequate level of reimbursement, by third-party payors in a timely manner for Shire's products may impact future revenues, financial condition and results of operations;
- Shire conducts its own manufacturing operations for certain of its products and is reliant on third party contractors to manufacture other products and to provide goods and services. Some of Shire’s products or ingredients are only available from a single approved source for manufacture. Any disruption to the supply chain for any of Shire’s products may result in Shire being unable to continue marketing or developing a product or may result in Shire being unable to do so on a commercially viable basis for some period of time.
- the development, approval and manufacturing of Shire’s products is subject to extensive oversight by various regulatory agencies. Submission of an application for regulatory approval of any of our product candidates, such as our planned submission of a New Drug Application to the FDA for Lifitegrast as a treatment for the signs and symptoms of dry eye disease in adults, may be delayed for any number of reasons and, once submitted, may be subjected to lengthy review and ultimately rejected. Moreover, regulatory approvals or interventions associated with changes to manufacturing sites, ingredients or manufacturing processes could lead to significant delays, increase in operating costs, lost product sales, an interruption of research activities or the delay of new product launches;
- the actions of certain customers could affect Shire's ability to sell or market products profitably. Fluctuations in buying or distribution patterns by such customers can adversely impact Shire’s revenues, financial conditions or results of operations;
- investigations or enforcement action by regulatory authorities or law enforcement agencies relating to Shire’s activities in the highly regulated markets in which it operates may result in the distraction of senior management, significant legal costs and the payment of substantial compensation or fines;
- adverse outcomes in legal matters and other disputes, including Shire’s ability to enforce and defend patents and other intellectual property rights required for its business, could have a material adverse effect on Shire’s revenues, financial condition or results of operations;
- Shire faces intense competition for highly qualified personnel from other companies, academic institutions, government entities and other organizations. Shire is undergoing a corporate reorganization and the consequent uncertainty could adversely impact Shire’s ability to attract and/or retain the highly skilled personnel needed for Shire to meet its strategic objectives;
- failure to achieve Shire’s strategic objectives with respect to the acquisition of ViroPharma Incorporated may adversely affect Shire’s financial condition and results of operations;

and other risks and uncertainties detailed from time to time in Shire’s filings with the US Securities and Exchange Commission, including its most recent Annual Report on Form 10-K.

Investor Day Agenda and Outline

Time	Topic	Speaker
8:00-8:30am	***Registration/Breakfast***	
8:30-8:45am	**Corporate Overview**	**Flemming Ornskov, M.D., MPH**
8:45-9:25am	**R&D Strategy Overview**	**Phil Vickers, Ph.D.**
9:25-10:00am	**Research Overview and Technology Platforms** *(mRNA, Protein Replacement, Gene Therapy, Antibody Platforms)*	**Albert Seymour, Ph.D.**
10:00-10:45am	**Rare Diseases: GI/Hepatology** *(SHP625 / LUM001, SHP626 / LUM002)*	**Ciara Kennedy, Ph.D.** **David Piccoli, M.D.**
10:45-11:15am	***Morning Break***	
11:15-11:45am	**Rare Diseases: Ophthalmology** *(SHP607 / ROP, SHP630 / BIKAM)*	**Norman Barton, M.D., Ph.D.**
11:45-12:15pm	**Morning Q&A**	
12:15-1:15pm	***Lunch***	
1:15-1:30pm	**Rare Diseases: Complement Pathway** *(SHP616 / CINRYZE new uses)*	**Howard Mayer, M.D.**
1:30-2:00pm	**Rare Diseases: CNS** *(SHP609 / Hunter CNS, SHP610 / Sanfilippo A, SHP611 / MLD, Armagen)*	**Howard Mayer, M.D.**
2:00-2:45pm	**Late Stage Update** *(SHP606 / Lifitegrast, BED, SHP465 / ADHD)*	**Howard Mayer, M.D.** **Randy Brenner** **Joe Tauber, M.D.**
2:45-3:00pm	**Program Wrap-Up**	**Phil Vickers, Ph.D.**
3:00-3:30pm	**Afternoon Q&A**	
3:30-4:30pm	**Reception**	

Corporate Overview

Flemming Ornskov, M.D., MPH, Chief Executive Officer

Our purpose
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Our Clear and Focused Strategy

PURPOSE

Enable people with life-altering conditions to lead better lives

ASPIRATION

- To become a leading global biotech delivering innovative medicines to patients with rare diseases and other specialty conditions
- Double product sales to $10B by 2020 (10 x 20)[1][2]

STRATEGIC DRIVERS

GROWTH

- Optimize in-line assets through commercial excellence
- Advance late-stage pipeline and launch new products
- Acquire core / adjacent assets

INNOVATION

- Expand Rare Diseases expertise through internal research and collaborations
- Extend existing portfolio to new indications / TAs[3]

EFFICIENCY

- Operate a lean and agile organization
- Meet milestones and deliver on commitments
- Maintain flexibility to reinvest in growth

PEOPLE

- Live our BRAVE values
- Foster and reward a high-performance culture
- Attract, develop and retain the best talent

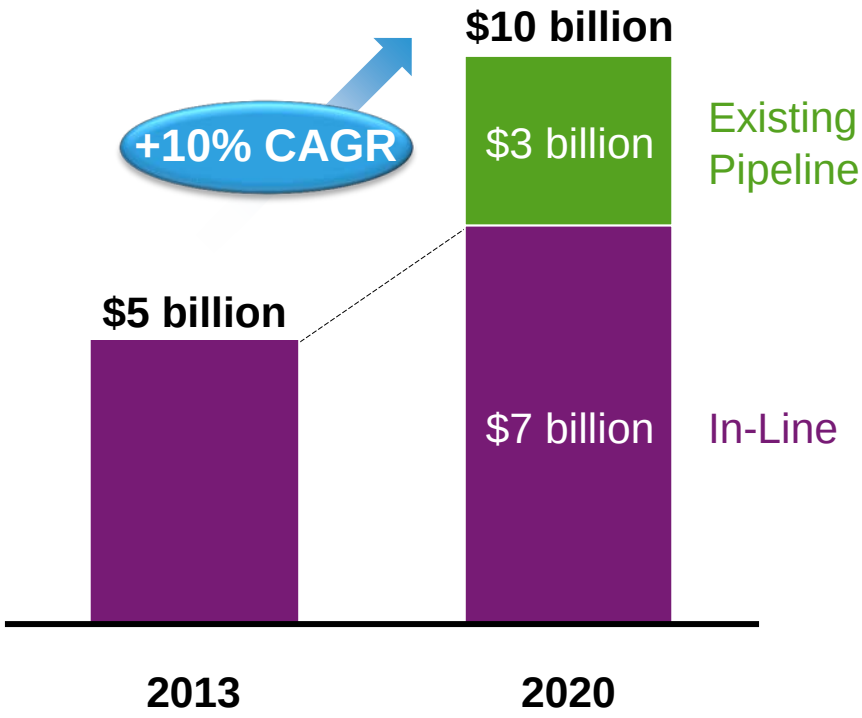
(1) Forecast growth includes ViroPharma product sales (ViroPharma Inc. was acquired by Shire on January 24, 2014). Further potential upside to this 10x20 target includes the closed Lumena and Fibrotech acquisitions and future M&A and licensing.

(2) 2013 product sales = $5B.

(3) TA refers to Therapeutic Area.

10 x 20: $10 Billion in Product Sales by 2020

Product sales; Percent CAGR

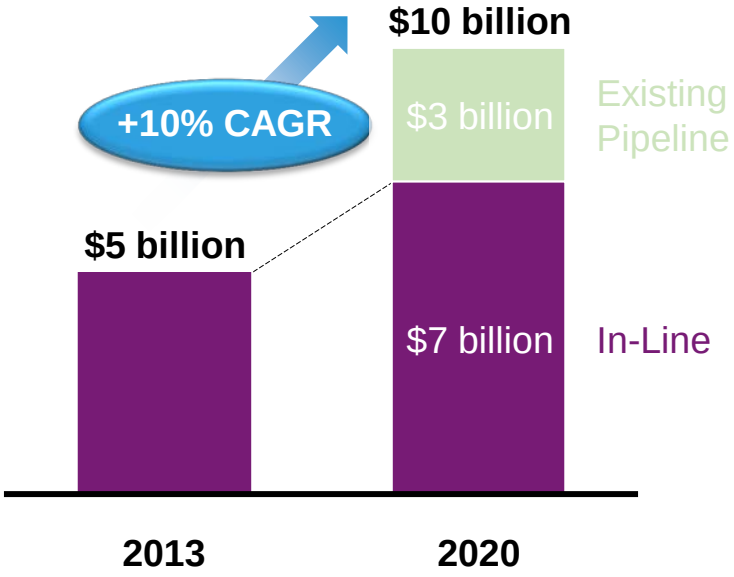


10 x 20 Details

1. **In-Line:** $7 billion expected from on-market products
2. **Pipeline:** $3 billion from existing pipeline
3. **Upside:** Lumena, Fibrotech, BIKAM, early stage pipeline and future BD provide additional upside to 10 x 20

$7 Billion from In-Line Products

Product sales; Percent CAGR



1 In Line: $7 billion expected from on-market products(1)(2)

Rare Diseases	Neuro-science	Gastro-Intestinal	Internal Medicine
REPLAGAL agalsidase alfa	Vyvanse lisdexamfetamine dimesylate	Lialda (mesalamine) 1.2g	XAGRID
CINRYZE C1 esterase inhibitor (human)	EQUASYM Methylphenidate Hydrochloride Modified Release Capsules	PENTASA (mesalamine) controlled-release capsules	ADDERALL XR
firazyr icatibant	intuniv (guanfacine)	Resolor prucalopride	FOSRENOL (lanthanum carbonate)
VPRIV velaglucerase alfa for injection	BUCCOLAM MIDAZOLAM OROMUCOSAL SOLUTION		
elaprase (idursulfase)			

(1) Products shown are not exhaustive
(2) $7 billion also includes pipeline extensions of existing in-line products

Diversified and durable in-line portfolio has delivered 6 straight quarters of double-digit product sales growth

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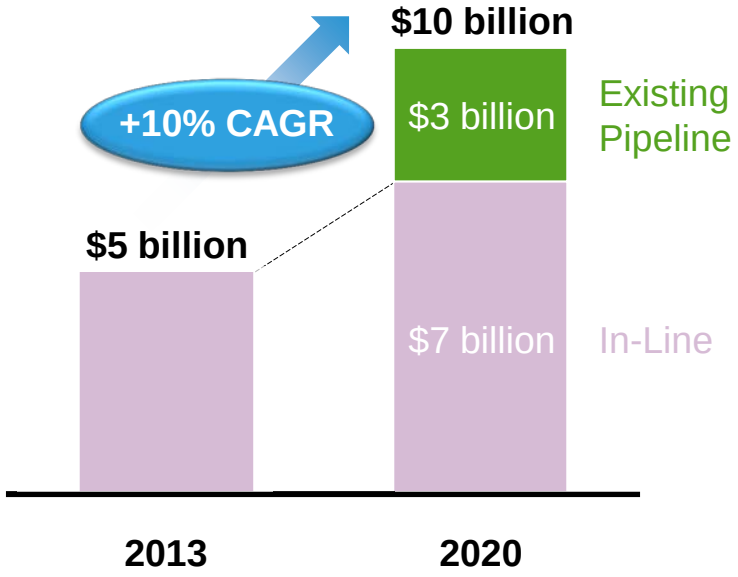
$3 Billion from Existing Pipeline

Product sales; Percent CAGR



2 Pipeline: $3 billion from existing pipeline

Included in $3 Billion

Preclinical	Phase 1	Phase 2		Phase 3	Registration
26 Research Programs	SHP611 MLD (Ph 1/2)	SHP602 Iron overload (clinical hold)	SHP616 – Cinryze Acute Antibody Mediated Rejection	Firazyr ACE inhibitor-induced AE	XAGRID® (Japan) Thrombocythaemia (Approved 3Q 2014)
SHP619 Duchenne's Muscular Dystrophy	SHP616 Cinryze SC HAE Prophylaxis	SHP610 Sanfilippo A	SHP625 (LUM001) Primary Biliary Cirrhosis	Firazyr (Japan) HAE	VPRIV (Japan) Gaucher (Approved 3Q 2014)
TH/GCH1 Gene Pod Parkinson's Subset	SHP622 Friedreich's Ataxia	SHP609 Hunter CNS	SHP625 (LUM001) Progressive Familial Intrahepatic Cholestasis	SHP616 Cinryze (Japan) HAE Prophylaxis	INTUNIV® (EU) ADHD
SHP608 Dystrophic E.Bullosa	SHP627 (FT011) Focal Segmental Glomerulosclerosis	SHP607 Prevention of ROP	SHP625 (LUM001) Alagille Syndrome	SHP555 (US) Chronic Constipation	Vyvanse BED
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SHP630 adRP	SHP626 (LUM002) Non-Alcoholic Steatohepatitis			SHP465 ADHD	
SHP624 Heme B Gene Edit					
SHP628 (FT-061) Renal Impairment					

Balanced pipeline across stages of development with multiple upcoming milestones that will support long-term growth

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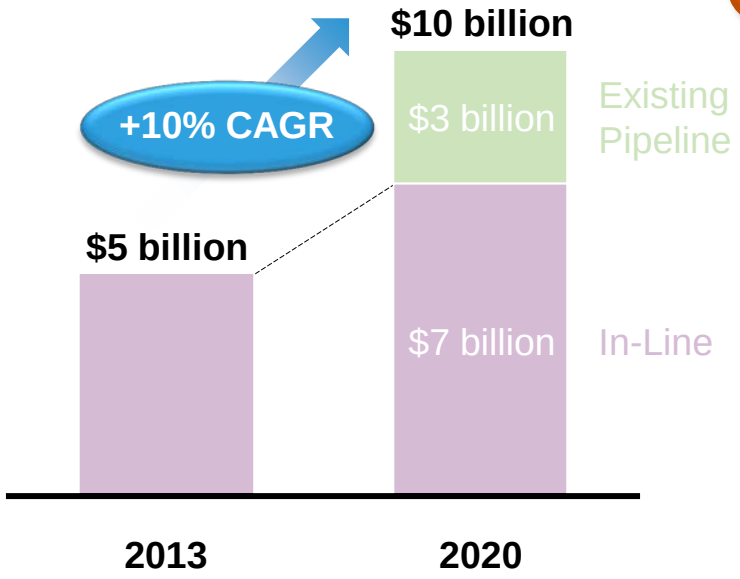
Upside from Recent and Future BD

Product sales; Percent CAGR



3 **Upside:** Lumena, Fibrotech, CINRYZE New Uses, early stage pipeline, and future BD provide additional upside to 10 x 20

Additional upside

Preclinical	Phase 1	Phase 2		Phase 3	Registration
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SHP628 (FT-061) Renal Impairment					

Rare Diseases domain expertise and significant cash generation creates an opportunity to become the industry's go-to-partner

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Focused Business Development Strategy

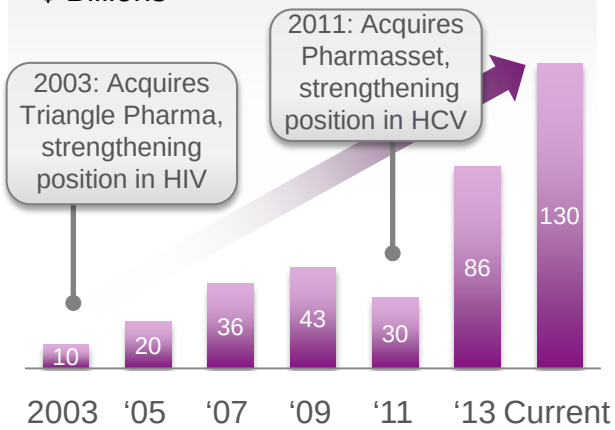
	Rationale	Recent Examples
Reinforce Core Therapeutic Areas (TAs)	• Existing infrastructure or expertise creates "ownership" advantage • Can generate and quickly capture synergies (revenue, cost, operational) to create value	CINRYZE® C1 esterase inhibitor (human) **SHP626 (LUM002)** Non-Alcoholic Steatohepatitis **SHP625 (LUM001)** Cholestatic Liver Diseases **SHP627 (FT011)** Focal Segmental Glomerulosclerosis
Expand Into High-value Adjacent TAs	• Informed entry into other specialist TAs with long-term growth potential where Shire has expertise or can build core competencies	**SHP606 (Lifitegrast)** Dry eye disease **SHP607** Prevention of ROP
Divest Non-Core Assets	• Divest non-core, underperforming businesses to refocus resources on core growth drivers	Dermagraft® Human fibroblast-derived dermal substitute

Domain Expertise Creates Substantial Value

Gilead (Virology)

M&A focused on Gilead's strength in anti-virals has contributed to ~$120B in shareholder value created since 2003

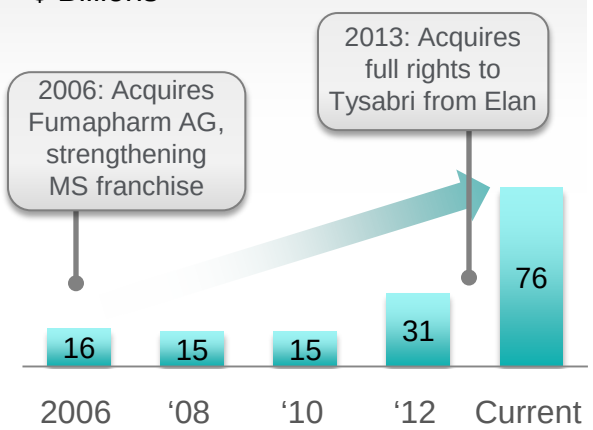
Market Capitalization(1)
$ Billions



Biogen Idec (MS)

Biogen has leveraged its dominant position in multiple sclerosis to create ~$60B of value since 2006

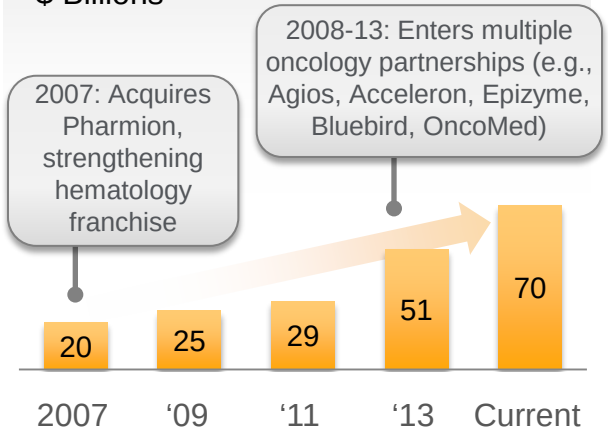
Market Capitalization(1)
$ Billions



Celgene (Hem / Onc)

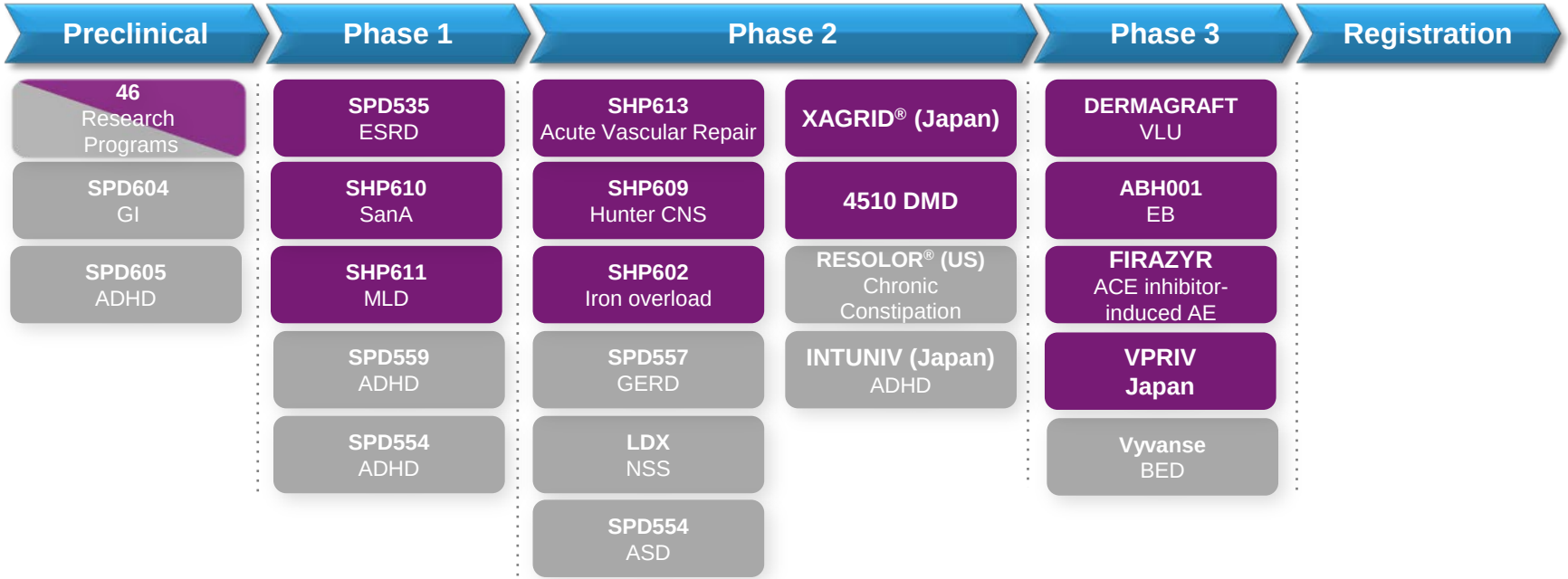
Since acquiring Pharmion in 2007, Celgene has created ~$50B of value, in part by executing a Hem / Onc licensing strategy

Market Capitalization(1)
$ Billions



Sources: Company filings, FactSet
(1) Average of market capitalizations at 1 January and 31 December each year except current, which is as at 2 July 2014

Research and Development Pipeline Pre-One Shire



Rare Diseases Programs

Current Research and Development Pipeline

Pipeline has Grown and is Increasingly Focused on Rare Diseases

Preclinical	Phase 1	Phase 2		Phase 3	Registration
26 Research Programs	**SHP611** MLD (Ph 1/2)	**SHP602** Iron overload (clinical hold)	**SHP616 (Cinryze)** Acute Antibody Mediated Rejection	**Firazyr** ACE inhibitor-induced AE	**XAGRID® (Japan)** Thrombocythaemia *(Approved 3Q 2014)*
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SHP628 (FT-061) Renal Impairment					

Rare Diseases Programs

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R&D Strategy Overview

Phil Vickers, Ph.D., Global Head of R&D

Our purpose
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R&D Pipeline Has Never Been Stronger

22 programs in the clinic, the most in the history of Shire

Well-positioned to deliver on ‘10 x 20’ expectations

Many **significant clinical milestones** in the next 18 months

On track to file at least **2 INDs** from internal programs every year

Establishing talent and capabilities appropriate to drive **future growth**

Continued excellence in acquiring **external assets with a strong strategic fit**

Establishing a leadership position in the treatment of Rare Diseases

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Our Clear and Focused Strategy

STRATEGIC DRIVERS

GROWTH

- Optimize in-line assets through commercial excellence
- Advance late-stage pipeline and launch new products
- Acquire core / adjacent assets

INNOVATION

- Expand Rare Diseases expertise through internal research and collaborations
- Extend existing portfolio to new indications / TAs

EFFICIENCY

- Operate a lean and agile organization
- Meet milestones and deliver on commitments
- Maintain flexibility to reinvest in growth

PEOPLE

- Foster and reward a high-performance culture
- Attract, develop and retain the best talent
- Live our BRAVE values

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R&D Strategy to Deliver Growth

GROWTH

INNOVATION

FOCUS IN AREAS OF HIGH UNMET MEDICAL NEED

- **Increasing emphasis on rare diseases** with high morbidity and / or mortality
- Focus on **specific platforms**
- Adapting existing therapeutic areas to a rare-disease focus
- Strategic focus, but flexibility in considering new opportunities

FOCUS IN AREAS OF HIGH VALUE TO PATIENTS, PAYORS AND SHAREHOLDERS

- **Alignment with all key stakeholders**, including patients
- Focus in areas which drive attractive commercial return
- Health economics assessments to support market access
- Prioritize programs where a single approach can address multiple rare diseases (e.g. Lumena, Cinryze) or expand to common indications

FOCUS ON INNOVATION

- **Innovation associated with every pipeline program**
- **Risk balance** across pipeline
- Foster a culture that ensures innovation and calculated risk-taking
- Creative partnerships and collaborations

ENSURE HIGH PRODUCTIVITY, OPERATIONAL EXCELLENCE

- Balance of internal programs and acquiring external assets
- Ensure industry-leading capabilities in **operational excellence**

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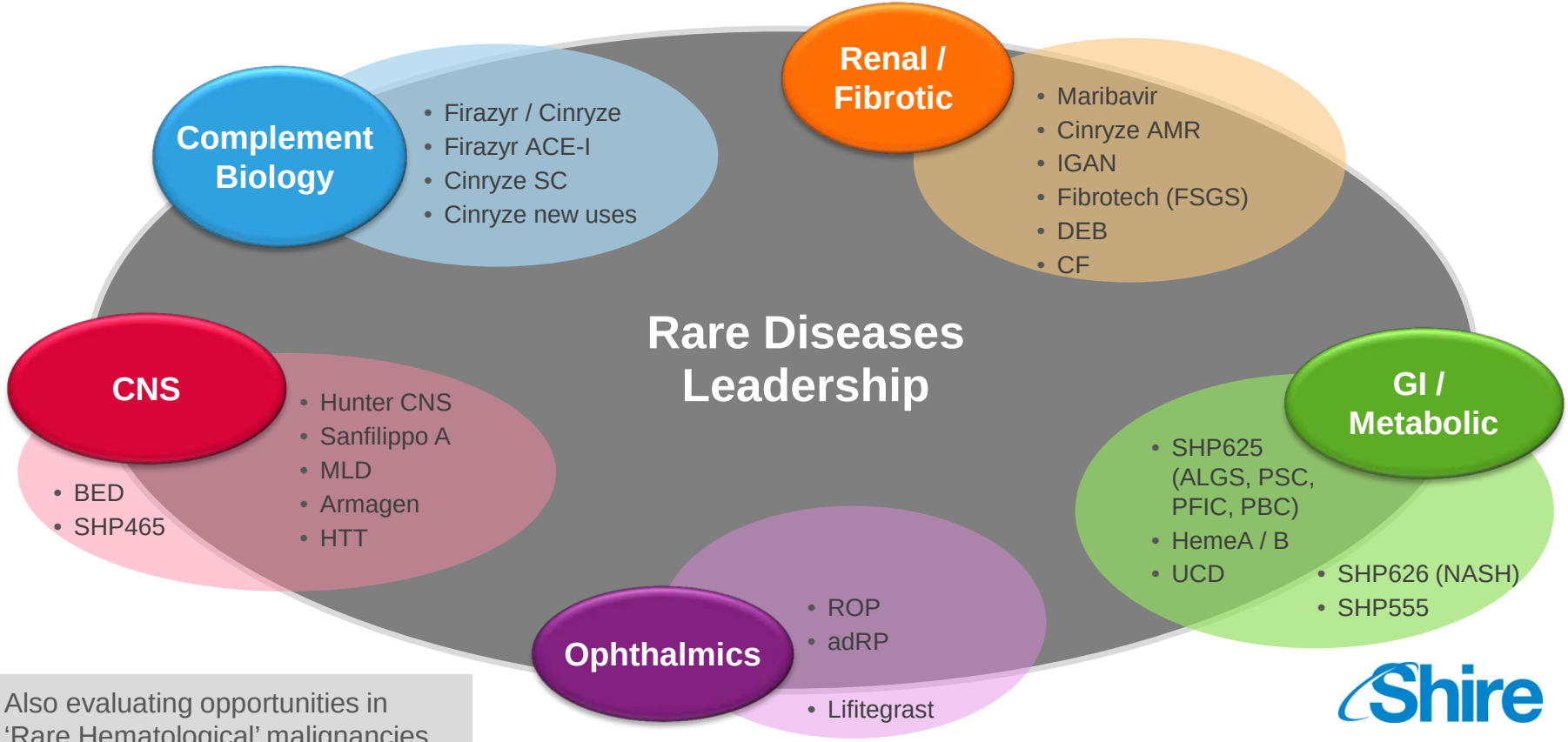
Main Therapeutic Areas Increasingly Focused on Rare Diseases

GROWTH

INNOVATION



Also evaluating opportunities in 'Rare Hematological' malignancies

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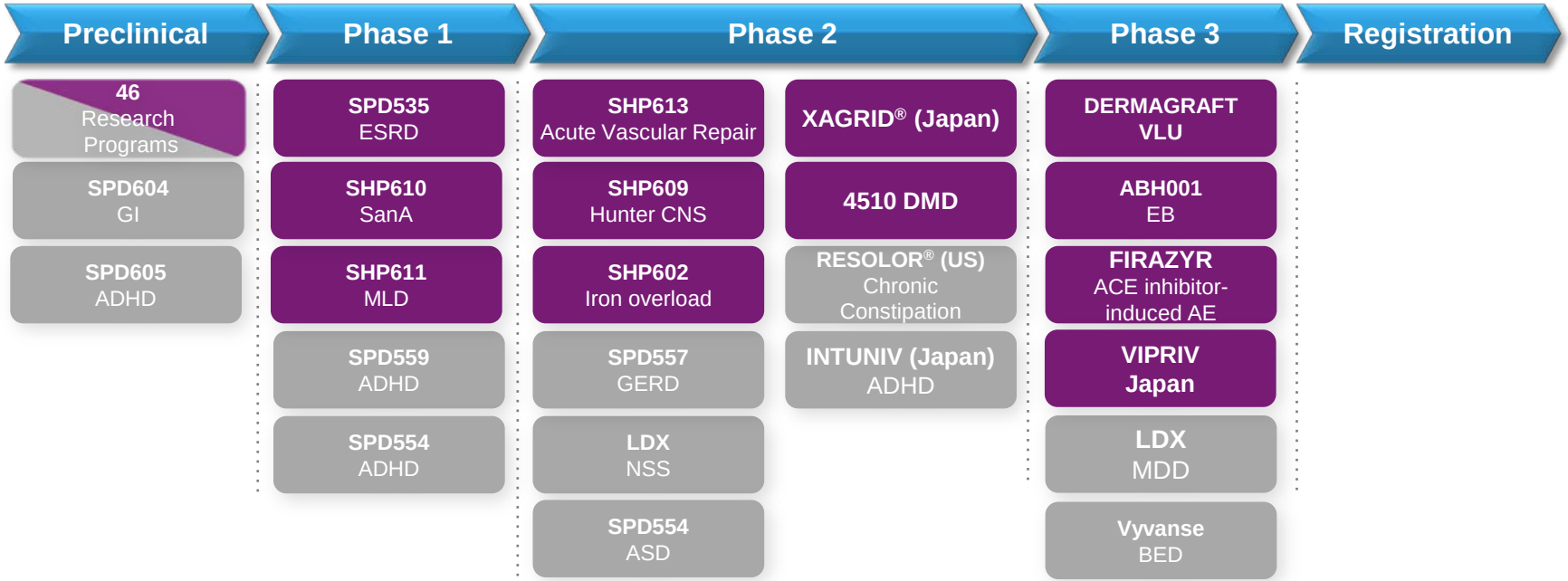
R&D Pipeline 1Q2013

GROWTH

INNOVATION



Rare Disease Programs

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Current R&D Pipeline

Pipeline has Grown and Increased its Focus on Rare Diseases

GROWTH

INNOVATION

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Rare Diseases Programs

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Recent Changes to Internal Programs Increase Portfolio Value

GROWTH

INNOVATION

Rare Diseases Platform

- Reinforced **Rare Diseases leadership through internal research and partnerships** with world-class organizations while extending the platform to new indications and adapting current TAs
- Future rare diseases strategy defined

Intrathecal Programs

- **Progressed intrathecal programs** to treat CNS manifestations of Hunter, Sanfilippo A and MLD
- Novel intrathecal device approved for use in US and EU

SHP465 ADHD

- Planning to **resubmit SHP465** for high-growth ADHD adult segment

Vyvanse BED

- **Positive Phase 3** results
- Filed NDA in 3Q14
- **PDUFA date Feb 2015**
- Expect to launch in 1H15 subject to FDA review
- Currently no approved Binge Eating Disorder treatments

Rationalization

- **Halted programs that did not fit** scientific, strategic or commercial criteria
- Discovery programs now focused on rare diseases

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Recent Acquisitions Have Significant Potential

GROWTH

INNOVATION

ViroPharma Incorporated

- Acquired Viropharma 1Q14
- **Cinryze** low volume SC program for HAE prophylaxis (Phase 1) complement IV program
- SHP620 (Maribavir) being developed for treatment of cytomegalovirus infection in transplant patients (Phase 2)
- **Cinryze new use** programs: PNH (Phase 1), NMO (Phase 1), AMR (Phase 2)

SARCode bioscience

- Acquired SARCode 2Q13
- **Lifitegrast** being evaluated for signs and symptoms of **Dry Eye Disease**
- No currently approved product treats signs and symptoms of disease
- Plan to file NDA in 1Q15

LUMENA PHARMACEUTICALS

- Acquired Lumena 2Q14
- **SHP625** (LUM001) **for 4 rare cholestatic liver diseases** (Phase 2)
- SHP626 (LUM002) for NASH (Phase 1)

premacure

- Acquired Premacure 1Q13
- SHP607 (Premiplex) novel **protein replacement therapy** with potential **to prevent retinopathy of prematurity**
- Clinical program paused to allow optimization during 2014
- Ongoing Phase 2 study, due to read out 2015

fibrotech therapeutics

- Acquired Fibrotech 3Q14
- SHP627 (FT011) **antifibrotic agent** with potential for Focal Segmental Glomerulosclerosis (Phase 1 completed)
- SHP628 (FT061)) with potential for renal impairment (Preclinical)
- Fibrotechs **library** of novel molecules **targeting fibrosis**

LOTUS TISSUE REPAIR

- Acquired Lotus Tissue Repair 1Q13
- SHP608 (recombinant collagen 7) novel protein replacement therapy with potential for Dystrophic **Epidermolysis Bullosa**

armagen

- AGT-182 licensed from Armagen in 3Q14
- Molecular '**Trojan Horse**' of ERT fused to human insulin receptor designed **to treat severe Hunter syndrome** - facilitates entry into CNS
- Currently in preclinical development

bikam pharmaceuticals

- Acquired BIKAM 3Q14
- SHP 630 is a **pharmacological chaperone** designed **to treat** autosomal-dominant retinitis pigmentosa (**adRP**)
- SHP 630 facilitates opsin folding, with the aim of restoring retinal function in adRP
- Currently in preclinical development

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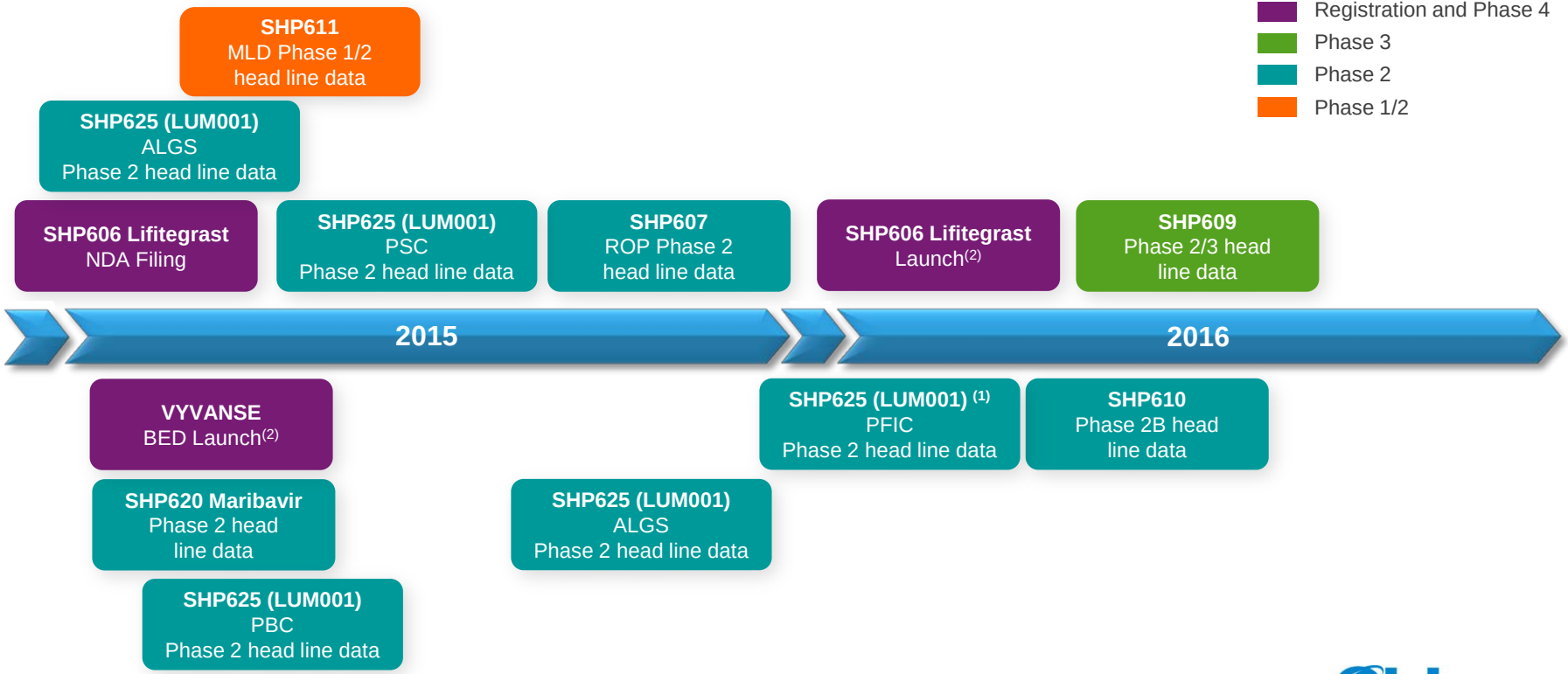
Upcoming Anticipated Pipeline Milestones

GROWTH

INNOVATION



Notes
(1) Interim 625 PFIC INDIGO data expected Q2 2015.
(2) Subject to regulatory approval.

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EFFICIENCY

- Operate a lean and agile organization
- Meet milestones and deliver on commitments
- Maintain flexibility to reinvest in growth

PEOPLE

- Foster and reward a high-performance culture
- Attract, develop and retain the best talent
- Live our BRAVE values

(1) TA refers to Therapeutic Area.

Unifying the Organization to Drive Efficiency

EFFICIENCY

3 SEPARATE R&D UNITS

Shire REGENERATIVE MEDICINE

Shire Human Genetic Therapies

Shire Specialty Pharmaceuticals

ONE INTEGRATED R&D ORG

ONE

Structure | Culture | Purpose

REPLAGAL agalsidase alfa

elaprase (idursulfase)

Vyvanse (lisdexamfetamine dimesylate)

intuniv (guanfacine)

SHP609
Hunter CNS

VPRIV velaglucerase alfa for injection

firazyr icatibant

FIRAZYR
ACE inhibitor-induced AE

XAGRID®

FOSRENOL (lanthanum carbonate)

CINRYZE C1 esterase inhibitor (human)

Lialda (mesalamine) 1.2g

INTUNIV ADHD

Resolor prucalopride

EQUASYM XL

PENTASA (mesalamine)

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Effective Decision Making in R&D

EFFICIENCY

PEOPLE

Science and Technology Committee

Composition: Subset of **board members with scientific backgrounds**

Role: **Reviews scientific aspects of R&D** and pipeline progress

- Evaluates in-licensing and acquisition opportunities
- Reviews internal pipeline programs and assesses R&D talent
- Provides view to the full board of directors on the above

Research Steering Committee

Composition: **Internal stakeholders responsible** for transition from "R" to "D"

Role: Makes **"go / no-go" decisions** on internal **research** programs

- Reviews research program progress and manages to go / no-go decisions
- Engages externally for input (e.g. payors)
- Makes recommendations to Pipeline Committee

Pipeline Committee

Composition: **Internal stakeholders** responsible for the **pipeline**

Role: Makes major **decisions on** programs in the **development pipeline**

- Makes recommendations to the Board whether to pursue external opportunities
- Aligns on an R&D strategy and priorities
- 'One stop shopping' for all major pipeline decisions

Scientific Advisory Board

Composition: **External experts** in science relevant to the R&D pipeline

Role: **Provides external perspective into science** underpinning R&D programs

- Contributes independent advice on science and technology
- Provides ideas and challenges based on their experience

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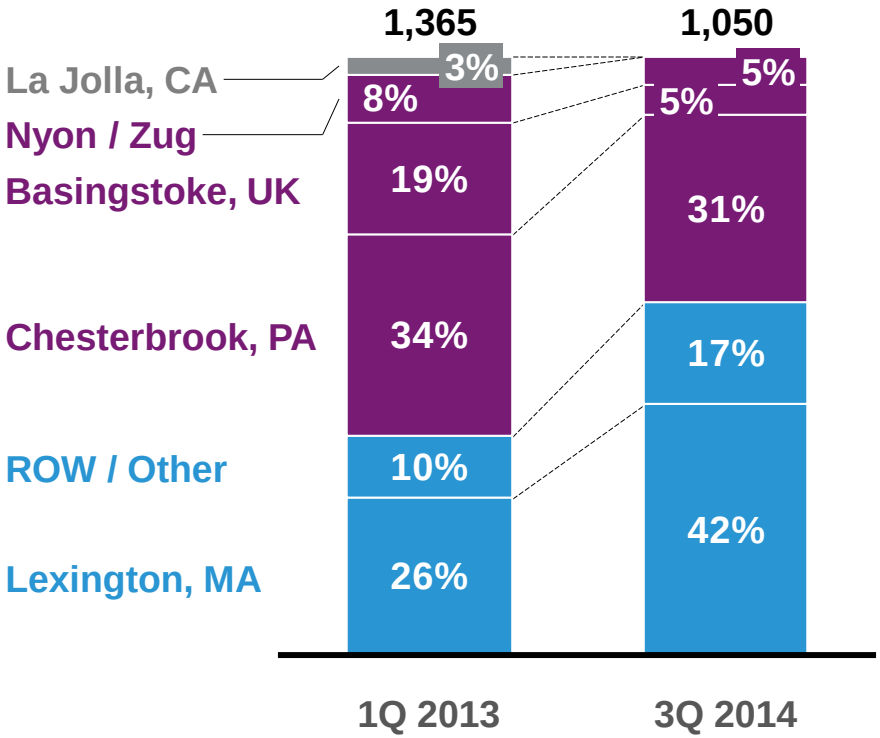
Centralization Increases Efficiency and Effectiveness

R&D Headcount; Percent of Total (1)



Impact

- **More efficient** footprint, structure and operating model
- **Reduced R&D headcount** drives cost savings
- **Increased access to talent** in global innovation hubs
- **Greater collaboration** with thought leaders (e.g., start-ups, research institutions, SAB)

(1) Permanent headcount as of August 30, 2014 including recent acquisitions; excludes contractors and open positions

R&D is Supported by a Network of Alliances and Creative Collaborations

EFFICIENCY

Shire

Experienced and Talented Team

PEOPLE

Presenting today

Phil Vickers
- Head of R&D
- Former Merck, Pfizer, BI, Resolvyx

Howard Mayer
- Head of Clinical Development
- Former CMO Merck Serono, ex-Pfizer

Ciara Kennedy
- Head of ex-Lumena Programs
- Former Lumena COO

Mike Heartlein
- Head of MRT Program
- Responsible for 3 marketed ERTs

Norman Barton
- Head of ROP Program
- Responsible for industry's first ERT

Albert Seymour
- Head of Research & Non-Clinical Development
- Former Pfizer Rare Diseases, Head of Human Genetics

Randy Brenner
- Head of Regulatory Affairs
- Former Pfizer Head of Regulatory, Emerging Markets

Rekha Abichandani
- Head of Intrathecal ERT Programs
- Former Genzyme, Rare Diseases & Hematological Malignancies

Clark Pan
- Head of Discovery Therapeutics
- Former Genzyme, Head of Protein Engineering

Jennifer Schranz
- Head of HAE Programs
- Former VP of Clinical Research, Viropharma

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Positioned for Leadership in Rare Diseases

PEOPLE

	Specific Rare Diseases R&D Challenges	Shire R&D Expertise
Research	• Few scientific experts • Incomplete knowledge of pathophysiology • Genotype-phenotype unclear	• Strong links to key opinion leaders • Research grants and partnerships • Ground-breaking R&D
Clinical / Regulatory	• Inefficient diagnosis • Few patients, geographically dispersed • Clinical endpoints unclear • Need for natural history studies • Challenges with placebo-controlled studies	• Clinical operations focus on specific challenges to open sites in novel therapeutic areas and recruit patients with rare diseases • Early engagement with regulatory authorities • Support for investigator-sponsored trials • Natural history studies
Medical Affairs / Post-Marketing	• Need for medical education • Post-marketing commitments • Patient registries / outcome surveys • Need for early access programs • Charitable access programs • Health economics challenges	• Strong links to patient associations • Numerous early access programs • Numerous registries / outcome surveys • Health economics focus

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Sessions for the Remainder of Today

Topic	Speaker	Time (EST)
Research Overview and Technology Platforms *mRNA, Protein Replacement, Gene Therapy, Antibody Platforms*	Albert Seymour, Ph.D.	9:25-10:00
Rare Diseases: GI / Metabolic *SHP625 (LUM001), SHP626 (LUM002)*	Ciara Kennedy, Ph.D. *David Piccoli, M.D.*	10:00-10.45
Rare Diseases: Ophthalmics *SHP607 / ROP, SHP630 / BIKAM*	Norman Barton, M.D., Ph.D.	11:15-11:45
Rare Diseases: Complement Biology and Renal / Fibrotic *SHP616 / Cinryze new uses*	Howard Mayer, M.D.	1:15-1:30
Rare Diseases: CNS *SHP609 / Hunter CNS, SHP610 / Sanfilippo A, SHP611 / MLD, Armagen*	Howard Mayer, M.D.	1:30-2:00
Late-Stage Update *SHP606 / Lifitegrast, BED, SHP465 / ADHD*	Howard Mayer, M.D. Randy Brenner *Joe Tauber, M.D.*	2:00-2:45

Research Overview and Technology Platforms

Albert Seymour, PhD, Head of Research and Nonclinical Development

Our purpose
We enable people with life-altering conditions to lead better lives.

