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Shire plc





## THE “SAFE HARBOR” STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

### "SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forwarding-looking statements. Such 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 plc's results could be materially affected. The risks and uncertainties include, but are not limited to: risks associated with the inherent uncertainty of pharmaceutical research, product development, manufacturing and commercialization; the impact of competitive products, including, but not limited to, the impact of those on Shire plc's Attention Deficit and Hyperactivity Disorder ("ADHD") franchise; patents, including but not limited to, legal challenges relating to Shire plc's ADHD franchise; government regulation and approval, including but not limited to the expected product approval dates of SPD503 (guanfacine extended release) (ADHD), SPD465 (extended release of mixed amphetamine salts) (ADHD), LIALDA™ (mesalamine) with MMX Technology (SPD476) (ulcerative colitis), and NRP104 (lisdexamfetamine dimesylate) (ADHD), including its scheduling classification by the Drug Enforcement Administration in the United States; Shire plc's ability to secure new products for commercialization and/or development; and other risks and uncertainties detailed from time to time in Shire plc's and its predecessor registrant Shire Pharmaceuticals Group plc's filings with the US Securities and Exchange Commission, particularly Shire plc's Annual Report on Form 10-K for the year ended December 31, 2005.

#### **The following are trademarks of Shire plc or its subsidiaries, which are the subject of trademark registrations in certain countries.**

ADDERALL XR® (mixed salts of a single-entity amphetamine product), AGRYLIN® (anagrelide hydrochloride), CARBATROL® (carbamazepine), DAYTRANA™ (methylphenidate transdermal), ELAPRASE™ (idursulfase), FOSRENOL® (lanthanum carbonate), LIALDA™ (mesalamine), MESAVANCE™ (mesalamine), MEZAVANT™ (mesalamine), REPLAGAL™ (agalsidase alfa), VYVANSE™ (lisdexamfetamine dimesylate), XAGRID® (anagrelide hydrochloride)

**The following are trademarks of third parties.** 3TC® (trademark of GlaxoSmithKline (GSK)), PENTASA® (trademark of Ferring AS), DYNEPO® (trademark of Aventis Pharma Holdings GmbH), ZEFFIX® (GSK), REMINYL/RAZADYNE® (trademark of Johnson & Johnson, excluding UK and Republic of Ireland)

## Ability to Execute

- Stated goals for Q3/Q4:
  - ✓ Launch DAYTRANA in the US
  - ✓ Launch ELAPRASE in the US & receive a positive opinion from the European authorities
  - ✓ Continue the international launch of FOSRENOL
  - ✓ File SPD465 with FDA
  - ✓ File SPD503 with FDA
  - ✓ Receive positive response on VYVANSE (NRP104 )
  - ✓ Settle patent litigation with Barr Laboratories, Inc.

## ADHD Progress

- ADDERALL XR US market share leader : 26.8%\*
  - YTD script growth of nearly 9% - nearly three times the rate of growth in the ADHD market
- DAYTRANA
  - Successful US launch continues ~ 2% market share
  - Very positive reaction from patients and physicians
- VYVANSE™ (NRP104)
  - Next generation stimulant
  - Second approvable letter received by NRP on December 21, 2006
- SPD465 - filed with the FDA on July 21 – PDUFA May 21, 2007
- SPD503 - filed with the FDA on August 24 – PDUFA June 24, 2007

## GI progress

- LIALDA (US) (ulcerative colitis)
  - Trade name agreed with FDA
  - US PDUFA January 21, 2007
  - Q1 launch planned
- MEZAVANT (Europe) (ulcerative colitis)
  - Core labelling language agreed with MAA for 15 European countries
    - For the induction of clinical and endoscopic remission in patients with mild to moderate, active ulcerative colitis and for maintenance of remission.
    - 2.4g/d to 4.8g/d (two to four tablets) taken once daily for induction of remission and 2.4g/d (two tablets) taken once daily for maintenance of remission.
  - National approvals to follow throughout Q1

## Renal

- FOSRENOL (hyperphosphatemia)
  - US co-promotion agreement signed with Abbott
    - Co-promotional activities will begin in Q1 07 and continue for a term of up to 5 years
  - Product performing well in launched European markets
  - Major European country launches continue
- DYNEPO (anemia)
  - Plans progressing for H1 2007 European rollout

## HGT Commercial Highlights

- ELAPRASE (Hunter syndrome)
  - US: over 110 patients on therapy and 140 additional patients consented for treatment
  - Positive opinion received from European Authorities
  - Pre-approval access received for France, Germany, Italy, Spain, Sweden, Denmark and Norway. Over 100 patients on therapy in these countries
- REPLAGAL (Fabry disease)
  - Agreement reached with Canadian government to support post-marketing research of patients on Fabry treatment
  - Licence variation granted by European Commission to include, in the product information data, from children with Fabry disease from 7 years of age