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Today's R&D Sessions

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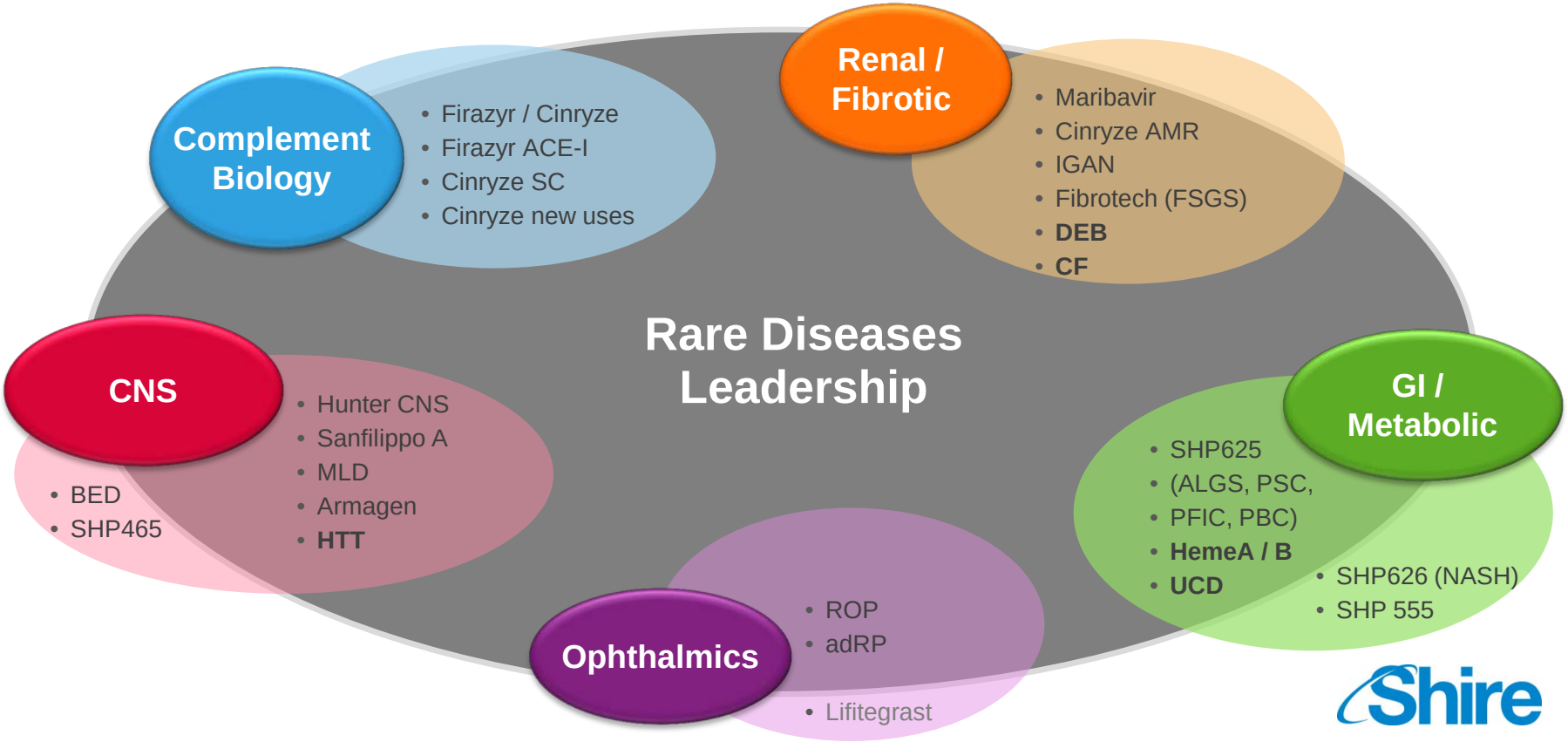
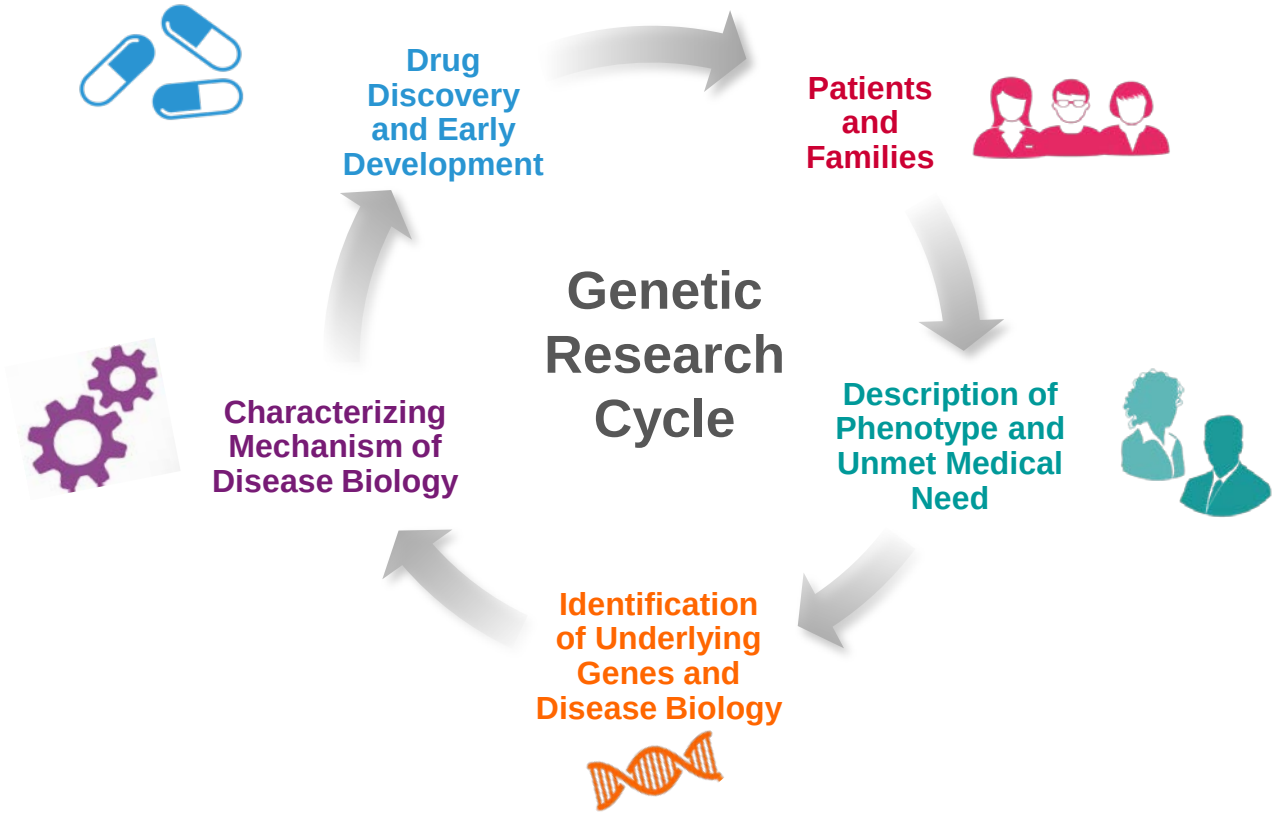
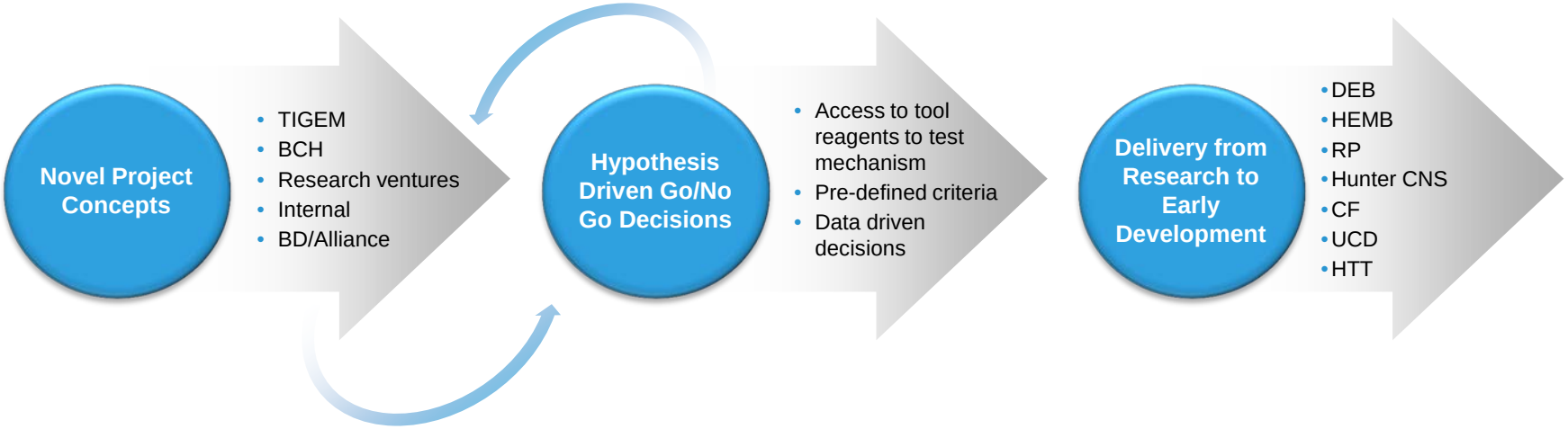
Rare Diseases Leadership Underpins Multiple TAs



Genetic-based Drug Discovery & Development



Research Model for Delivering the Portfolio in Rare Diseases



1. Research portfolio built around high confidence targets in diseases with significant unmet medical need

2. Culture of rapid and clear data driven go/no go decisions

3. Efficient and focused team integrating internal and external flexible model to deliver early alignment with process and clinical development

4. ~26 active programs with a goal of delivering 3 programs from research to early development per year with a focus on quick to clinical POC

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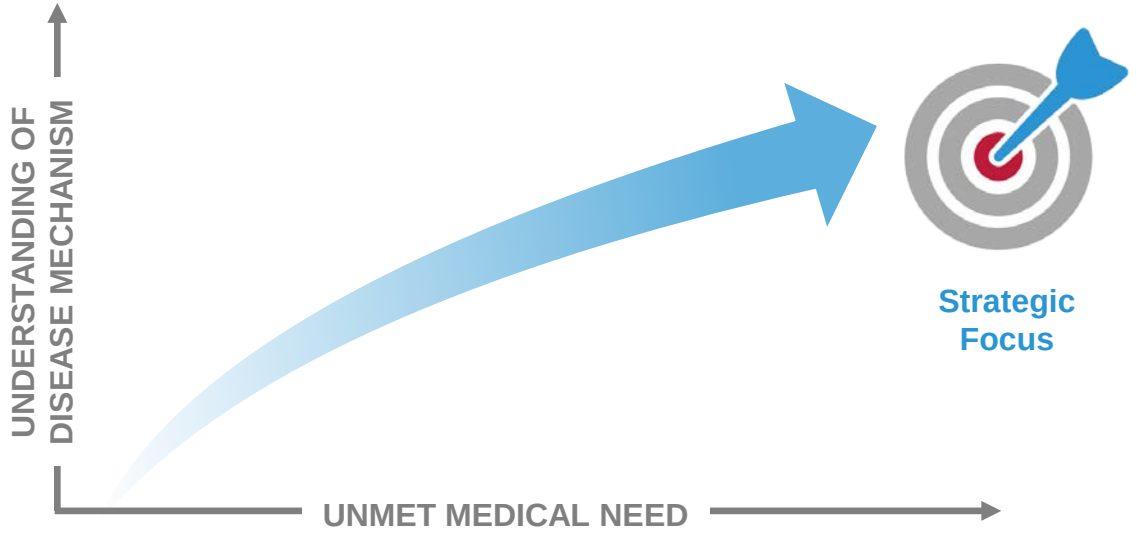
Identifying Rare Diseases Opportunities

Follow the biology to select the right target and focus on diseases with high unmet medical need and well-understood disease pathophysiology

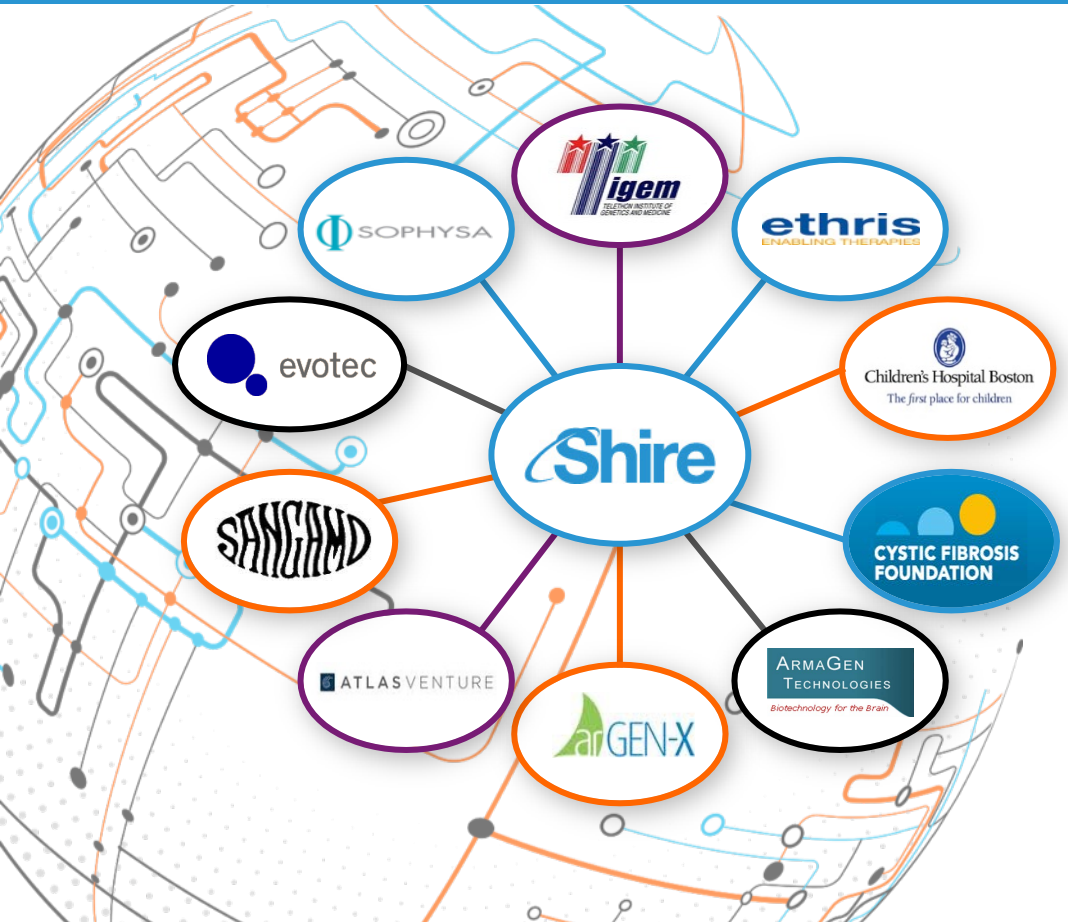


ELICIT PHARMACOLOGY

TARGET ENGAGED

EXPOSURE IN TARGET TISSUE

External Innovation is Core to Research



Early Stage Opportunities

- Translate existing science into diseases of interest
- Develop lead assets
- Build relationships

Development Opportunities

Inception Sciences

Nimbus Discovery

Co-Investment

- Externally fund programs and manage research and develop
- Create novel investment structures

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Rare Disease Leadership through Innovative Technology Platforms – Internal and External

TARGET CONCEPT

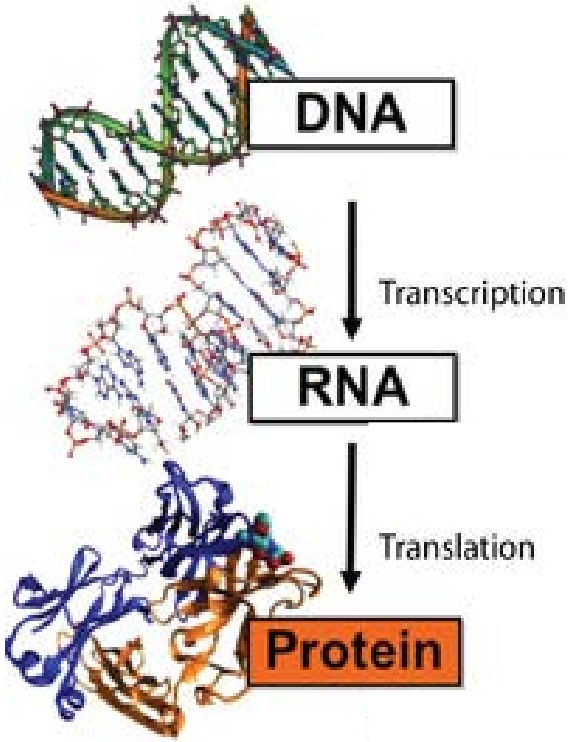
BIOLOGY
Best modality to affect Biology

POC
Quickest way to test POC

TECHNOLOGY PLATFORMS

	Gene Therapy	MRT	Proteins	Antibody	Small Molecule
Description	Therapeutic delivery of cDNA for gene correction Gene editing	Reagent mRNA to test mechanism Therapeutic mRNA	Reagent protein constructs Therapeutic delivery of novel proteins	Reagent antibodies to test mechanism Therapeutic antibodies	Reagent tools to test mechanism Therapeutic lead molecules Internal expertise to manage outsourced expertise
Partners	SANGAMO	ethris, CYSTIC FIBROSIS FOUNDATION	LOTUS TISSUE REPAIR	arGEN-X	NIMBUS, Inception Sciences, evotec

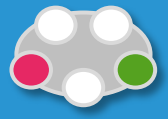
DNA, RNA, and Protein Technology Platforms



Technology platforms	Description
Gene Therapy	• Therapeutic delivery of cDNA for gene correction • Gene editing
MRT	• Reagent mRNA to test mechanism • Therapeutic mRNA
Proteins	• Reagent protein constructs • Therapeutic delivery of novel proteins

Gene Therapy

Transformational Therapy for Monogenic Diseases



	Gene Therapy	MRT	Proteins
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Research Programs	1 Hemophilia A / B Gene Editing 2 Huntington Mutant Allele Repression	3 Cystic Fibrosis 4 Citrullinemia	5 Dystrophic Epidermolysis Bullosa

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Shire – Sangamo Collaboration

Gene Therapy

Goal: *Using Zinc Finger Protein (ZFP) Technology as Disease Therapeutics*

Shire + SANGAMO

Agreement announced in Feb 2012

- Shire innovative approach to address root-cause of life-threatening diseases
- Entry into gene editing therapies

Milestone-driven agreement

- Cross-functional collaboration aimed to deliver multiple therapeutics
- Technology affords exploration of multiple approaches for disease-modifying therapies
- Initial focus on Hemophilia and Huntington Disease

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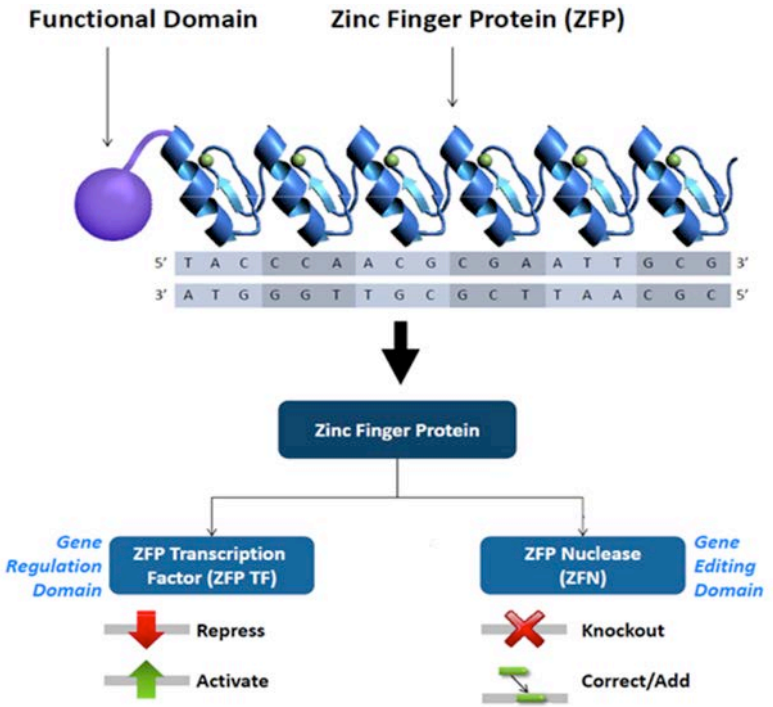
Engineered ZFPs Enables Sequence Specificity and Function

ZFP attached to a functional domain or nuclease

- Regulation of target gene expression (up-regulation or repression)
- Double strand break in the DNA (gene disruption or correction)



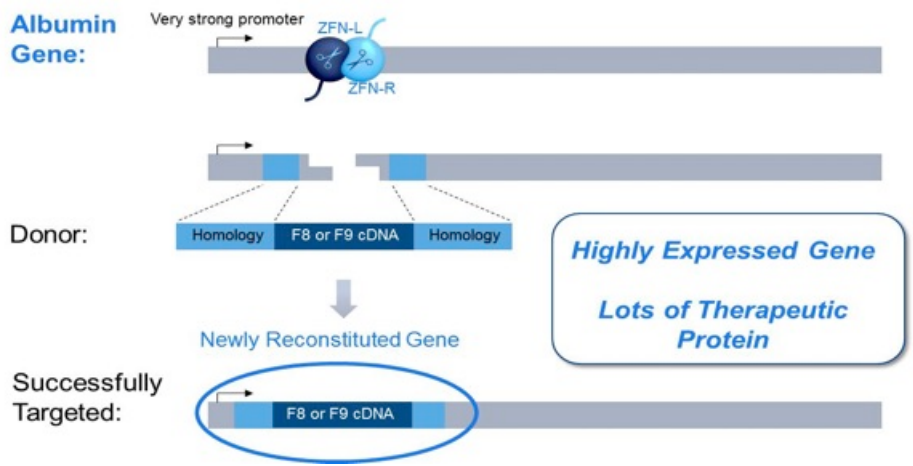
Gene Therapy in Albumin
Safe Harbor Locus: Factor VIII & Factor IX

Gene Therapy

DISEASE

- Rare hereditary disorder in which the ability of patients' blood to clot is impaired due to impaired FIX or FVIII production – leads to excessive and uncontrolled internal bleeding, pain and eventual permanent damage to joints and muscles
- **Epidemiology:** 1 / 5000 male births (~8 out of 10 people who have hemophilia have type A)
- **Disease severity:** severe, moderate, mild – dependent on percentage of FVIII / FIX level in blood, (<1%, 1-5%, >5%)

MECHANISM



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1 Systemic Delivery of ZFP Therapeutics® via AAV Vectors

Gene Therapy

ZFN Pair and Corrective Gene

ZFN

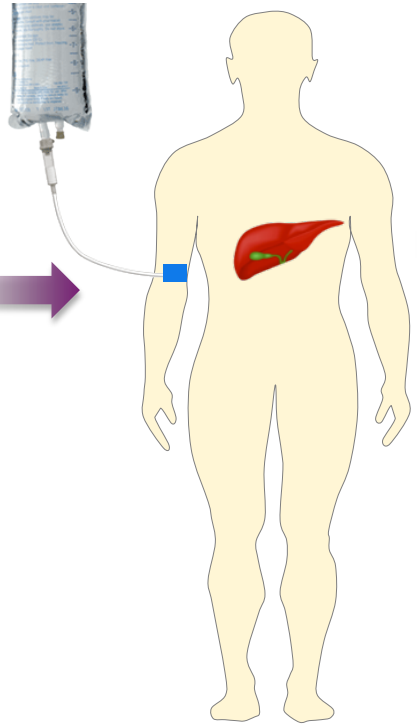
ZFN

Homology | Corrective Gene | Homology

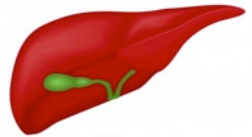
Nucleic Acids Coding for ZFNs and Corrective Gene in AAV Vectors

AAV Vectors

Peripheral IV Administration

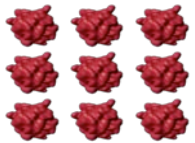


AAV Traffics to Liver And Permanently Corrects Gene



Liver Cells Secrete Corrected Protein

In Vivo **Protein Replacement (e.g. Factor IX)**

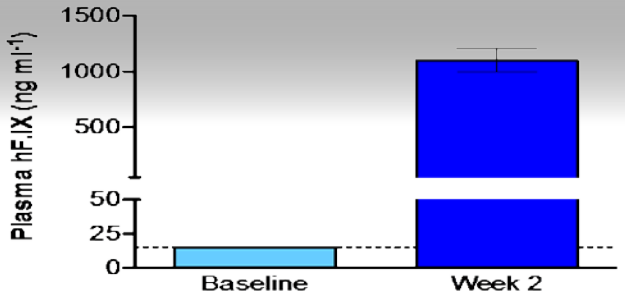


Factor IX Gene Therapy Development Candidate for Hemophilia B: Murine POC

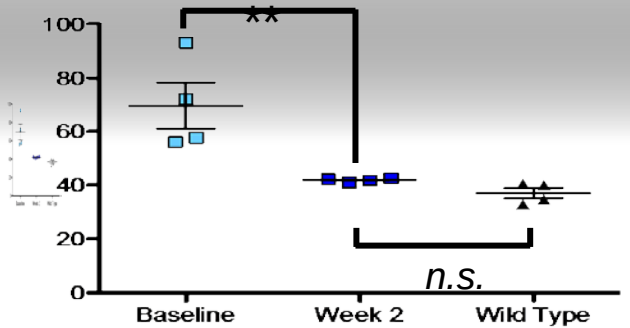
1

Gene Therapy

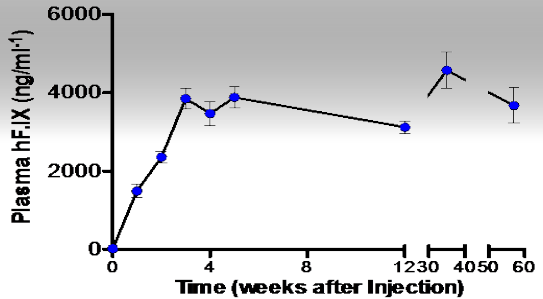
Factor 9 Expression Elevated



Clotting Time Reduced



Duration of Expression Beyond 60 Weeks



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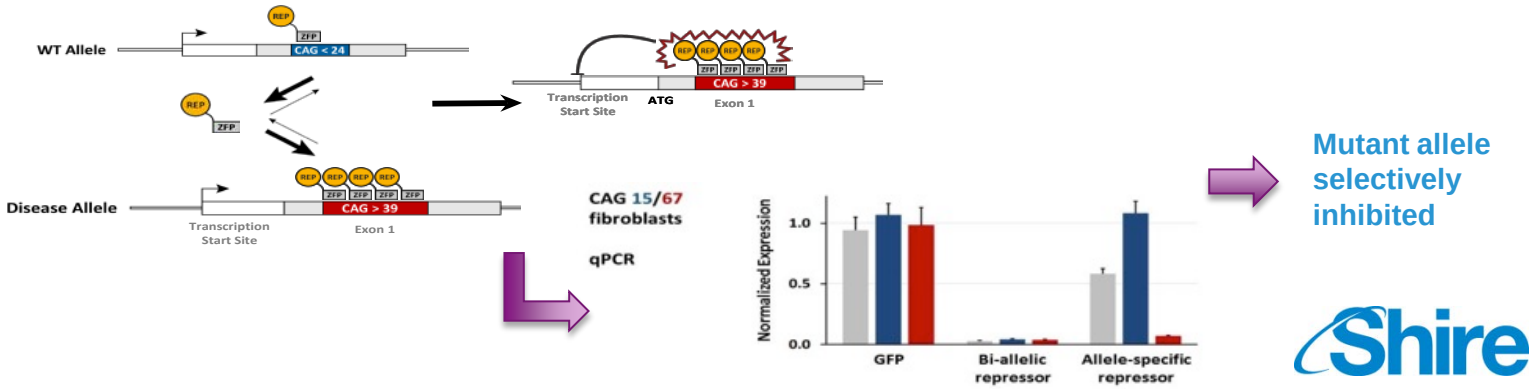
2 Huntington's Disease: Selective Inhibition of Disease Causing Mutation

Gene Therapy

DISEASE

- Huntington's disease is an autosomal dominant neurodegenerative disease characterized by cognitive, behavioral and motor dysfunction. It is a progressive disease initiating typically at mid-life, with an average death 15 years after onset.
- Caused by expansion of a CAG nucleotide repeat within the first exon of the huntington gene causing a misfolding and pathologic conformation of the huntington protein
- **Epidemiology**: 8 / 100,000 (prevalence)

MECHANISM



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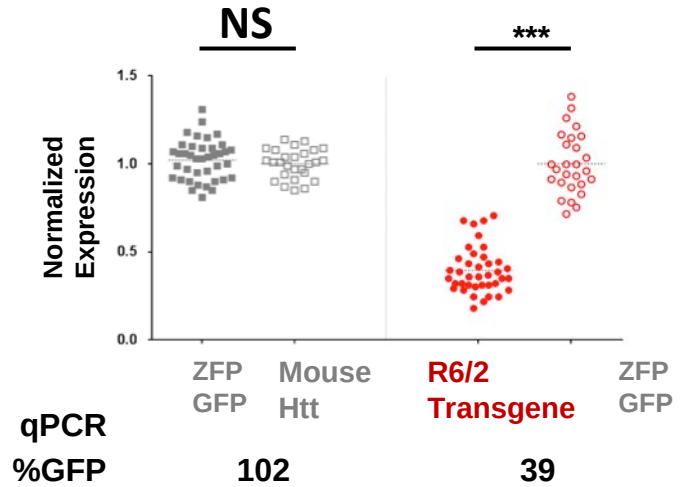
Huntington's Disease Gene Therapy: Murine POC

Gene Therapy

CURRENT DATA

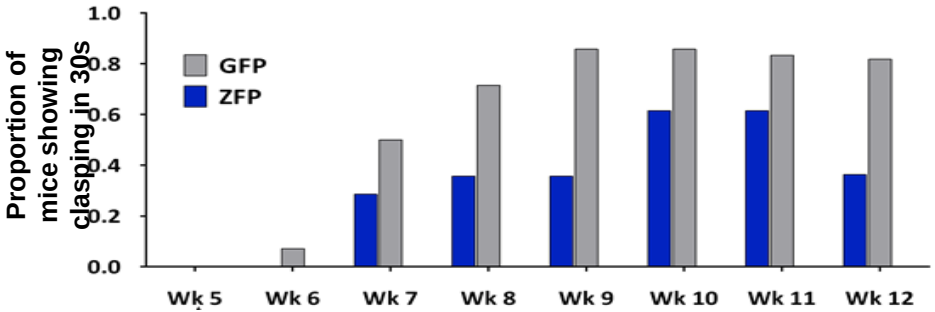
61% knock-down of HD mutant allele in ZFP-treated striata 7 weeks after injection



qPCR %GFP: 102 | 39

*** P < 0.001

Reduced clasping (primary motor phenotype) In HD model



AAV-ZFP delivery

Statistical longitudinal analysis:
Generalized Estimated Equation (GEE)
* GFP vs. ZFP = OR 2.4, p = 0.015

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mRNA Replacement Therapy (MRT)

MRT for Monogenic Diseases

	Gene Therapy	MRT	Proteins
Description	Therapeutic delivery of cDNA for gene correction Gene editing	Reagent mRNA to test mechanism Therapeutic mRNA	Reagent protein constructs Therapeutic delivery of novel proteins
Partners	SANGAMO	ethris; CYSTIC FIBROSIS FOUNDATION	LOTUS TISSUE REPAIR
Research Programs	1 Hemophilia A / B Gene Editing 2 Huntington Mutant Allele Repression	3 Cystic Fibrosis 4 Citrullinemia	5 Dystrophic Epidermolysis Bullosa

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mRNA Therapeutics Platform Overview

MRT

Transformational Technology	• Novel therapeutic – Messenger RNA designed to enable the *in vivo* production of both intracellular and secreted proteins – ability to treat diseases that cannot be addressed with current technologies
Broad Applicability	• As patient's own cells produce endogenous protein, downstream processes (e.g., glycosylation, protein processing and trafficking) remain unaffected • Unlike gene therapy, does not alter the genome • Potent, dose-dependent pharmacology is reversible upon cessation of treatment in animal models
Proof-of-Principle In Multiple Disease Models	• Rapid normalization of clinical biomarkers in liver disease models • Successful delivery of therapeutic protein to lungs via nebulization in pulmonary model • Successful delivery of mRNA in mouse models via intrathecal, intra-ocular and intra-articular administration; efficient production of therapeutic antibodies
Scalable Manufacturing In Place	• "Plug-and-play" platform with ability to use same reagents, same cell-free production process and same proprietary delivery vehicle – rapid, cost-effective, small footprint manufacturing
Other	• Protected by extensive IP portfolio: 26 patent families & 70+ pending applications • Repeat dosing treatment algorithm – no need to define new commercial model (e.g., gene therapy "one-and-done")

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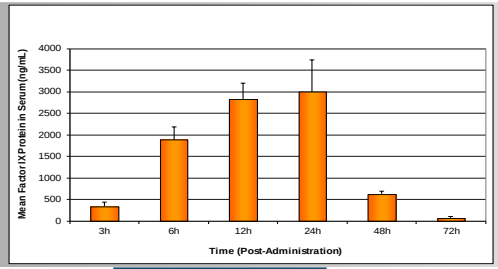
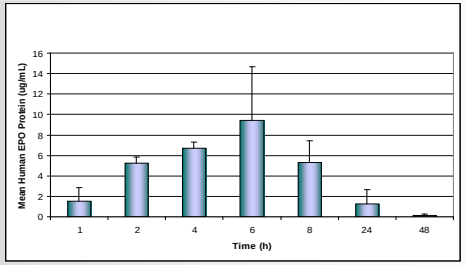
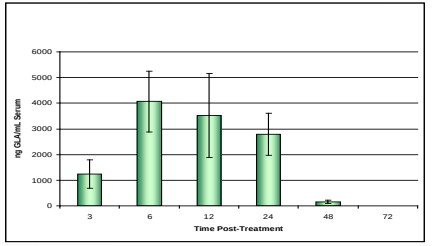
MRT has demonstrated Potential for Broad Therapeutic Applicability

MRT

Proteins produced systemically





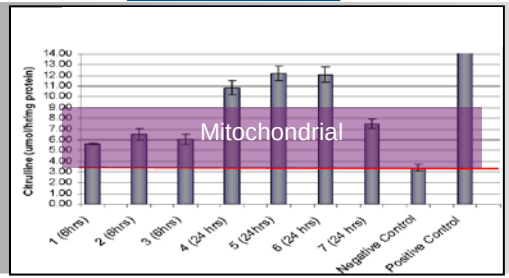


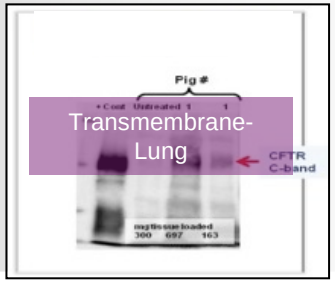
Factor IX | EPO | AGAL

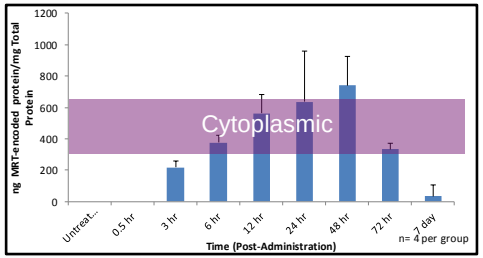
MRT Technology

OTC | CFTR | ASS1

Proteins produced locally







MRT demonstrated across species:
Mouse, Rat, Rabbit, Pig, Non-human Primate

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3 MRT CFTR: Development Candidate to Treat Cystic Fibrosis

MRT

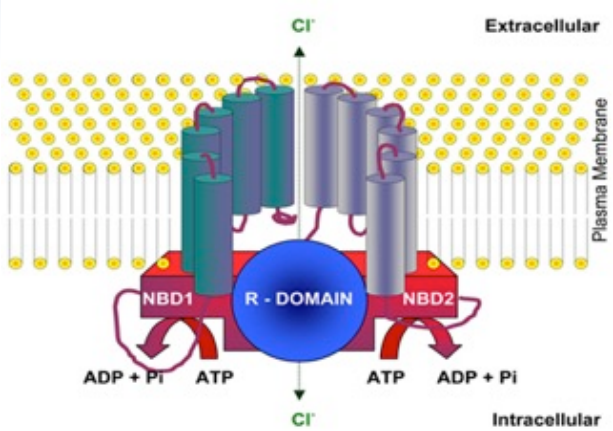
DISEASE

- Autosomal recessive disorder
- DF508 is most common mutation (>70% of patient population)
- Results in improper folding and mis-trafficking of protein away from membrane surface
- Results in clogging of the airways due to mucus build-up

INCIDENCE / PREVALENCE & TREATMENT OPTIONS

- ~60,000 Patients in US and EU
- Recent treatments focus on small subset of patients
- Significant unmet medical need remains

Human CFTR Protein



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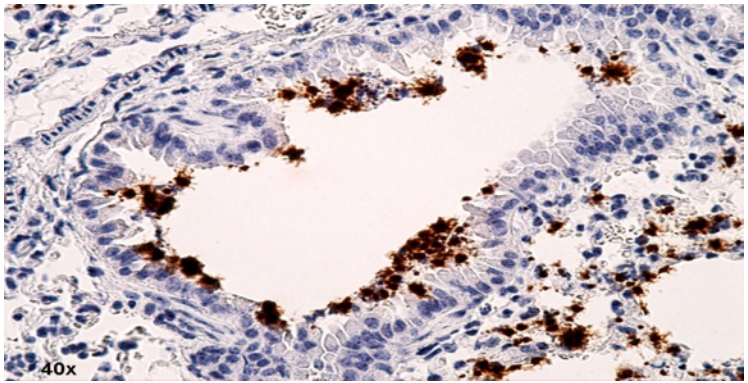
3 Pulmonary Delivery: Functional Translation of CFTR MRT *In Vitro* and *In Vivo* in mice

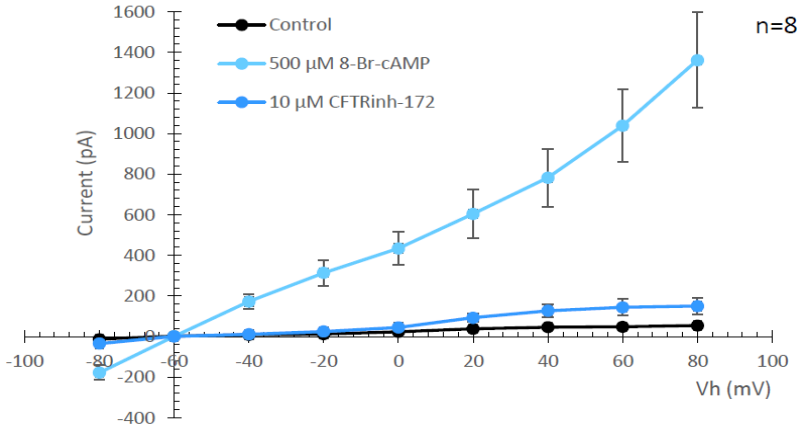
MRT

Nanoparticle delivered hCFTR mRNA can be observed in target epithelial cells *in vivo*[1]…



[1]High magnification (40x) representation of i*n situ* hybridization analysis of lungs from CFTR KO mice treated with hCFTR mRNA nanoparticles. hCFTR mRNA is observed in apical cytoplasm of target epithelial cells within bronchus. Tissues were harvested 24 hours post-administration.

…and creates functional ion channels *in vitro*[2]



[2]Current-voltage plot comparing chloride ion-generated current of various treated HEK293T cells 24 hours after transfection of hCFTR mRNA. The light blue represents cells that have been transfected with hCFTR mRNA 24 hours prior, followed by treatment with activator 8-Br-cAMP (4 min prior to analysis). The dark blue line represents similarly treated cells which were subjected to further exposure of 10 mM $CFTR_{inh}$-172. The black line represents untreated HEK 293T cells (untreated).

Shire

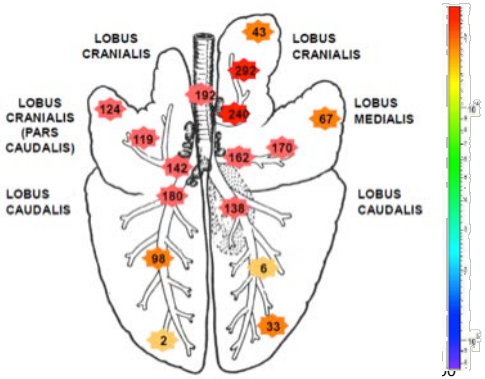
3 Animal Proof-of-Principle for Lung Delivery of CFTR Shows Broad Biodistribution of Functional Protein

MRT

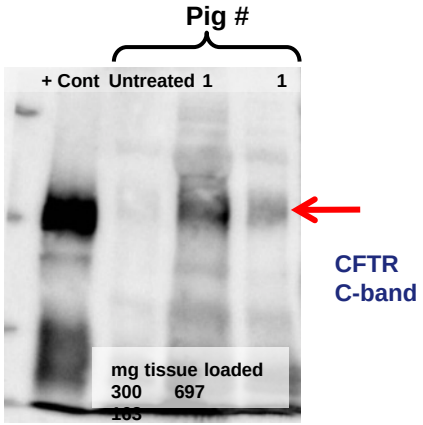
MRT aerosolized for delivery to Lung epithelia

Firefly luciferase (FFL) MRT used as a measure of biodistribution in pig lung tissue

Dorsal View of the Pig Lung



CFTR expression detected in FFL + lung tissue



Demonstration of exogenous expression of CFTR in a large animal model system

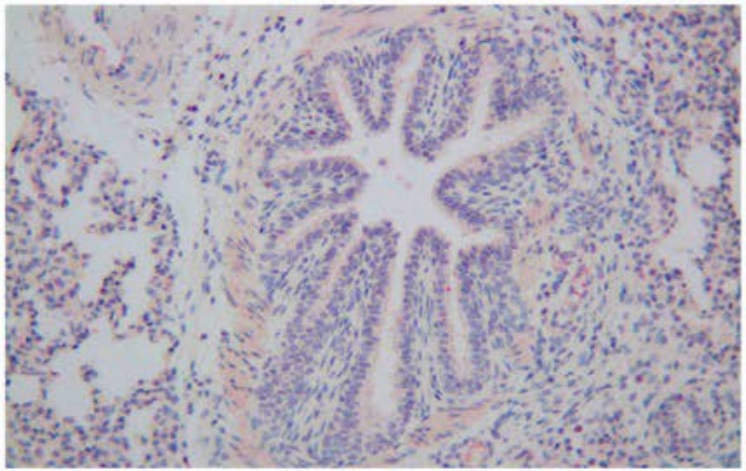
Shire

3 IHC in Normal Pig Lung: Anti-hCFTR Antibody Detection of MRT-Derived hCFTR

MRT

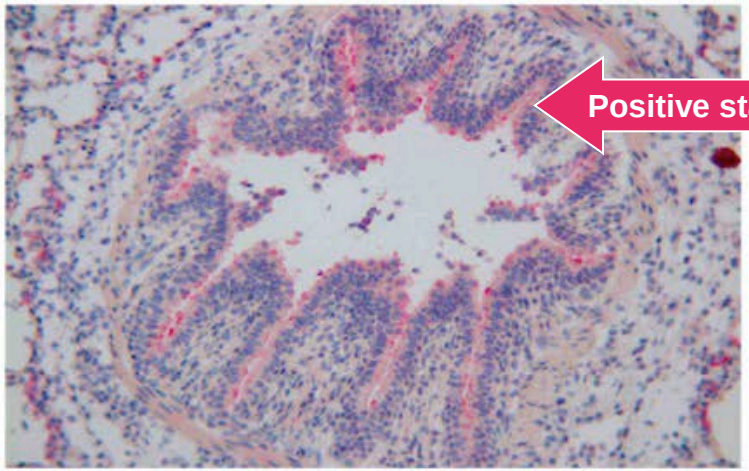
Immunohistochemistry images of one representative pig from either vehicle treated (A) or 10 mg human CFTR mRNA dose group (B)

A)



Vehicle

B)



10 mg human CFTR mRNA

Shire

3 Summary of Pulmonary Delivery Results

- CFTR MRT offers potential for disease modification in an area of significant unmet medical need
- Pulmonary delivery and expression of hCFTR:FFL to the porcine lung by nebulized mRNA formulation was demonstrated
  - Tissue regions with expression of Luciferase also co-expressed hCFTR
    - Luciferase negative regions lacked hCFTR expression
  - Provides evidence that target lung tissue, i.e. bronchial epithelial cells, expresses hCFTR following mRNA delivery
- Tolerance to 5 doses at weekly intervals in pigs demonstrated
  - No tissue pathology detected
  - No adverse clinical signs observed
  - No increase in liver enzymes or inflammatory cytokines detected
- Early development to date has demonstrated:
  - Strong preclinical data package
  - Clear development strategy

Shire

4 MRT ASS1: Development Candidate to Treat Citrullinemia

MRT

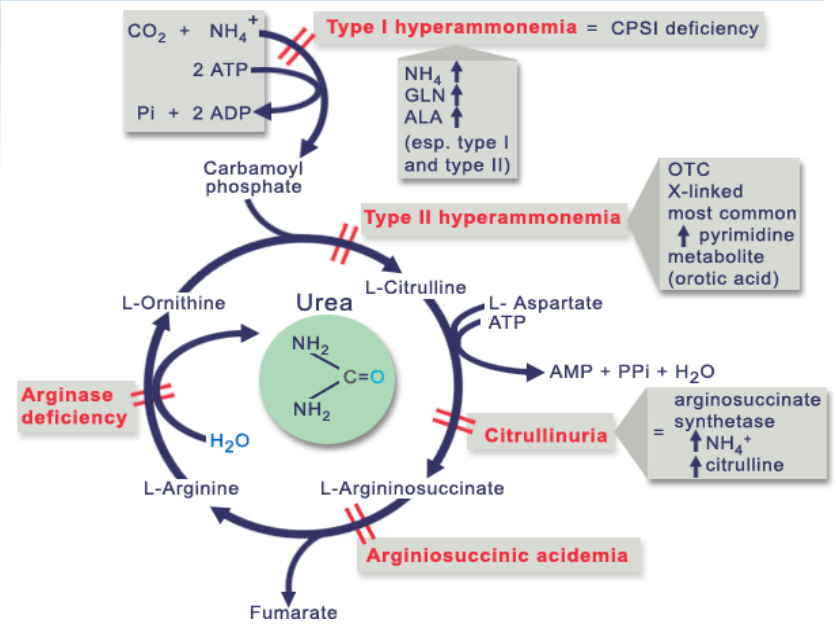
DISEASE

- Citrullenemia is an autosomal recessive metabolic disorder
- Due to mutations in argininosuccinate synthetase (ASS1)
- ~14% of all urea cycle disorders
- Results in high levels of plasma ammonia, leading to lethargy, vomiting, seizures, and failure to thrive

INCIDENCE / PREVALENCE & TREATMENT OPTIONS

- 1: 57,000 live births
- Expressed in liver and kidney
- No disease modifying therapies available

Human urea cycle pathway



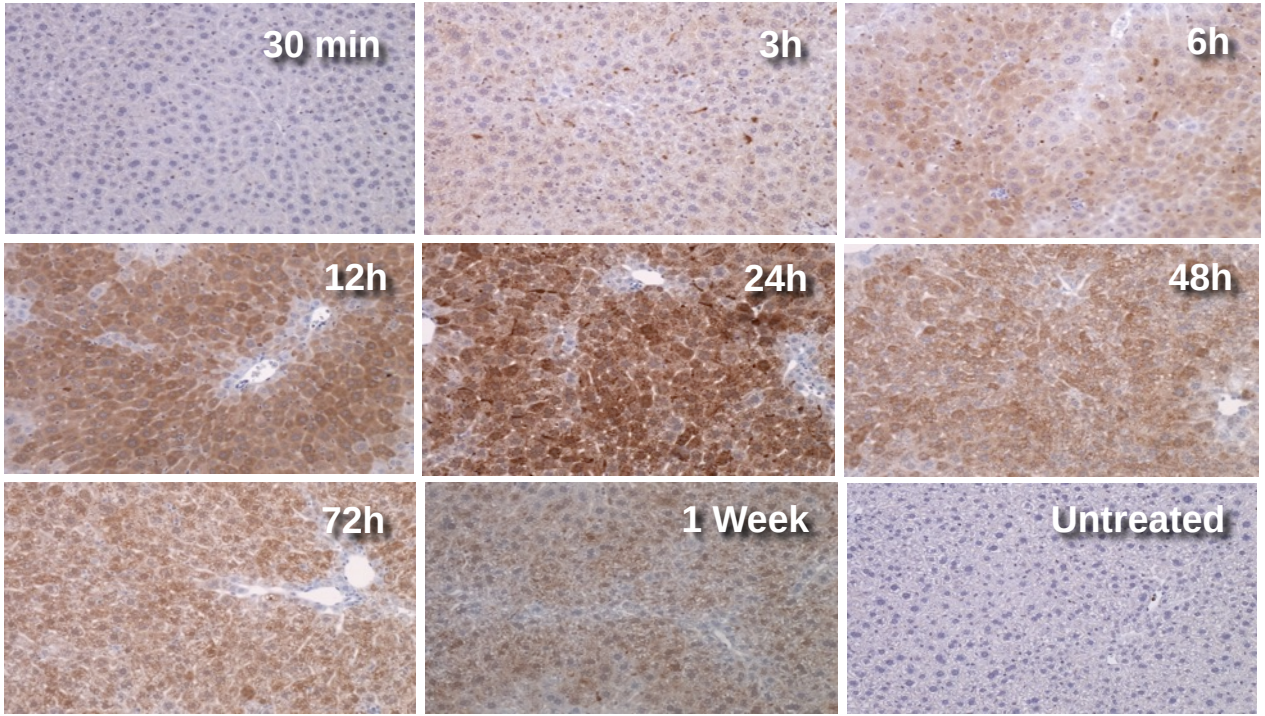
Shire

4 Immunohistochemical (IHC) Detection of Human ASS1 Protein Encoded by MRT

MRT

Pharmacokinetic profile studied after single dose of MRT

1.0 mg / kg MRT, single dose, IV, WT mice



- IHC staining of MRT-encoded protein
- Positive staining in hepatocytes and Kupffer cells
- Widespread distribution in liver
- Protein detectable up to 1 week post-dose

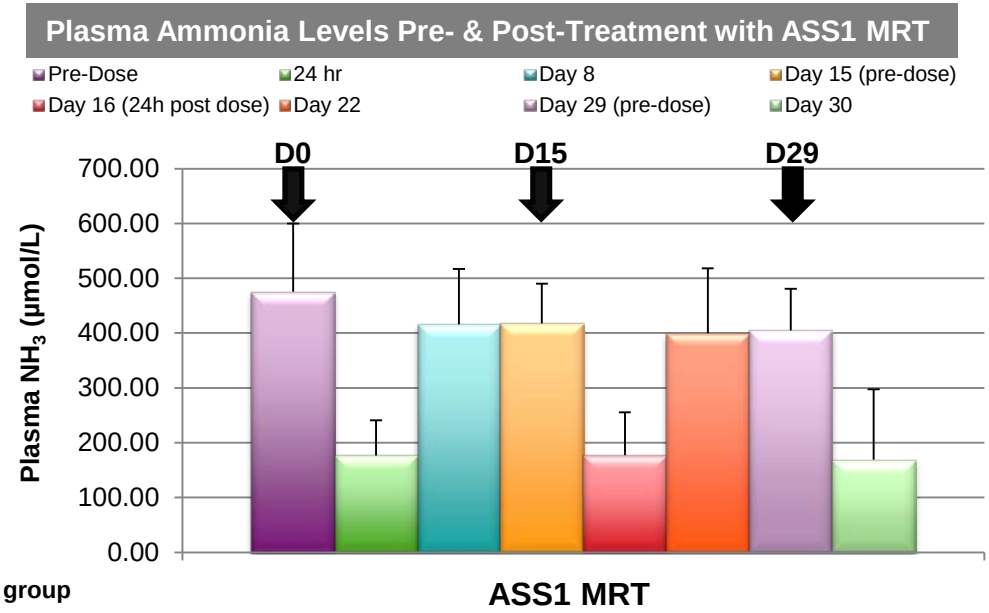
Shire

4 Evidence of Efficacy in Citrullinemia Mouse Model

MRT

Initial efficacy study performed in ASS1 deficiency model; hypomorphic mutation with ~10% of normal ASS1 activity

- Single dose (1.0 mg / kg) of either ASS1 mRNA loaded LNP or empty LNP (control)
- Measure plasma ammonia levels pre- & post-dose
- Compare model with WT levels



N=6 / group

Shire

4 Summary of Intravenous MRT for Urea Cycle Diseases

- We have focused initially on urea cycle defects for IV MRT as they allow rapid clinical proof-of-concept and compelling market opportunity
  - Clinical path clarity
  - High unmet need in a sizeable market
  - Clear MRT advantage

- Mouse model results demonstrate approximately 50-100% of normal liver ASS1 and ammonia reduction following MRT
  - Human ASS1 mutational spectrum in Citrullinemia suggests activity >10% would be disease-modifying

Shire

mRNA Replacement Therapy (MRT)

MRT for Monogenic Diseases

	Gene Therapy	MRT	Proteins
Description	Therapeutic delivery of cDNA for gene correction Gene editing	Reagent mRNA to test mechanism Therapeutic mRNA	Reagent protein constructs Therapeutic delivery of novel proteins
Partners	SANGAMO	ethris CYSTIC FIBROSIS FOUNDATION	LOTUS TISSUE REPAIR
Research Programs	1 Hemophilia A / B Gene Editing 2 Huntington Mutant Allele Repression	3 Cystic Fibrosis 4 Citrullinemia	5 Dystrophic Epidermolysis Bullosa

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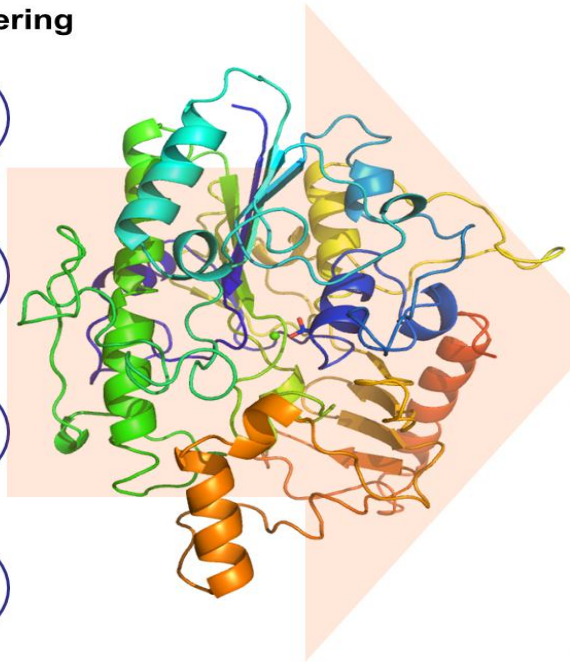
Novel Therapeutics via Protein Engineering

Proteins

Protein Engineering

- Amino Acid Sequence Optimization
- Post Translational Modification
- Domain Selectivity
- Fusion Proteins



- Improve Efficacy
- Enhance Drug Bioavailability
- Structure-based Drug Design
- Reduce Cost of Goods
- Novel Drug Design
- Lifecycle Extension

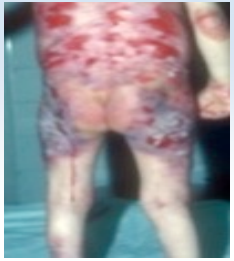
Shire

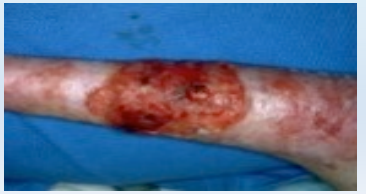
Human rCollagen 7: Development Candidate to Treat Dystrophic Epidermolysis Bullosa (DEB)

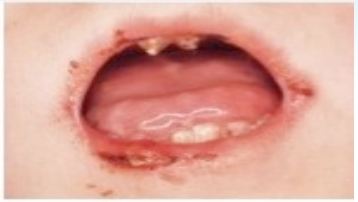
Proteins

DISEASE

- Rare genetic disease: fragile blistering skin, deformed limbs, numerous co-morbidities, early death
- Mutations in gene encoding Collagen Type VII (C7): autosomal dominant (DDEB) & autosomal recessive (RDEB)
- Aberrant function / absence of C7 at dermal-epidermal junction affect attachment of epidermis to dermis







INCIDENCE / PREVALENCE & TREATMENT OPTIONS

- ~5000 diagnosed patients: 2,000 addressable patients (base case) with IV protein replacement therapy; all genders and races affected
- No disease modifying treatment available: only recurrent, symptomatic treatments; painful and costly disease

HYPOTHESIS

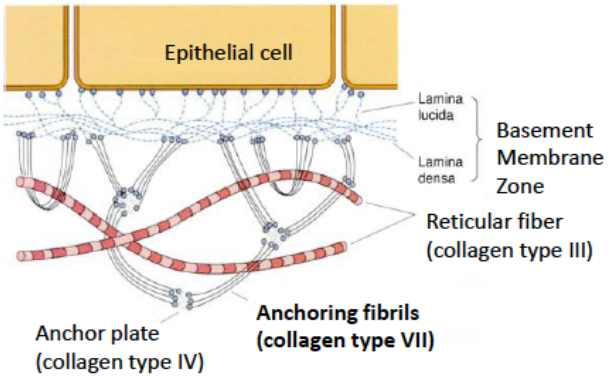
IV rC7 as protein replacement therapy will:

- Reach the lamina densa at dermal-epidermal surfaces
- Incorporate into matrix to normalize function
- Correct blistering abnormalities and complications

5 rC7 Forms Anchoring Fibrils Critical for Dermal-Epidermal Adhesion in Animal Models

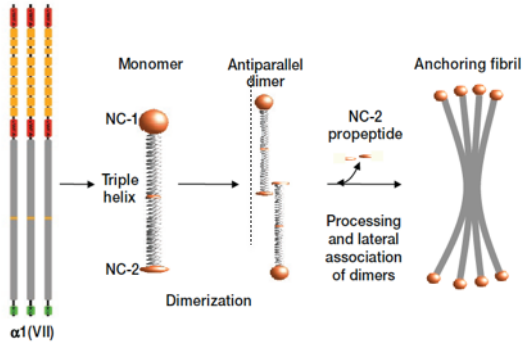
Proteins

- C7 forms anchoring fibrils, attachment structures in the basement membrane zone (BMZ) responsible for adhering the epidermis to the dermis
- Loss-of-function mutations in COL7A1 lead to abnormal, decreased or absent anchoring fibrils

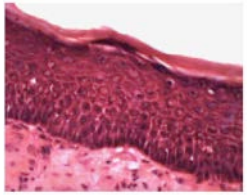


Recombinant C7 (rC7) incorporates into basement membrane zone forming anchoring fibrils, reversing separation of dermal-epidermal junction in animal models

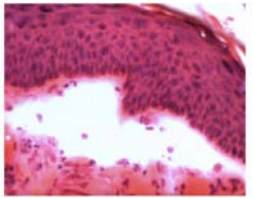
Formation of anchoring fibrils



Normal



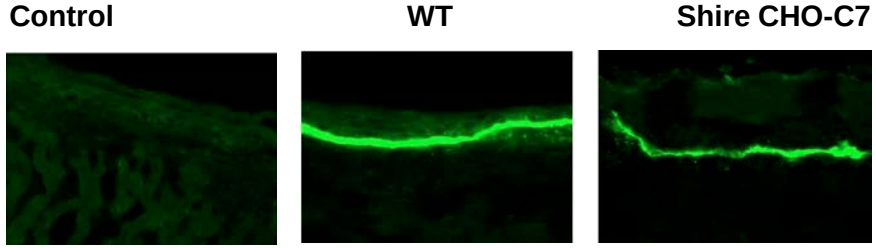
DEB Recessive



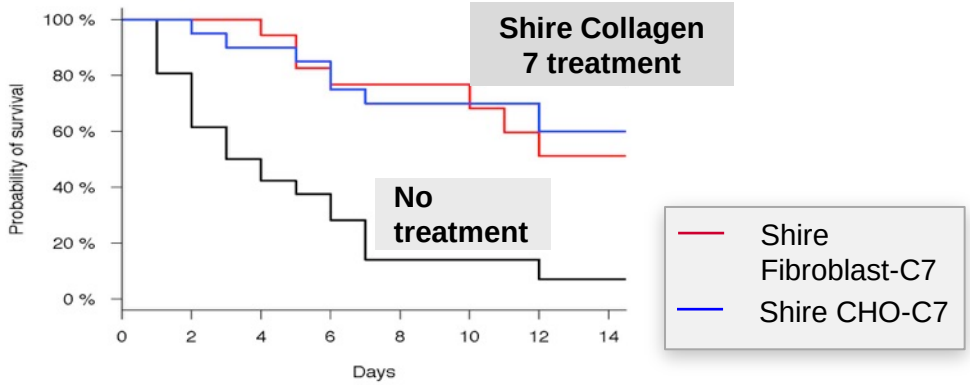
5 Tissue Distribution of Shire Collagen 7

Proteins

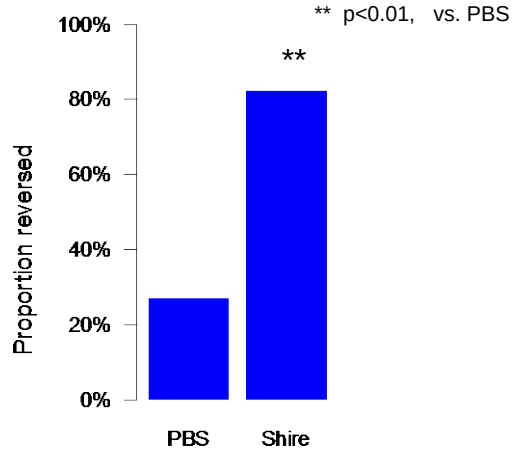
Shire Collagen 7 was Distributed to the Proper Location within the Dermal-Epidermal Junction in Multiple Tissues in Mouse Models

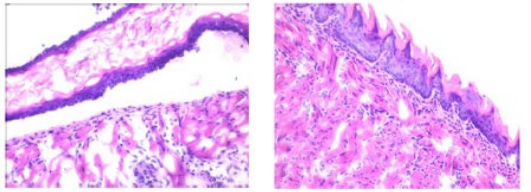


Mice Treated with a Single Injection of Recombinant Collagen 7 Lived Longer



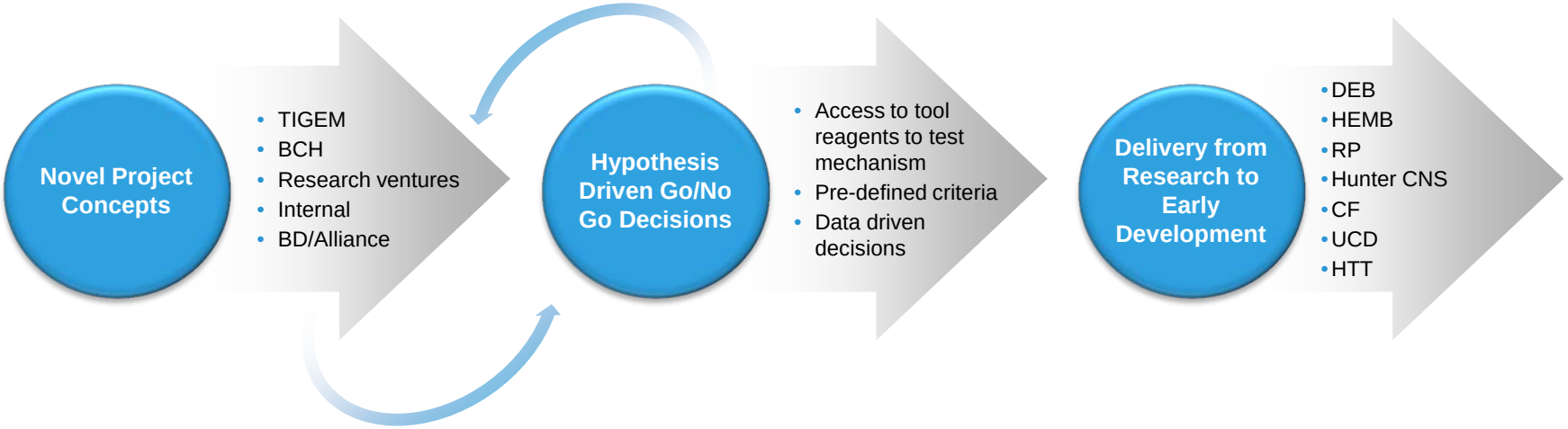
Shire Collagen 7 Reversed Dermal-Epidermal Separation in a Dose-Dependent Manner in Mouse Models





DEB (Control) DEB (Shire Collagen 7)

Research Model for Delivering the Portfolio in Rare Diseases



1. Research portfolio built around high confidence targets in diseases with significant unmet medical need

2. Culture of rapid and clear data driven go/no go decisions

3. Efficient and focused team integrating internal and external flexible model to deliver early alignment with process and clinical development

4. ~26 active programs with a goal of delivering 3 programs from research to early development per year with a focus on quick to clinical POC

Shire

Rare Diseases:

GI / Metabolic

Ciara Kennedy, PhD, MBA – Head of Cholestatic Liver Disease
David Piccoli, MD – Chief of Gastroenterology, Hepatology & Nutrition, Children's Hospital Of Philadelphia

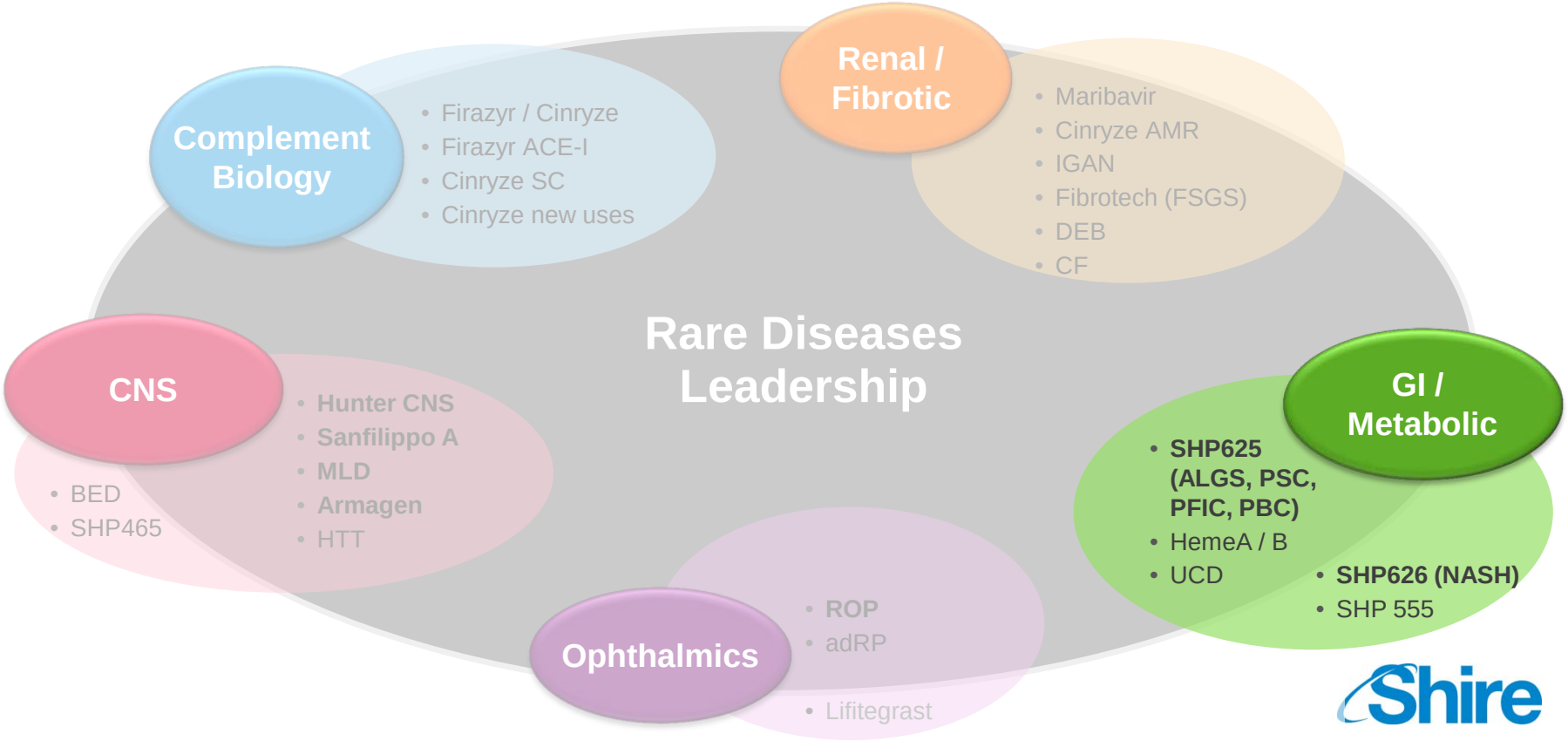
Our purpose
We enable people with life-altering conditions to lead better lives.

Shire

Today's R&D sessions

Topic	Speaker	Time (EST)
Research Overview and Technology Platforms *mRNA, Protein Replacement, Gene Therapy, Antibody Platforms*	Albert Seymour, PhD	9:25-10:00
Rare Diseases: GI / Metabolic *SHP625 (LUM001), SHP626 (LUM002)*	Ciara Kennedy, PhD *David Piccoli, MD*	10:00-10.45
Rare Diseases: Ophthalmics *SHP607 / ROP, SHP630 / BIKAM*	Norman Barton, MD, PhD	11:15-11:45
Rare Diseases: Complement Biology and Renal / Fibrotic *SHP616 / Cinryze new uses*	Howard Mayer, MD	1:15-1:30
Rare Diseases: CNS *SHP609 / Hunter CNS, SHP610 / Sanfilippo A, SHP611 / MLD, Armagen*	Howard Mayer, MD	1:30-2:00
Late-Stage Update *SHP606 / Lifitegrast, BED, SHP465 / ADHD*	Howard Mayer, MD Randall Brenner *Joe Tauber, MD*	2:00-2:45

Multiple Rare Diseases Programs in GI / Metabolic



Cholestasis is Present in Several Adult and Pediatric Diseases

Cholestasis is characterized by:

- Impaired bile flow
- Reduction of bile in intestine
- Retention of bile in liver and tissues
- Elevated serum bile acids

Extra-hepatic causes

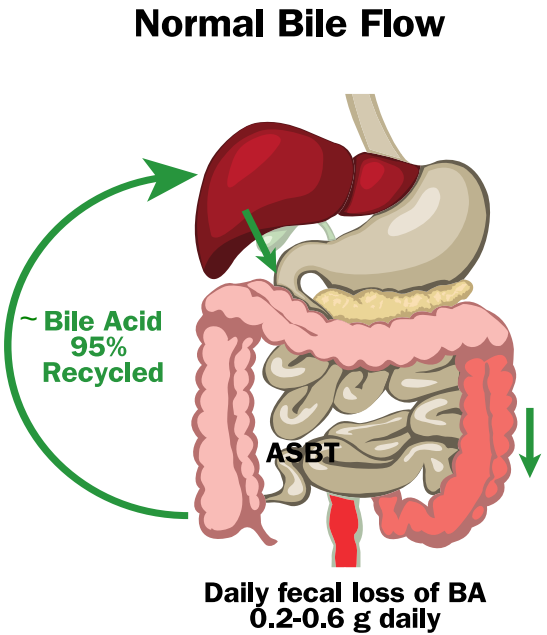
- Stones
- Cysts
- Bile duct tumors

Intrahepatic causes

- Pregnancy
- Viral hepatitis
- Alcoholic liver disease
- Primary sclerosing cholangitis (PSC)
- Primary biliary cirrhosis (PBC)
- Congenital diseases (ALGS, PFIC, Biliary Atresia)

The Role of Bile Acids

- Bile acids are synthesized in the liver from cholesterol
  - Recovered from GI tract via the apical sodium bile acids transporter (ASBT) and returned to liver
  - Facilitate digestion and absorption of dietary fats and fat-soluble vitamins
  - Regulate lipid and glucose metabolism
- Excess bile acids are associated with liver damage and pruritus
- ASBT inhibition:
  - Reduces serum bile acid levels
  - Decreases serum and hepatic cholesterol
  - Lowers plasma glucose
  - Reduces insulin resistance



SHP625 (LUM001): Cholestatic Liver Disease

Preclinical	Phase 1	Phase 2		Phase 3	Registration
26 Research Programs	**SHP611** MLD (Ph 1/2)	**SHP602** Iron overload (clinical hold)	**SHP616 (Cinryze)** Acute Antibody Mediated Rejection	**Firazyr** ACE inhibitor-induced AE	**XAGRID® (Japan)** Thrombocythaemia *(Approved 3Q 2014)*
SHP619 Duchenne's Muscular Dystrophy	**SHP616 (Cinryze SC)** HAE Prophylaxis	**SHP610** Sanfilippo A	**SHP625 (LUM001)** Primary Biliary Cirrhosis	**Firazyr** (Japan) HAE	**VPRIV (Japan)** Gaucher *(Approved 3Q 2014)*
TH / GCH1 Gene Pod Parkinson's Subset	**SHP622** Friedreich's Ataxia	**SHP609** Hunter CNS	**SHP625 (LUM001)** Progressive Familial Intrahepatic Cholestasis	**SHP616 (Cinryze) (Japan)** HAE Prophylaxis	**INTUNIV® (EU)** ADHD
SHP608 Dystrophic E.Bullosa	**SHP627 (FT011)** Focal Segmental Glomerulosclerosis	**SHP607** Prevention of ROP	**SHP625 (LUM001)** Alagille Syndrome	**SHP555 (US)** Chronic Constipation	**LDX** BED
SHP614 IgA Nephropathy	**SHP616 (Cinryze)** Paroxysmal Nocturnal Hemoglobinuria	**SHP620 (Maribavir)** CMV in transplant patients	**SHP625 (LUM001)** Primary Sclerosing Cholangitis	**INTUNIV (Japan)** ADHD	
Armagen Hunter CNS	**SHP616 (Cinryze)** Acute Neuromyelitis Optica	**LDX (Japan)** ADHD		**SHP606 (Lifitegrast)** Dry eye disease	
SHP630 adRP	**SHP626 (LUM002)** Non-Alcoholic Steatohepatitis			**SHP465** ADHD	
SHP624 Heme B Gene Edit					
SHP628 (FT-061) Renal Impairment					

- Complement Biology
- Renal / Transplant
- Ophthalmics
- GI / Metabolic
- CNS
- Rare Diseases Leadership

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SHP625 (LUM001): Novel Therapy with Potential to Address Four Rare Hepatic Conditions

SHP625 (LUM001)
Cholestatic Liver Disease

Significant unmet need

Alagille Syndrome (ALGS)

- Present at 3 months
- Markedly elevated bile acids and cholesterol
- Very intense pruritus
- No approved therapy
- ~13% bile diversion surgery, 21-31% liver transplant
- ~25K prevalence in U.S. / EU

Progressive Familial Intrahepatic Cholestasis (PFIC)

- Present at 3-6 months
- Very intense pruritus
- No approved therapy
- ~35% bile diversion surgery, ~50% liver transplant
- Without surgery, fatal by 2nd decade
- ~13K prevalence in U.S. / EU

Primary Biliary Cirrhosis (PBC)

- >40 years old, 90% female
- ~50% of patients respond to approved therapy (UDCA*)
- Intense pruritus
- Slow progression
- ~275K prevalence U.S. / EU

Primary Sclerosing Cholangitis (PSC)

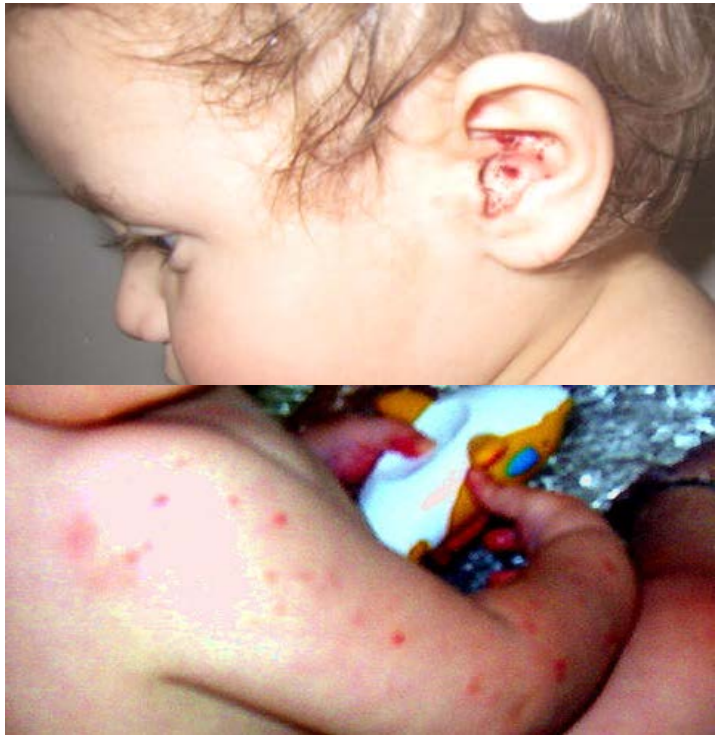
- Mean age at diagnosis: 40 years, 70% Male
- Intense pruritus
- No approved therapy
- Aggressive, life expectancy 8-10 years from diagnosis
- ~60K prevalence in U.S. / EU

Pediatric Adult

Shire

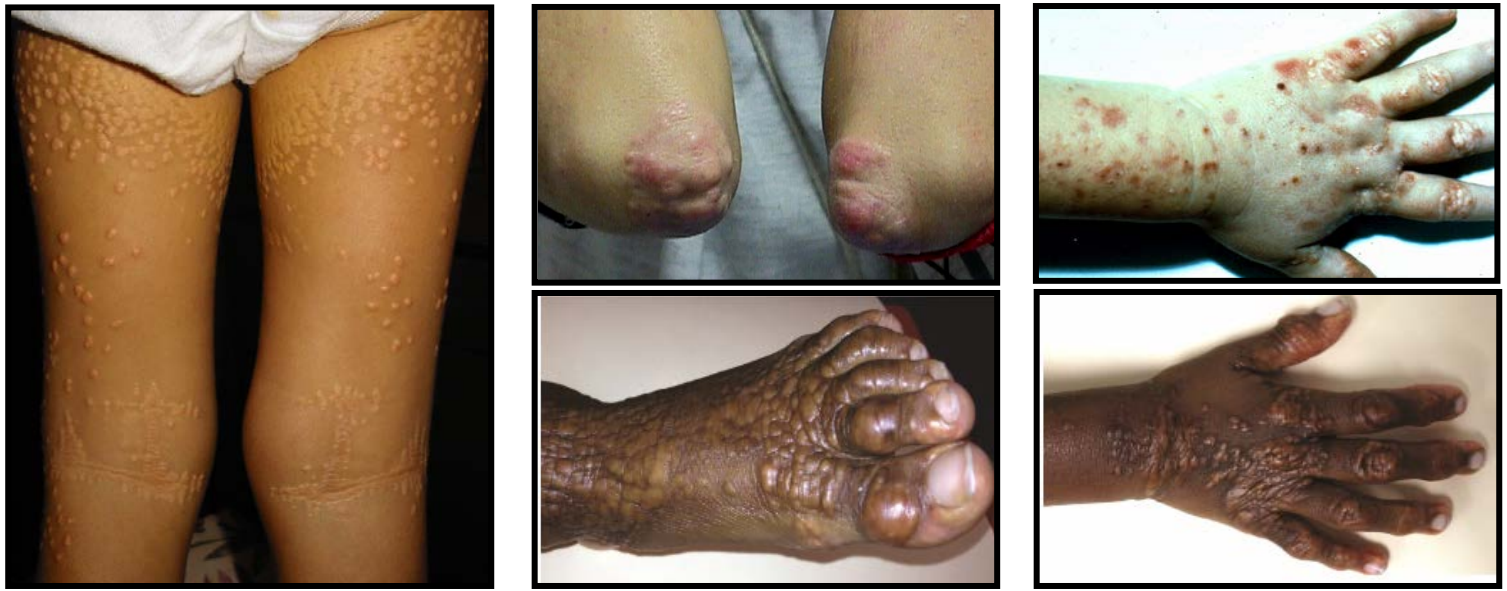
* Ursodeoxycholic acid (UDCA)

Cholestatic Pruritus: Not Simply Itching



John would sleep about 20-40 min at a time, then he would be up with us holding him for 1-2 hours itching. This was all night long.
– Robin (Mother of 2 children with PFIC)

Xanthomathosis
Manifestation of Elevated Cholesterol



In severe cases xanthomas can be “disfiguring” causing distortion of the face or extremities, and “disabling” interfering with function (such as hand use or ability to walk)

Management of Cholestatic Liver Disease

SHP625 (LUM001)
Cholestatic Liver Disease

- Limited options for pharmaceutical management of cholestasis
- UDCA only approved for treatment of PBC
- Bile acid resins can reduce pruritus in some patients
- Rifampicin may alleviate pruritus in some cases
- In a 15 year retrospective review of Alagille syndrome patients from Kings College London; <20% of patients experience relief of pruritus following treatment with UDCA and with cholestyramine:

Treatment Effect	UDCA		Cholestyramine	
	Frequency (n = 40)	Percentage (%)	Frequency (n = 18)	Percentage (%)
None – Some	32	80	15	83.4
Good – Very Good	8	20	3	16.7
Adverse Effects	3	7.5	6	33.3

- Many patients resort to invasive interventions to manage disease

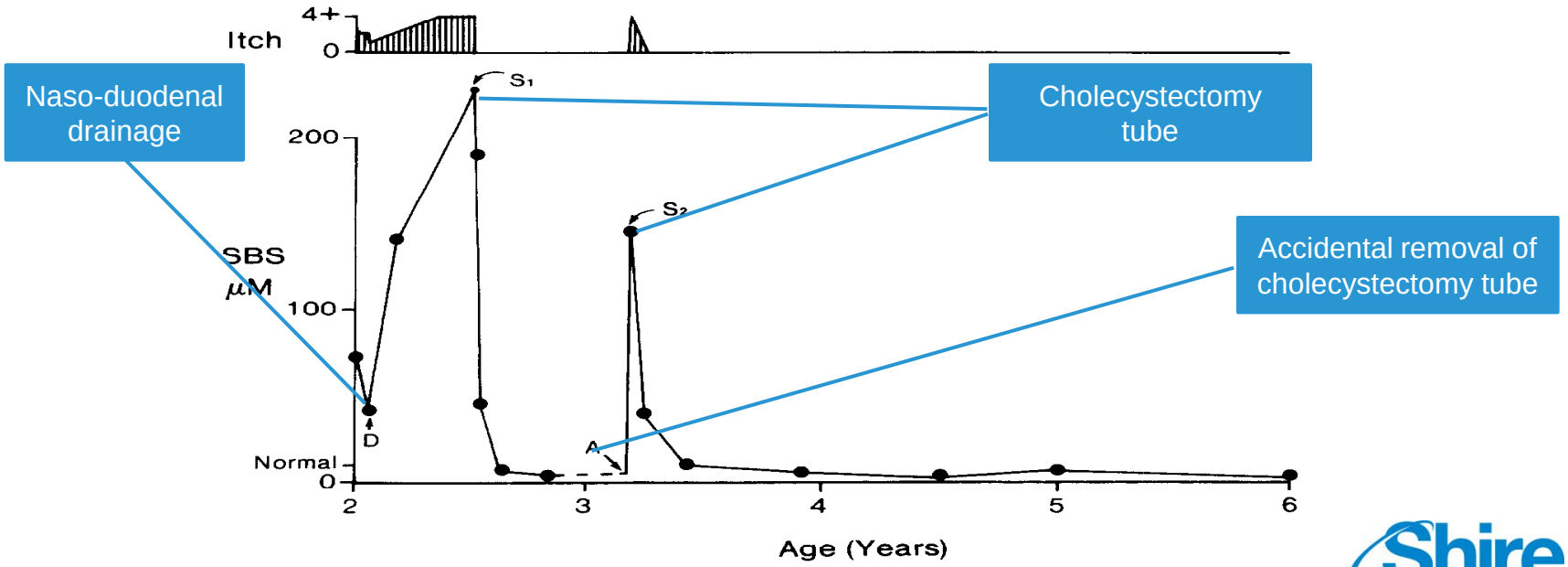
Shire

Kronsten, JPGN (2013); 149-154

Reduction of Serum Bile Acid Levels Associated With Pruritus Control in a Patient with PFIC

SHP625 (LUM001)
Cholestatic Liver Disease

Serum Bile Salt Concentration and Degree of Itch in a PFIC Patient Over a 4-year Course



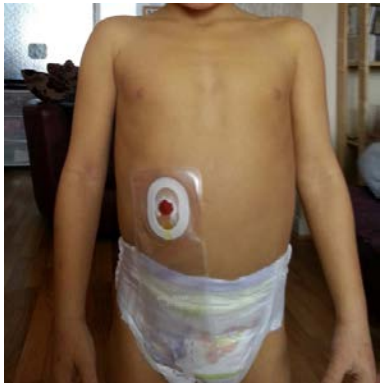
Whitington, Gastroenterology 1988

Lowering Bile Acids Results in Significant Clinical Benefits

SHP625 (LUM001)
Cholestatic Liver Disease

Removing bile acids through surgical intervention:

- ✓ Reduces serum bile acids
- ✓ Improves biochemical markers of liver disease
- ✓ Rapidly reduces itching
- ✓ Slows disease progression
- ✘ Disfiguring and associated with serious complications



ALGS			PFIC		
	Before Surgery(1)	After Surgery(1)		Before Surgery(2)	After Surgery(2)
Bile Acids (μmol/L)	115	28	Bile Acids (μmol/L)	337	11
Bilirubin (mg/dL)	2.4	1.6	Bilirubin (mg/dL)	2.4	1.5
Itching (0 no scratching-4 cutaneous mutilation)	4	1	Itching (0-4)	3	1

BMC Gastroenterology (2008), Hepatology (2002), J Ped Surgery (2012)
(1) Mean
(2) Median

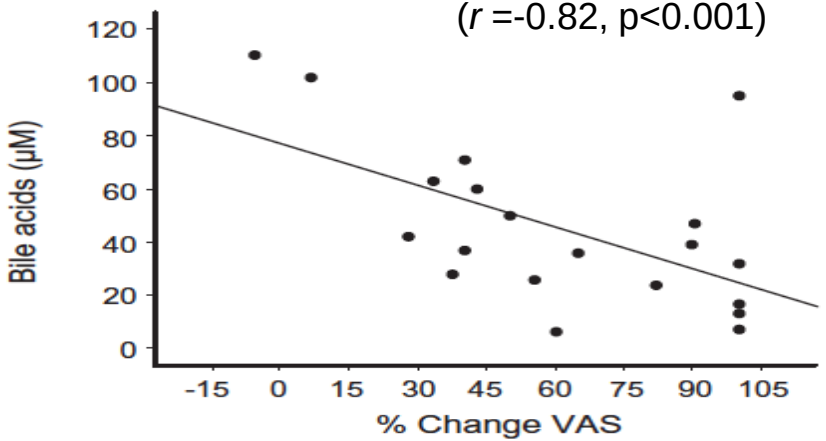
Treatment of Severe Pruritus in Patients With Cholestasis With Extracorporeal Albumin Dialysis *(PBC, PSC, ALGS)*

SHP625 (LUM001)
Cholestatic Liver Disease

Molecular adsorbent recirculating system (MARS) reduces serum bile acid levels and controls pruritus

- 20 patients (12 females), mean age: 51 ± 3.4 years with chronic cholestatic liver disease or chronic liver-graft rejection
- Pruritus assessed with VAS before and after MARS, and 30 days thereafter
- Liver tests, including total bilirubin, ALP, GGT and total bile acid levels were determined

(r =-0.82, p<0.001)



Pares A. Journal of Hepatology 2010

Animal Models of Cholestasis

Partial bile duct ligation (pBDL)

- Mimics the paucity of bile ducts or narrowing of bile ducts observed in clinical cases of cholestasis

MDR2 knockout mouse model

- Model for PFIC3 (MDR2 deficiency)
- Primary sclerosing cholangitis (PSC)

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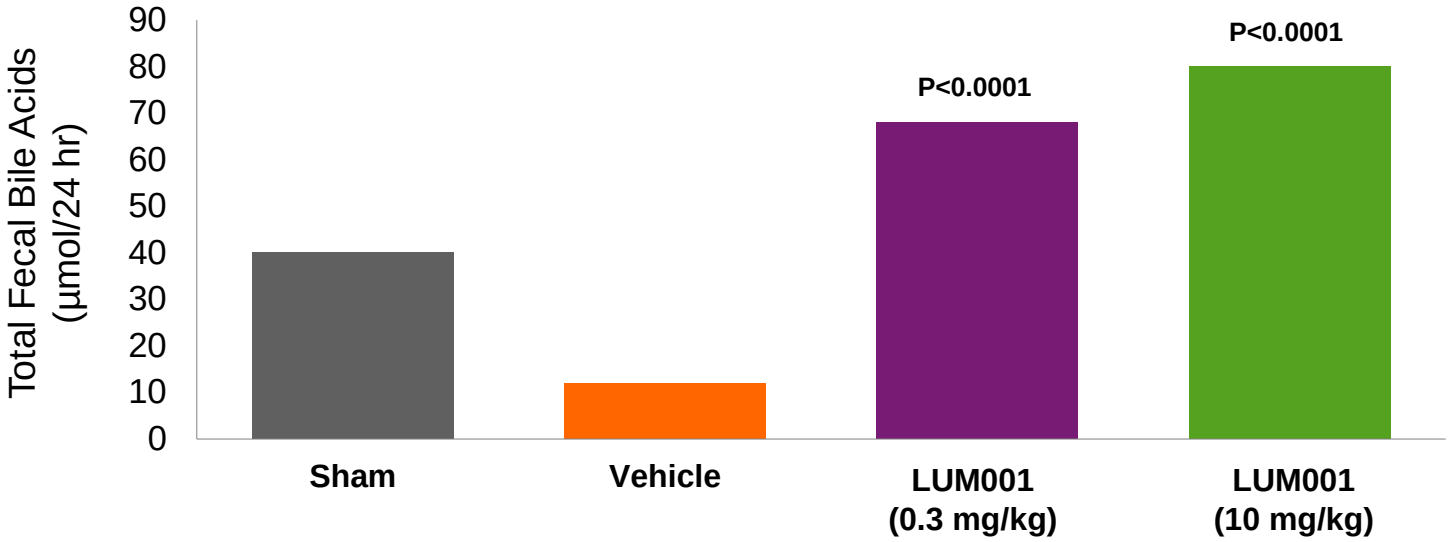
SHP265 (LUM001) Increased Total Fecal Bile Acid Excretion

10 Days of Treatment in Rat Model of Cholestasis

SHP625 (LUM001)
Cholestatic Liver Disease



LUM001 causes a 4.8- and 5.9-fold increase in total FBA after 10 days treatment with 0.3 and 10 mg/kg/d, respectively

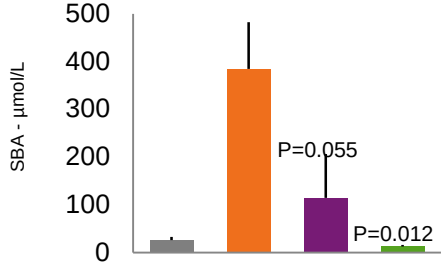
Shire

Data Presented at AASLD

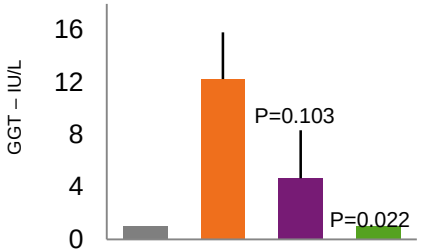
SHP625 (LUM001) Improved Biochemical Markers of Liver Damage *pBDL Rat Cholestasis Model*

SHP625 (LUM001) Cholestatic Liver Disease

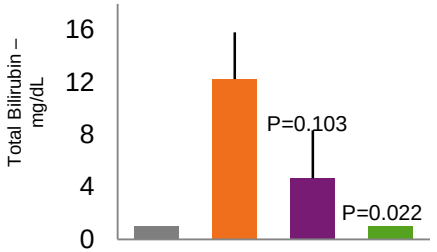
Total Serum Bile Acids



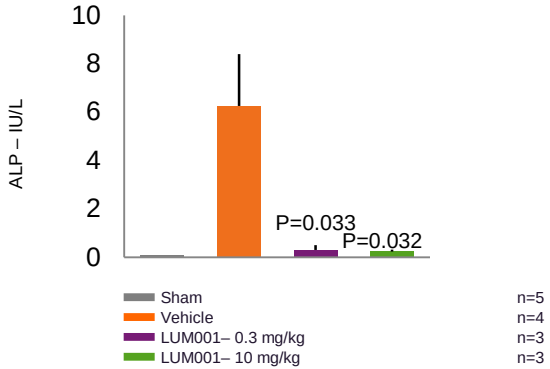
g-Glutamyl Transpeptidase



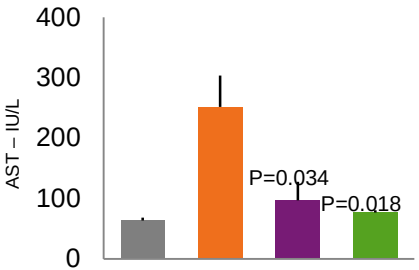
Total Bilirubin



Alkaline Phosphatase

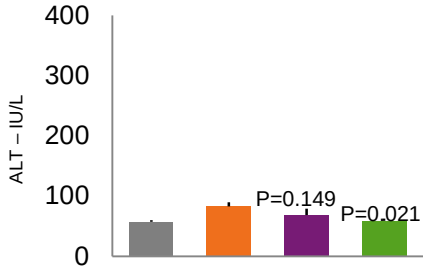


Aspartate Aminotransferase



P value: LUM001-treated vs. Vehicle Group

Alanine Aminotransferase



Shire

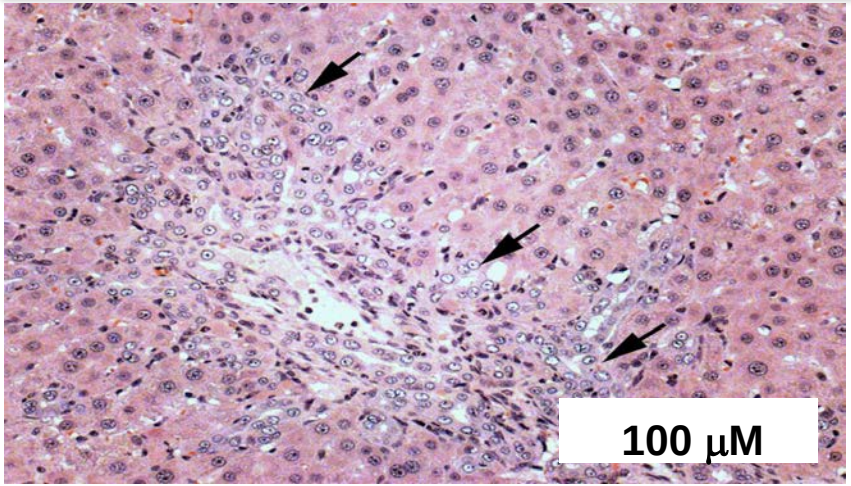
Data Presented at AASLD

SHP625 (LUM001) Reduced Liver Injury

pBDL Rat Cholestasis Model

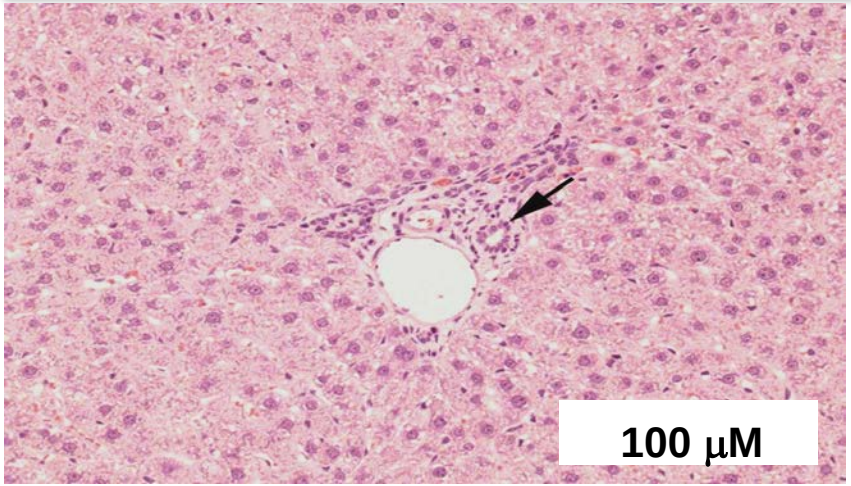
SHP625 (LUM001)
Cholestatic Liver Disease

Vehicle



Moderate bile duct epithelial cell proliferation (arrow), cell necrosis and inflammatory cell infiltration

LUM001 (10 mg/kg)



Normal bile duct morphology within the portal region with minimal epithelial cell proliferation

Shire

Data Presented at AASLD

Animal Models of Cholestasis

Partial bile duct ligation (pBDL)

- Mimics the paucity of bile ducts or narrowing of bile ducts observed in clinical cases of cholestasis

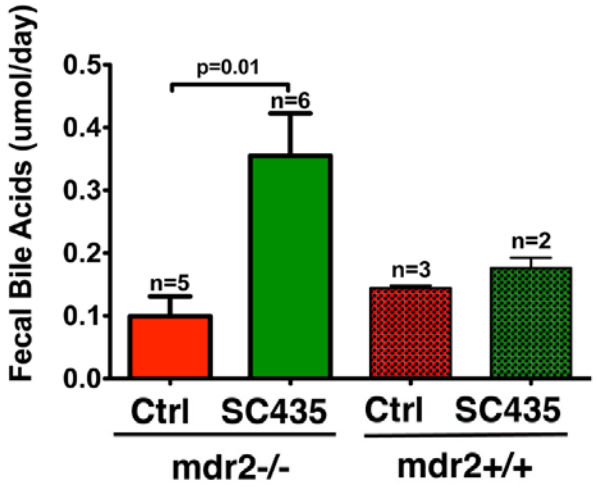
MDR2 knockout mouse model

- Model for PFIC3 (MDR2 deficiency)
- Primary sclerosing cholangitis (PSC)

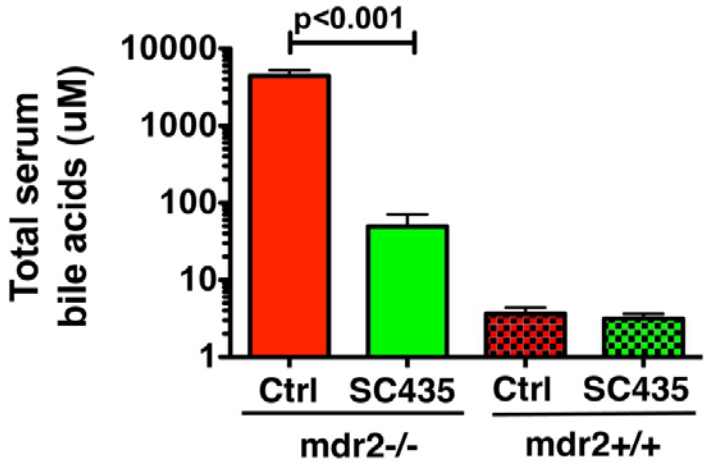
ASBTi* Promoted Fecal Bile Acid Losses and Reduced Serum Bile Acid Levels in MDR2-/- Model

SHP625 (LUM001)
Cholestatic Liver Disease

Fecal Bile Acid Levels (48 hr collection)



Serum Bile Acid Levels

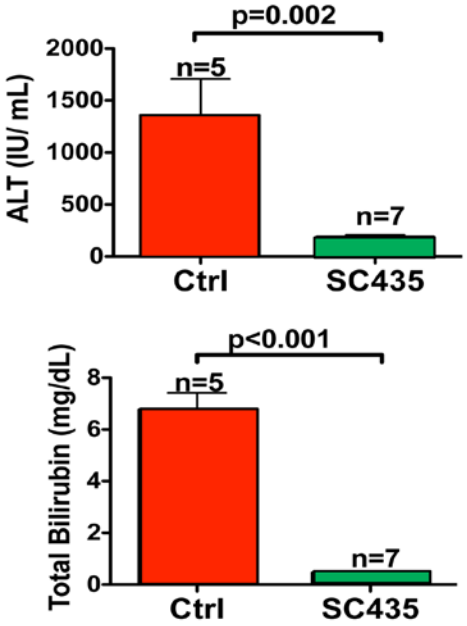


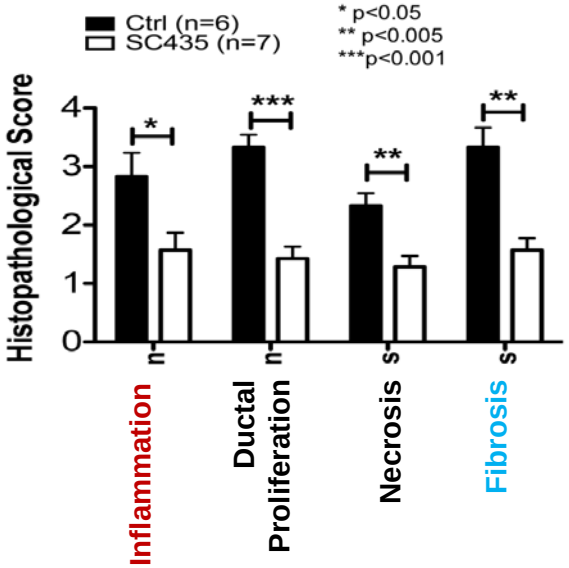
*ASBTi used is SC-435, a research analogue of LUM001

Data Presented at AASLD

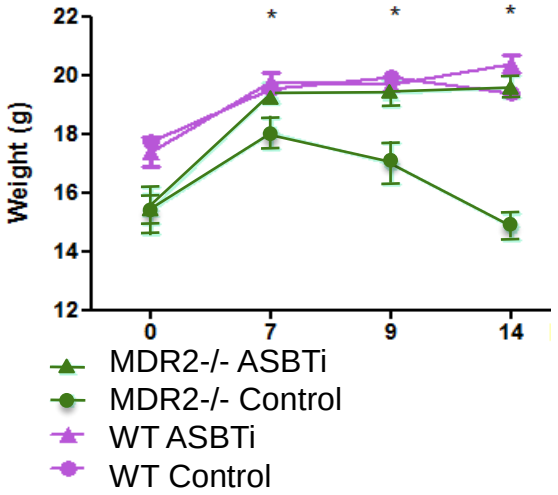
ASBTi* Blocked Wasting and Attenuated Hepatocellular Injury and Cholestasis in MRD2-/- Model