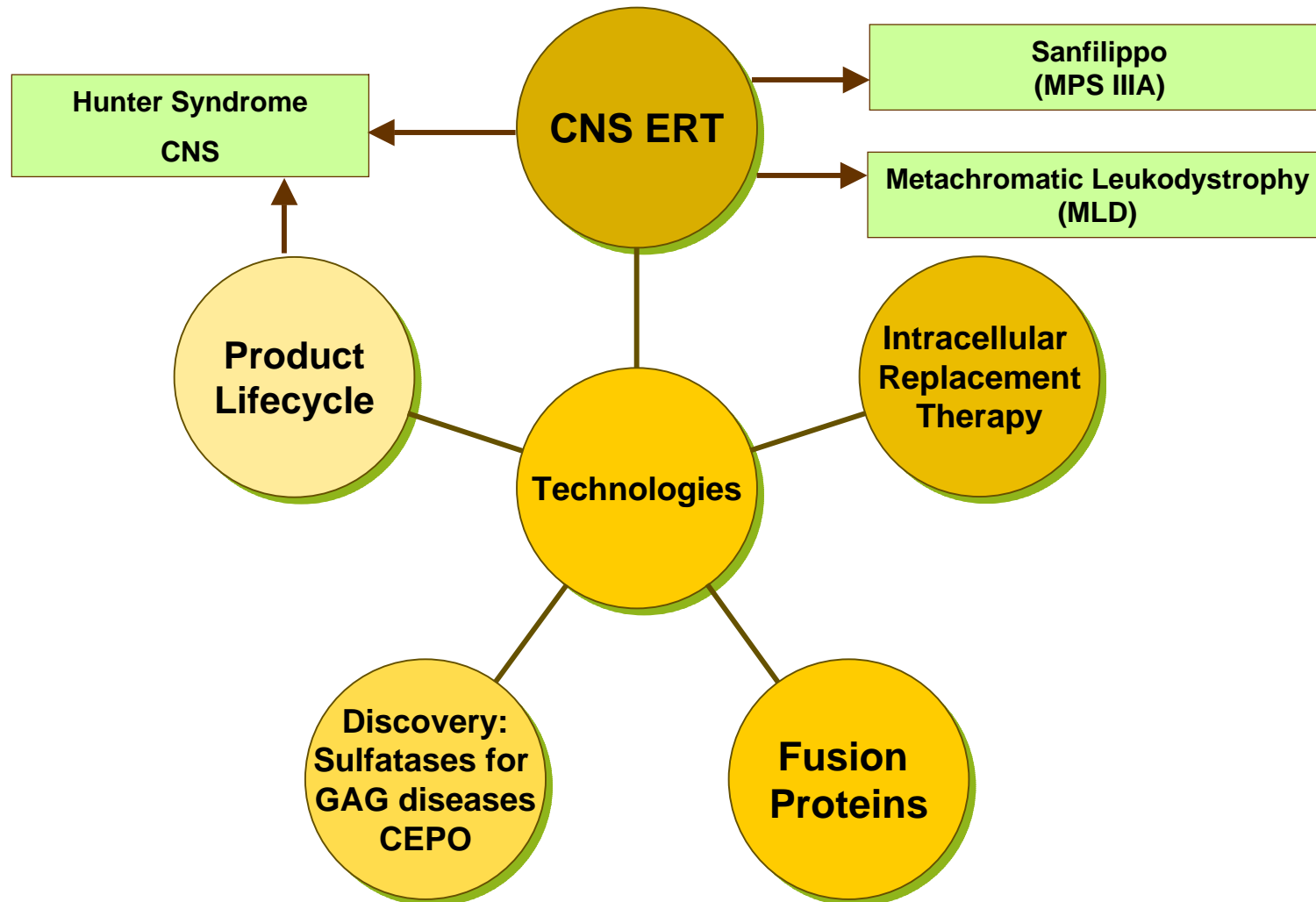
# HGT Pipeline Update



## HGT Research Overview

- Goal:
  - One new drug candidate every 12 months starting in 2007
- Capacity:
  - Three research projects to proof of concept every 18 months
- Principles:
  - Disease targets resulting from single gene deficiencies amenable to protein therapy
  - Limited proof of concept experiments
  - Discovery mainly via external collaborations

# HGT Product Pipeline: Technologies for Genetic Diseases



# Enzyme Replacement Therapy for CNS Lysosomal Storage Diseases

- Treatment concept
  - Direct administration of lysosomal enzymes into the cerebrospinal fluid
  - Peripheral administration for enzymes with demonstrated capacity to cross the blood brain barrier
  - Enzymes reach target cells and tissues by active transport via M6P Receptor-mediated uptake
  - Proof of concept has been demonstrated

# Sanfilippo Syndrome, MPS IIIA

## ■ Overview

- Caused by deficiency of the lysosomal enzyme, sulfamidase (heparan N-sulfatase)
- Primarily CNS disease; diagnosis within 2-6 years of age
- Severe, progressive neurodegeneration in most patients with mild somatic disease
- Incidence: approximately 1/70,000 births
- Enzyme production uses FGE\* converting technology

## ■ Rationale for Therapy

- Intrathecal direct delivery concept
- CNS delivery proof-of-concept established in dog and mouse models

\*Formylglycine Generating Enzyme (FGE) is a unique technology specific to Shire that allows for the development of high productivity manufacturing cell lines for sulfatases.