SHP625 (LUM001)
Cholestatic Liver Disease





Score validated in rat BDL model He et al., Hepatology, 2011



*p<0.05 for MDR2-/- ASBTi vs MDR2-/- Control (n=8/group)

*ASBTi used is SC-435, a research analogue of LUM001

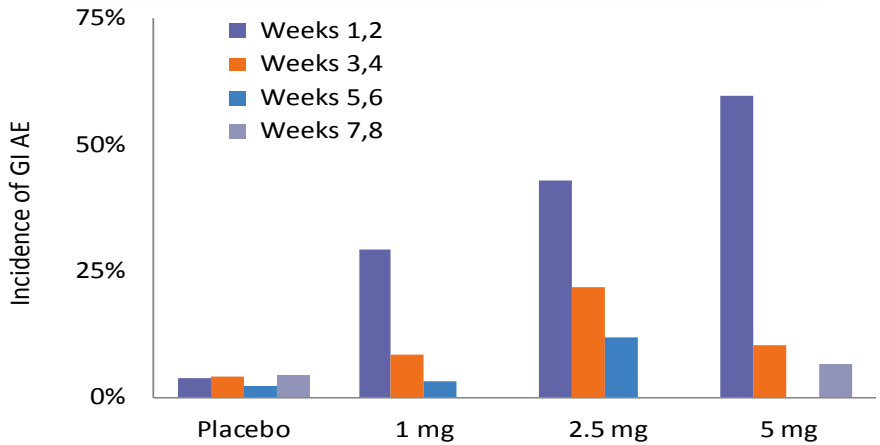
Data Presented at AASLD

SHP625 (LUM001): Safety Profile

SHP625 (LUM001)
Cholestatic Liver Disease

- SHP625 (LUM001) was designed to be minimally absorbed
- Extensive non-clinical data package with good safety margins
- Experience in over 1,400 human subjects in 12 clinical studies
- Most common AEs in completed studies were gastrointestinal in nature; 1 possibly related SAE

Typically dissipate in 2-3 weeks



May be mitigated by gradual dose increases

	Placebo (n=20)	5 mg (n=26)	0.5-5 mg* (n=16)
GI ADVERSE EVENTS (Once Daily Dosing)			
Abdominal pain	2 (10%)	5 (17%)	1 (6.3%)
Constipation	2 (10%)	0	0
Diarrhea	1 (5%)	2 (7%)	0
Nausea	0	1 (4%)	0
Pruritus Ani	0	4 (15%)	0

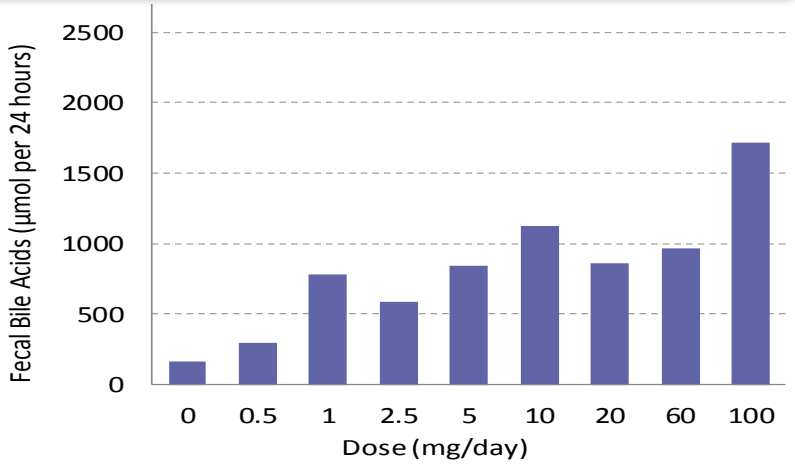
* Week 1: 0.5mg, Week 2: 1.0mg, Week 3: 2.5mg, Week 4: 5.0mg

SHP625 (LUM001): Increased Fecal Bile Acids Excretion and Lowered Serum Bile Acids in Clinical Trials

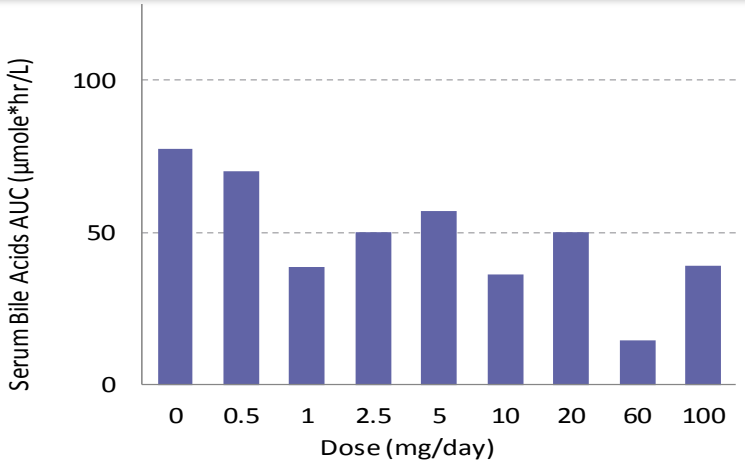
SHP625 (LUM001)
Cholestatic Liver Disease

A Potent and Selective Inhibitor of ASBT Lowers Bile Acids in Clinical Trials

Fecal Bile Acids (day 23-28)



Serum Bile Acids AUC(0-15h) day 14



- SHP625 (LUM001) once daily dosing for 28 days in healthy volunteers (n=167)
- Data are shown as the mean (mmol/24 hours) for fecal bile acids and mean AUC(0-15 hr) (mmol/24 hours) for serum bile acids
- AUC, or area under the curve, is a measure of drug concentration in the blood

Shire

Development Program Covers Multiple Indications

SHP625 (LUM001)
Cholestatic Liver Disease

Indication	Trial, Stage and Design	# of Patients	Trial Location	Initiation	Target Completion
PEDIATRIC					
ALGS	**IMAGO**: Phase 2, registration 13 week double blind, placebo-controlled study	Enrollment Complete 18	UK	Q3 2013	H1 2015
	IMAGINE-I: Phase 2, long term 72 week extension study	18	UK	Q4 2013	H2 2016
	ITCH: Phase 2, registration 13 week double blind, placebo-controlled study	24	US/CA	Q2 2014	H2 2015
	IMAGINE-II: Phase 2, long term 48 week extension study	24	US/CA	Q3 2014	H2 2016
	ICONIC: Phase 2, 48 week open label study with randomized drug withdrawal period	30	EU/CA/ AUS	Q2 2014	H1 2016
PFIC	**INDIGO**: Phase 2, 72 week open label study with interim efficacy analysis at week 13	24	US/UK/EU /AUS	Q1 2014	H2 2016
ADULT					
PBC	**CLARITY**: Phase 2, 13 week double blind, placebo-controlled study in combination with UDCA	Enrollment Complete 60	US/CA/UK	Q3 2013	H1 2015
	CASCADE: Phase 2, 2 year open label extension study	60	US/CA/UK	Q1 2014	H2 2017
PSC	**CAMEO**: Phase 2, 14 week open label study	20	US	Q1 2014	H1 2015

Shire

SHP625 (LUM001): Summary

SHP625 (LUM001)
Cholestatic Liver Disease

- SHP625 (LUM001) is a highly potent and selective, minimally-absorbed ASBT inhibitor
- Orphan drug designation for ALGS, PFIC, PBC, PSC in US and EU
- Parallel development in all 4 high unmet need indications
  - Data from Phase 2 studies in first half of 2015
- Phase 3 studies in PBC and PSC will be required for approval
- Plan to file NDA/MAA for pediatric indications (ALGS/PFIC) using Phase 2 registration studies in the first half of 2016

Shire

SHP626 (LUM002): Non-Alcoholic Steatohepatitis (NASH)

Preclinical	Phase 1	Phase 2		Phase 3	Registration
26 Research Programs	**SHP611** MLD (Ph 1/2)	**SHP602** Iron overload (clinical hold)	**SHP616 (Cinryze)** Acute Antibody Mediated Rejection	**Firazyr** ACE inhibitor-induced AE	**XAGRID® (Japan)** Thrombocythaemia *(Approved 3Q 2014)*
SHP619 Duchenne's Muscular Dystrophy	**SHP616 (Cinryze SC)** HAE Prophylaxis	**SHP610** Sanfilippo A	**SHP625 (LUM001)** Primary Biliary Cirrhosis	**Firazyr** (Japan) HAE	**VPRIV (Japan)** Gaucher *(Approved 3Q 2014)*
TH / GCH1 Gene Pod Parkinson's Subset	**SHP622** Friedreich's Ataxia	**SHP609** Hunter CNS	**SHP625 (LUM001)** Progressive Familial Intrahepatic Cholestasis	**SHP616 (Cinryze) (Japan)** HAE Prophylaxis	**INTUNIV® (EU)** ADHD
SHP608 Dystrophic E.Bullosa	**SHP627 (FT011)** Focal Segmental Glomerulosclerosis	**SHP607** Prevention of ROP	**SHP625 (LUM001)** Alagille Syndrome	**SHP555 (US)** Chronic Constipation	**LDX** BED
SHP614 IgA Nephropathy	**SHP616 (Cinryze)** Paroxysmal Nocturnal Hemoglobinuria	**SHP620 (Maribavir)** CMV in transplant patients	**SHP625 (LUM001)** Primary Sclerosing Cholangitis	**INTUNIV (Japan)** ADHD	
Armagen Hunter CNS	**SHP616 (Cinryze)** Acute Neuromyelitis Optica	**LDX (Japan)** ADHD		**SHP606 (Lifitegrast)** Dry eye disease	
SHP630 adRP	**SHP626 (LUM002)** Non-Alcoholic Steatohepatitis			**SHP465** ADHD	
SHP624 Heme B Gene Edit					
SHP628 (FT-061) Renal Impairment					

- Complement Biology
- Renal / Transplant
- Ophthalmics
- GI / Metabolic
- CNS
- Rare Diseases Leadership

Shire

NASH – A Growing Problem

SHP626 (LUM002)
Non-Alcoholic Steatohepatitis

Disease Overview

- Non-alcoholic Fatty Liver Disease (NAFLD) is the hepatic manifestation of metabolic syndrome; NAFLD affects ~27% of adults in U.S. / EU
- Non-Alcoholic Steatohepatitis (NASH) is the progressive form of NAFLD characterized by accumulation of fat, fibrous tissue, inflammation and damage to the liver; characteristics resemble those of alcoholic steatohepatitis
- Underlying cause of NASH-associated liver injury is not fully known; strong association with obesity, Type 2 diabetes, high cholesterol and triglycerides
- ~10% of the NAFLD population has NASH (1)
  - Estimated ~6 million individuals in the U.S. have NASH and ~600K have NASH-related cirrhosis
  - NASH projected to surpass Hepatitis C and alcoholic liver disease to become leading cause for liver transplant by 2020
- Despite increasing incidence of nonalcoholic fatty liver disease (NAFLD) and NASH, there are no treatments currently approved for these common liver disorders

(1) National Digestive Diseases Information Clearinghouse

Rationale for SHP626 (LUM002) in NASH

SHP626 (LUM002)
Non-Alcoholic Steatohepatitis

Lipid Lowering

- Blocking bile acid reabsorption decreases level of bile acids returning to the liver via the enterohepatic circulation
- Stimulating bile acid synthesis from cholesterol
- Reduction of hepatic cholesterol reduces oxidative stress
  - Preclinical data demonstrates reduction of serum and hepatic LDL-cholesterol
  - Clinical data demonstrates reduction of serum LDL-cholesterol in healthy volunteers

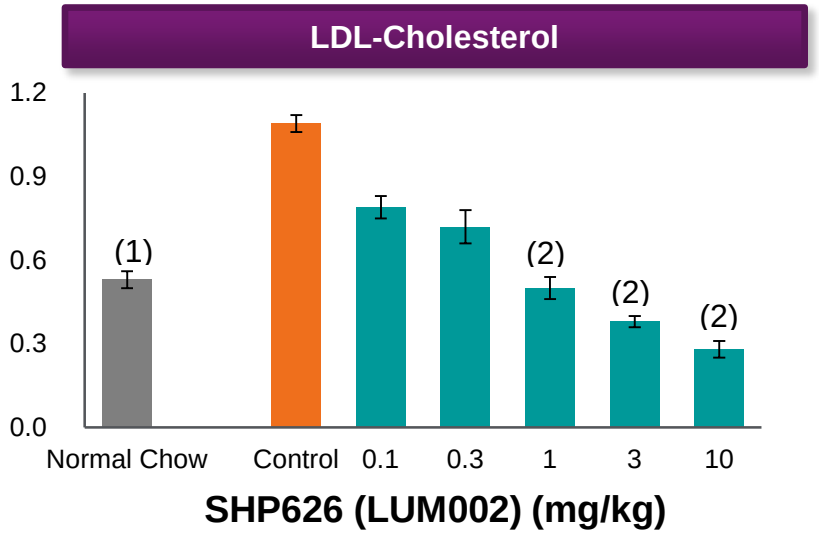
Regulation of Metabolic Function

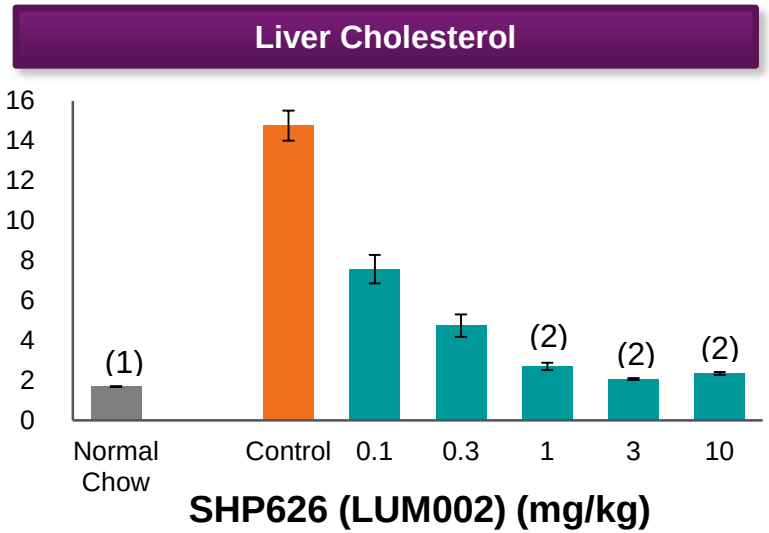
- Blocking bile acid reabsorption increases colonic bile acids levels
- Bile acids have a signaling function in the intestine, liver and other tissues that is mediated by receptors including TGR5; these signaling pathways have key functions in regulating insulin homeostasis
  - Preclinical data supports improved metabolic function
  - Clinical data shows that SHP626 (LUM002) reduced fasting glucose levels, and suggested improvements in glucose homeostasis

SHP626 (LUM002) Demonstrated Efficacy in Cholesterol-fed Hamsters; Reducing Serum LDL and Hepatic Cholesterol Levels

SHP626 (LUM002)
Non-Alcoholic Steatohepatitis

- SHP626 (LUM002) lowered Serum LDL and Hepatic Cholesterol in Cholesterol-fed hamsters after 3 weeks
- Normal chow group received standard chow, control group and all other groups a cholesterol-enriched diet (0.1%, w/w) [n = 6]
- Mean ± SEM, (1) p<0.05 normal chow versus control, (2) p<0.05 versus control

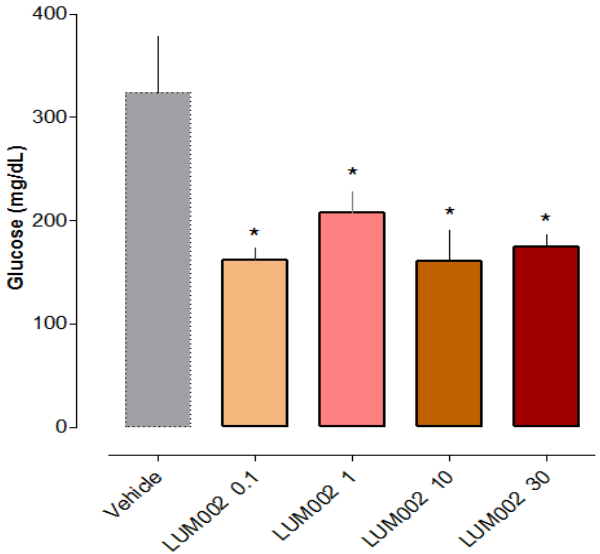




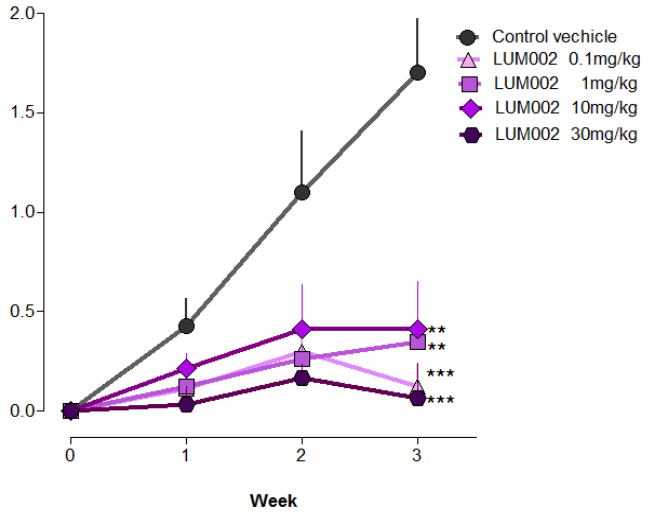
SHP626 (LUM002) Demonstrated Reduction in Plasma Glucose and HbA1c in ZDF Rats

SHP626 (LUM002)
Non-Alcoholic Steatohepatitis

Fasting Plasma Glucose Concentration – Week 3



Baseline-corrected Percent Hemoglobin A1c



* P<0.05, ** P<0.01 and *** P<0.001 vs. vehicle group

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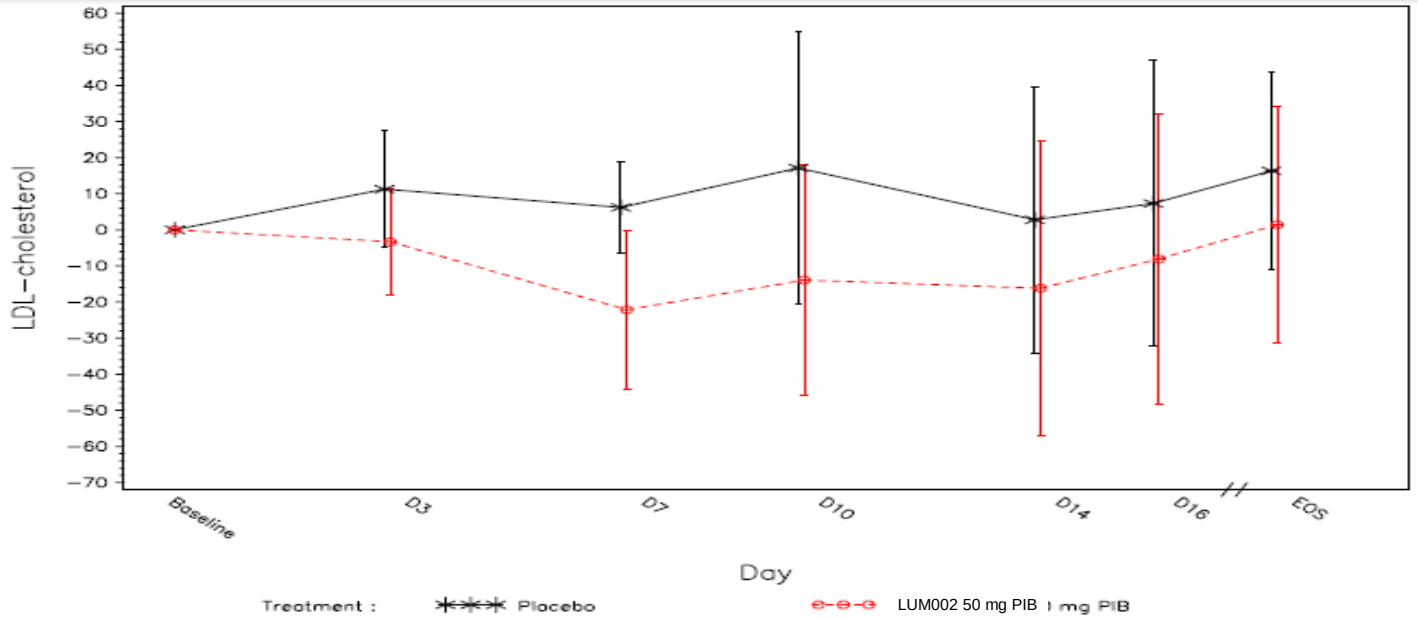
SHP626 (LUM002) Treatment Lowered LDL Cholesterol After 14 Days Oral Administration in Healthy Subjects

SHP626 (LUM002)
Non-Alcoholic Steatohepatitis

Data expressed as percent change from the baseline value (Day -1)



Subjects (n=12) were dosed once daily with SHP626 (LUM002) (50 mg/kg) for 14 days and followed for an additional 7-day period after the termination of dosing

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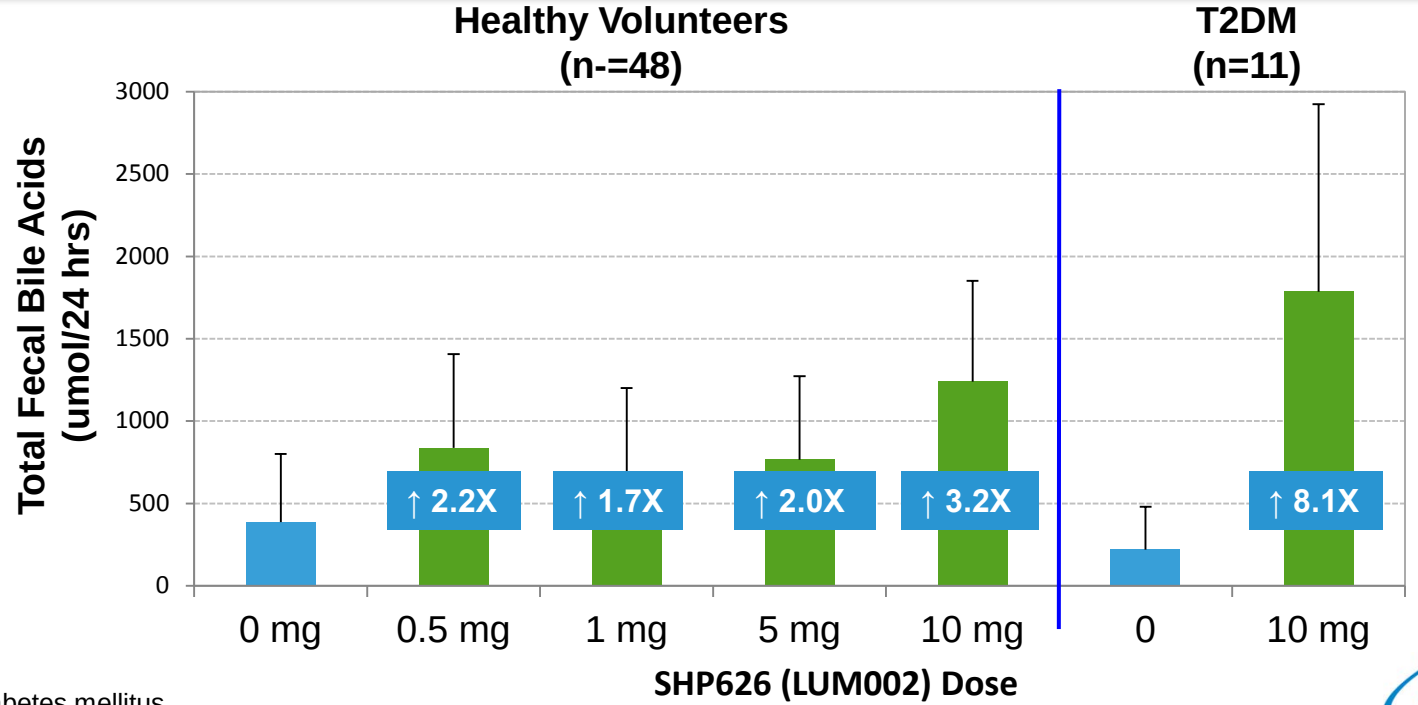
SHP626 (LUM002) Increased Fecal Bile Acid Levels in Healthy Volunteers, as Well as in T2DM[(1)] Patients

SHP626 (LUM002)
Non-Alcoholic Steatohepatitis

Total fecal bile acids days 26-28 [48 hrs] in T2DM patients (mean ± SD)



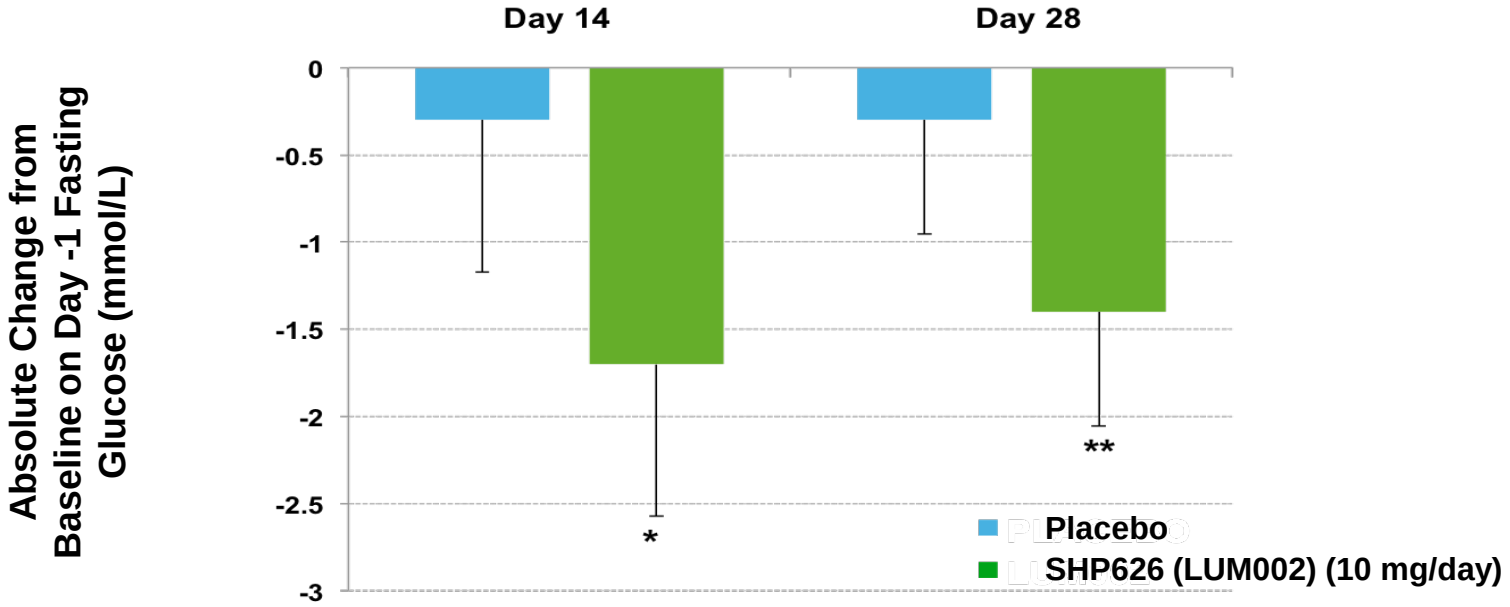
(1) Type 2 diabetes mellitus

Pre-specified analysis *P ≤ 0.05, ** P ≤0.01 vs. placebo

SHP626 (LUM002) Showed Statistically Significant Reduction in Fasting Blood Glucose Levels at Day 14 and Day 28 in T2DM Patients

SHP626 (LUM002)
Non-Alcoholic Steatohepatitis

Fasting blood glucose, absolute change from baseline (Day-1) SHP626 (LUM002) in T2DM patients (n=11) (mean ± SD)

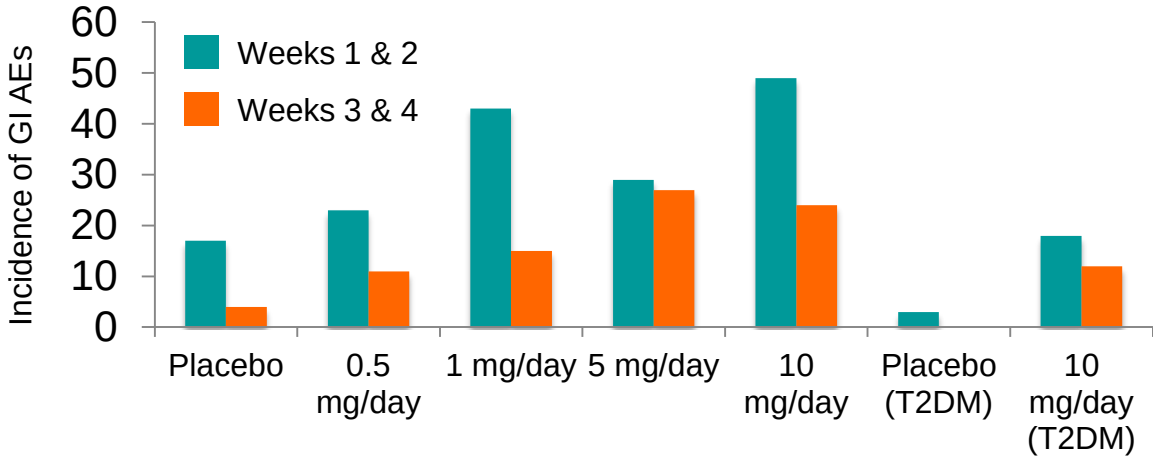


Pre-specified analysis *P ≤ 0.05, ** P ≤0.01 vs. placebo

SHP626 (LUM002): Safety Profile

SHP626 (LUM002)
Non-Alcoholic
Steatohepatitis

- SHP626 (LUM002) is minimally absorbed
- Single and multiple ascending dose and food effect studies complete (n = 153)
- 28 day study in T2DM patients (n = 11)
- Adverse events were mostly mild GI events
  - The total rate of AEs decreased following first 2 weeks of treatment



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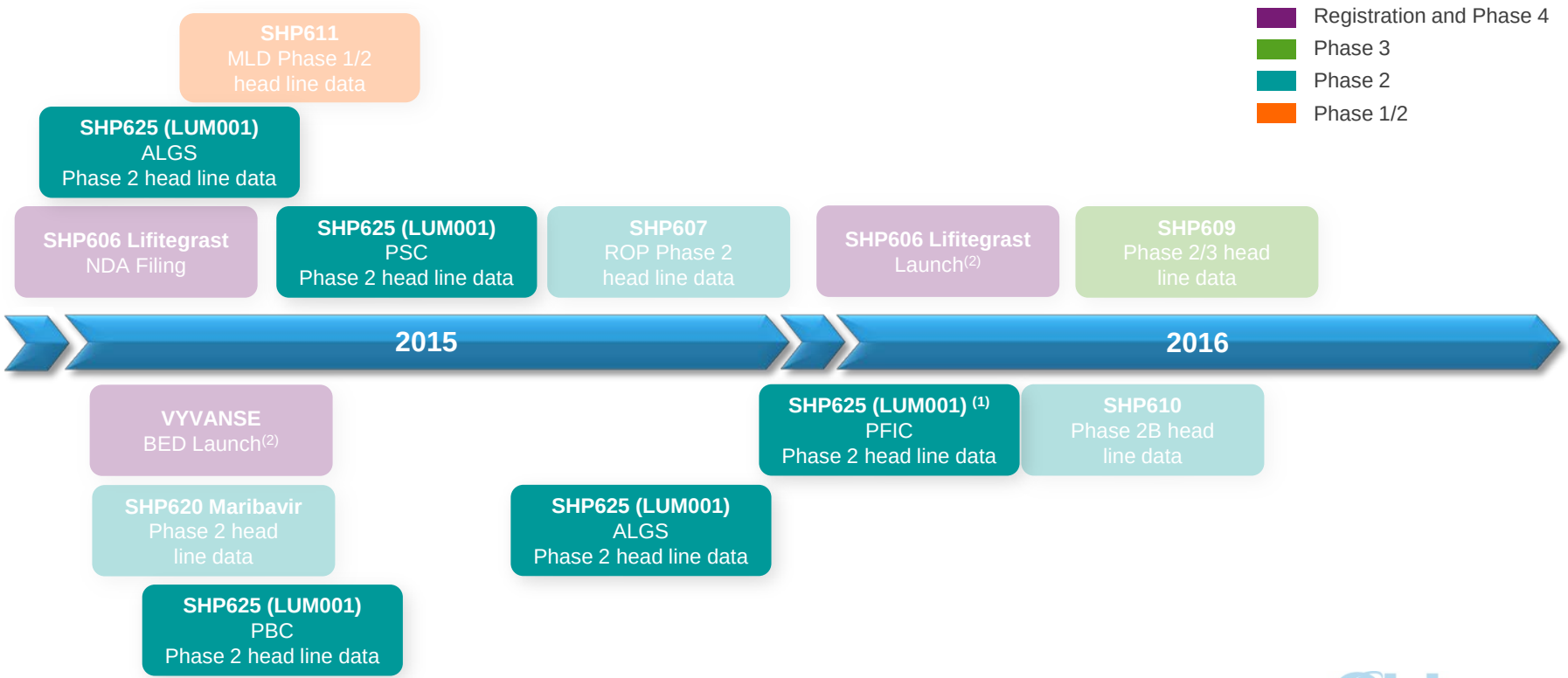
SHP626 (LUM002): Summary

SHP626 (LUM002)
Non-Alcoholic Steatohepatitis

- Highly potent and selective, minimally absorbed ASBT inhibitor
- Safety:
  - Adverse events were mostly mild GI events
  - No clinically significant elevations in lipids or triglycerides
- Phase 1 data supports:
  - Increased fecal bile acid excretion
  - Lowering of LDL
  - Reduction in fasting blood glucose and trends towards insulin sensitivity in T2DM
- Phase 2 NASH study in planning:
  - 52-week double-blind, randomized, placebo-controlled study
  - Endpoints include: biopsy, biochemical markers, and imaging

Shire

Upcoming GI / Metabolic Rare Diseases Milestones



Notes
(1) Interim 625 PFIC INDIGO data expected Q2 2015.
(2) Subject to regulatory approval.

Break

Our purpose
We enable people with life-altering conditions to lead better lives.

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Rare Diseases:

Ophthalmics

Norman Barton, M.D., PhD, Global Development Team Leader

Our purpose
We enable people with life-altering conditions to lead better lives.

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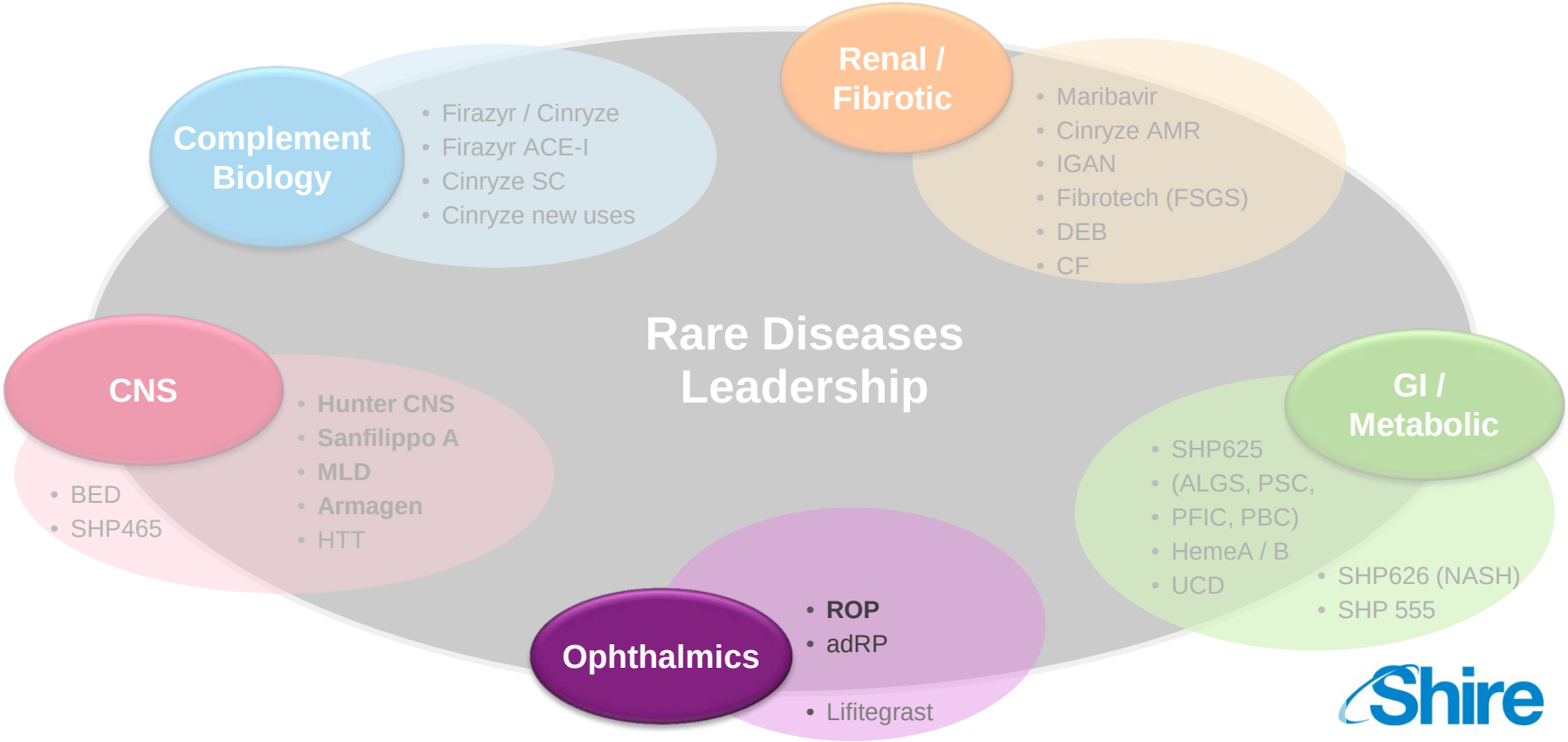
Today's R&D Sessions

Topic	Speaker	Time (EST)
Research Overview and Technology Platforms *mRNA, Protein Replacement, Gene Therapy, Antibody Platforms*	Albert Seymour, Ph.D	9:25-10:00
Rare Diseases: GI / Metabolic *SHP625 (LUM001), SHP626 (LUM002)*	Ciara Kennedy, Ph.D *David Piccoli, M.D.*	10:00-10.45
Rare Diseases: Ophthalmics *SHP607 / ROP, SHP630 / BIKAM*	Norman Barton, M.D., Ph.D	11:15-11:45
Rare Diseases: Complement Biology and Renal / Fibrotic *SHP616 / Cinryze new uses*	Howard Mayer, M.D.	1:15-1:30
Rare Diseases: CNS *SHP609 / Hunter CNS, SHP610 / Sanfilippo A, SHP611 / MLD, Armagen*	Howard Mayer, M.D.	1:30-2:00
Late-Stage Update *SHP606 / Lifitegrast, BED, SHP465 / ADHD*	Howard Mayer, M.D. Randy Brenner *Joe Tauber, M.D.*	2:00-2:45

Shire

Rare Diseases Programs in Ophthalmics



Shire

SHP607: Prevention of Retinopathy of Prematurity (ROP)

IGF-1 / IGFBP3

Preclinical	Phase 1	Phase 2		Phase 3	Registration
26 Research Programs	**SHP611** MLD (Ph 1/2)	**SHP602** Iron overload (clinical hold)	**SHP616 (Cinryze)** Acute Antibody Mediated Rejection	**Firazyr** ACE inhibitor-induced AE	**XAGRID® (Japan)** Thrombocythaemia *(Approved 3Q 2014)*
SHP619 Duchenne's Muscular Dystrophy	**SHP616 (Cinryze SC)** HAE Prophylaxis	**SHP610** Sanfilippo A	**SHP625 (LUM001)** Primary Biliary Cirrhosis	**Firazyr** (Japan) HAE	**VPRIV (Japan)** Gaucher *(Approved 3Q 2014)*
TH / GCH1 Gene Pod Parkinson's Subset	**SHP622** Friedreich's Ataxia	**SHP609** Hunter CNS	**SHP625 (LUM001)** Progressive Familial Intrahepatic Cholestasis	**SHP616 (Cinryze) (Japan)** HAE Prophylaxis	**INTUNIV® (EU)** ADHD
SHP608 Dystrophic E.Bullosa	**SHP627 (FT011)** Focal Segmental Glomerulosclerosis	**SHP607** Prevention of ROP	**SHP625 (LUM001)** Alagille Syndrome	**SHP555 (US)** Chronic Constipation	**Vyvanse** BED
SHP614 IgA Nephropathy	**SHP616 (Cinryze)** Paroxysmal Nocturnal Hemoglobinuria	**SHP620 (Maribavir)** CMV in transplant patients	**SHP625 (LUM001)** Primary Sclerosing Cholangitis	**INTUNIV (Japan)** ADHD	
Armagen Hunter CNS	**SHP616 (Cinryze)** Acute Neuromyelitis Optica	**LDX (Japan)** ADHD		**SHP606 (Lifitegrast)** Dry eye disease	
SHP630 adRP	**SHP626 (LUM002)** Non-Alcoholic Steatohepatitis			**SHP465** ADHD	
SHP624 Heme B Gene Edit					
SHP628 (FT-061) Renal Impairment					

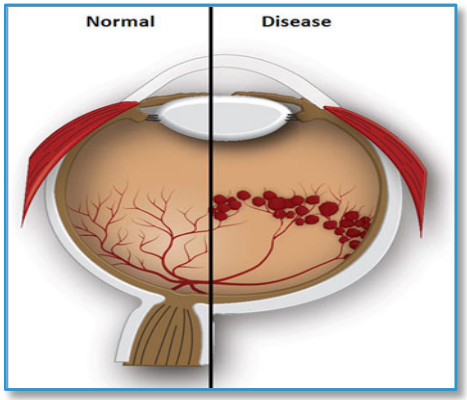
- Complement Biology
- Renal / Transplant
- Ophthalmics
- GI / Metabolic
- CNS
- Rare Diseases Leadership

Shire

Prevention of Retinopathy of Prematurity (ROP)

SHP607
Prevention of ROP

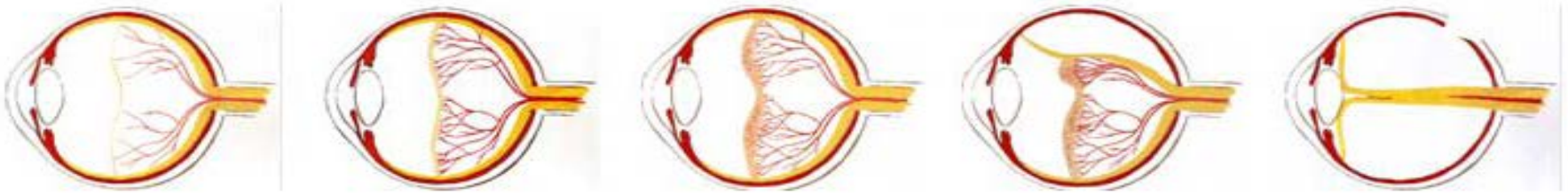
Patients	• ~30K patients < 28 weeks gestational age (GA) in the US and a similar number in the EU per year • Surgery is currently only widely recognized treatment option
Product	• IGF-1 protein replacement therapy administered preventatively by continuous IV infusion beginning within the first 24-48 hours of life • Delivered until endogenous production of IGF-1 begins at ~30 weeks GA
Progress	• Phase 2 studies ongoing with headline data expected 2H 2015 • Dose selection completed
Potential	• Significant opportunity to treat a serious unmet need



Shire

Retinopathy of Prematurity (ROP): Extent of Disease (Stages)

ROP STAGES



Stage 1
Demarcation line

Stage 2
Demarcation ridge

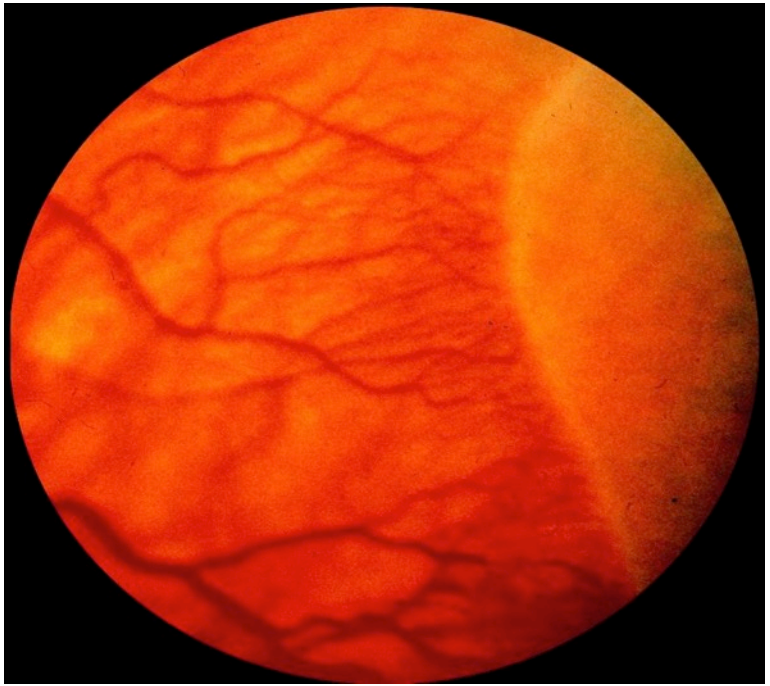
Stage 3
Neovascularization

Stage 4
Subtotal retinal detachment

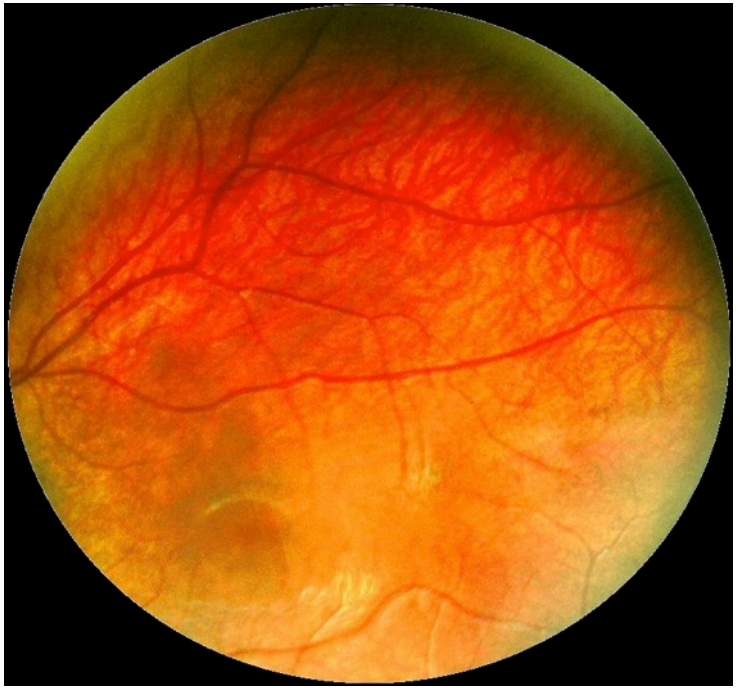
Stage 5
Total retinal detachment

ROP Images

Premature Retina with ROP
(34 Weeks PMA /Birth at 28 Weeks GA)



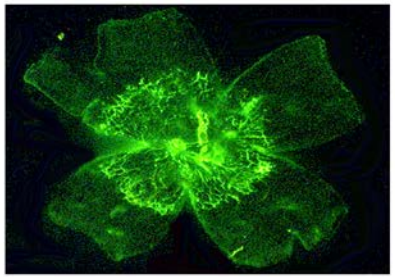
Mature Healthy Retina
(40 Week Term Infant)



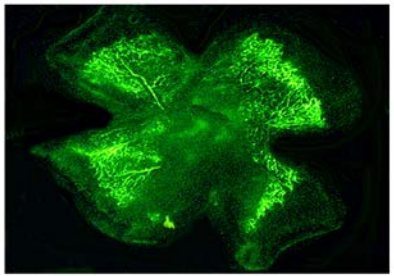
Compelling Pre-clinical Evidence

- Retinal vascularization is inhibited in IGF-1 KO mice despite the presence of other growth factors (VEGF)
- IGF-1 supplementation preserves retinal vasculature in oxygen induced retinopathy model
- IGF-1 receptor blockade in mice prevents retinal vascularization despite the presence of IGF-1

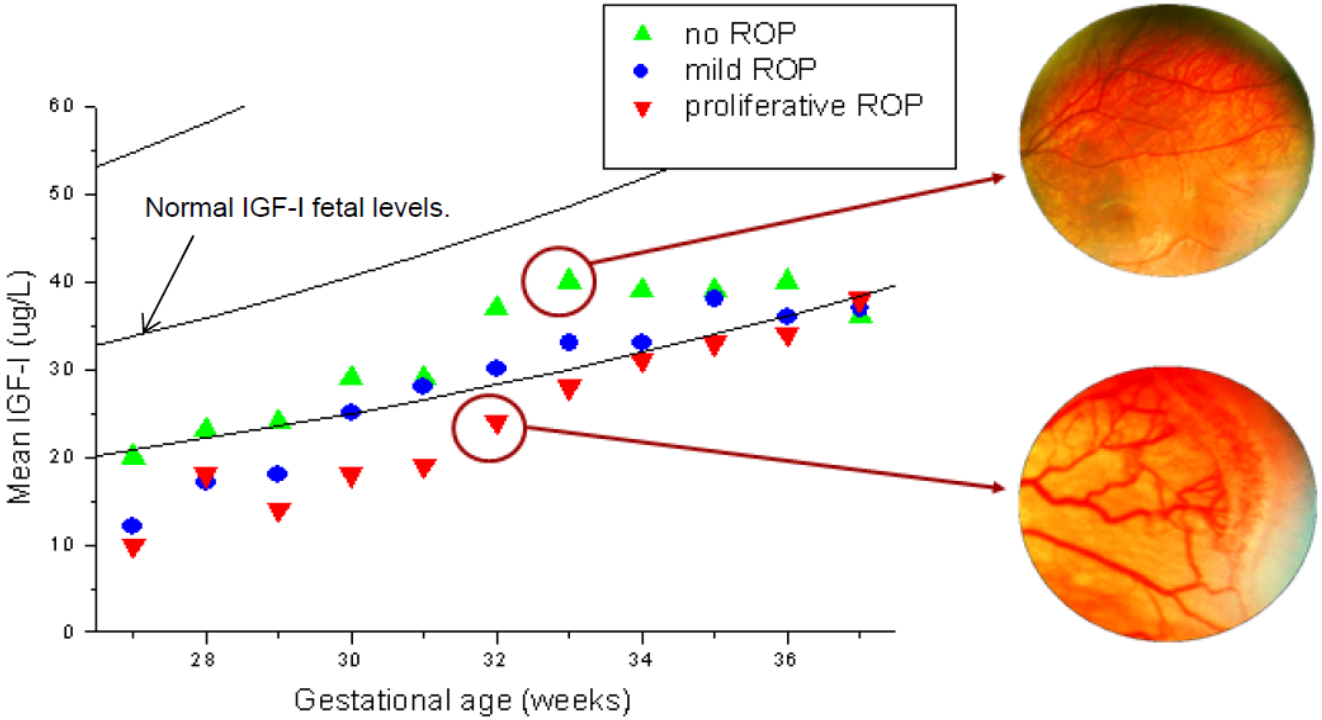
IGF-I -/- mouse



WT mouse

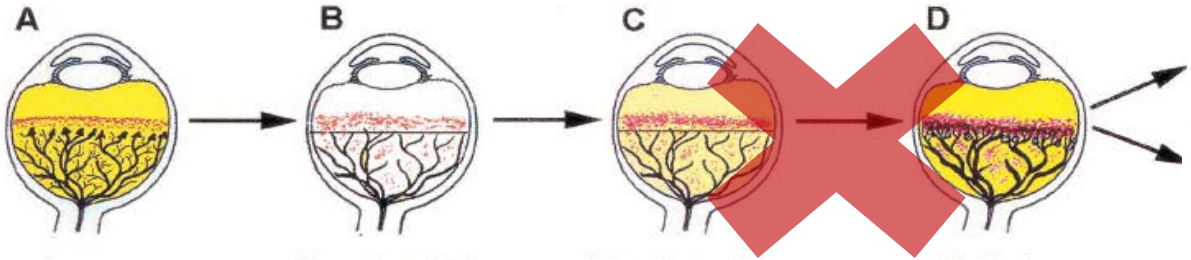


Intra-uterine IGF-1 Levels and the Correlation Between ROP and Serum IGF-1 Levels in Premature Infants



Retinopathy of Prematurity (ROP)

IGF-1 and VEGF Roles in Development



A	B	C	D
In utero Normal vessel growth	Premature birth Vessel growth stops	Maturing retina Hypoxia	Retinal neovascularization
IGF-1 nl VEGF nl	↓IGF-1 nl (↓VEGF)	Slow ↑IGF-1 ↑↑VEGF	↑IGF-1 to "threshold" ↑↑VEGF

↑ NI vessel growth in retina
↑VEGF
Resolution of ROP

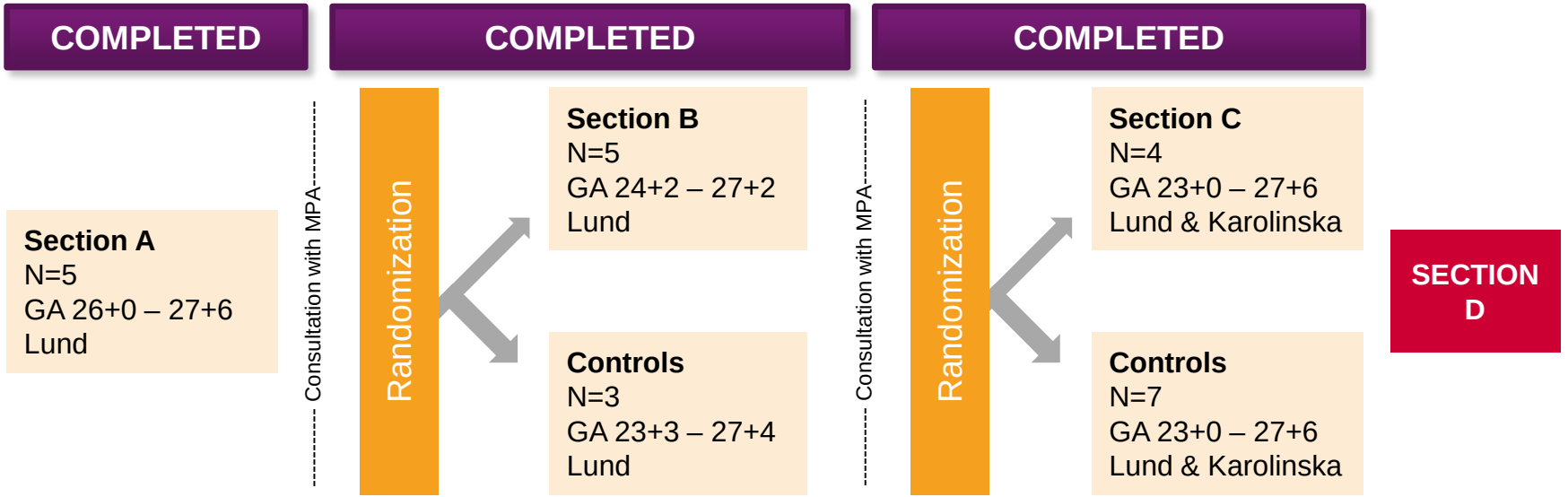
↑VEGF
Proliferative retinopathy
Retinal detachment

VEGF
IGF-1

IGF-1

Phase II Trial Design

A Phase II, Open-Label, Multicenter, Dose Evaluation Study to Determine Safety and Efficacy of rhIGF-1 / rhIGFBP-3 in Premature Infants (Sections A, B, and C)



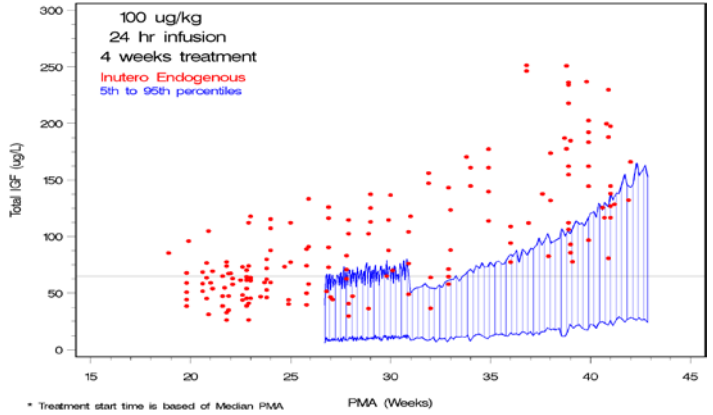
Trial designed in phased sections – sections A, B and C completed by Premacure

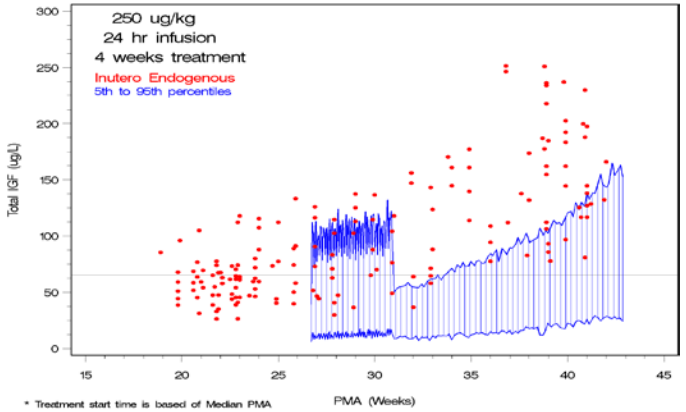
- 24 patients included in Sections A, B and C
- Dosing per individualized algorithm and intense serum IGF-1 monitoring

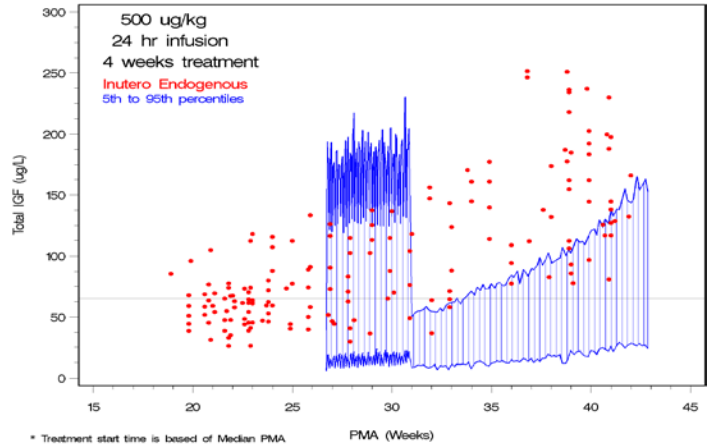
Results: Phase 1 and Phase 2 Sections A, B and C

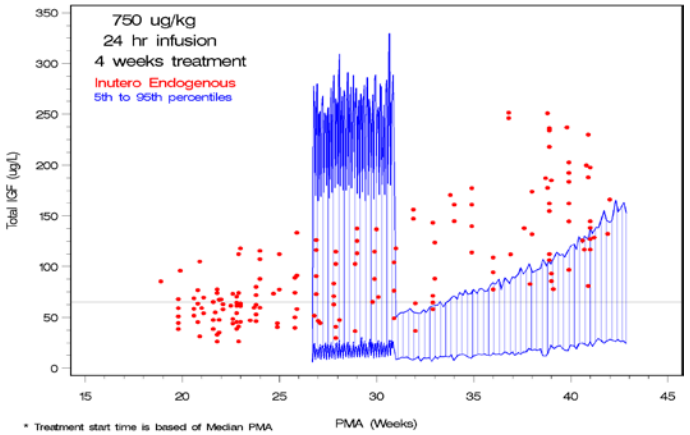
- Number of exposures
  - Phase 1: 5 active
  - Phase 2: Sections A, B and C: 9 active and 10 SOC controls
- Results
  - Elimination is rapid ($T_{½}$ < 1hour); IGF-1/IGFBP-3 placement requires continuous IV infusion
  - Average administered dose (~100 µg/kg/day) was insufficient to achieve physiologic replacement (range: 21-124 µg/kg/day)
  - No safety signals
  - Fewer total days of NICU care required for active treatment vs SOC
  - One SOC control required laser treatment for ROP; none in the active treatment group

Simulated IGF-1 Levels Versus Dose Superimposed on Normal in Utero Levels









Dose of ≥ 250 ug/kg/24h is necessary to achieve therapeutic target

Next Steps: Ongoing Phase II in ROP

SHP607
Prevention of ROP

A **Phase II**, Open-Label, Multicenter, **Dose Evaluation Study** to Determine Safety and Efficacy of rhIGF-1 / rhIGFBP-3 in Premature Infants (Section D)

- Randomized, treated versus standard of care control, assessor-masked trial
- Extremely pre-term infants (23 weeks – 27 weeks + 6 days GA) included in trial
- **Standardized dose** developed: continuous IV infusion (250µg/kg/24hrs) of rhIGF-1/rhIGFBP-3
- **Primary endpoint: maximum severity of ROP** stage across all retinal examinations (assessed at 40 weeks corrected gestational age)
    - Key **secondary endpoint: time to discharge** from neonatal intensive care
        - Additional secondary endpoints: incidence of BPD at 36 weeks PMA and brain volume by MRI at 40 weeks term equivalent
    - 120 patients at 15-20 sites across Europe, US and Canada
    - MOH approval in UK, Sweden, Italy, Netherlands, Poland, Canada;
      US IND accepted Nov 17, 2014 **and fast track designation granted** in December

Headline data expected 2H2015

Shire

SHP630: Autosomal Dominant Retinitis Pigmentosa (adRP)

Preclinical	Phase 1	Phase 2		Phase 3	Registration
26 Research Programs	**SHP611** MLD (Ph 1/2)	**SHP602** Iron overload (clinical hold)	**SHP616 (Cinryze)** Acute Antibody Mediated Rejection	**Firazyr** ACE inhibitor-induced AE	**XAGRID® (Japan)** Thrombocythaemia *(Approved 3Q 2014)*
SHP619 Duchenne's Muscular Dystrophy	**SHP616 (Cinryze SC)** HAE Prophylaxis	**SHP610** Sanfilippo A	**SHP625 (LUM001)** Primary Biliary Cirrhosis	**Firazyr** (Japan) HAE	**VPRIV (Japan)** Gaucher *(Approved 3Q 2014)*
TH / GCH1 Gene Pod Parkinson's Subset	**SHP622** Friedreich's Ataxia	**SHP609** Hunter CNS	**SHP625 (LUM001)** Progressive Familial Intrahepatic Cholestasis	**SHP616 (Cinryze) (Japan)** HAE Prophylaxis	**INTUNIV® (EU)** ADHD
SHP608 Dystrophic E.Bullosa	**SHP627 (FT011)** Focal Segmental Glomerulosclerosis	**SHP607** Prevention of ROP	**SHP625 (LUM001)** Alagille Syndrome	**SHP555 (US)** Chronic Constipation	**Vyvanse** BED
SHP614 IgA Nephropathy	**SHP616 (Cinryze)** Paroxysmal Nocturnal Hemoglobinuria	**SHP620 (Maribavir)** CMV in transplant patients	**SHP625 (LUM001)** Primary Sclerosing Cholangitis	**INTUNIV (Japan)** ADHD	
Armagen Hunter CNS	**SHP616 (Cinryze)** Acute Neuromyelitis Optica	**LDX (Japan)** ADHD		**SHP606 (Lifitegrast)** Dry eye disease	
SHP630 adRP	**SHP626 (LUM002)** Non-Alcoholic Steatohepatitis			**SHP465** ADHD	
SHP624 Heme B Gene Edit					
SHP628 (FT-061) Renal Impairment					

- Complement Biology
- Renal / Transplant
- Ophthalmics
- GI / Metabolic
- CNS
- Rare Diseases Leadership

Shire

Autosomal Dominant Retinitis Pigmentosa (adRP)

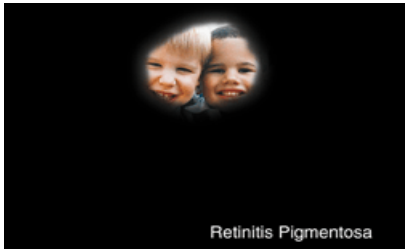
SHP630
adRP

The Disease

- adRP is an orphan genetic disease of the eye characterized by onset of night blindness in late childhood or adolescence followed by progressive loss of peripheral vision
- Most patients meet legal criteria for blindness between 40 and 70
- Genetically heterogeneous with several disease causing genes; mutations in the opsin gene are a frequent cause of adRP

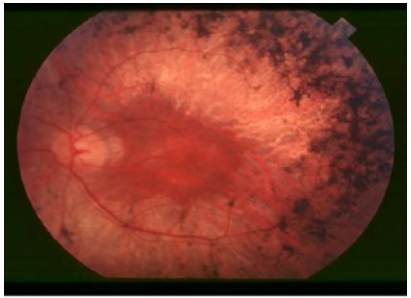
Prevalence & Gene Mutations

- ~ 75,000 patients with adRP worldwide
- ~ 15,000 carry a Class II mutation (mis-folded opsin)
- P23H, T17M, R135W account for 75% of Class II opsin mutations



Diagnosis

- Retinal specialist (fundoscopic exam, visual field testing, electroretinogram and optical coherence tomography)
- Genotype provides confirmation of diagnosis
- No approved treatments for adRP



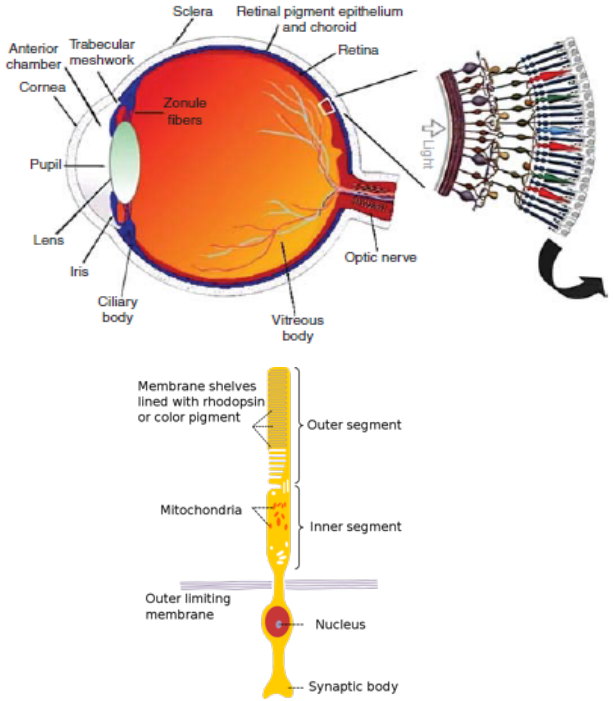
Treatment Strategy

- SHP630 is designed to stabilize misfolded opsin, facilitate trafficking to the cell membrane and restore function

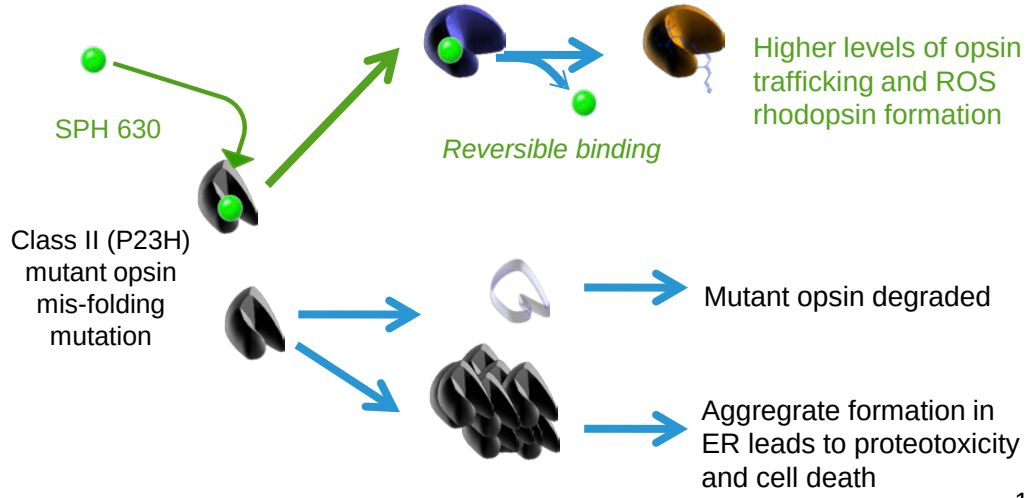
Opsin is Critical for Rod Photoreceptor Function

SHP630
adRP

- Opsin binds to cis-retinal in membrane discs located in rod outer segment (ROS); opsin comprises 90% of all ROS protein
- Binding of opsin to cis-retinal is the first step in the visual cycle
- Class II mutations in opsin lead to reduced protein in ROS, leading to loss of ROS followed by rod photoreceptor cell death



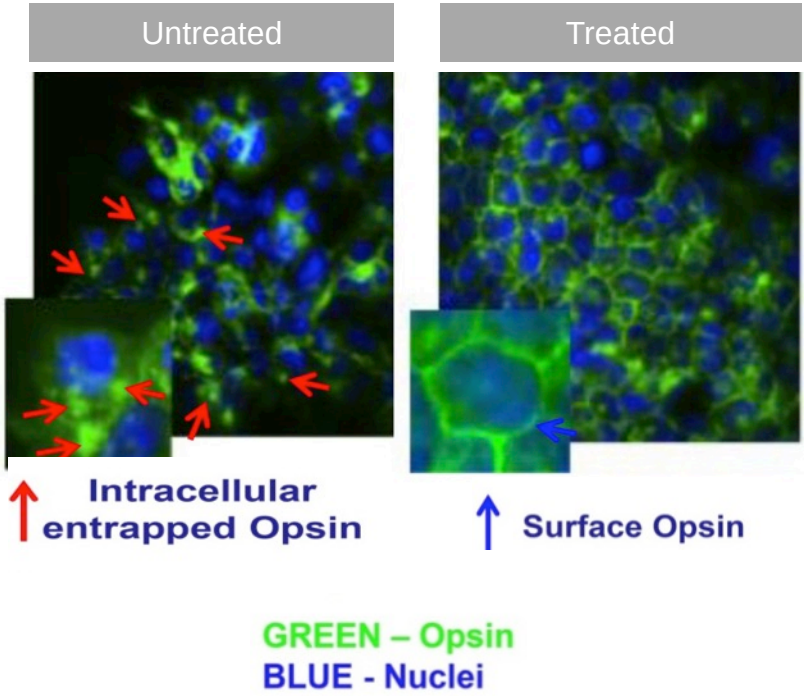
SHP630 is an orally available, non-retinal small molecule chaperone designed to facilitate opsin trafficking to the correct cellular location



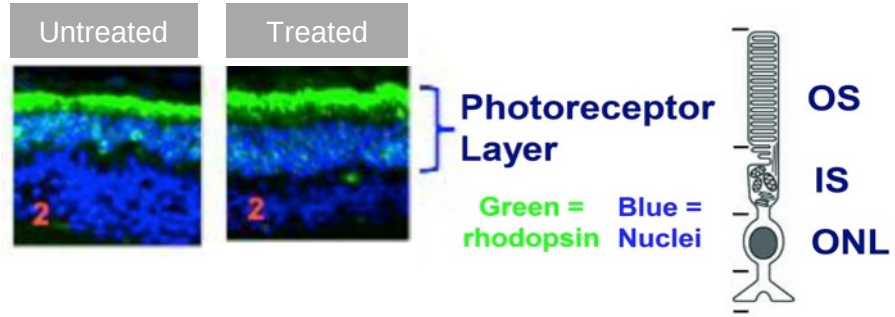
SHP630 is Designed to Preserve Rod Photoreceptor Structure and Function

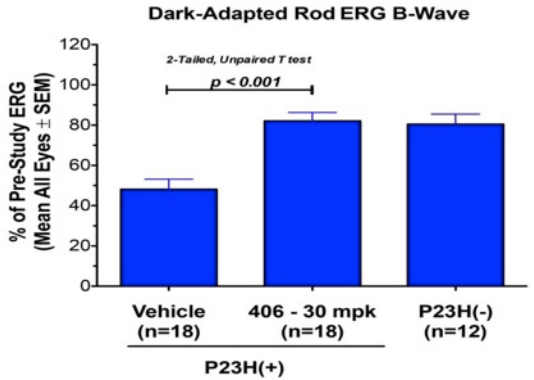
SHP630
adRP

In vitro studies show SPH630 facilitates localization of mutant opsin in the cell surface membrane

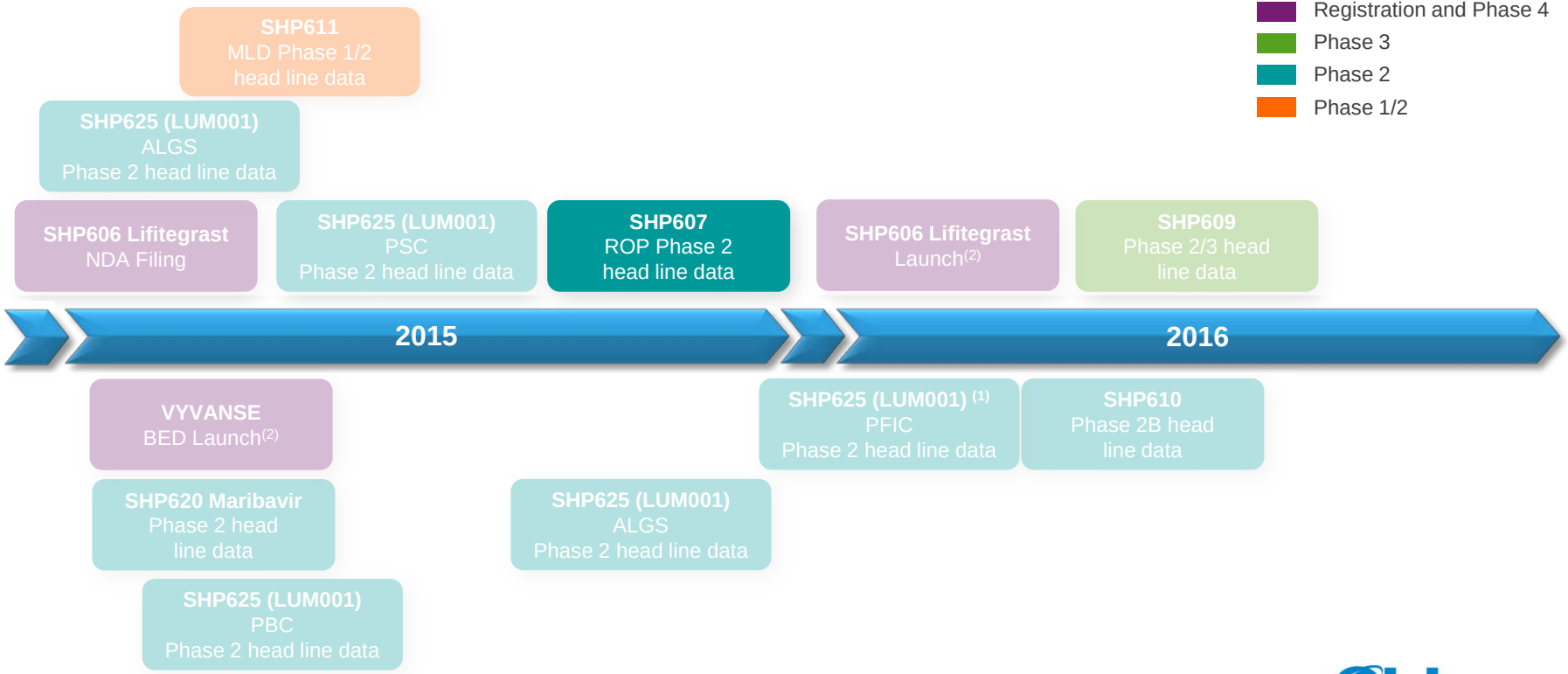


In vivo studies show SPH630 restores ROS structure and retinal function in adRP disease mouse model





Upcoming Anticipated Ophthalmics Rare Diseases Milestones



Notes
(1) Interim 625 PFIC INDIGO data expected Q2 2015.
(2) Subject to regulatory approval.

Question & Answer

Our purpose
We enable people with life-altering conditions to lead better lives.

Shire

Lunch

Our purpose
We enable people with life-altering conditions to lead better lives.

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Rare Diseases:

Complement Biology and Renal / Fibrotic CINRYZE® New Uses

Howard Mayer, M.D., Head of Clinical Development

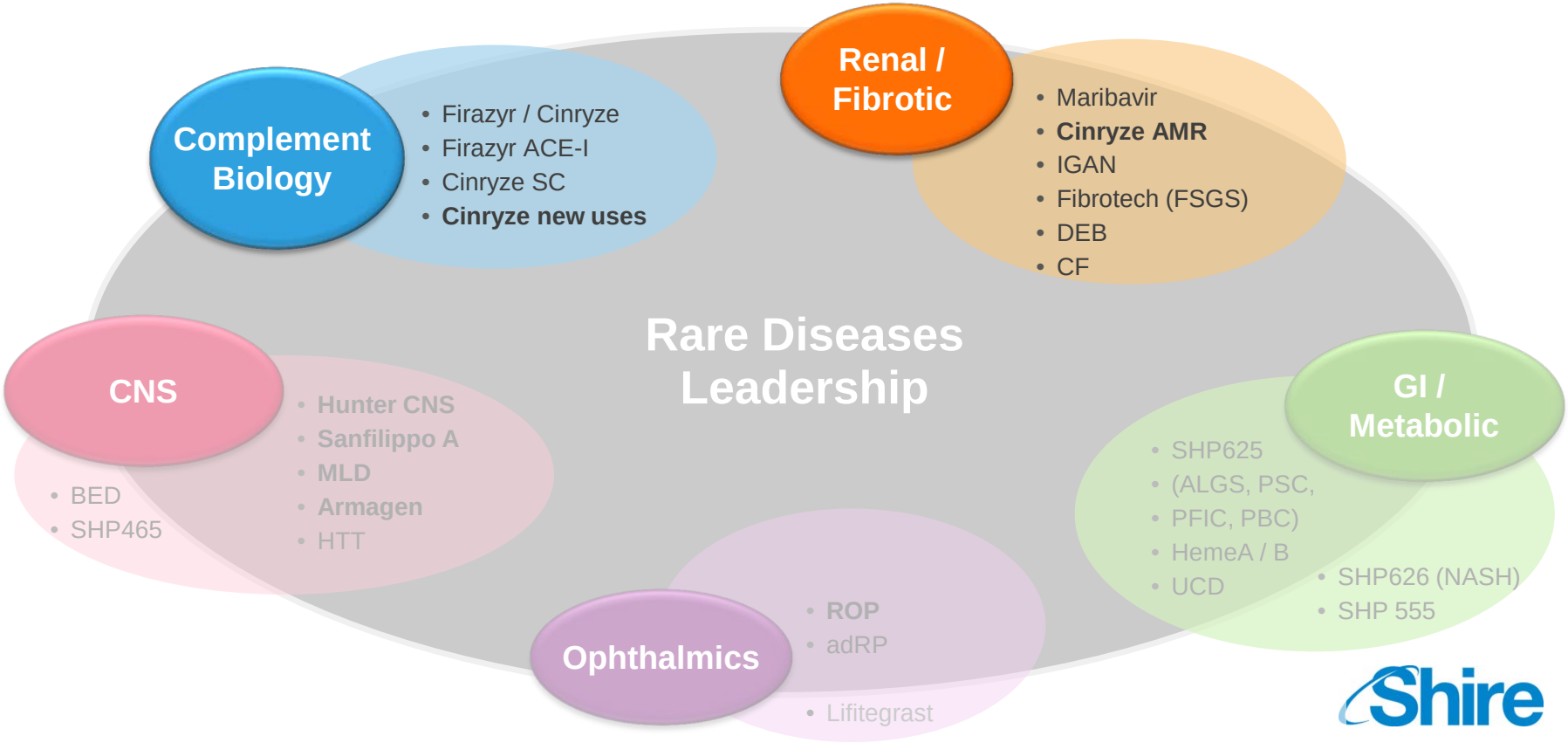
Our purpose
We enable people with life-altering conditions to lead better lives.

Shire

Today's R&D Sessions

Topic	Speaker	Time (EST)
Research Overview and Technology Platforms *mRNA, Protein Replacement, Gene Therapy, Antibody Platforms*	Albert Seymour, Ph.D.	9:25-10:00
Rare Diseases: GI / Metabolic *SHP625 (LUM001), SHP626 (LUM002)*	Ciara Kennedy, Ph.D. *David Piccoli, M.D.*	10:00-10.45
Rare Diseases: Ophthalmology *SHP607 / ROP, SHP630 / BIKAM*	Norman Barton, M.D., Ph.D.	11:15-11:45
Rare Diseases: Complement Biology and Renal / Fibrotic *SHP616 / Cinryze new uses*	Howard Mayer, M.D.	1:15-1:30
Rare Diseases: CNS *SHP609 / Hunter CNS, SHP610 / Sanfilippo A, SHP611 / MLD, Armagen*	Howard Mayer, M.D.	1:30-2:00
Late-Stage Update *SHP606 / Lifitegrast, BED, SHP465 / ADHD*	Howard Mayer, M.D. Randy Brenner *Joe Tauber, M.D.*	2:00-2:45

Cinryze New Use Programs in Complement and Renal



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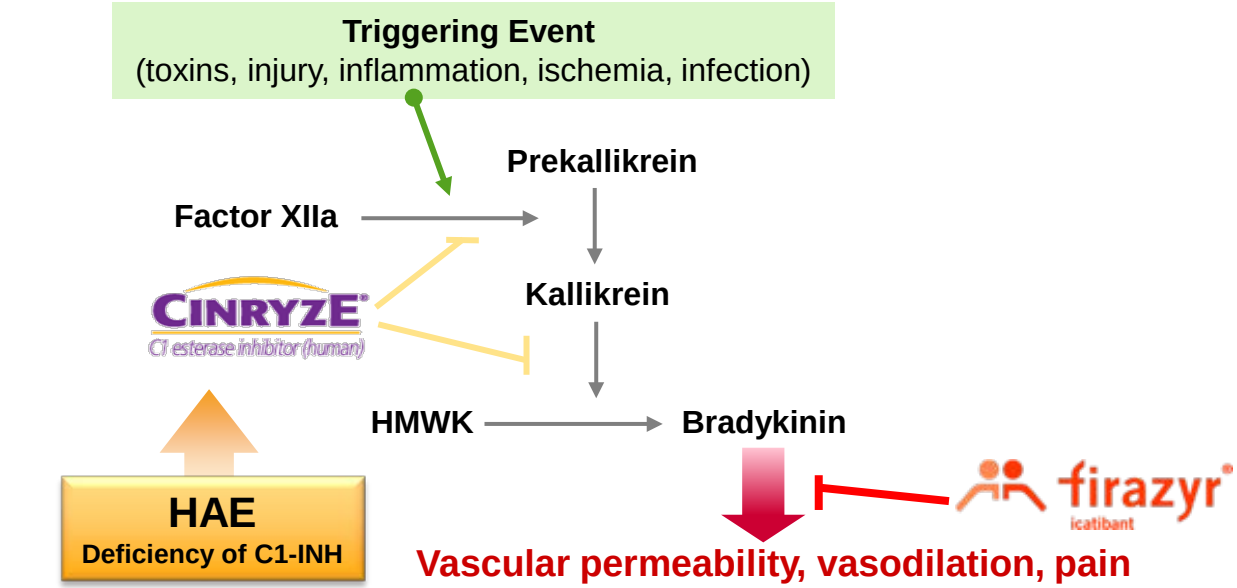
CINRYZE (C1 INH): Regulator of Inflammatory Cascades

- Member of serine proteinase inhibitors (“serpins”)
- Heavily glycosylated 478 amino acid protein
- Regulates several inflammatory cascades
  - Contact system: inhibition of factor XIIa and kallikrein
  - Complement: inhibition of C1s, C1r and MASPs
  - Amplification loop of coagulation: inhibition of factor XIa
  - Inhibition of Factor VII activating protease (FSAP)

- Physiological role: to mitigate the pro-inflammatory phase of the acute phase response
  - Doubling of plasma concentrations later in acute phase reaction

Shire

CINRYZE Reduces Frequency of HAE Attacks by Regulating Contact Inflammatory Pathway Preventing Excess Bradykinin

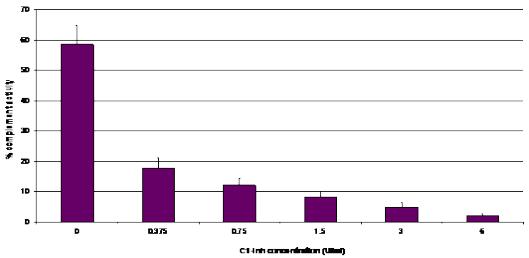


Normal Condition | Mild/Moderate | Severe | Very Severe

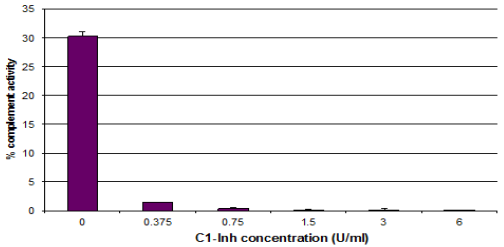
Shire

CINRYZE (C1 INH) Also Has Inhibitory Activity On All Three Complement Inflammatory Pathways*

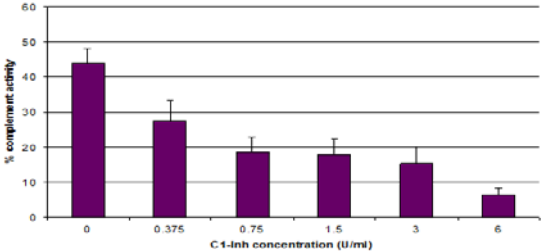
Classical Pathway



Lectin Pathway



Alternative Pathway



Antibody-Mediated Disease – Classical Complement Pathway

- **Neuromyelitis Optica (NMO)**
- **Antibody Mediated Rejection (AMR) in Kidney Transplantation**
- Autoimmune Hemolytic Anemia (AIHA)

Ischemia Reperfusion Injury – Lectin Complement Pathway

- Delayed Graft Function (DGF)

Other Diseases – Alternative Complement Pathway Mediated

- **Paroxysmal Nocturnal Hemoglobinuria (PNH)**

Shire

Data on file, Sponsored Study UMCG *Human Serum / Weilisa Assays

SHP616 (Cinryze): Acute Neuromyelitis Optica

Preclinical	Phase 1	Phase 2		Phase 3	Registration
26 Research Programs	**SHP611** MLD (Ph 1/2)	**SHP602** Iron overload (clinical hold)	**SHP616 (Cinryze)** Acute Antibody Mediated Rejection	**Firazyr** ACE inhibitor-induced AE	**XAGRID® (Japan)** Thrombocythaemia *(Approved 3Q 2014)*
SHP619 Duchenne's Muscular Dystrophy	**SHP616 (Cinryze SC)** HAE Prophylaxis	**SHP610** Sanfilippo A	**SHP625 (LUM001)** Primary Biliary Cirrhosis	**Firazyr** (Japan) HAE	**VPRIV (Japan)** Gaucher *(Approved 3Q 2014)*
TH / GCH1 Gene Pod Parkinson's Subset	**SHP622** Friedreich's Ataxia	**SHP609** Hunter CNS	**SHP625 (LUM001)** Progressive Familial Intrahepatic Cholestasis	**SHP616 (Cinryze) (Japan)** HAE Prophylaxis	**INTUNIV® (EU)** ADHD
SHP608 Dystrophic E.Bullosa	**SHP627 (FT011)** Focal Segmental Glomerulosclerosis	**SHP607** Prevention of ROP	**SHP625 (LUM001)** Alagille Syndrome	**SHP555 (US)** Chronic Constipation	**Vyvanse** BED
SHP614 IgA Nephropathy	**SHP616 (Cinryze)** Paroxysmal Nocturnal Hemoglobinuria	**SHP620 (Maribavir)** CMV in transplant patients	**SHP625 (LUM001)** Primary Sclerosing Cholangitis	**INTUNIV (Japan)** ADHD	
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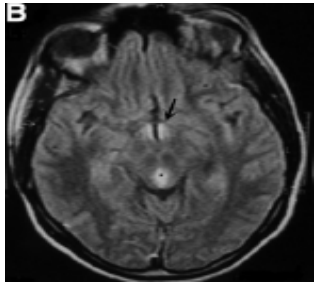
SHP630 adRP	**SHP626 (LUM002)** Non-Alcoholic Steatohepatitis			**SHP465** ADHD	
SHP624 Heme B Gene Edit					
SHP628 (FT-061) Renal Impairment					

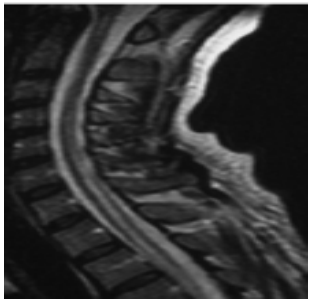
Complement Biology
Renal / Transplant
Ophthalmics
GI / Metabolic
CNS
Rare Diseases Leadership

Shire

Neuromyelitis Optica (NMO)

- Inflammatory disease of the CNS that selectively attacks the optic nerve and spinal cord
- NMO disability accumulates through relapses; even a single relapse can have severe clinical consequence
- Prevalence: 1 – 3 / 100,000
- Associated with circulating IgG auto-antibodies against the astrocyte water channel protein aquaporin-4 (AQP4) “NMO-IgG”
- Results in antibody-mediated classical complement activation
- No approved treatment
  - Steroids and plasmapheresis for acute attacks
  - Immunosuppressants for prevention





Wingerchuk D. *AAN Continuum.* 2010

NMO Pilot Clinical Study Design

SHP616 (Cinryze)
Acute Neuromyelitis Optica

Study enrolled between January – August 2013

N = 10 patients with NMO / NMOSD

Dosing Regimen	• CINRYZE 2000 units/day on days 1-3 at onset of acute NMO attack • Added on to 'standard of care': IV Solumedrol
Outcomes	• Primary: safety/tolerability • Secondary: effectiveness as measured by EDSS
Top Line Results	• No SAEs reported • Generally well tolerated; no patients discontinued from study • AE profile c/w known product profile

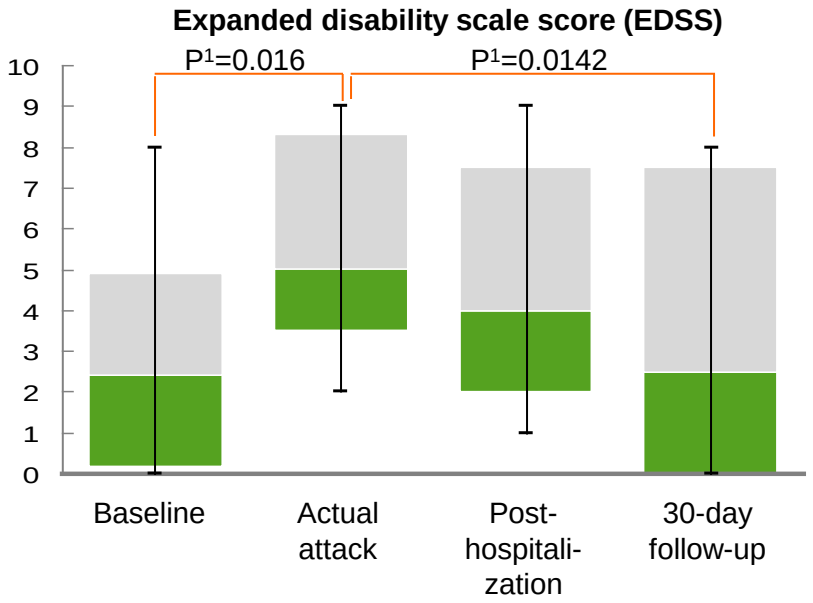
*Expanded Disability Status Scale quantifies disability across eight functional systems with an overall score ranging from 0 (normal) to 10 (death). Scores above 5 indicate impaired ambulation.

Levy M,Mealy MA. Purified human C1-esterase inhibitor is safe in acute relapses of neuromyelitis optica. Neurol Neuroimmunol Neuroinflammation vol 1 no.1 Published online April 24,2014

Shire

NMO Pilot Clinical Study Results

SHP616 (Cinryze)
Acute Neuromyelitis Optica



Data suggest that C1 INH may be effective to limit neurologic damage and clinical disability from acute relapses:

- Majority of patients returned to their pre-attack level of neurologic function
- Only 2 patients required plasmapheresis (historical rate of about 40 – 50%)

Clinical Development next steps

Meet with FDA in 1Q2015 to agree on the design of a Phase 2/3 placebo controlled trial in patients with acute NMO relapses

*Expanded Disability Status Scale quantifies disability across eight functional systems with an overall score ranging from 0 (normal) to 10 (death). Scores above 5 indicate impaired ambulation.

Levy M,Mealy MA. Purified human C1-esterase inhibitor is safe in acute relapses of neuromyelitis optica. Neurol Neuroimmunol Neuroinflammation vol 1 no.1 Published online April 24,2014

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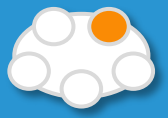
SHP616 (Cinryze): Antibody-Mediated Rejection (AMR) in Kidney Transplantation



Preclinical	Phase 1	Phase 2		Phase 3	Registration
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SHP624 Heme B Gene Edit					
SHP628 (FT-061) Renal Impairment					

- Complement Biology
- Renal / Transplant
- Ophthalmics
- GI / Metabolic
- CNS
- Rare Diseases Leadership

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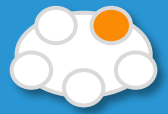
Antibody-Mediated Rejection (AMR) in Kidney Transplantation



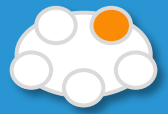
SHP616 (Cinryze)
Acute Antibody Mediated Rejection

- Kidney transplant patients with donor specific antibody (DSA) have worse outcomes because of the high rate of AMR and resultant transplant glomerulopathy (tg)
- Patients with tg have a lower graft survival at one year (67% vs 97%; p<0.001)
  - Loss of graft = poor quality of life, significant costs related to dialysis and related complications of renal failure
- 6,000 US patients have willing live donor but are DSA+ and do not get transplanted
- Acute AMR affects ~2,500 in US and EU5
  - 2.5% of standard transplants; >25% of DSA+ patients
- No approved treatments for AMR and current treatments not sufficient
  - 50% fail standard of care (Plasmapheresis and IVIG)

Sharif et al. Transplantation 2014;97: 541-547, Montgomery RA. Am J Transpl 2010;10: 449-457,
Bentall et al. Am J Transpl 2013;13: 76-85, Haririan et al. Am J Transpl 2009;9: 2758-2767.

Shire

Antibody-Mediated Rejection in Kidney Transplantation Phase 2 Study Design



SHP616 (Cinryze)
Acute Antibody Mediated Rejection

Double-blind, randomized, placebo-controlled, multicenter Phase 2 study of acute AMR in kidney transplant patients with donor specific antibody

18 patients enrolled [CINRYZE (n=9); Placebo (n=9)]

Dosing Regimen

- CINRYZE 20,000 Units IV over 13 days
  (5,000 U bolus followed by 2,500 U on Days 3, 5, 7, 9, 11, 13)
- Placebo: IV 0.9% sodium chloride solution for infusion administered on Days 1, 3, 5, 7, 9, 11, and 13
- Add on to standard of care: IVIG and / or plasmapheresis

Objectives

- Safety, PK, Clinical Effect

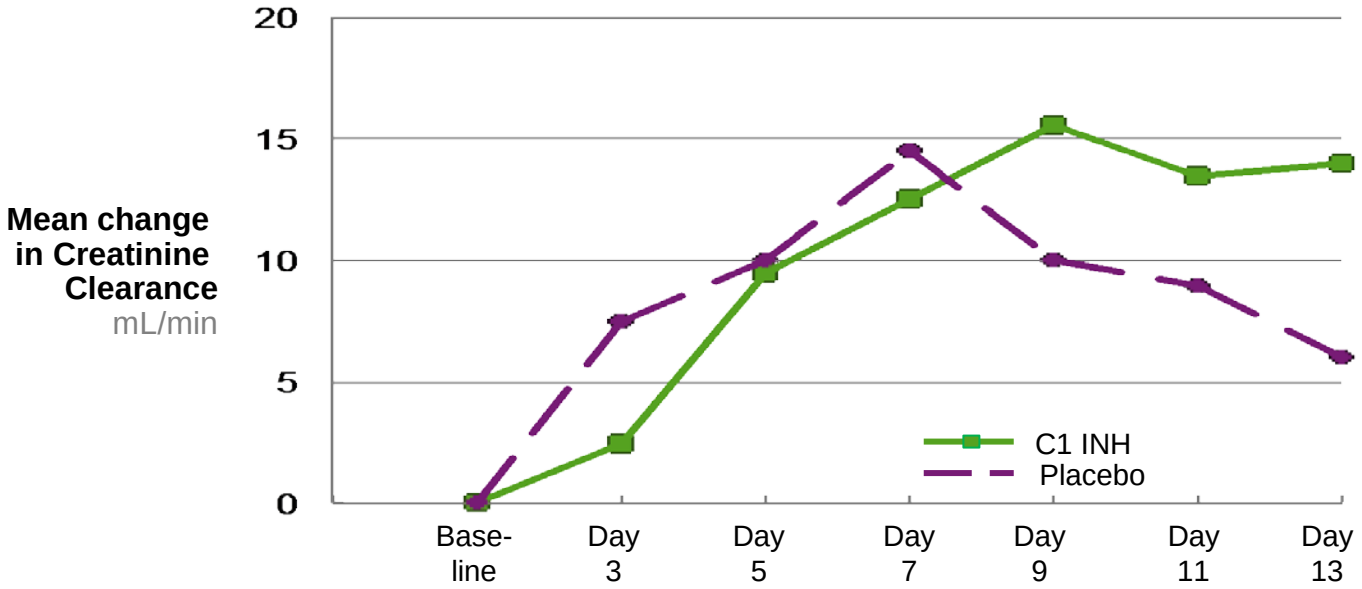
Top Line Results

- No discontinuations, study drug-related SAEs or deaths
- CINRYZE-treated subjects achieved higher exposure of C1 INH functional activity on Day 13, with baseline-corrected steady-state Cmax and AUClast for functional activity ranging from 3.7- to 8.8-fold higher than placebo subjects
- No difference in renal histopathological outcome 7 days after last dose

Antibody-Mediated Rejection in Kidney Transplantation Phase 2 Study Results (1/2)

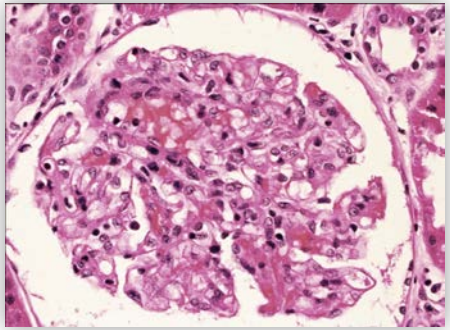
SHP616 (Cinryze)
Acute Antibody Mediated Rejection

Renal function (mean by cohort), measured as mean change in Creatinine Clearance (mL/min)



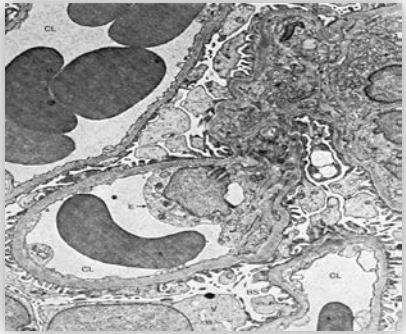
Montgomery R, et al. *Am J Transplant*. 2014; 14(S3):129-130. In: Supplement: 2014 World Transplant Congress Abstracts, 26-31 July, 2014; San Francisco, CA. Abstract 2252.

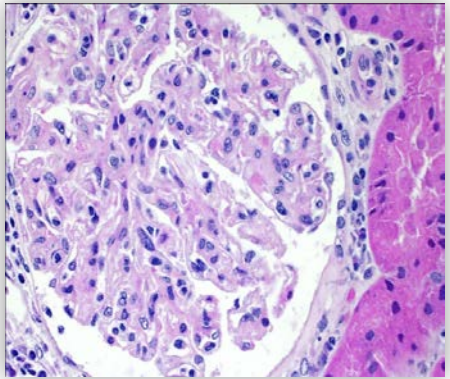
Transplant Glomerulopathy (tg) Seen in 3/7 PBO Patients and 0/7 CINRYZE Patients at 6 Months



normal

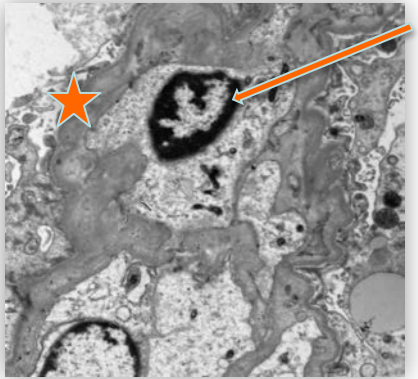
CINRYZE subject





tg

Placebo subject



WBC(2): inflammation

Multilayered GBM (1)

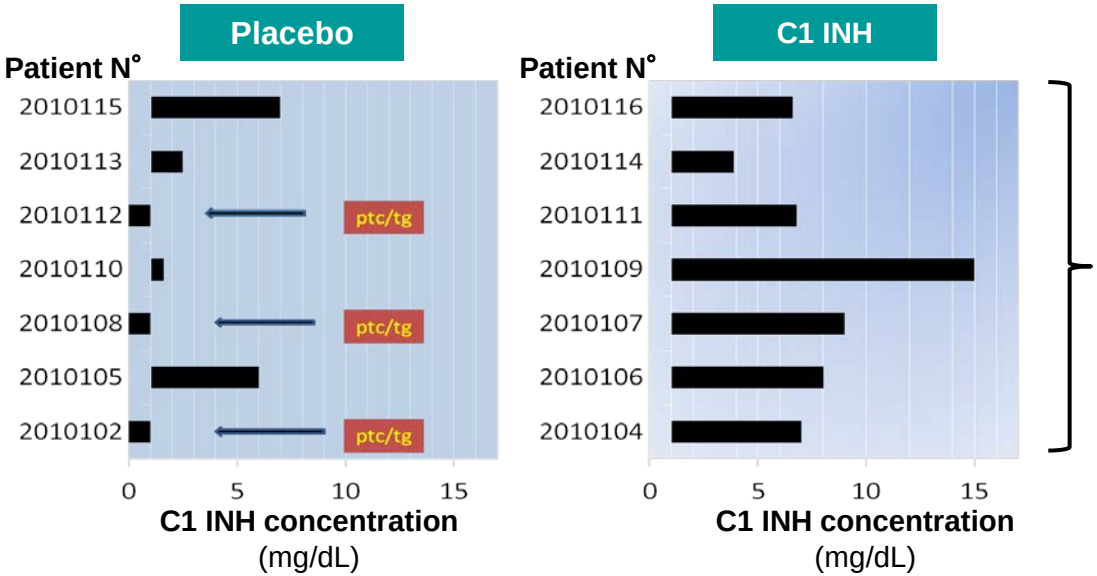
Chronic rejection = new onset transplant glomerulopathy (tg), a clinically accepted surrogate for accelerated loss of a kidney allograft

(1) GBM refers to the glomerular basement membrane

(2) White Blood Cells

Study Results (2/2): tg May be Related to Lower C1 INH Antigen Levels During Therapy for AMR

Patients developing post-transplantation glomerulopathy in the placebo arm had no C1 INH level above baseline



- None of the patients who received C1 INH had post-transplant glomerulopathy
- This suggests that C1 INH may reduce the risks of AMR

Clinical Development Next Steps

- Positive EOP2 feedback from FDA on the use of the accelerated approval pathway based on tg, with longer term confirmatory clinical data in the same study
- Pivotal registrational trial to start in 2015

Montgomery R, et al. *Am J Transplant*. 2014; 14(S3):129-130. In: Supplement: 2014 World Transplant Congress Abstracts, 26-31 July, 2014; San Francisco, CA. Abstract 2252.

SHP616 (Cinryze): Paroxysmal Nocturnal Hemoglobinuria

Preclinical	Phase 1	Phase 2		Phase 3	Registration
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SHP628 (FT-061) Renal Impairment					

- Complement Biology
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- Ophthalmics
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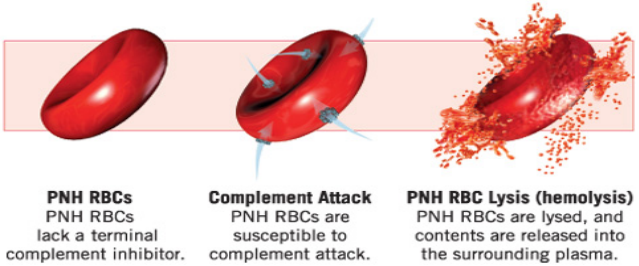
- CNS
- Rare Diseases Leadership

Shire

Paroxysmal Nocturnal Hemoglobinuria (PNH)

SHP616 (Cinryze)
Paroxysmal Nocturnal Hemoglobinuria

- Clonal hematopoietic stem cell disorder
- Worldwide prevalence estimated at 1-5 cases / million
- Hemolytic anemia, bone marrow failure, thrombosis
- Acquired mutation of PIG-A gene
- PIG-A required for GPI–anchored protein biosynthesis
  - CD55 inhibits C3 convertase
  - CD59 blocks membrane attack complex (MAC) formation
- PNH cells have deficiency or absence of both CD 55/59
- Eculizumab is an FDA-approved monoclonal antibody vs C5 protein that compensates for CD59 deficiency and reduces intravascular hemolysis and thrombosis risk in PNH patients
- Eculizumab does not compensate for CD55 deficiency which may result in extravascular hemolysis and persistent anemia



DeZern AE et al, Exp Hematol 2014;42:857-861
Brodsky RA, Blood 2014;124:2804-2811

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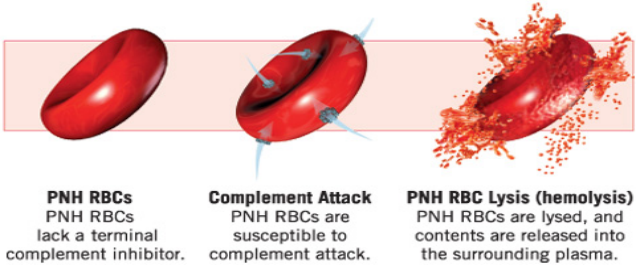
PNH *ex vivo* Study Design

Sera from 6 PNH patients with type III proportion >5%

All patients had been treated with eculizumab

Clinical criteria for hemolysis noted at time of sampling



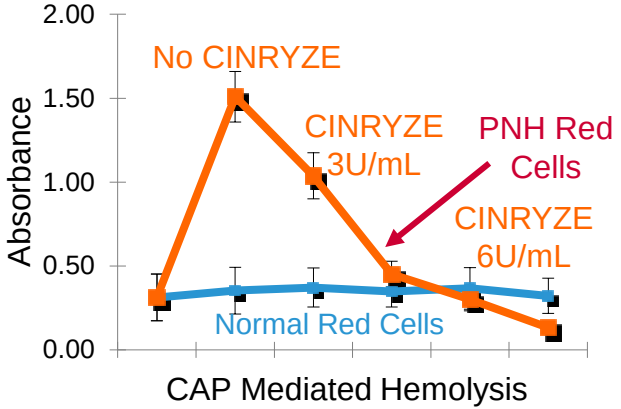
Study Design

- PNH Erythrocytes were incubated with 25% acidified human serum with or without CINRYZE
- Part A – optical density by spectrophotometry at 415 nm was used to calculate the percentage PNH RBC lysis
- Part B – Flow cytometry was used to analyze deposition of C3 activation fragments on intact and lysed PNH erythrocytes (ghosts)

Shire

DeZern AE et al, Exp Hematol 2014;42:857-861

PNH *ex vivo* Study Results



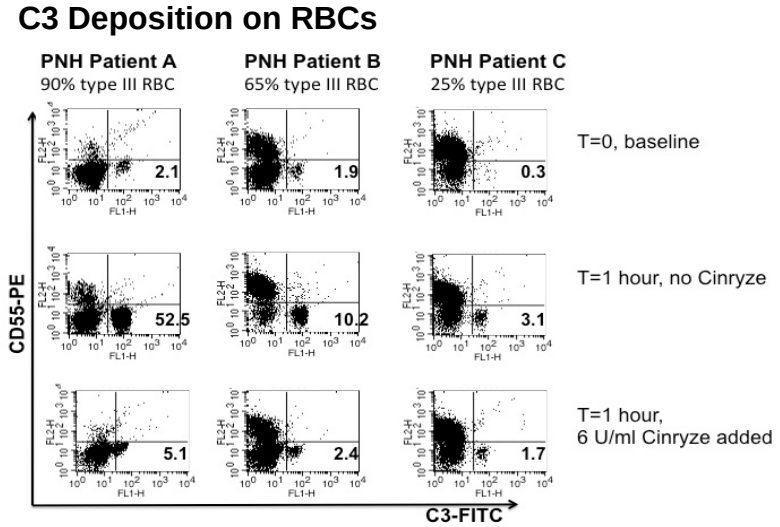


Figure 3 Part A. Flow cytometric profiles of C3 deposition on intact PNH RBCs and PNH RBC ghosts that were recovered after one-hour incubation in acidified normal serum without and with Cinryze (Row 2 and 3). Numbers in dot plots indicate the percentage of $C3^{pos}$ $CD55^{neg}$ cells.

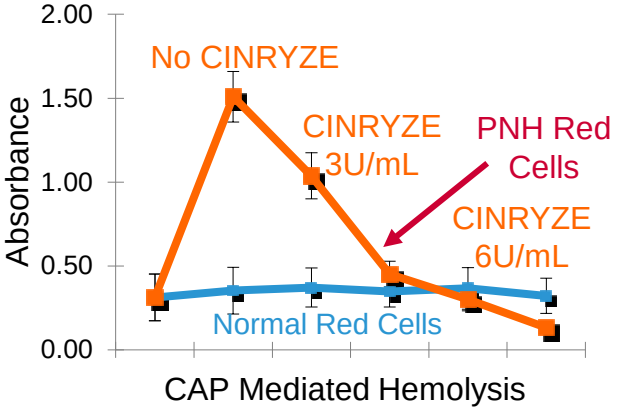
- CINRYZE (C1 INH) **attenuated hemolysis** of PNH erythrocytes in a dose-dependent fashion
- CINRYZE (C1 INH) **blocked accumulation of C3** degradation products on PNH erythrocytes from patients on eculizumab

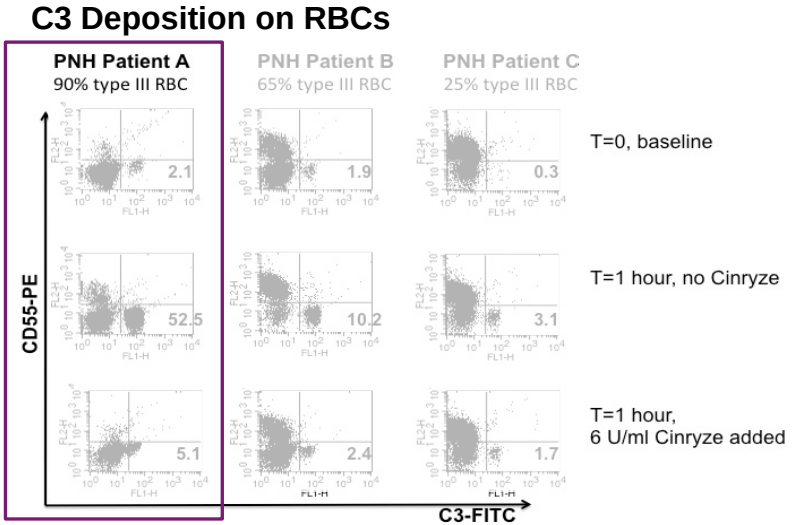
Clinical Development Next Steps

- IND planned 1H 2015
- Dose ranging safety/PK 2015

DeZern AE et al, American Society of Hematology: Abstract #594, Dec 7, 2013
DeZern AE et al, Exp Hematol 2014;42:857-861

PNH *ex vivo* Study Results





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Next Steps for *CINRYZE*® New Uses Programs

Acute Neuromyelitis Optica	• Meet with FDA in 1Q2015 on the design of a Phase 2/3 trial in patients with acute NMO relapses
Acute Antibody Mediated Rejection	• Positive feedback from FDA on accelerated approval pathway based on transplant glomerulopathy • Pivotal registrational trial to start in 2015
Paroxysmal Nocturnal Hemoglobinuria	• IND planned 1H 2015 • Dose ranging safety/PK study planned for 2015

Shire

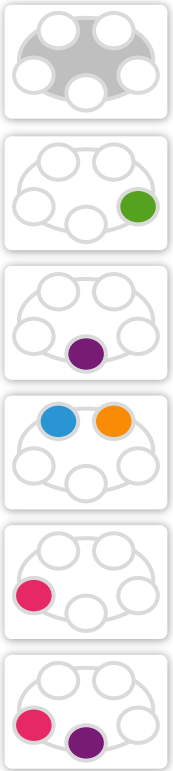
Rare Diseases:
CNS

Howard Mayer, M.D., Head of Clinical Development

Our purpose
We enable people with life-altering conditions to lead better lives.

Shire

Today's R&D Sessions



Research Overview and Technology Platforms *mRNA, Protein Replacement, Gene Therapy, Antibody Platforms*	Albert Seymour, Ph.D.	9:25-10:00
Rare Diseases: GI / Metabolic *SHP625 (LUM001), SHP626 (LUM002)*	Ciara Kennedy, Ph.D. *David Piccoli, M.D.*	10:00-10.45
Rare Diseases: Ophthalmology *SHP607 / ROP, SHP630 / BIKAM*	Norman Barton, M.D., Ph.D.	11:15-11:45
Rare Diseases: Complement Biology and Renal / Fibrotic *SHP616 / Cinryze new uses*	Howard Mayer, M.D.	1:15-1:30
Rare Diseases: CNS *SHP609 / Hunter CNS, SHP610 / Sanfilippo A, SHP611 / MLD, Armagen*	Howard Mayer, M.D.	1:30-2:00
Late-Stage Update *SHP606 / Lifitegrast, BED, SHP465 / ADHD*	Howard Mayer, M.D. Randy Brenner *Joe Tauber, M.D.*	2:00-2:45

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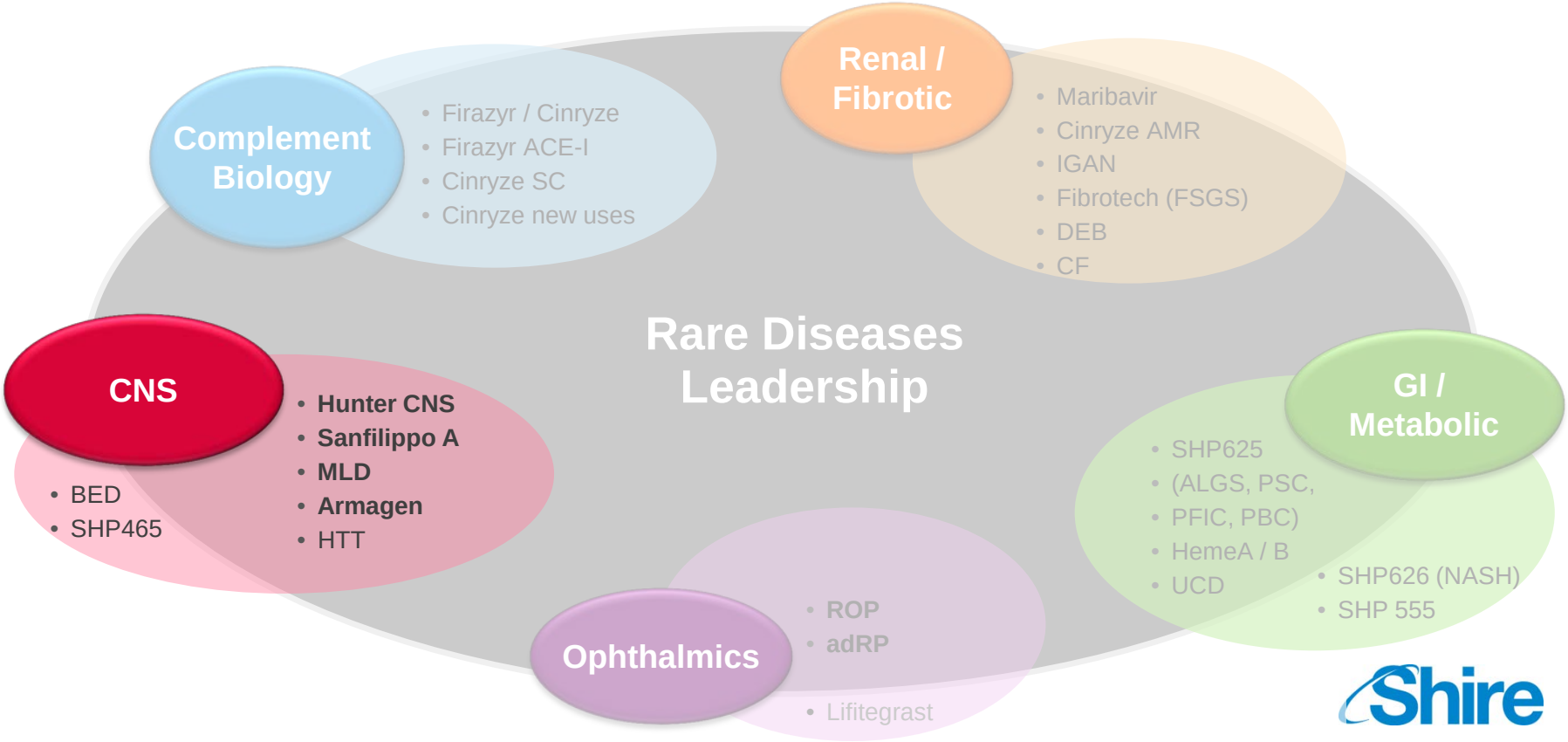
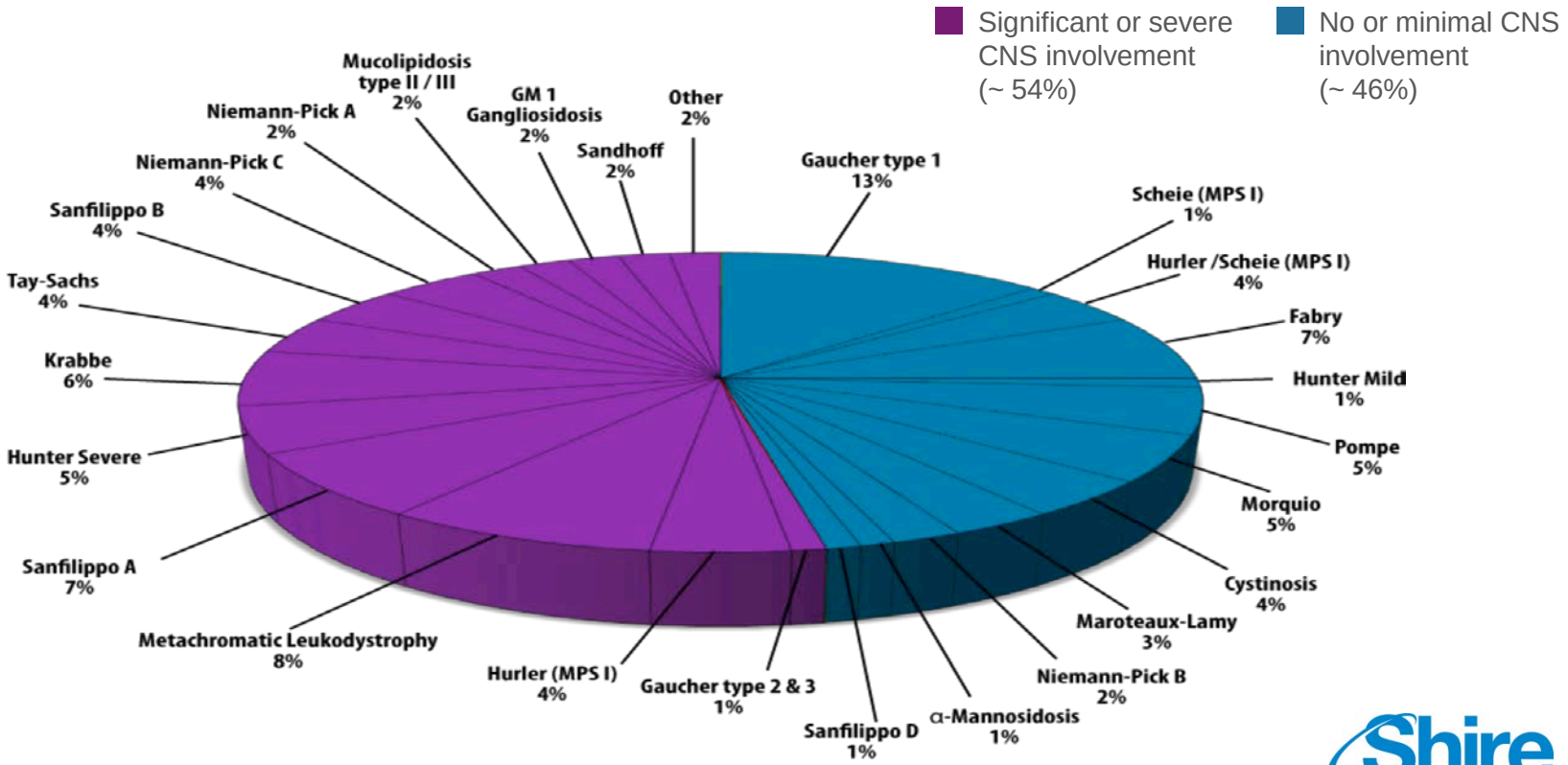
Multiple Rare Diseases Programs in CNS



Shire

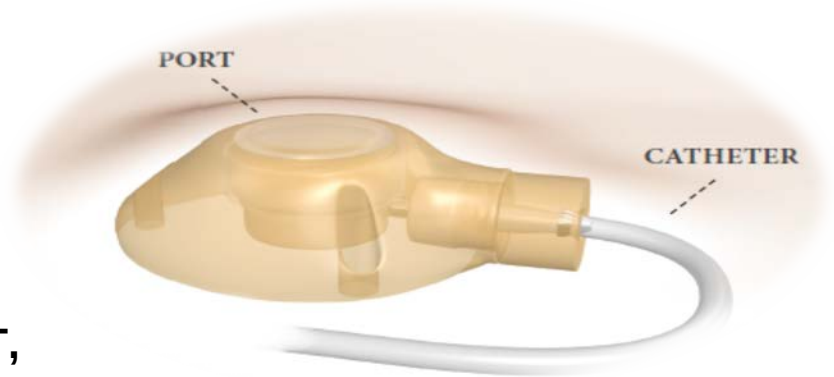
CNS Involvement by Lysosomal Storage Diseases (LSDs)



Meikle et al., JAMA 1999

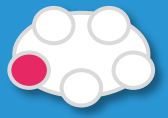
Intrathecal Drug Delivery Device (IDDD)

- To circumvent the Blood Brain Barrier, recombinant enzymes are administered into the subarachnoid space, via a transcutaneously accessible indwelling intrathecal drug delivery device (IDDD)
- Soph-A-Port® Mini S is an implantable access system designed to provide repeated access to the intrathecal space for drug delivery
- It is CE marked in Europe and approved for investigational use in the US
- It is **currently being used in Shire's Hunter-IT, Sanfilippo A and MLD** clinical development programs



SHP609: Hunter Syndrome (MPS II)

Recombinant human idursulfase-IT



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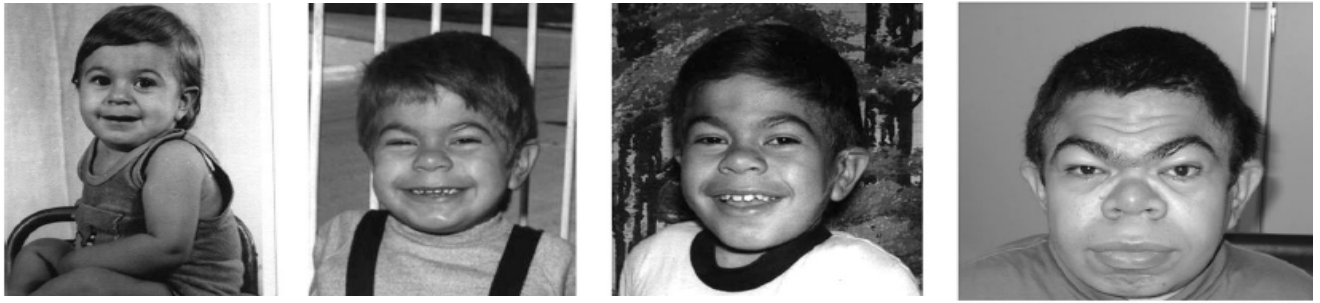
Shire

Mucopolysaccharidosis II – Hunter Syndrome

SHP609
Hunter CNS



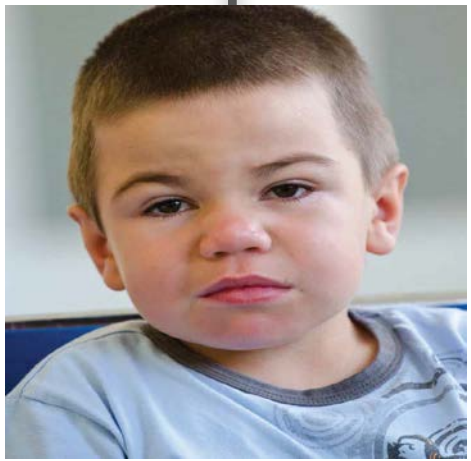
A series of photographs showing the progression of the characteristic facial features of Hunter syndrome.
The ages of the boy from left to right are 6 months and 5, 9 and 30 years.

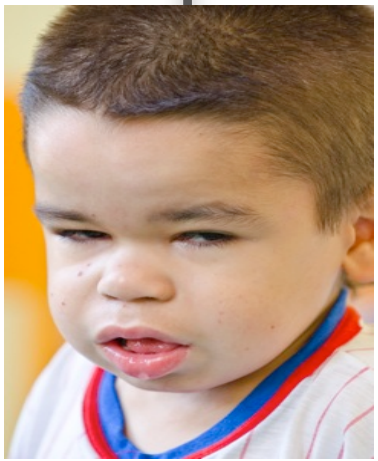
- Extremely rare X-linked lysosomal storage disease
- Incidence ~ 1 in 170,000 male births
- Absence or deficient activity of the lysosomal enzyme iduronate-2-sulfatase (I2S)
- Diagnosis typically at 2-6 years, prompted by typical appearance (coarse facial features), organomegaly or developmental delays
- Multiple physical issues caused by deposits of glycosaminoglycans in the soft tissues of upper respiratory tract, joints, heart, liver and spleen
- 2/3 of patients experience progressive developmental delay and cognitive decline, usually leading to death in the teenage years
- Idursulfase (ELAPRASE) is an intravenous enzyme replacement therapy which addresses some of the somatic issues but does not address the cognitive issues

Muenzer et al., Pediatrics 2009; Martin et al., 2008

Spectrum of Disease in Hunter Syndrome

Attenuated — Severe



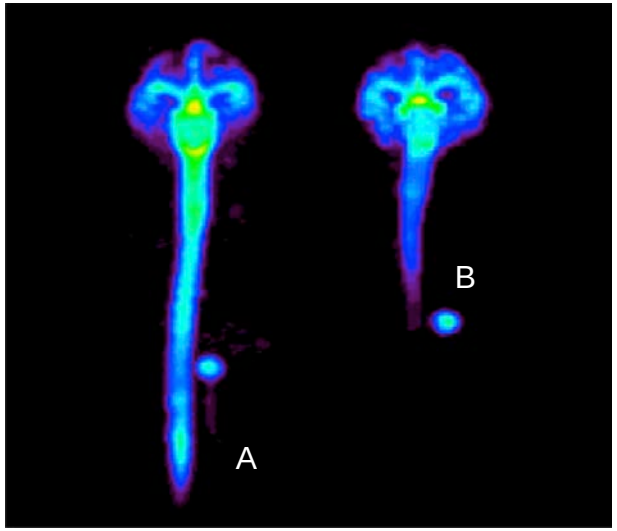


- Insidious onset
- Normal intelligence
- Variable life expectancy

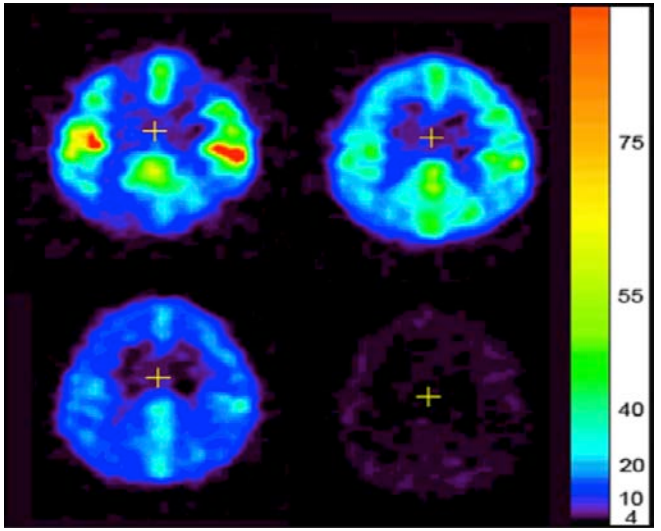
- Onset by 2 to 4 years of age
- Impaired intelligence
- Life expectancy 10 to 15 years

Uptake of Labeled Iduronate-2-Sulfatase (I2S) in Cynomolgus Monkey After Intrathecal and ICV(1) Delivery

In vivo distribution of 124I -labeled I2S (3 mg/animal) in cynomolgus monkeys by PET



Distribution of I2S administered through the lumbar (left) and ICV (right) catheters 30 minutes after the administration as demonstrated by a projection PET image (sum of all slices). Relative linear color scale.

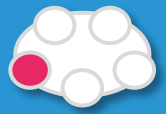


The distribution of I2S in the brain at 0.5, 2.5, 5 and 24 hours after lumbar administration; PET image, 1.2 mm slice through the corpus callosum region in the plane parallel to the occipital bone. The color scale is calibrated in mg/ml of I2S.

1 Intracerebroventricular

Papisov et al., PLOS 2012

Phase 1/2:
Multiple-dose Dose-escalation Study in MPS II



SHP609
Hunter CNS

- Study drug was idursulfase-IT, a formulation of recombinant iduronate-2-sulfatase that is different from that used for IV idursulfase treatment

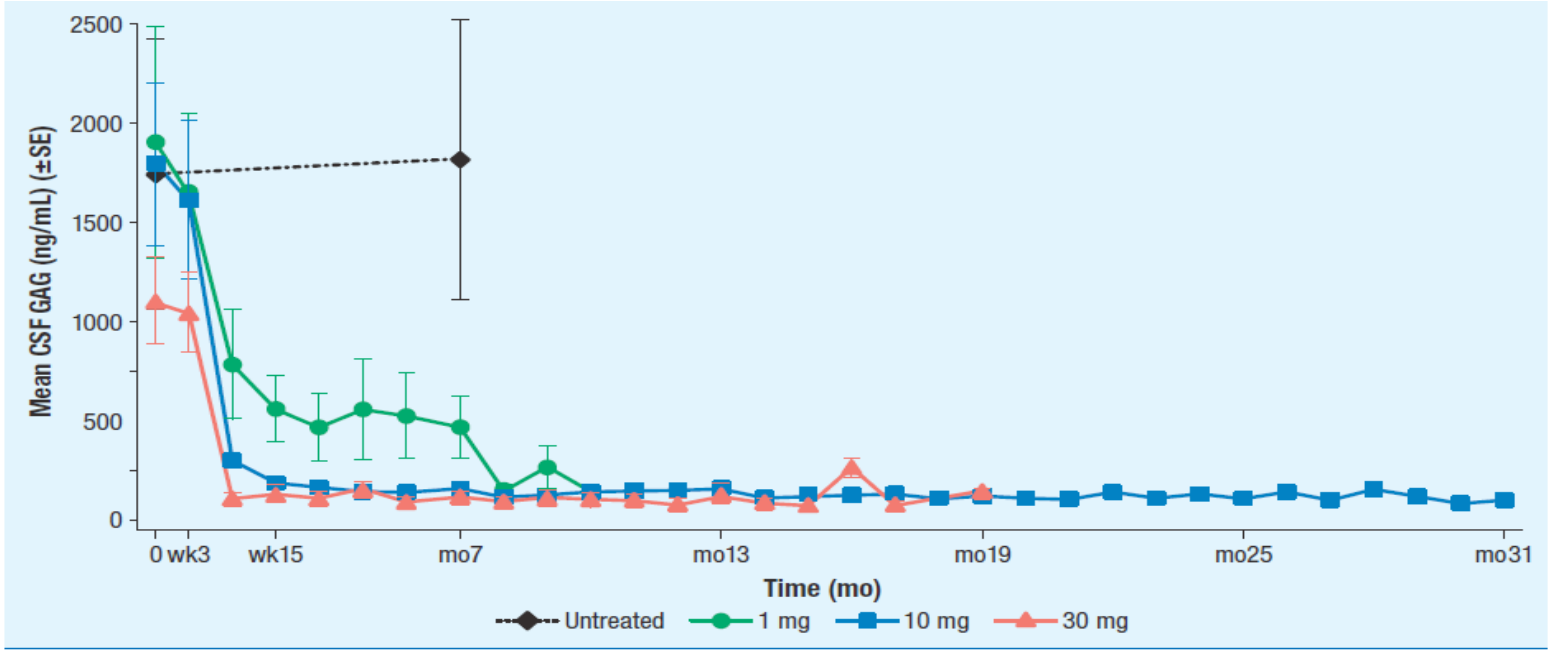
- Four patients per treatment arm (n=16)

Treatment Arms	• 10, 30 and 1 mg of idursulfase-IT and no-treatment • Administered via IDDD or lumbar puncture • Dosed monthly for 6 months • All patients received weekly IV idursulfase 0.5 mg/kg IV
Inclusion Criteria	• Ages 3 to18 years • Cognitive impairment due to MPS II (GCA ≤ 77) • History of tolerating weekly IV idursulfase 0.5 mg/kg for at least 6 months
Primary Endpoint	• Safety and tolerability of ascending doses of idursulfase-IT
Secondary Endpoint	• Change From Baseline in CSF Glycosaminoglycans [GAGs] at 6 months

Exploratory Efficacy Endpoints	• Cognitive / adaptive behavioral testing at 0 and 6 months
	• Differential Abilities Scale-II (DAS-II)
	  • Preferred method in the study and can be performed with cognitively impaired children
	  • Yields the **General Conceptual Ability** (GCA), which is constructed like an IQ

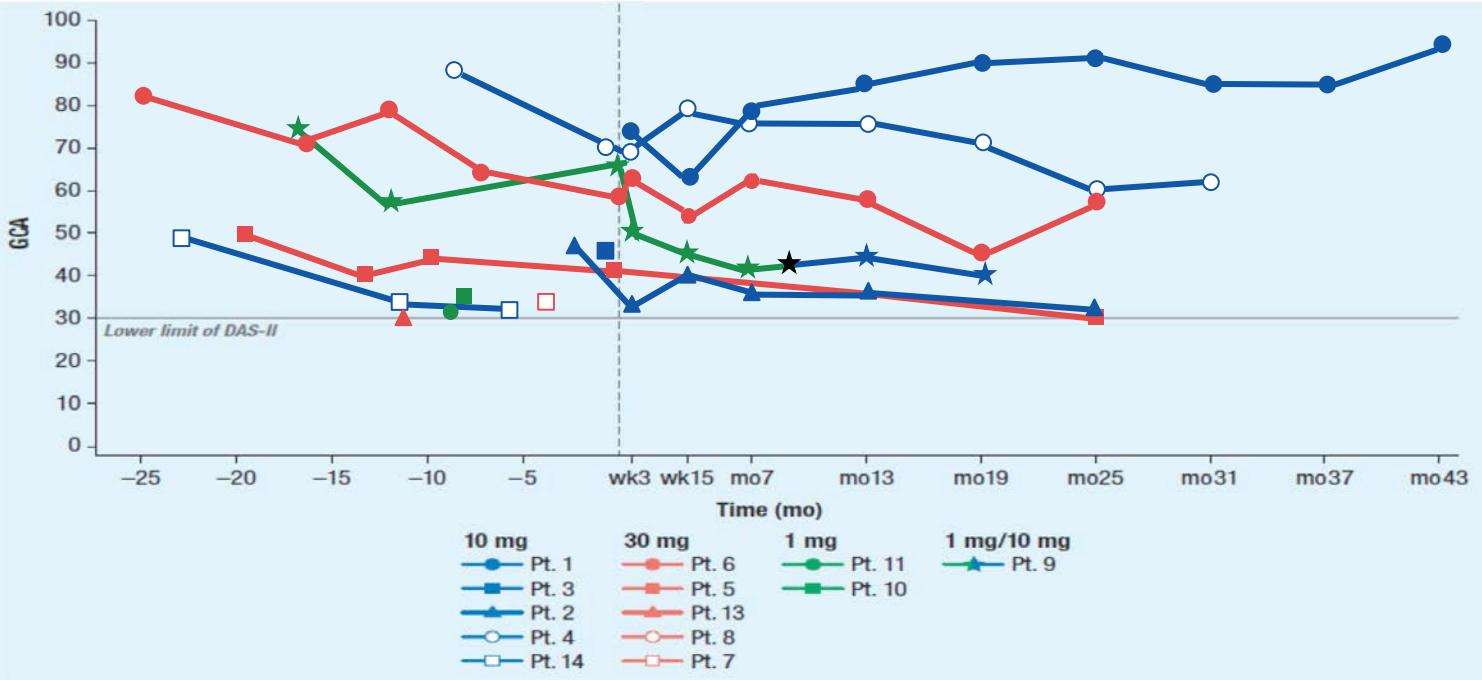
- All eligible patients rolled over into an extension trial, currently there are 14 patients in the extension trial

MPSII: Effect of Idursulfase-IT Administration on Biomarkers in a Phase I-II Study and Extension



Note: Time 0 is the phase ½ (HGT-HIT-045) randomization date for treated patients in HGT-HIT-045 and is the date of receipt of the informed consent form for the extension study (HGT-HIT-046) from untreated patients in HGT-HIT-045. Week 3 is the date of the first dose of idursulfase-IT.
CSF, cerebrospinal fluid; GAG, glycosaminoglycan; IT, intrathecal.

MPSII: Effect of Idursulfase-IT on Cognitive Performance in a Phase I-II Study and Extension



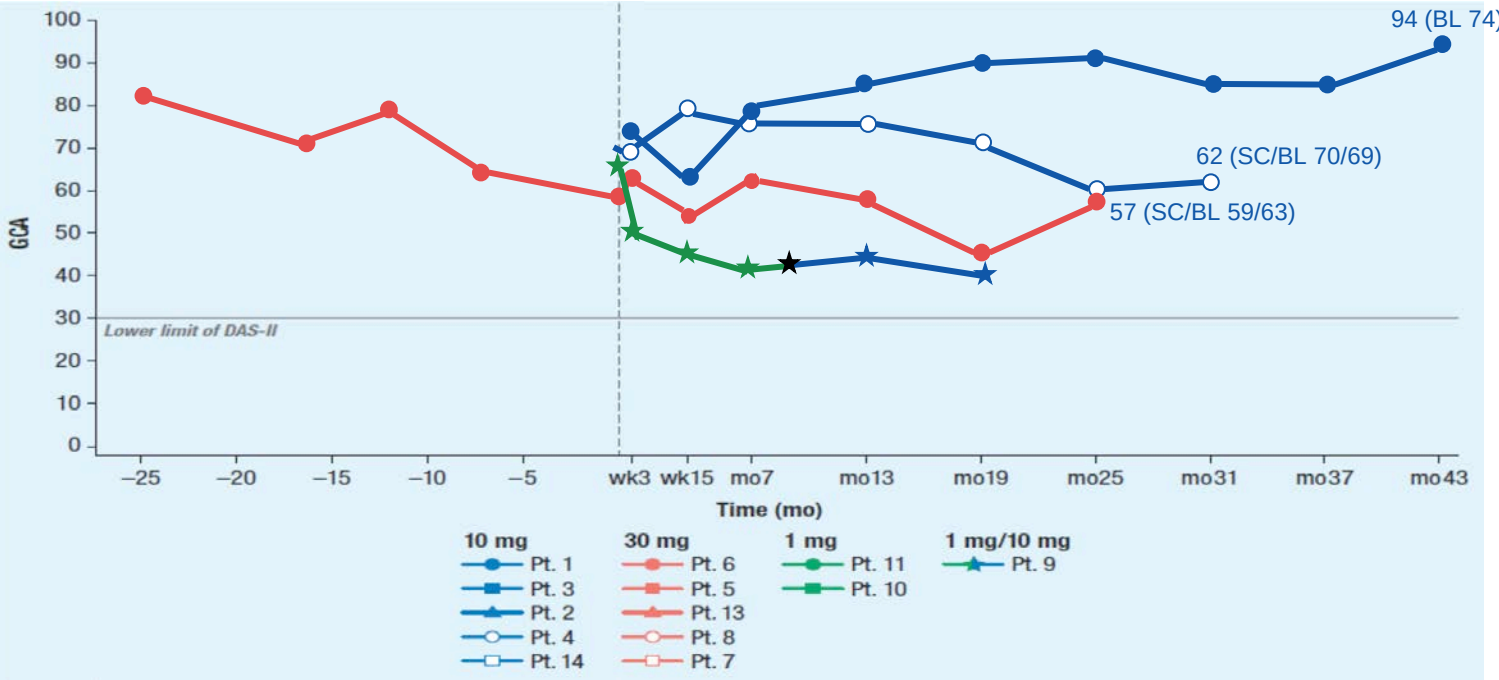
At Month 9, Patient 9 was switched from 1 mg idursulfase-IT monthly in the phase ½ trial to 10mg monthly in the extension study.

Note: Time 0 is the phase ½ (HGT-HIT-045) randomization date for treated patients in HGT-HIT-045 and is the date of receipt of the informed consent form for the extension study (HGT-HIT-046) from untreated patients in HFT-HIT-045. Week 3 is the date of the the first dose of idursulfase-IT.

DAS-II, Differential Ability Scales-Second Edition; GCA, general conceptual ability; IT, intrathecal.

MPSII: Effect of Idursulfase-IT on Cognitive Performance in Mild-Moderate Impaired Patients

SHP609
Hunter CNS



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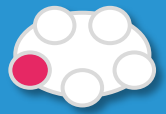
Note: Time 0 is the phase ½ (HGT-HIT-045) randomization date for treated patients in HGT-HIT-045 and is the date of receipt of the informed consent form for the extension study (HGT-HIT-046) from untreated patients in HFT-HIT-045. Week 3 is the date of the the first dose of idursulfase-IT.
DAS-II, Differential Ability Scales-Second Edition; GCA, general conceptual ability; IT, intrathecal.

Shire

Hunter-IT Current Phase II/III Pivotal Study

Actively Enrolling, Headline Data Expected Mid 2016*



SHP609
Hunter CNS

Phase II-III (094 study)

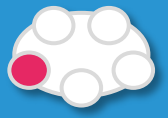
- Multicenter, international, randomized, assessor-blinded
- 42 patients, to be randomized 2:1 (28 treated, 14 untreated)

Inclusion Criteria	• Ages 3 to18 years • Hunter Syndrome and mild to moderate cognitive impairment (between 85 and 55 GCA as measured by DAS-II)
Dosage	• 12 monthly doses via IDDD • Dose level of idursulfase-IT - 10 mg
Primary Endpoint	• Change in General Conceptual Ability (GCA) obtained by the Differential Abilities Scale (DAS-II)
Key Secondary Endpoint	• Independent / adaptive function, measured by Vineland Adaptive Behavior Scales (VABS)

Shire

* Subject to enrollment timelines and interactions with Regulatory Authorities

SHP610: SANFILIPPO A (MPS IIIA)

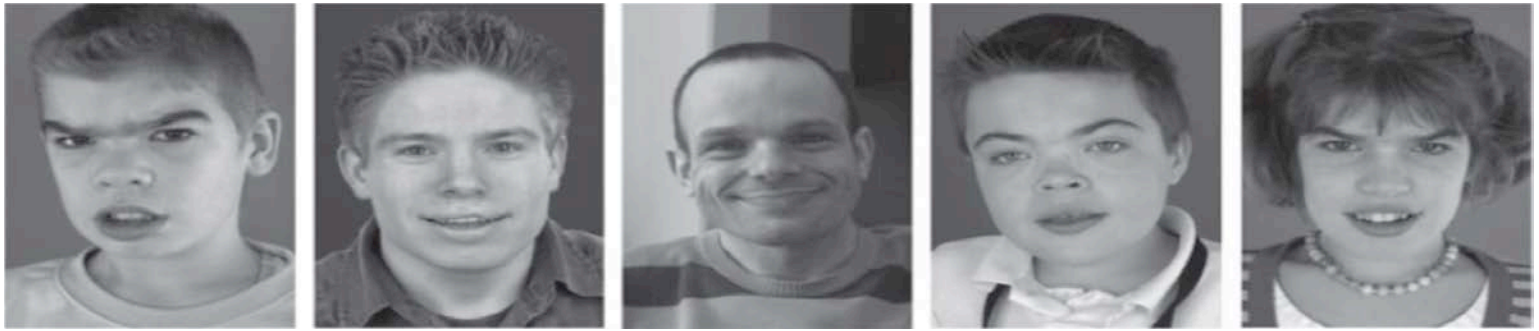


Preclinical	Phase 1	Phase 2		Phase 3	Registration
26 Research Programs	**SHP611** MLD (Ph 1/2)	**SHP602** Iron overload (clinical hold)	**SHP616 (Cinryze)** Acute Antibody Mediated Rejection	**Firazyr** ACE inhibitor-induced AE	**XAGRID® (Japan)** Thrombocythaemia *(Approved 3Q 2014)*
SHP619 Duchenne's Muscular Dystrophy	**SHP616 (Cinryze SC)** HAE Prophylaxis	**SHP610** Sanfilippo A	**SHP625 (LUM001)** Primary Biliary Cirrhosis	**Firazyr** (Japan) HAE	**VPRIV (Japan)** Gaucher *(Approved 3Q 2014)*
TH / GCH1 Gene Pod Parkinson's Subset	**SHP622** Friedreich's Ataxia	**SHP609** Hunter CNS	**SHP625 (LUM001)** Progressive Familial Intrahepatic Cholestasis	**SHP616 (Cinryze) (Japan)** HAE Prophylaxis	**INTUNIV® (EU)** ADHD
SHP608 Dystrophic E.Bullosa	**SHP627 (FT011)** Focal Segmental Glomerulosclerosis	**SHP607** Prevention of ROP	**SHP625 (LUM001)** Alagille Syndrome	**SHP555 (US)** Chronic Constipation	**Vyvanse** BED
SHP614 IgA Nephropathy	**SHP616 (Cinryze)** Paroxysmal Nocturnal Hemoglobinuria	**SHP620 (Maribavir)** CMV in transplant patients	**SHP625 (LUM001)** Primary Sclerosing Cholangitis	**INTUNIV (Japan)** ADHD	
Armagen Hunter CNS	**SHP616 (Cinryze)** Acute Neuromyelitis Optica	**LDX (Japan)** ADHD		**SHP606 (Lifitegrast)** Dry eye disease	
SHP630 adRP	**SHP626 (LUM002)** Non-Alcoholic Steatohepatitis			**SHP465** ADHD	
SHP624 Heme B Gene Edit					
SHP628 (FT-061) Renal Impairment					

- Complement Biology
- Renal / Transplant
- Ophthalmics
- GI / Metabolic
- CNS
- Rare Diseases Leadership

Shire

MPSIIIA Disease Overview



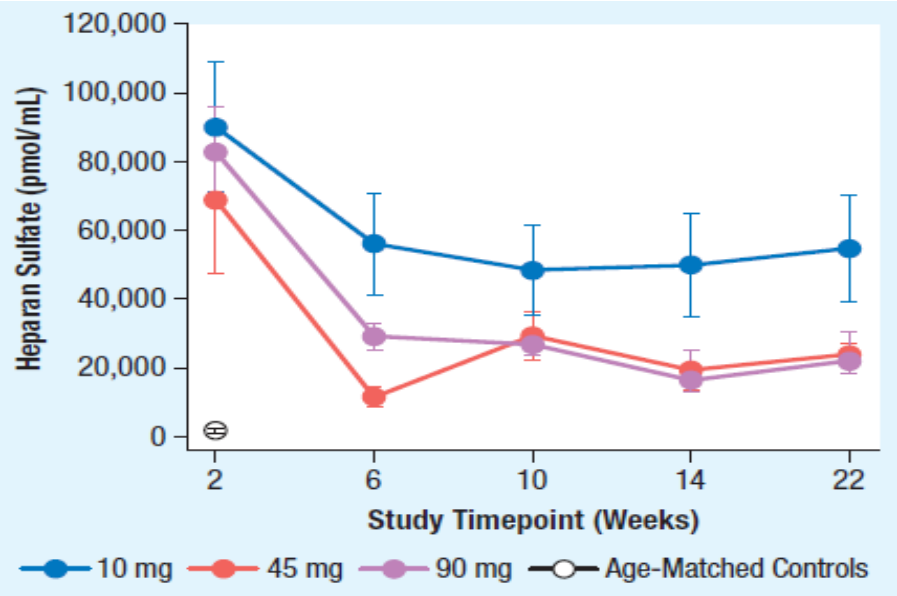
- Autosomal recessive lysosomal storage disease: mutations in *SGSH*, encoding heparan N sulfatase (HNS)
- Live birth incidence ~ 1 in 100,000
- Enzyme defect causes accumulation of heparan sulfate
- Clinical features are overwhelmingly neurological
  - Normal early infancy
  - Developmental delays often first manifestations
  - Severe behavioral disturbances are a prominent feature of middle childhood
  - Progressive dementia leads to a “quiet phase” of withdrawal and developmental regression
  - Survival to late teens / early 20s
- Primary accumulation of the glycosaminoglycan (GAG) heparan sulfate triggers poorly understood pathological cascade with primarily CNS manifestations

Shire

Wijburg, Acta Pediatrica 2013

Phase 1/2 Study with Once-Monthly IT-rHNS

Pharmacodynamic Analysis Revealed Dose-dependent Suppression of CSF GAG* in MPS IIIA



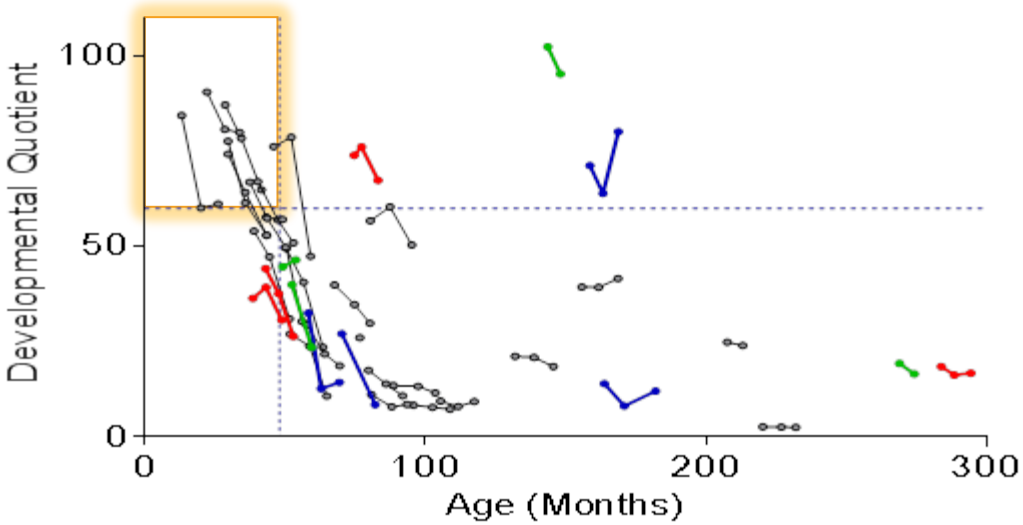
- Pharmacodynamic data demonstrated *in vivo* biological activity and provide basis for Phase IIB dose selection
- Safety results
  - No deaths
  - No discontinuations
  - No SAEs related to investigational drug

*GAG: glycosaminoglycans

Shire

Wijburg et al. Am Coll Med Human Genetics Meeting 2013, poster 392

SanA Phase IIB Study Focusing on Patient Population Believed Most Likely to Benefit from IT rhHNS

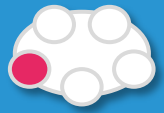


Phase IIB entry criteria: Age ≤ 48 months, DQ ≥ 60

- No children in Phase I/II (SAN-055) met these criteria vs 8/25 in Natural history study
- Median decline in DQ: 23 points in 12 months among the 8/25 patients in Natural history study

SHP610: Phase IIb Proof-of-Concept Study

Actively Enrolling, Headline Data Expected Mid 2016*



SHP610
Sanfilippo A

- A randomized, open-label, parallel group, controlled, multicenter study
- 45 mg rHNS-IT administered either every 2 weeks (Q2W) or every 4 weeks (Q4W) via an IDDD, versus no treatment – 6 patients per group

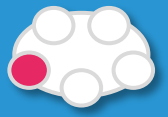
Primary Objective	To assess the potential clinical efficacy of rHNS administered via a surgically implanted IDDD in patients with MPS IIIA. Efficacy will be measured as the number of patients with no more than 10 point loss over 12 months as measured by the Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III).

Shire

* Subject to enrollment timelines and interactions with Regulatory Authorities

SHP611: METACHROMATIC LEUKODYSTROPHY (MLD)

Recombinant human arylsulfatase A (rhASA)



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SHP619 Duchenne's Muscular Dystrophy	**SHP616 (Cinryze SC)** HAE Prophylaxis	**SHP610** Sanfilippo A	**SHP625 (LUM001)** Primary Biliary Cirrhosis	**Firazyr** (Japan) HAE	**VPRIV (Japan)** Gaucher *(Approved 3Q 2014)*
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SHP628 (FT-061) Renal Impairment					

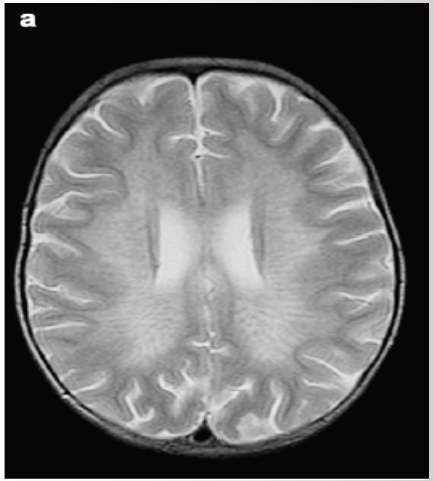
- Complement Biology
- Renal / Transplant
- Ophthalmics
- GI / Metabolic
- CNS
- Rare Diseases Leadership

Shire

Metachromatic Leukodystrophy: Disease Overview

SHP611
MLD

Manifestations of MLD



- MLD results from deficiency of the lysosomal enzyme arylsulfatase-A
- Arylsulfatase-A breaks down sulfatides and accumulation causes nerve demyelination

Disease Summary

- An inherited leukodystrophy
- Inheritance is autosomal recessive
- Birth incidence 1 in 100,000
- Three different phenotypic presentations classified by age of onset: late-infantile, juvenile, and adult
- Motor weakness and cognitive loss the most prominent symptoms
- Uniformly fatal; earlier onset correlates with more rapid decline
- Management focused on palliative care
- No treatments currently available
- Significant negative impact on patients & caregiver quality of life
- High economic costs

Shire

Haberlandt et al., Eur. J. Ped Neuro 2009

Distribution & PK of ^{124}I-labeled ARSA

SHP611
MLD

In vivo Distribution & PK of ^{124}I-labeled ARSA (6 mg) at t=1hr Post-dose in Cynomolgus Monkeys by PET / CT Imaging

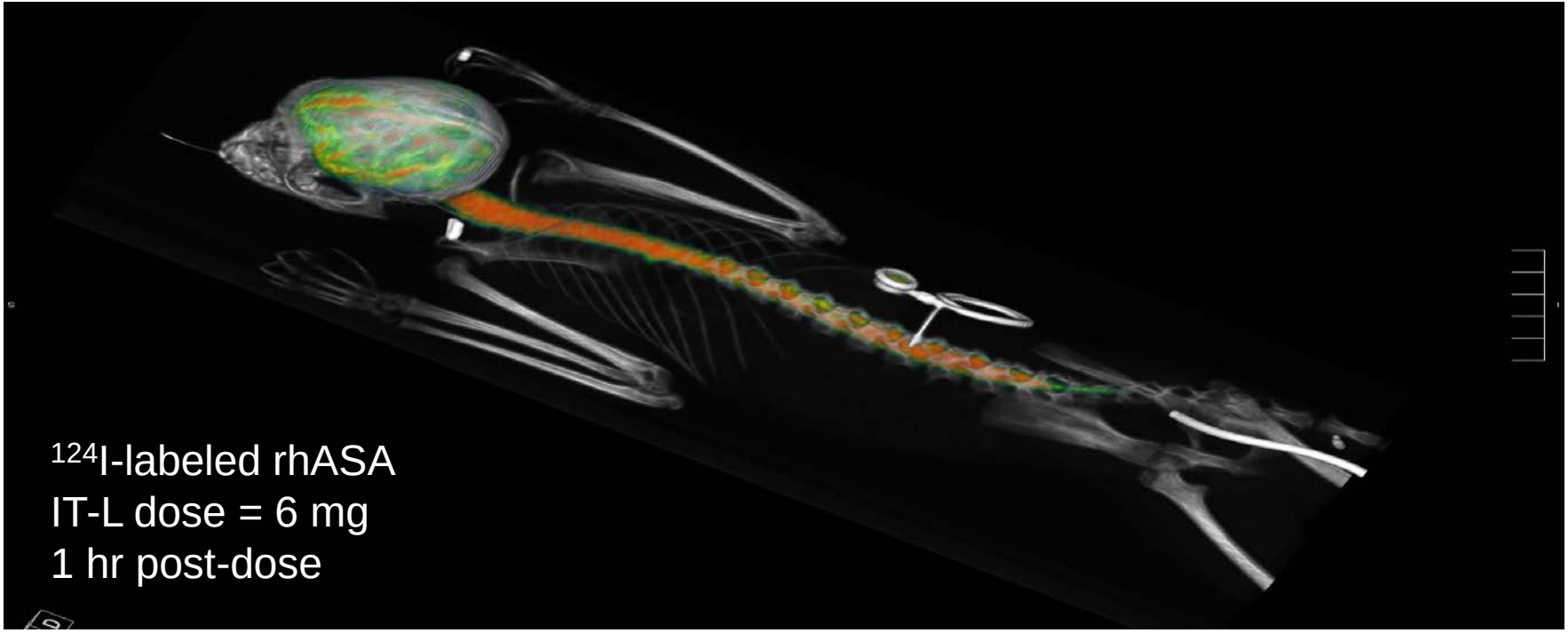
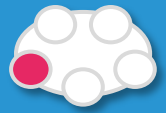


Image courtesy of Papisov group at MGH

SHP611: Phase I/II Dose Escalation Study with rASA

Fully Enrolled [1], Headline Data Expected Mid 2015



SHP611
MLD

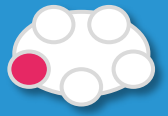
- Dose escalation study to evaluate safety of 3 doses administered EOW
- Study duration is 40 weeks
- 18 patients have been enrolled in 3 dosing cohorts (10, 30, 100 mg every other week)

Primary Objective	• Safety of ascending doses in children
Secondary Objectives	• Clinical activity on gross motor function • Effects on other key clinical signs and symptoms • On serum / CSF pharmacokinetics
Key Inclusion Criteria	• Appearance of first symptoms at or before 30 months of age • Able to walk at the time of screening • Neurological signs must be present at screening
Key Exclusion Criteria	• History of bone marrow transplantation

[1] All But 1 Eligible Patient In Extension Study

* Subject to enrollment timelines and interactions with Regulatory Authorities

AGT-182: HUNTER SYNDROME



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SHP628 (FT-061) Renal Impairment					

Complement Biology
Renal / Transplant
Ophthalmics
GI / Metabolic
CNS
Rare Diseases Leadership

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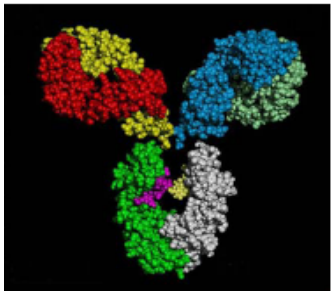
Armagen's Platform For Delivery to Target the Brain: IgG molecular Trojan-Horse Fusion Protein

Armagen
Hunter CNS

Fusion protein consisting of chimeric MAb against the human insulin receptor(HIR) fused with a recombinant protein (e.g. iduronate-2-sulfatase, L-iduronidase)

HEAD



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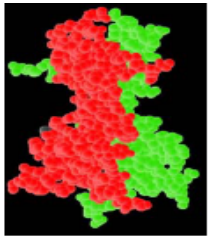
TAIL



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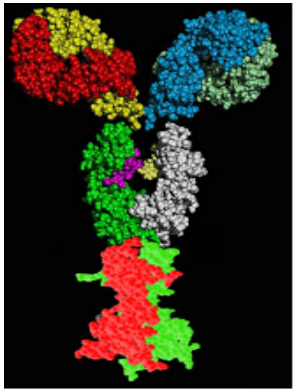


Molecular Trojan Horse
A genetically engineered monoclonal antibody (MAb) against the human insulin receptor (HIR)

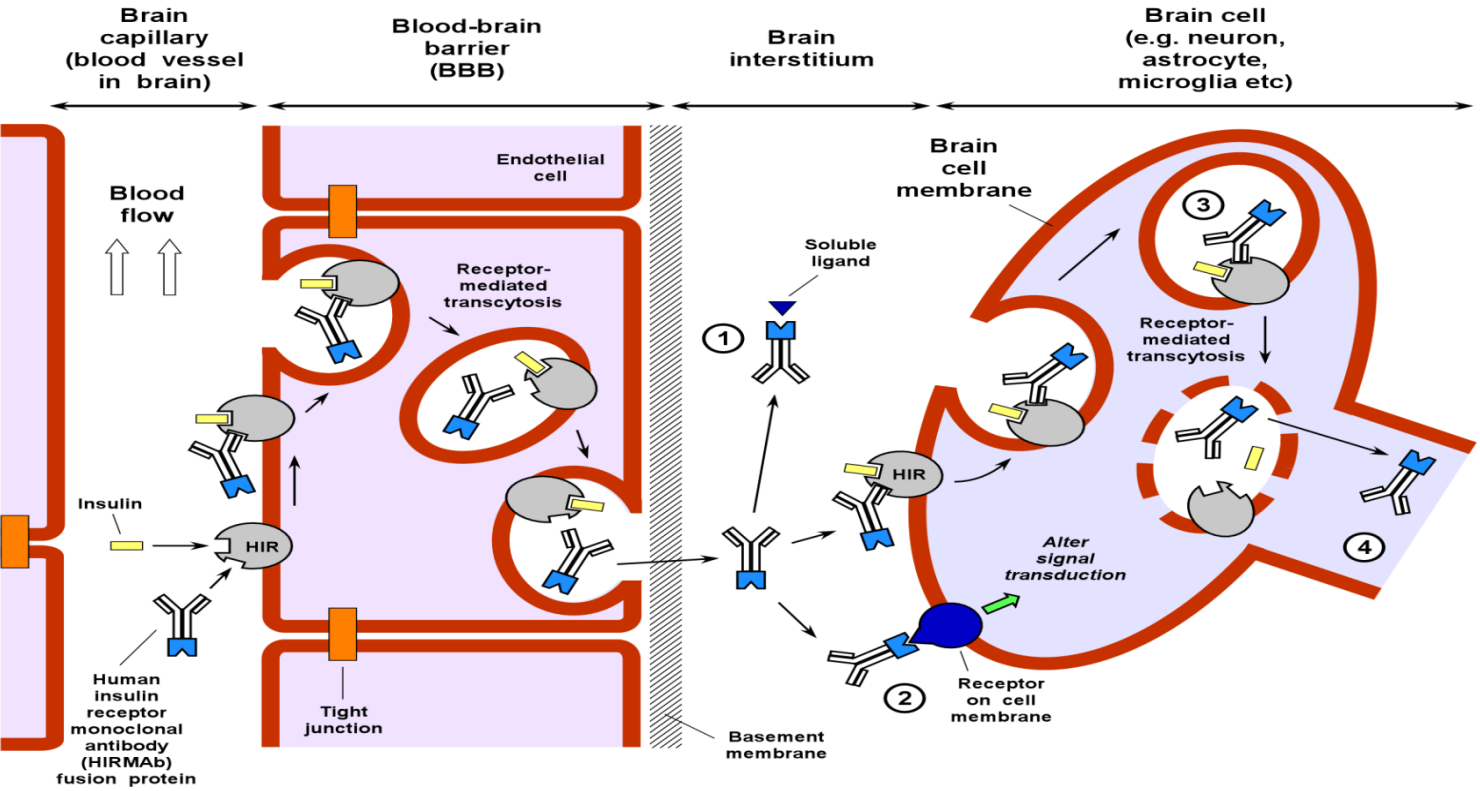
Recombinant Protein

IgG Fusion Protein:
A new chemical entity

Shire

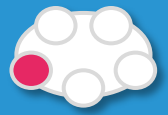
Data provided by Armagen

Utilizing Endogenous Transporter To Cross Blood Brain Barrier



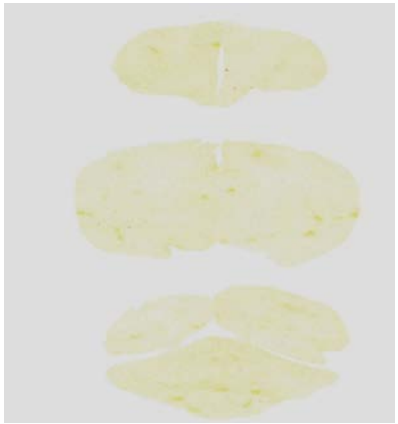
Fusion protein consisting of chimeric MAb against the human insulin receptor(HIR) fused with a recombinant protein (e.g. iduronate-2-sulfatase, L-iduronidase).

Data to Support MOA: Distribution to Brain Tissue in Rhesus Monkey

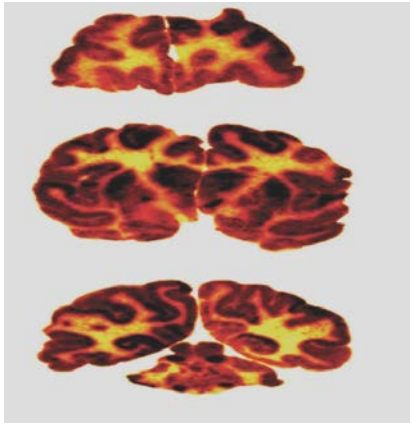


Armagen
Hunter CNS

- Systemic distribution similar to ELAPRASE®
- Autoradiography demonstrated the extensive distribution of drug into all regions of the brain (at 2 hours after IV injection) versus ELAPRASE



ELAPRASE-alone



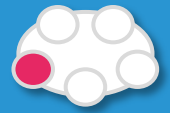
AGT-182

Shire

Published Bioconjugate Chem. 2013, 24, 1741−1749

AGT-182: Next Steps

Phase 1/2 Expected to Start Early 2015*



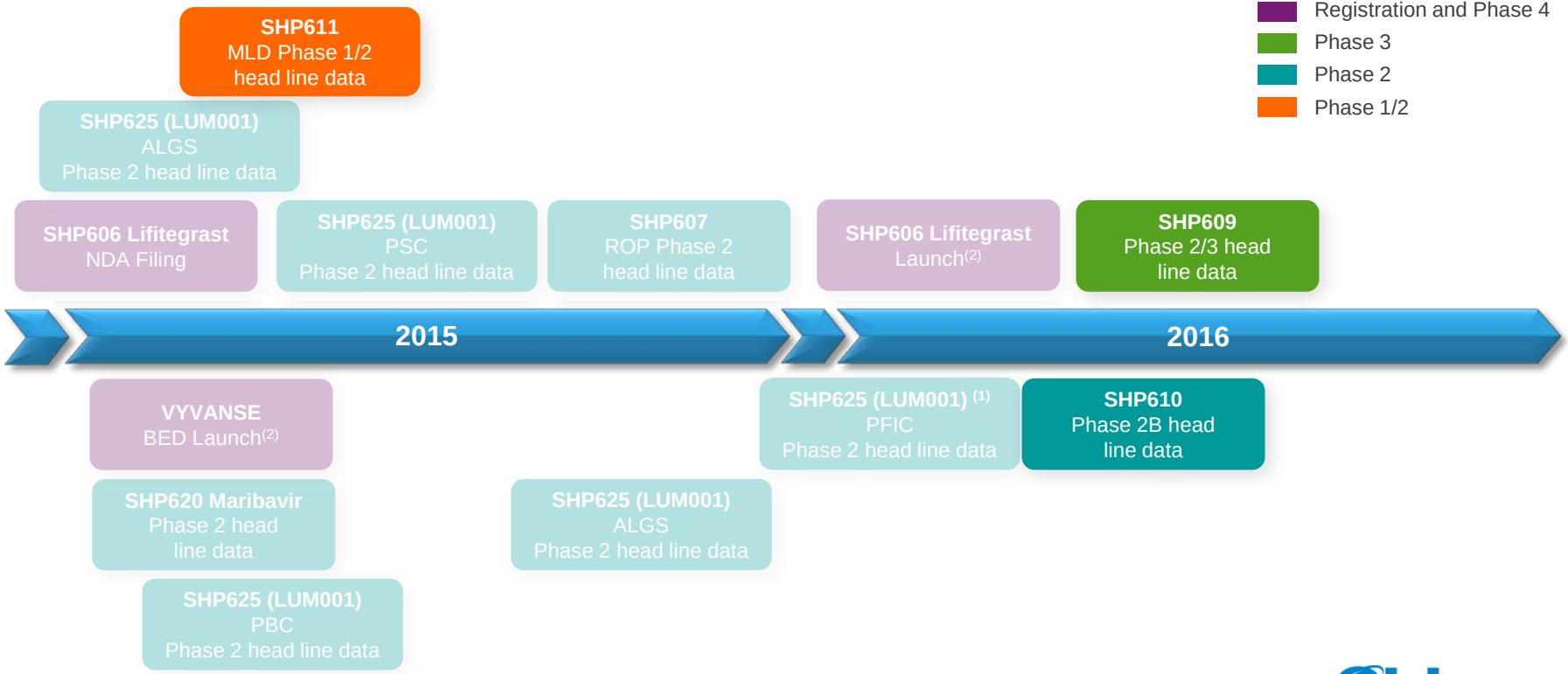
Armagen
Hunter CNS

- US IND submitted October 2014
- A Phase 1/2, Dose-Exploratory, Clinical Study of Human Insulin Receptor Monoclonal Antibody-Human Iduronate-2-Sulfatase (IDS) Fusion Protein, AGT-182 in adult patients with MPSII is being planned to start in early 2015
- Next study – is expected to be in children with cognitive impairment due to Hunter Syndrome

Shire

* Subject to enrollment timelines and interactions with Regulatory Authorities

Upcoming Anticipated CNS Rare Diseases Milestones



Notes
(1) Interim 625 PFIC INDIGO data expected Q2 2015.
(2) Subject to regulatory approval.

Late-Stage Pipeline Update

Howard Mayer, M.D., Head of Clinical Development
Randy Brenner, Head of Regulatory Affairs
Joe Tauber, M.D., Tauber Eye Center, Kansas City, MO

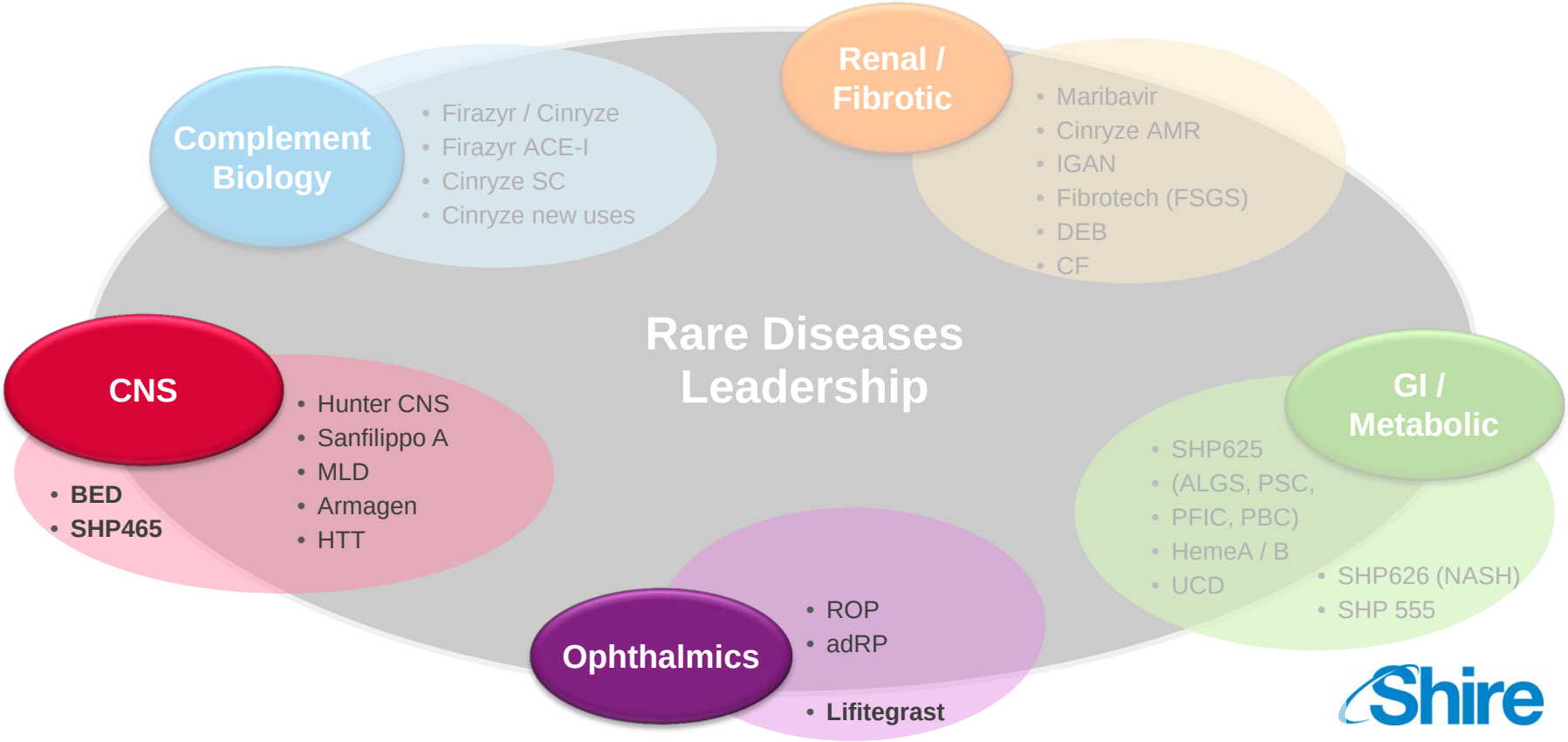
Our purpose
We enable people with life-altering conditions to lead better lives.

Shire

Today's R&D Sessions

Topic	Speaker	Time (EST)
Research Overview and Technology Platforms *mRNA, Protein Replacement, Gene Therapy, Antibody Platforms*	Albert Seymour, Ph.D.	9:25-10:00
Rare Diseases: GI / Metabolic *SHP625 (LUM001), SHP626 (LUM002)*	Ciara Kennedy, Ph.D. *David Piccoli, M.D.*	10:00-10.45
Rare Diseases: Ophthalmics *SHP607 / ROP, SHP630 / BIKAM*	Norman Barton, M.D., Ph.D.	11:15-11:45
Rare Diseases: Complement Biology and Renal / Fibrotic *SHP616 / Cinryze new uses*	Howard Mayer, M.D.	1:15-1:30
Rare Diseases: CNS *SHP609 / Hunter CNS, SHP610 / Sanfilippo A, SHP611 / MLD, Armagen*	Howard Mayer, M.D.	1:30-2:00
Late-Stage Update *SHP606 / Lifitegrast, BED, SHP465 / ADHD*	Howard Mayer, M.D. Randy Brenner *Joe Tauber, M.D.*	2:00-2:45

Late-Stage Programs in CNS and Ophthalmics



Shire

Late-Stage Pipeline Update – Agenda

Dry Eye 2014

Joe Tauber, M.D.

Lifitegrast for the treatment of Dry Eye Disease

Howard Mayer, M.D.

Late-Stage Regulatory Update

- Vyvanse for Binge Eating Disorder
- SHP465 for Attention Deficit Hyperactivity Disorder

Randy Brenner

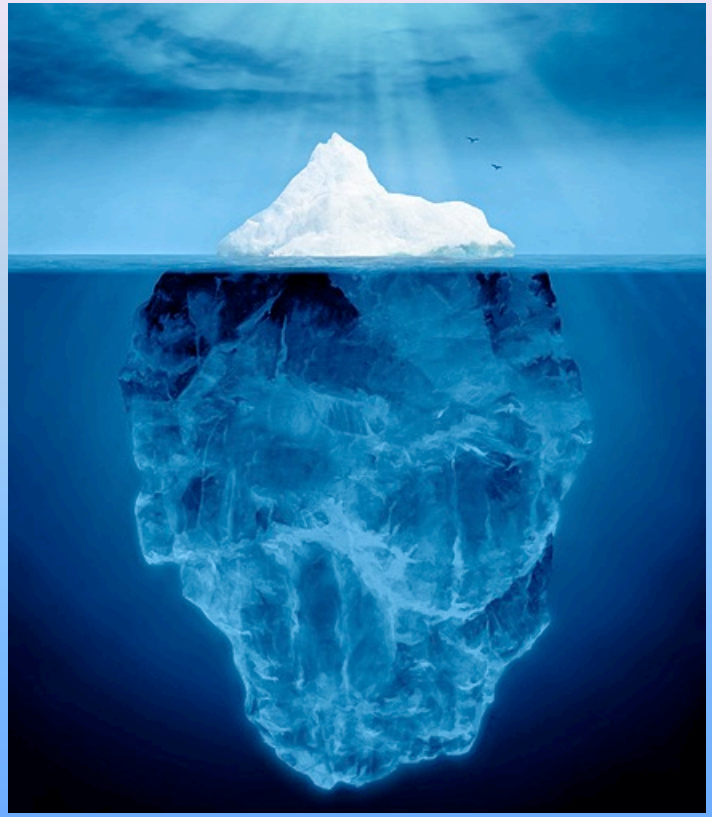
Shire

Dry Eye 2014

JOSEPH TAUBER, M.D.

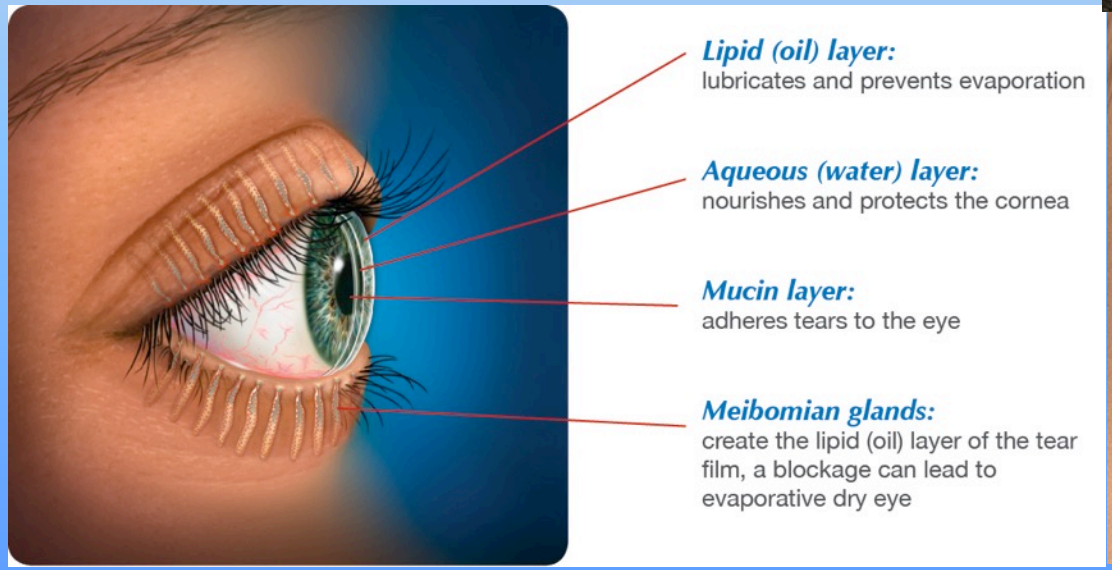
TAUBER EYE CENTER

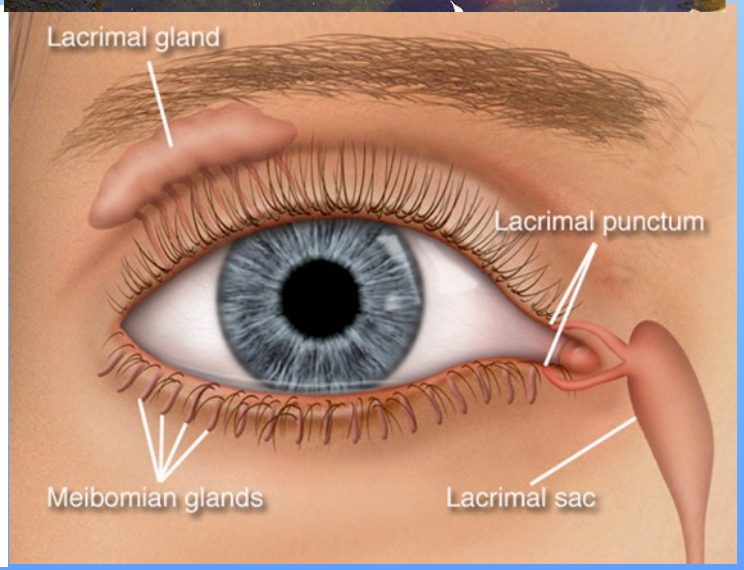
KANSAS CITY, MO



The Eye Surface Requires Lubrication to Adequately Perform its Primary Functions of:

1. Barrier protection
2. Visual function





Dry Eye is a Significant Market Opportunity…
It is the Primary or Related Cause of 40% of Eye Care Visits

DRY EYE PREVALENCE IN THE U.S.(1)

Dry Eye Category	Severe	Moderate	Episodic	Total
Sjögren's Disease	1,427,847	1,223,869	407,956	3,059,672
Post-menopausal Women	1,933,486	3,093,577	7,733,943	12,761,006
Men Over Age 65	518,751	864,585	1,729,169	3,112,505
LASIK Patients	4,722	9,444	141,667	155,833
Past LASIK Patients	34,027	68,053	340,266	442,346
Other	196,924	393,848	2,888,221	3,478,994
Total U.S.	**4,115,757**	**5,653,377**	**13,241,222**	**23,010,355**

Women: 4% @ 40 → 15% @ 65

Men: 4% @ 50 → 7.7% @ 80+

- 1/10 dry eye patients in U.S. has Sjogren's syndrome
- 1.5 M Rheumatoid Arthritis (CDC, 2005)
- 37% of diabetics (Canadian Dry Eye Epidem. Study)
- $4B in health care costs (Yu J, et al, Cornea 2011)

(1) Shire has used the following prevalence estimates: patients diagnosed with DED from U.S. studies vary from 0.39% in 1998 to 18.8% of patients seeking treatment in VA eye clinics from 2006-2011. Overall U.S. prevalence by self-reported symptoms has been estimated to be 7.8% of females aged 50 and older and 4.34% of males aged 50 and older. Using this self-reported symptom data and U.S. census estimates for 2012, over 2.1 M males and over 4.3 M females over the age of 50 have either been clinically diagnosed with DED or have severe dry eye symptoms.

Market Scope. 2010 Comprehensive Report on The Global Dry Eye Products Market.

For <u>all</u> Eye Care Providers…

Contact lens discomfort

Blurred vision

Address pre-surgical risk proactively

Dry Eye Rx Skill is Critical

Better surgical outcomes

Happy patients ↓ ***referrals***

Practice Building ($)

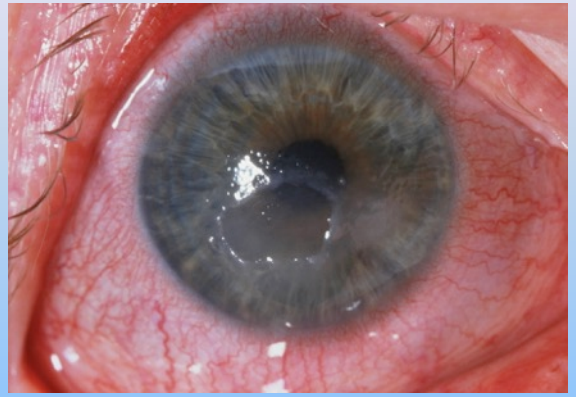
If you found it before surgery and there are postop issues – it is because of the disease.

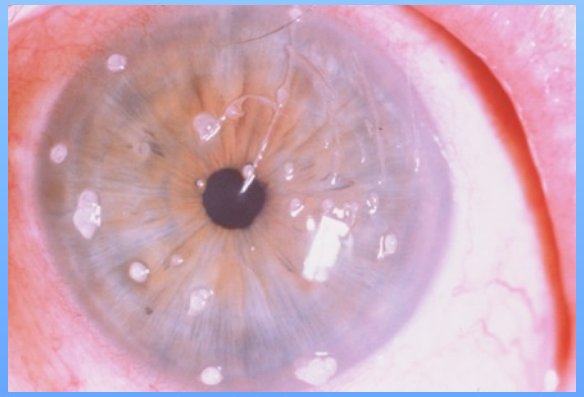
If you didn't – patients will believe it's your fault.

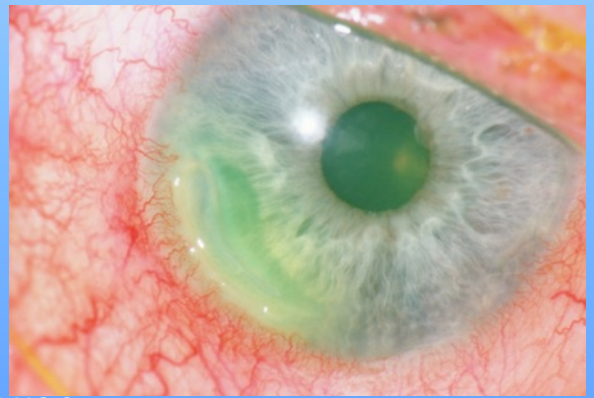
For Patients, Dry Eye is not a Trivial Matter

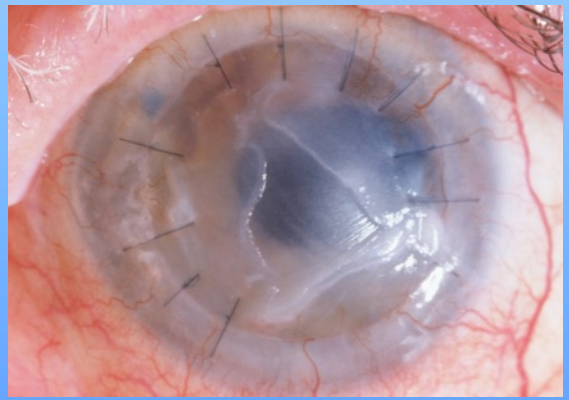
Health State	Mean Score
Moderate Dry Eye Disease*	0.78
Moderate Angina*	0.75

☹ LASIK patients: 48% have dry eye









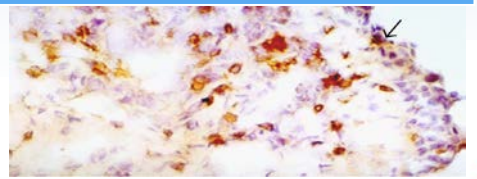
Schiffman RM, et al. Ophthalmology 2003 Jul;110(7):1412-9.
Salomão MQ et al. J Cataract Refract Surg. 2009 Oct;35(10):1756-60. doi: 10.1016/j.jcrs.2009.05.032.
Raoof D et al. Semin Ophthalmol. 2014 Nov;29(5-6):358-62. doi: 10.3109/08820538.2014.962663.

Unmet Needs in Dry Eye

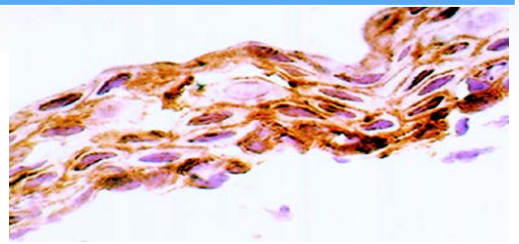
- Cure is rare or non-existent
- Disease incidence may be growing, independent of improved diagnosis
  - Aging population, increasing incidence with age, menopause
  - Growth of prostaglandin eye drop Rx for glaucoma
- Increasing patient demand for better control of symptoms
- Growth of premium IOL cataract surgery, with increased insistence on high grade vision after more expensive surgery

Dry Eye is an Inflammatory Disease

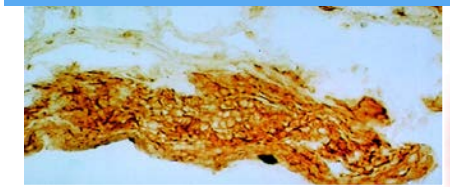
CD4+ T Cell Infiltration

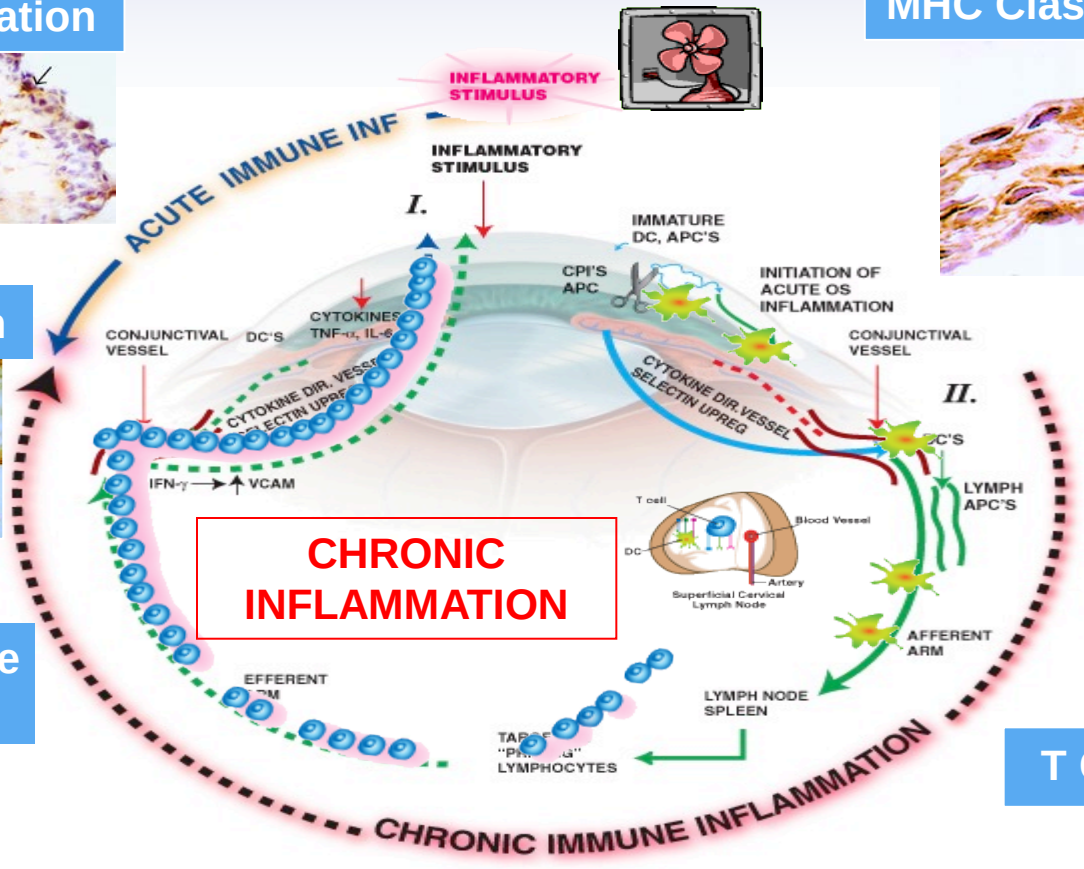


MHC Class II Upregulation



ICAM-1 Upregulation





T Cell Homing to the Ocular Surface

Antigen Presentation

T Cell Activation

ABC's of "First Line" Treatment

In "Doctor speak"

Supplementation	Stimulation	Retention
Add tears	Stimulate more tears	Block tears from leaving

in Patient's Terms

NB – Only 1/3 of these strategies reduces inflammation

Clinical Research in Dry Eye (human)

- Lifitegrast (Shire) – LFA-1 receptor antagonist
- EBI-005 (ElevenBio) – IL-1 antagonist
- Rebamipide (Otsuka) – mucin secretagogue
- Resolvyx – resolvins (RX10045)
- Sirolimus – (Macusight) / subconjunctival injection
- Lacritin – naturally occurring, “prosecretory mitogen
- LP-MPP 0.25% (Kala) “enhanced” lotoprednol
- Civamide (OPKO) - TRPV1 receptor / tear stimulant
- CP-6900550 (Pfizer) – JAK 3 kinase inhibitor (IL-2,4,7,9,15,21)
- MIM-D3 (Mimetogen) – NGF mucomimetic / peptidomimetic
- CF101 – A3 adenosine receptor agonist, anti-inflammatory
- Ikervis /CSA (Novagli-Santen) proprietary vehicle
- Restasis-X (Allergan)

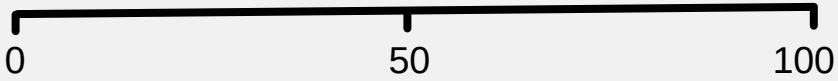
How Do We Measure Symptoms?

CATEGORICAL SCALES 0 - 3

Dryness	None, mild, moderate severe
Pain, soreness	None, mild, moderate severe
Burning	None, mild, moderate severe
Sandiness, grittiness	None, mild, moderate severe
Blurred vision	None, mild, moderate severe
Discharge	None, mild, moderate severe
Itching	None, mild, moderate severe

VISUAL ANALOGUE SCALES

VISUAL ANALOGUE SCALES WITH ANCHORS

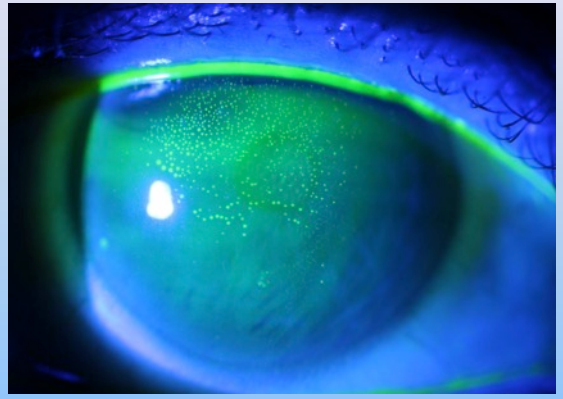


How Do We Measure Symptoms?

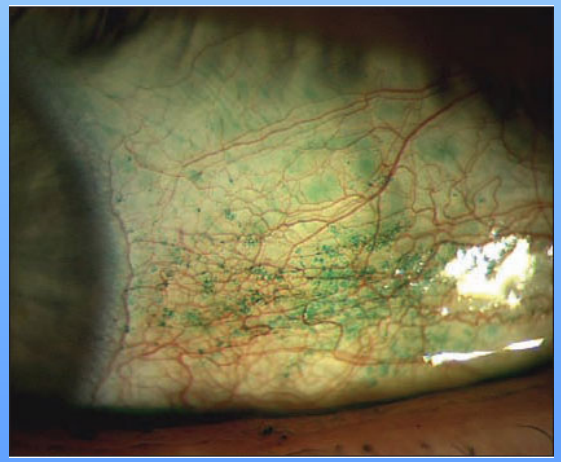
1. McMonnies Questionnaire
2. DEQ, The Dry Eye Questionnaire
3. VFQ-25 NEI-devised Visual Functioning Questionnaire
4. VT-HRQ, Vision-Targeted Health-Related Quality of Life, a questionnaire that evaluates QOL activities related to or dependent upon vision
5. NEI-VFQ NEI, Visual Function Questionnaire, a questionnaire developed by the National Eye Institute to evaluate vision function inactivities of daily life
6. OSDI, Ocular Surface Disease Index, a set of questions assessing the level of discomfort and interference with activities of daily living produced by ocular surface disease.

Gothwal et al. Invest Ophthamol Vis Sci 2010;51:1401-1407.
2007 Report of the International Dry Eye Workshop (DEWS). The Ocular Surface 2007; 5:65-204.

How Do We Measure Signs?



Fluorescein
cornea



Lissamine Green conjunctiva

Grading Schemes for Staining

Oxford	0-3, entire cornea
NEI	0-4, 5 zones
Modified	0-4, 5 zones
NEI	micro, macropunctate
ORA	unique system of conj/cornea zones

Degree of staining increases over time (1-2-3-4 min)
– only recent trials have specified time in grading method

Dry Eye Development – *Ten+ Years of Terminated Clinical Trials*

- Diquafasol
- Rebamipide
- Hyaluronidase tears
- Androgen tears
- Ecabet sodium

ORA’s Controlled Adverse Environment (CAE) for Dry Eye

- Controlled airflow
- Controlled humidity
- Monitored blink rate
- Quantitative tear film breakup
- Functional visual assessment

Ocular Surface Disease Rx Algorithm

Tear Underproduction

Supplement | **Stimulate** | **Retain**

Uncontrolled | **Controlled**

- Higher viscosity Tears
- P.F. Tears
- Supradose Restasis
- Serum Tears
- Secretagogue (oral, SL)
- Clinical Trials

Lid Disease

Posterior

- **Lid Hygiene**
- **Oral Rx (macrolides)**
- **OM-3 supplements**
- **MG Duct Probing**
- **Anti-keratin Rx** (Vitamin A, “scraping”)
- **Lipiflow**

Anterior

- **Soaks / Scrubs**
- **Demodex**
- **Vitamin A**

Late-Stage Pipeline Update – Agenda

Dry Eye 2014

Joe Tauber, MD

Lifitegrast for the treatment of Dry Eye Disease

Howard Mayer, M.D.

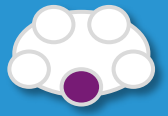
Late-Stage Regulatory Update

- Vyvanse for Binge Eating Disorder
- SHP465 for Attention Deficit Hyperactivity Disorder

Randy Brenner

Shire

SHP606 (Lifitegrast): Dry Eye Disease



Preclinical	Phase 1	Phase 2		Phase 3	Registration
26 Research Programs	**SHP611** MLD (Ph 1/2)	**SHP602** Iron overload (clinical hold)	**SHP616 (Cinryze)** Acute Antibody Mediated Rejection	**Firazyr** ACE inhibitor-induced AE	**XAGRID® (Japan)** Thrombocythaemia *(Approved 3Q 2014)*
SHP619 Duchenne's Muscular Dystrophy	**SHP616 (Cinryze SC)** HAE Prophylaxis	**SHP610** Sanfilippo A	**SHP625 (LUM001)** Primary Biliary Cirrhosis	**Firazyr** (Japan) HAE	**VPRIV (Japan)** Gaucher *(Approved 3Q 2014)*
TH / GCH1 Gene Pod Parkinson's Subset	**SHP622** Friedreich's Ataxia	**SHP609** Hunter CNS	**SHP625 (LUM001)** Progressive Familial Intrahepatic Cholestasis	**SHP616 (Cinryze) (Japan)** HAE Prophylaxis	**INTUNIV® (EU)** ADHD
SHP608 Dystrophic E.Bullosa	**SHP627 (FT011)** Focal Segmental Glomerulosclerosis	**SHP607** Prevention of ROP	**SHP625 (LUM001)** Alagille Syndrome	**SHP555 (US)** Chronic Constipation	**Vyvanse** BED
SHP614 IgA Nephropathy	**SHP616 (Cinryze)** Paroxysmal Nocturnal Hemoglobinuria	**SHP620 (Maribavir)** CMV in transplant patients	**SHP625 (LUM001)** Primary Sclerosing Cholangitis	**INTUNIV (Japan)** ADHD	
Armagen Hunter CNS	**SHP616 (Cinryze)** Acute Neuromyelitis Optica	**LDX (Japan)** ADHD		**SHP606 (Lifitegrast)** Dry eye disease	
SHP630 adRP	**SHP626 (LUM002)** Non-Alcoholic Steatohepatitis			**SHP465** ADHD	
SHP624 Heme B Gene Edit					
SHP628 (FT-061) Renal Impairment					

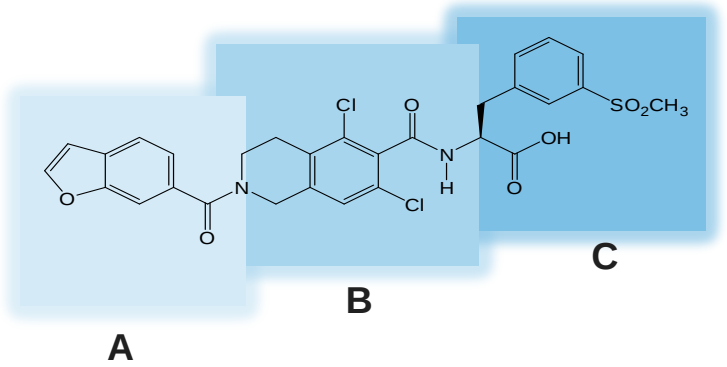
- Complement Biology
- Renal / Transplant
- Ophthalmics
- GI / Metabolic
- CNS
- Rare Diseases Leadership

Shire

Lifitegrast – A Purpose-Built Molecule

SHP606 (Lifitegrast)
Dry eye disease

- Selected from 1500 candidate molecules
- Specifically engineered as topical ophthalmic
- Built to potently block LFA-1 / ICAM-1 interaction
  - Adhesion to ICAM-1 (IC_{50} = 2 nM)
  - Cytokine release (SEB stimulated IL-2) IC_{50} >> 60nM
- Highly stable and hydrophilic
  - water/ saline/ pH 7 >>2 years
  - >200 mgs/mL at pH 7
- No systemic accumulation with rapid clearance
- Selectively targets LFA-1 on infiltrating leukocytes
- Selected based on its properties for further development as a candidate to treat Dry Eye Disease



Lifitegrast (formerly SAR 1118)
MW 610 g/mol

1. Ref.:USAN/INN (Jan 2012)
2. Zhong et al., Med Chem Lett (2012)

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Summary of the Overall Lifitegrast Program

SHP606 (Lifitegrast)
Dry eye disease

Phase	Study Number	Indication	Subjects	Status
1a	SAR1118-001	Healthy Volunteers, Safety, PK	28	Complete
1b	1118-DME-100 (Johns Hopkins, IST	PK Vitrectomy	30	Complete
2	1118-ACJ-100	Allergic Conjunctivitis	60	Complete
2	**Phase 2**	**Dry Eye**	**230**	**Complete**
3	**OPUS-1**	**Dry Eye**	**588**	**Complete**
3	**OPUS-2**	**Dry Eye**	**718**	**Complete**
3	SONATA	Dry Eye	332	Complete

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Results and Findings From 3 Key Efficacy Studies

SHP606 (Lifitegrast)
Dry eye disease

Phase 2

- **Dose response relationship** for signs and symptoms; 5% solution chosen for further evaluation
- Met pre-specified secondary sign endpoint **change from baseline to Day 84 in ICSS**; established as the sign endpoint for future studies
- Several pre-specified symptom endpoints trended or met significance particularly in patients with **history of artificial tear use**

Learnings and development progression

OPUS-1

- **Co-primary sign endpoint met significance** validating Phase 2 findings (p=0.0007)
- Co-primary symptom endpoint (Visual Related Function Subscale) not met
- Pre-specified subpopulation of subjects with **history of AT use** showed greater treatment effect on EDS
- Post hoc analysis of more symptomatic **AT subgroup with EDS≥40** met significance vs placebo (nominal p=0.0178)

Learnings and development progression

OPUS-2

- **Co-primary symptom endpoint met significance** validating OPUS-1 findings in this population of moderate to severely symptomatic subjects (EDS≥40) with history of AT use (p<0.0001)
- **All pre-specified secondary symptom endpoints** achieved statistical significance
- Co-primary sign endpoint failed to separate from placebo in this **more symptomatic population** and did not demonstrate significance vs placebo

ICSS: Inferior Corneal Staining Score **EDS:** Eye Disease Score

Why Different Outcomes in Different Studies?

Multifactorial Etiologies but Likely Influenced by Population Differences

SHP606 (Lifitegrast)
Dry eye disease

	Phase 2 and OPUS-1	OPUS-2
DESIGN	• CAE[1] for subject selection • Inclusion and exclusion • Similar sites (New England) • Similar seasonality (fall / winter)	• No CAE[1] • Thresholds • West / South • All year
SIGN	**Mild-moderate[2]**	**Moderate-severe[3]**
SYMPTOM	**Mild-moderate[2]**	**Moderate-severe[3]**
KEY OBSERVATION	• Mild-to-moderate subjects enhance detection of the sign • Moderate-to-severe subjects enhance detection of symptoms • Enriching population for one variable lead to loss of detection of the co-variable • Co-primary may not be practical	

1. Studies 1 and 2 were conducted in collaboration with ORA and utilized ORA's Controlled Adverse Environment (CAE℠) as a clinical model to study the treatment of dry eye disease with lifitegrast.
2. As defined per protocol, subjects with ICSS of greater than 3.0 were not allowed in the trial. As defined per protocol, subjects had to have worsening of ODS by +3 points and as such severely symptomatic subjects could not enroll.
3. As defined per protocol, subjects with EDS of greater than or equal to 40 could only enroll into the trial and there were no outer limits to the ICSS and as such subjects with the highest degree of staining (+4) could also enroll.

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Feedback from FDA

SHP606 (Lifitegrast)
Dry eye disease

Pre-NDA meeting held on May 15 with the division of Ophthalmology and Transplant Medicine of the FDA

- With respect to the evidence collected from the current program to date and its suitability for an NDA submission, the Agency acknowledged that:
  The clinical portion of an NDA with the current clinical data package was likely fileable. Approvability of a submitted NDA would be a review issue.

- Regarding totality of clinical evidence and the paradoxical relationship between the sign and symptom co-variables, FDA acknowledged that:
  Safety and efficacy is recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials. You may wish to consider demonstrating efficacy based on subjective findings in a different patient group or in a different clinical study than the patient group or clinical study which demonstrates efficacy based on objective findings.

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Evidence of Replication in Sign

Inferior Corneal Staining Score

SHP606 (Lifitegrast)
Dry eye disease

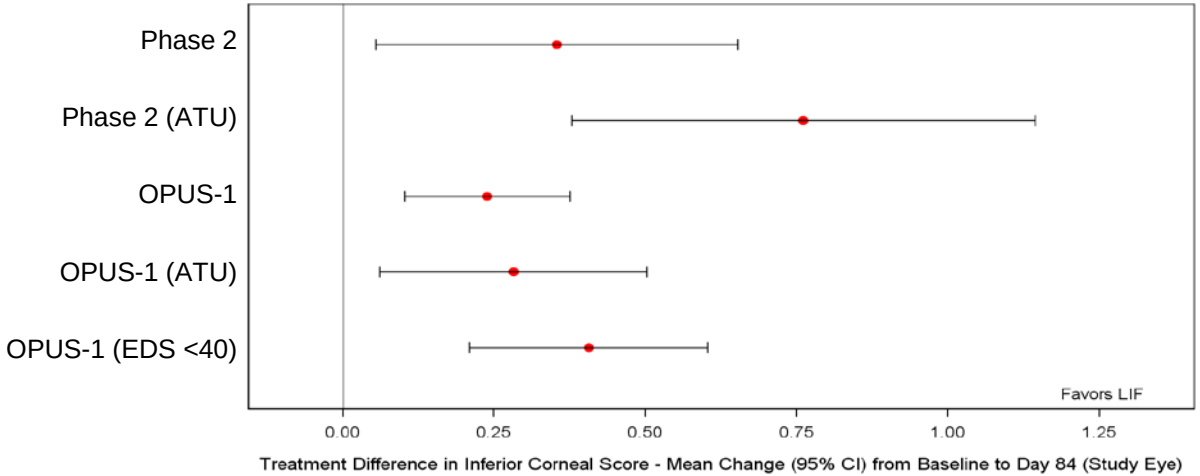


Table 1. Inferior Corneal Staining Score (ICSS)

	All Subjects		Artificial Tear Users		Phase 2 All Subjects PBO vs. 5.0% LIF (N=55:N=54) [a]	OPUS-1 Subjects with Baseline EDS<40 (N=147:N=137) [c]
	Phase 2 PBO vs. 5.0% LIF (N=55:N=54) [a]	OPUS-1 PBO vs. 5.0% LIF (N=294:N=293) [b]	Phase 2 PBO vs. 5.0% LIF (N=29:N=28) [c]	OPUS-1 PBO vs. 5.0% LIF (N=128:N=128) [d]		
Treatment Effect (95% CI)	0.35 (0.05, 0.65)	0.24 (0.10, 0.38)	0.76 (0.38, 1.14)	0.28 (0.06, 0.5)	0.35 (0.05, 0.65)	0.41 (0.21, 0.60)
P-value	0.0209	0.0007	0.0002	0.0127	0.0209	<0.0001

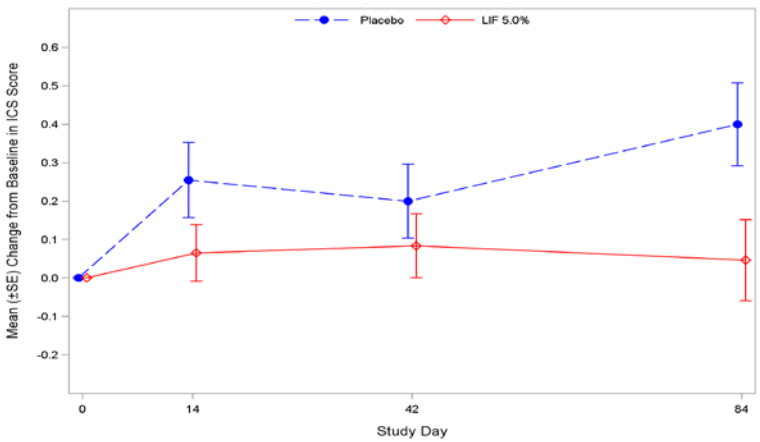
[a] Pre-specified secondary [b] Pre-specified co-primary [c] Post-hoc [d] Pre-specified tertiary

Treatment Effect on Inferior Corneal Staining Score Over the Course of Studies

SHP606 (Lifitegrast)
Dry eye disease

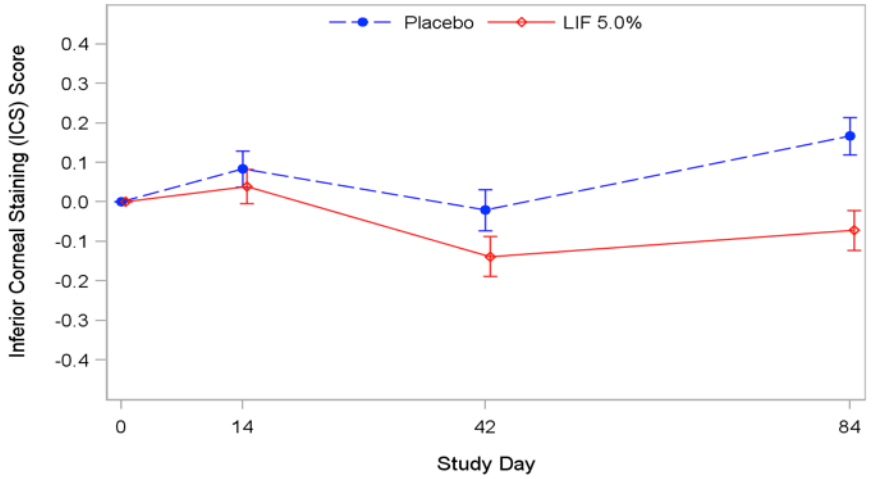
Phase 2

ITT Population with LOCF
Mean (±SE) Change from Baseline



OPUS-1

ITT Population with LOCF
Mean (±SE) Change from Baseline



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Evidence of Replication in Symptom

Eye Dryness Score

SHP606 (Lifitegrast)
Dry eye disease

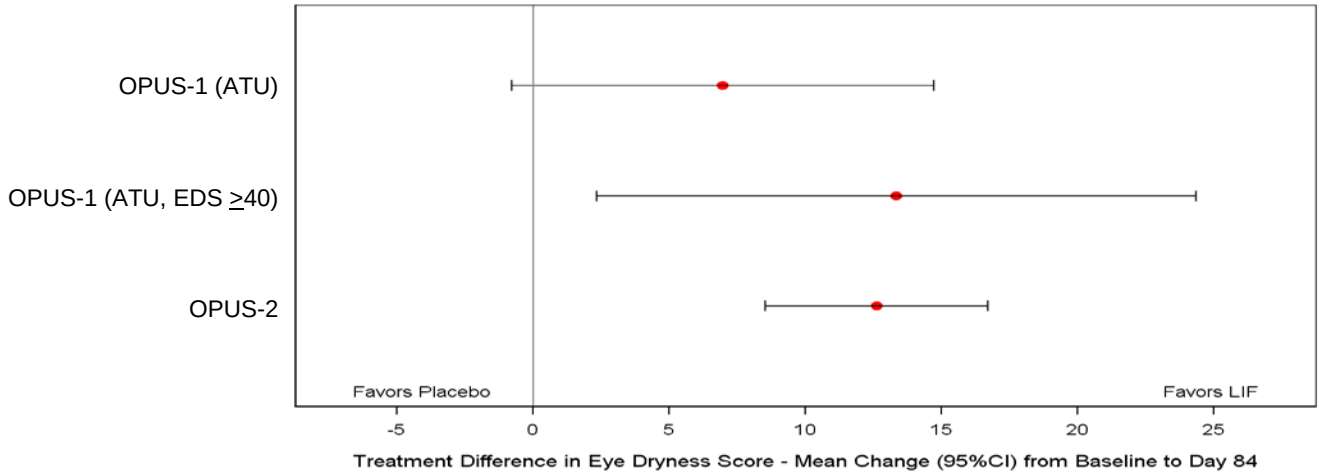


Table 2. Eye Dryness Score (EDS)

	Artificial Tear Users		Artificial Tear Users, EDS ≥ 40	
	OPUS-1 PBO vs. 5.0% LIF (N=129:N=128) [a]	**OPUS-2 PBO vs. 5.0% LIF (N=294:N=293) [b]**	**OPUS-1 PBO vs. 5.0% LIF (N=67:N=63) [c]**	**OPUS-2 PBO vs. 5.0% LIF (N=294:N=293) [b]**
Treatment Effect (95% CI)	6.96 (-0.79, 14.71)	12.61 (8.51, 16.70)	13.34 (2.35, 24.33)	12.61 (8.51, 16.70)
P-value	0.0783	<0.0001	0.0178	<0.0001

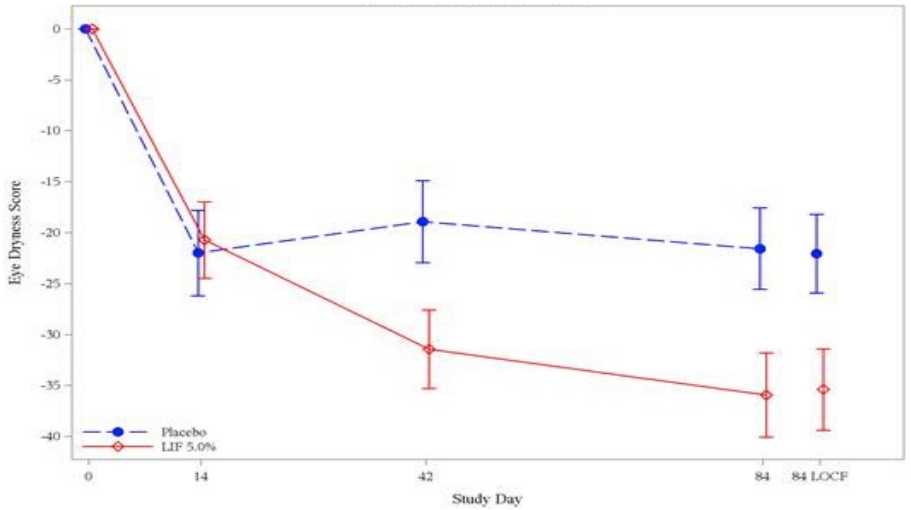
[a] Pre-specified tertiary [b] Pre-specified co-primary [c] Post-hoc

Treatment Effect on Eye Dryness Score Over the Course of the Study

SHP606 (Lifitegrast)
Dry eye disease

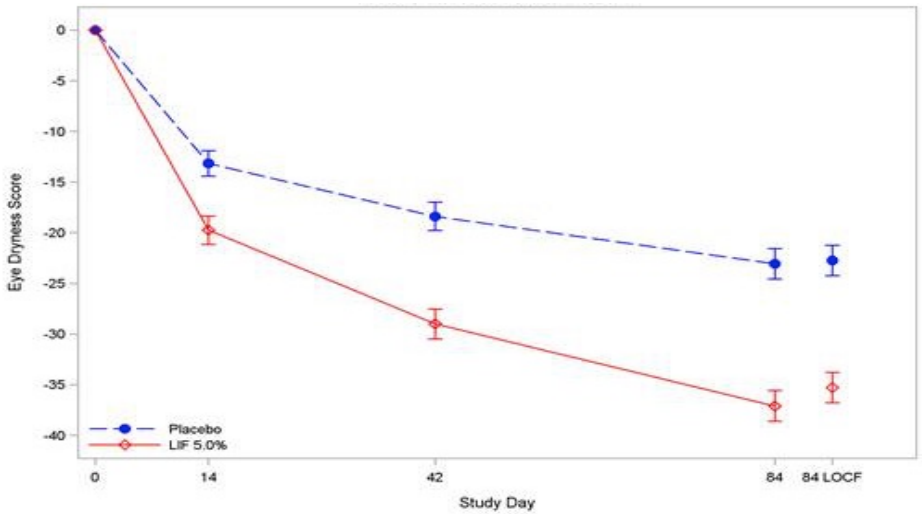
OPUS-1

ITT Population Observed Data plus ITT with LOCF at Day 84
Mean (±SE) Change from Baseline



OPUS-2

ITT Population Observed Data plus ITT with LOCF at Day 84
Mean (±SE) Change from Baseline



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Regulatory Position Based on our Pre-NDA Meeting - May 15, 2014

SHP606 (Lifitegrast)
Dry eye disease

- We are confident that the totality of the data from our existing clinical development program supports the submission of an NDA for Lifitegrast

- However, we are continuing to gather clinical data in support of US and potential international regulatory submissions

- OPUS-3 will not delay our plans to submit an NDA for Lifitegrast for signs and symptoms of dry eye disease in the first quarter of 2015

Shire

Why Conduct OPUS-3?

SHP606 (Lifitegrast)
Dry eye disease

- OPUS-3 (a Phase 3 safety and efficacy study) is to bolster our potential US label and further support international markets and will be conducted concurrent to the US NDA review
- Identical to OPUS-2 Population: DED, history of artificial tear use, and Eye Dryness Score ≥ 40
- Study designed to strengthen our existing efficacy data by evaluating the following symptom endpoints:
  - Primary efficacy endpoint: Superiority against placebo on **eye dryness score** as shown by change from baseline to day 84
  - Key Secondary efficacy endpoints: Superiority against placebo on **eye dryness score** as shown by change from baseline to day 42 and day 14

Shire

Late Stage Pipeline Update – Agenda

Dry Eye 2014

Joe Tauber, MD

Lifitegrast for the treatment of Dry Eye Disease

Howard Mayer, MD

Late-Stage Regulatory Update

- Vyvanse for Binge Eating Disorder
- SHP465 for Attention Deficit Hyperactivity Disorder

Randy Brenner

Shire

Vyvanse for Binge Eating Disorder (BED)

Preclinical	Phase 1	Phase 2		Phase 3	Registration
26 Research Programs	**SHP611** MLD (Ph 1/2)	**SHP602** Iron overload (clinical hold)	**SHP616 (Cinryze)** Acute Antibody Mediated Rejection	**Firazyr** ACE inhibitor-induced AE	**XAGRID® (Japan)** Thrombocythaemia *(Approved 3Q 2014)*
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SHP624 Heme B Gene Edit					
SHP628 (FT-061) Renal Impairment					

- Complement Biology
- Renal / Transplant
- Ophthalmics
- GI / Metabolic
- CNS
- Rare Diseases Leadership

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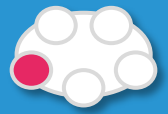
Vyvanse for BED



LDX
BED

Development Program Status

- SPD489-208: Fixed-dose study *(completed, included in sNDA)*
- SPD489-343: Dose optimization study #1 *(completed, included in sNDA)*
- SPD489-344: Dose optimization study #2 *(completed, included in sNDA)*
- SPD489-345: Open-label long-term safety study *(Interim data cuts included in sNDA with final CSR planned March 2015)*
- SPD489-346: Long term maintenance of efficacy study
  (ongoing, final CSR planned for September 2015, not included in sNDA)

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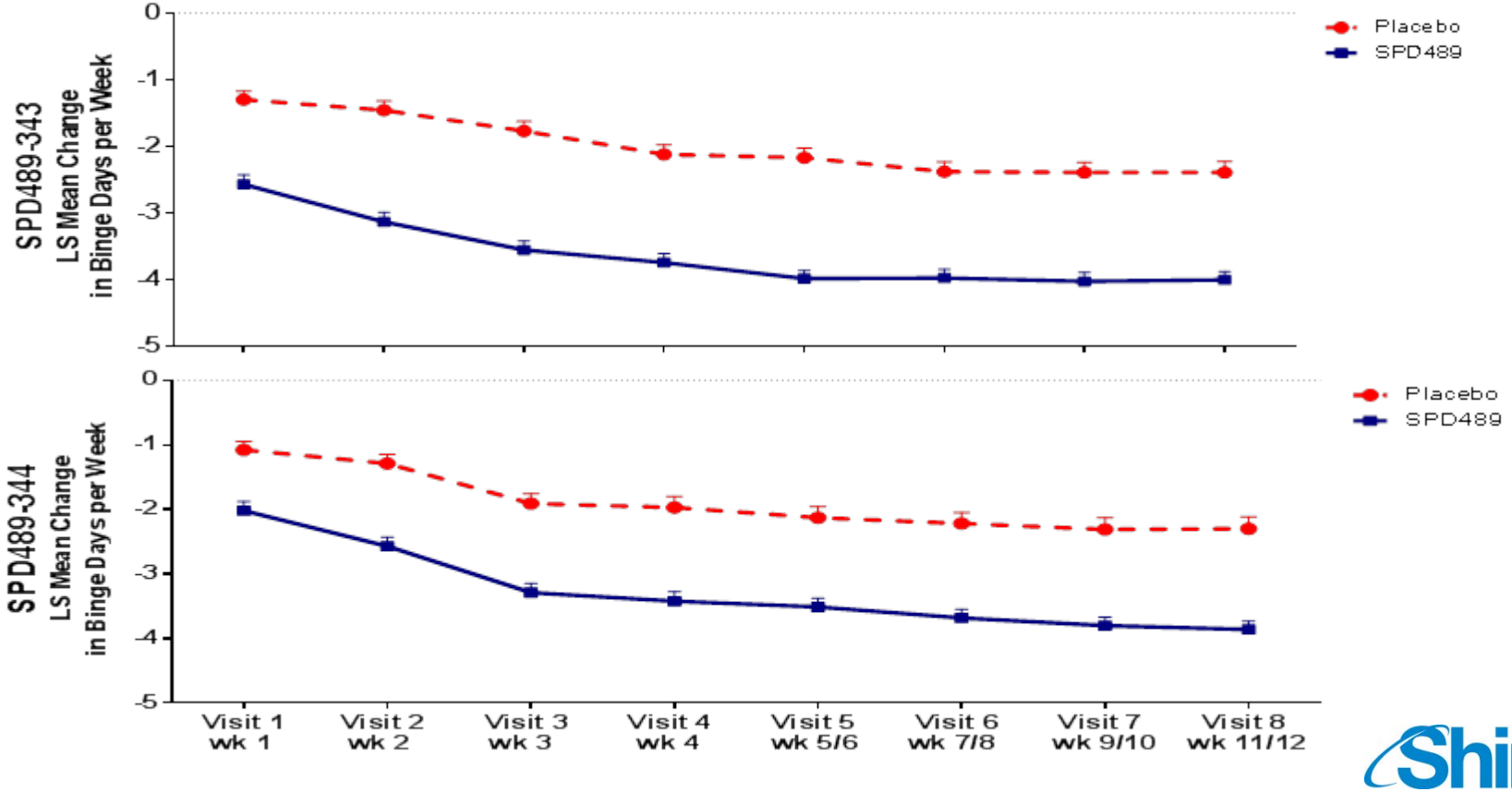
SPD489-343/344: Primary Efficacy Endpoint*: LS Mean (±SEM) Change from Baseline in the Number of Binge Days/Week



*p-value <0.001 at Visit 8 (Weeks 11 and 12) for both studies.

Data Source: Table 3.1.1.1 and 3.1.1.2

BED Regulatory Update

LDX
BED

Site inspections complete

Ongoing Q&A

Timeline

August 1
Submission

Sept 30
Accepted for filing

PRIORITY REVIEW

No filing issues identified

Mid Cycle
Review

No AC currently planned

Nov 21
Safety Update submission

Feb 1
PDUFA

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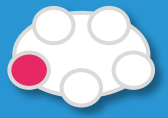
SHP465: ADHD



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- Complement Biology
- Renal / Transplant
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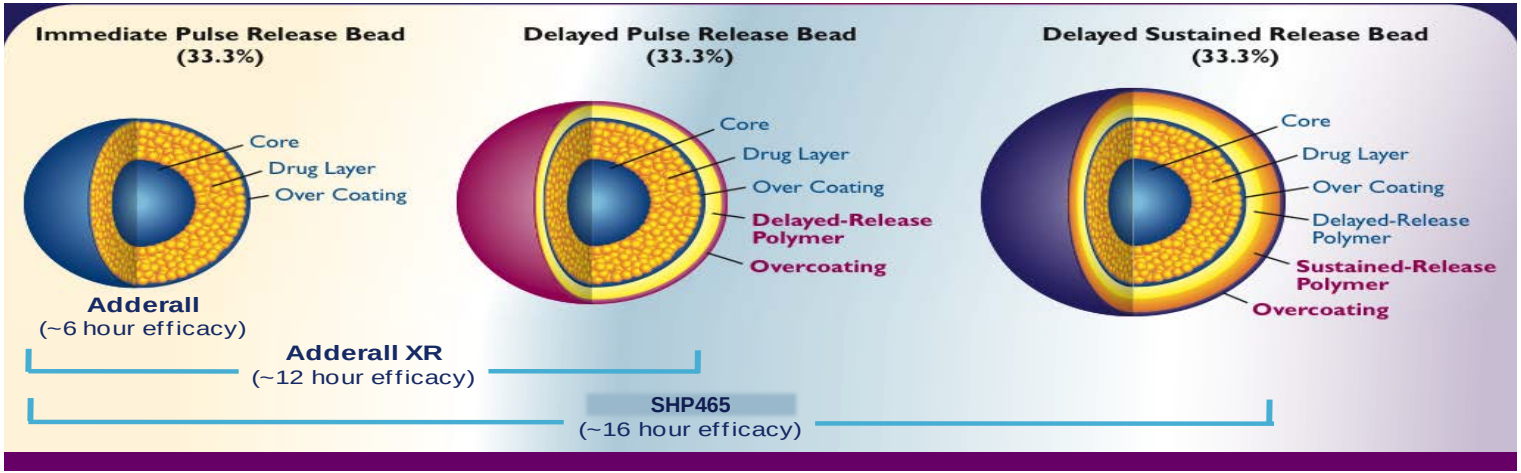
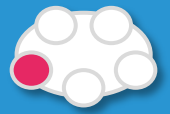
SHP465: ADHD

- A three bead formulation of mixed amphetamine salts provides ADHD symptom control at 16 hours post-dose (Adult ADHD).



SHP465: ADHD Development Status



SHP465
ADHD

Development Program Status

- SPD465-201: Adult workplace laboratory study *(completed)*
- SPD465-202: Adolescent analog classroom study *(completed)*
- SPD465-203: Adult workplace laboratory study *(completed)*
- SPD465-301: Adult dose-optimization study *(completed)*
- SPD465-303: Adult fixed-dose study *(completed)*
- SPD465-304: Adult open-label long-term safety study *(completed)*

Part of initial submission in 2006

- SHP465-305: Pediatric and adolescent dose-optimization study *(planning)*

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SHP465 Regulatory Update

SHP465
ADHD

Initial NDA Review

Ongoing dialogue regarding Peds requirements

Timeline Slide

2006
Submission

2007
Approvable letter

Feb 2014
Reinitiation with FDA discussions started

April
Initial FDA comments received. began discussions on peds requirements

October
General alignment on plan and peds plan submitted

Nov
Full protocol provided to FDA

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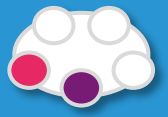
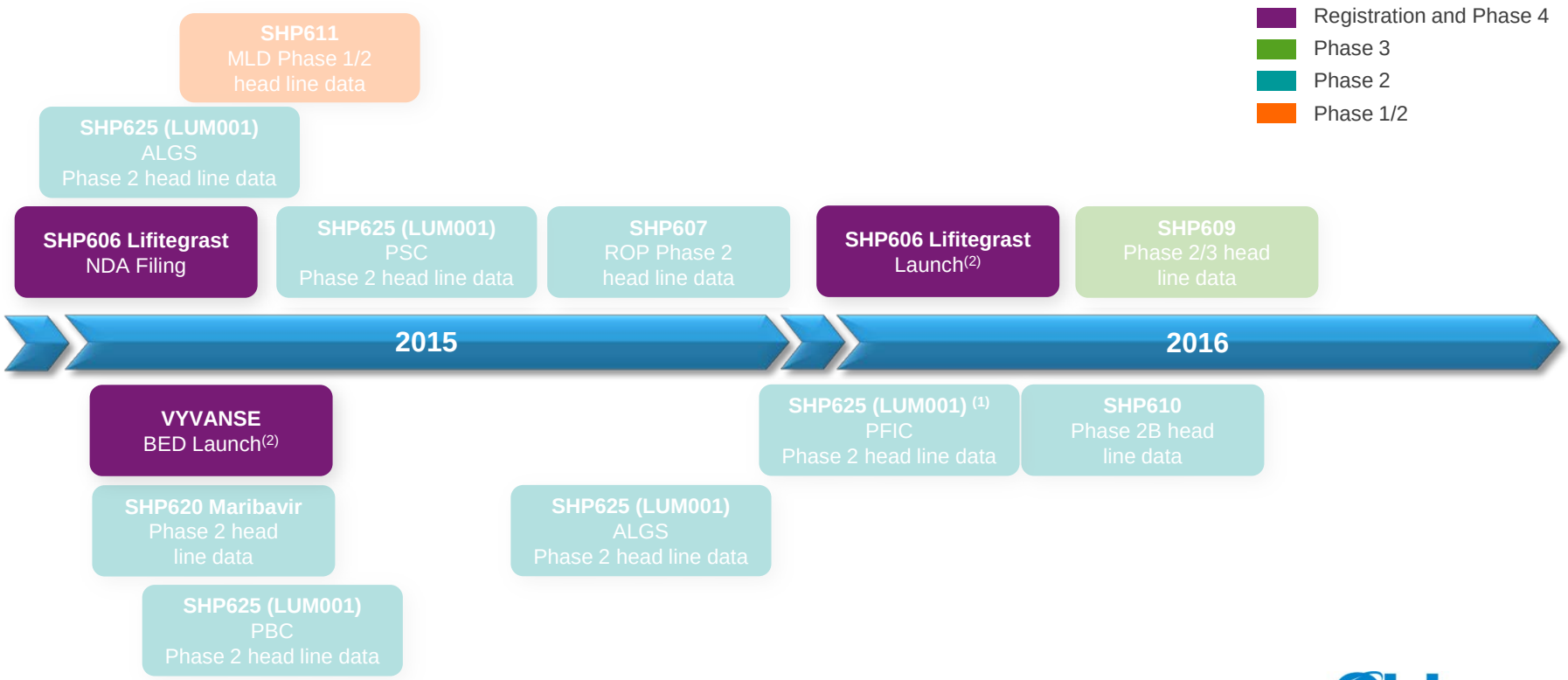
Upcoming Anticipated Late-Stage Pipeline Milestones





Notes
(1) Interim 625 PFIC INDIGO data expected Q2 2015.
(2) Subject to regulatory approval.

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Program Wrap-Up

Phil Vickers, Ph.D., Global Head of R&D

Our purpose
We enable people with life-altering conditions to lead better lives.

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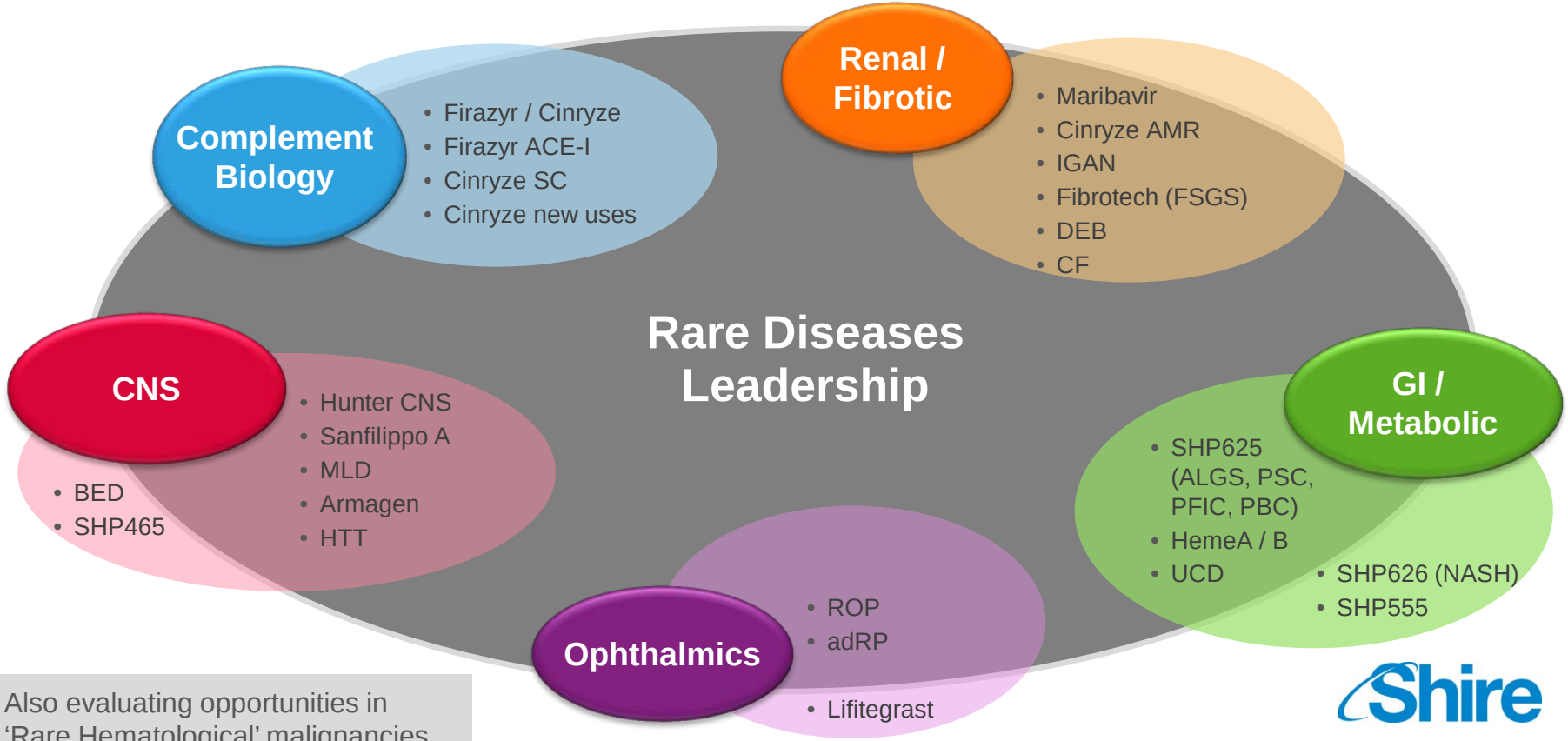
R&D Focused on Five Therapeutic Areas



Also evaluating opportunities in 'Rare Hematological' malignancies

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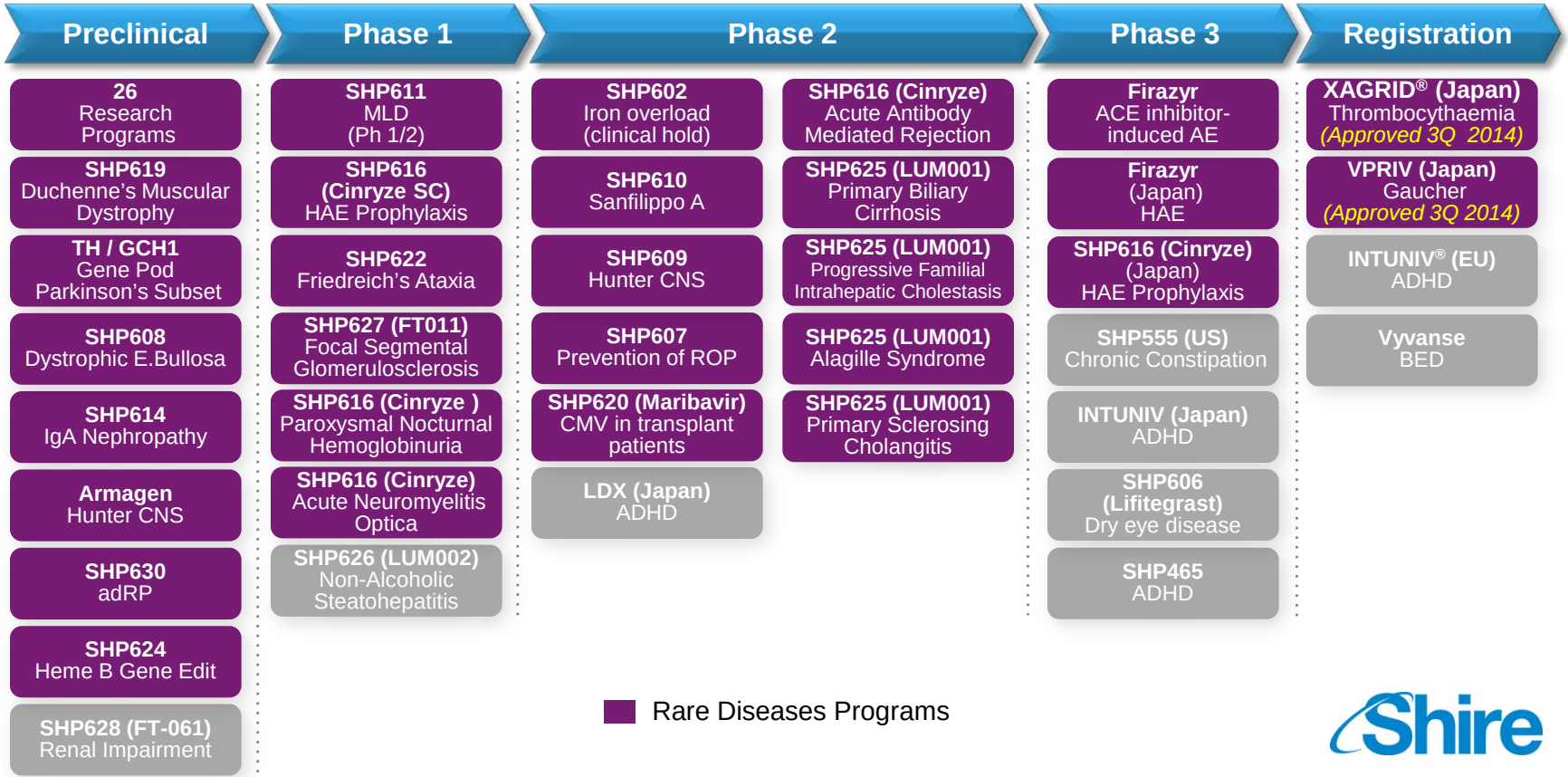
Pipeline Increasingly Focused on Rare Diseases



Programs Reviewed Today

GROWTH

INNOVATION

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- Rare Diseases Leadership
- Programs not specifically discussed today

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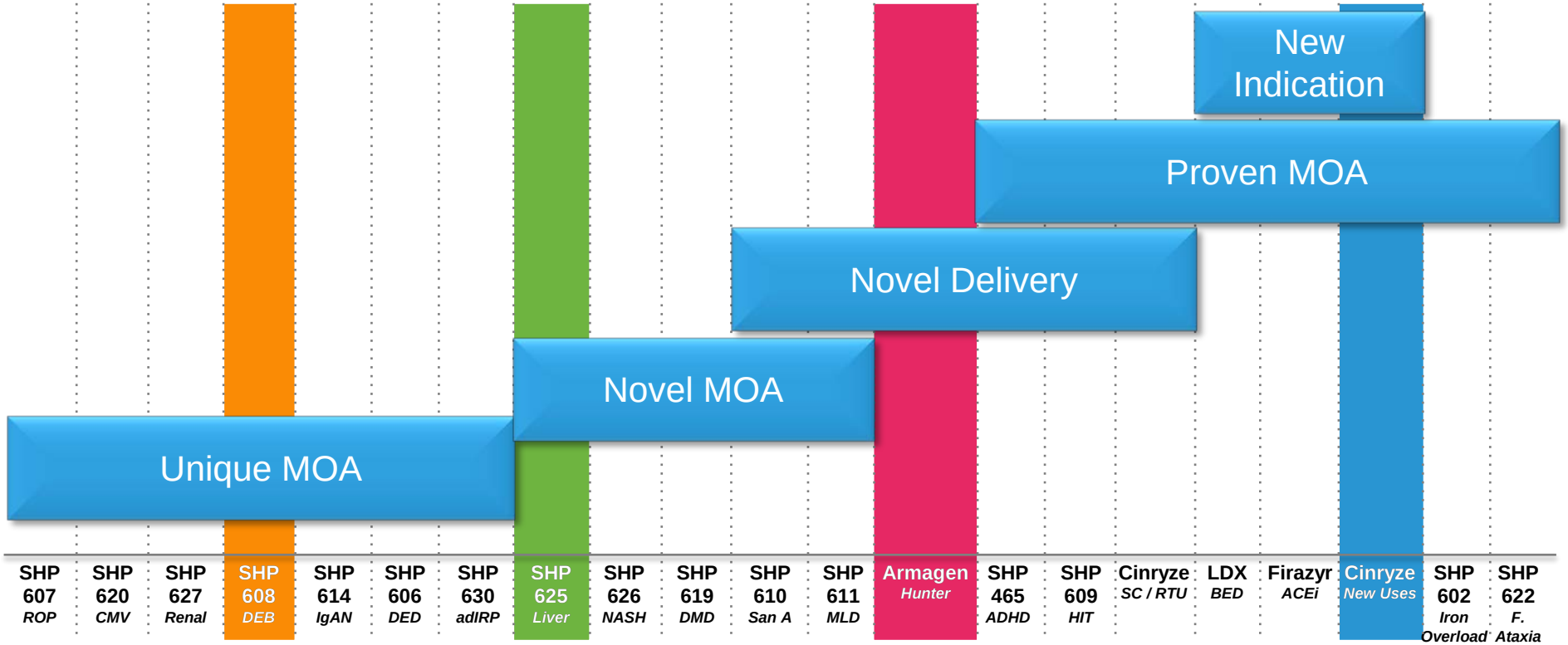
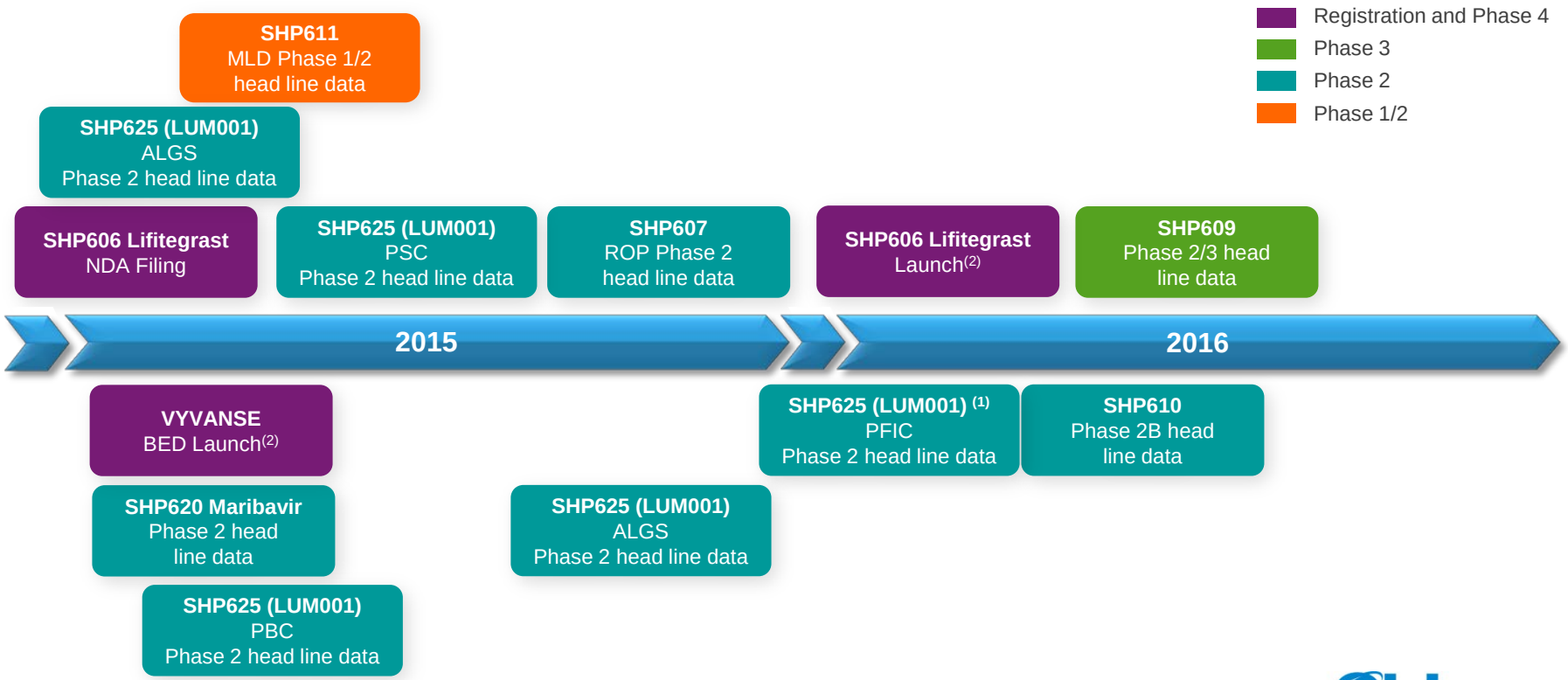
Pipeline Balances Innovation and Risk



Upcoming Anticipated Pipeline Milestones



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Pipeline Has Never Been Stronger

22 programs in the clinic, the most in the history of Shire

Well-positioned to deliver on ‘10 x 20’ expectations

Many **significant clinical milestones** in the next 18 months

On track to file at least **2 INDs** from internal programs every year

Establishing talent and capabilities appropriate to drive **future growth**

Continued excellence in acquiring **external assets with a strong strategic fit**

Establishing a leadership position in the treatment of Rare Diseases

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Question & Answer

Our purpose
We enable people with life-altering conditions to lead better lives.

Shire

Executing on our Corporate Strategy through R&D

- We plan to increase product sales to $10 Billion by 2020 – our 10 x 20 plan
- $3 Billion expected to come from our pipeline, excluding recent and future M&A
- Highly focused R&D organization
  - Prioritizing Rare Diseases (18 of 22 independent clinical programs)
  - Attracting, developing and retaining best talent
  - Ensuring organizational simplicity through two major geographic hubs
- Our R&D strategy is driving shareholder value
  - Addressing indications with high unmet medical need
  - Delivering a high-value late-stage pipeline to market
  - Optimizing asset value across the portfolio
  - Expanding expertise and access to innovation through collaborations

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Shire R&D Day

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