# Metachromatic Leukodystrophy (MLD)

- Overview
  - Deficiency of lysosomal arylsulfatase A (ASA)
  - Results in buildup of sulfatide leading to demyelination in central and peripheral nervous system
  - Clinical signs show variable onset and severity
  - Strong evidence links disease severity to residual enzyme level
  - Most patients normal at birth, but die before age 20
  - Incidence: 1/70,000 (range: 1:40,000-1:100,000)
  - Enzyme production uses FGE technology

# Metachromatic Leukodystrophy (MLD)

- Rationale for therapy
  - ASA will be taken-up into the peripheral and central nervous system through M6P receptor active transport
  - Published data in mouse model established the proof-of-concept for peripheral dosing of ASA
  - High doses of enzyme may be required due to the need for enzyme in both the peripheral and central nervous system, unlike Sanfilippo
  - Administration route could be either intrathecal or intravenous, depending on dose required

# Hunter Syndrome Overview

## ■ Overview

- X-linked disorder, incidence ~1:150,000
- Accumulation of dermatan sulfate and heparan sulfate (GAGs) occurs as a result of iduronate 2-sulfatase (I2S) deficiency
- Progressive accumulation of GAGs occurs in all cell types, including CNS
- Spectrum of disease, ranging from attenuated to severe
- The more severe end of the spectrum most often has CNS involvement
  - Intellectual deterioration, developmental delay
  - Moderate-severe communicating hydrocephalus (excessive Cerebro Spinal Fluid in brain ventricles)
  - Spinal cord compression
  - Seizures
  - Retinal dysfunction
  - Markedly reduced lifespan (age 10-15)

# Hunter Syndrome CNS

- Rationale for therapy
  - Line extension of I2S ERT for Hunter patients with CNS involvement
  - Direct delivery concept
  - CNS delivery proof-of-concept achieved for I2S
    - Single and repeat intrathecal dosing in normal dogs (no large animal model of Hunter syndrome): Measured enzyme levels throughout CNS
    - Enzyme was found widely distributed into target cells and tissues in both surface and deep brain structures
    - Single 30 mg dose provided 10 to 15-fold over normal enzyme activity levels throughout the brain

## Outlook - 2006

- Shire's business continues to perform strongly - 2006 revenue growth is now anticipated to be in the range of **12% to 14%** (previous guidance: low double digit growth).
- Earnings for 2006 impacted by costs associated with the continued development and launch of five new products in 2006 and H1 2007 in addition to the roll-out of FOSRENOL across Europe and new higher strengths of FOSRENOL in the US.
  - These launches require additional A&P spend and in some cases additional sales reps. In addition, Shire is seeking to maximize the level of ADDERALL XR market share. Consequently, SG&A costs are expected to be at the **top end** of the original forecast range (\$770 – 800 million);
  - 2006 activity includes regulatory filings for ELAPRASE, SPD465, SPD503 & MESAVANCE, Phase 3(b) and Phase 4 studies to support new product launches, the transfer of three HGT projects into pre-clinical development & the commencement of P3 trials on GA-GCB. R & D is expected to be at the **lower end** of the original guidance range (\$310 – 330 million);
  - D & A approximately **30% higher** than 2005 charge (previous guidance 50% higher).
- Estimated tax rate - approximately 28%.

## Outlook - 2006

- The financial outlook for the full year stated above excludes the accounting impact of the following items:
  - The milestone payment of \$50m paid to New River in February 2006 following the FDA's acceptance of the filing of NRP104;
  - **Upfront payments of \$30.5m paid to Duramed (\$25m) and Warren (\$5.5m);**
  - **The gain of \$63m made on disposal of ADDERALL product rights to Duramed;**
  - A US GAAP adjustment to cost of product sales, of **\$47m** (previous guidance: \$50m) to reflect the difference between the accounting fair value and book value of acquired REPLAGAL inventory, **all of which has now been consumed;**
  - HGT integration costs estimated at **\$6m** in 2006 (previous guidance: \$7m) of which \$4m was incurred to date;
  - The adoption from January 1, 2006 of US GAAP accountancy standard SFAS 123R for share based compensation; approximately \$45m of which \$25.8m charged YTD.

## Concluding Remarks

- Continuing to demonstrate our ability to execute
  - ADDERALL XR – leading US market share, litigation settled with Barr Laboratories
  - DAYTRANA - strong US launch, 2.0% share
  - ELAPRASE - approved in US, positive opinion in EU, over 210 patients globally on therapy
  - FOSRENOL - strong start in Europe
  - SPD465 - filed with FDA
  - SPD503 - filed with FDA
- Additional product launches by mid-2007 - on track
  - NRP104
  - LIALDA/MEZAVANT
  - DYNEPO
  - ELAPRASE – EU
- Earlier stage HGT pipeline advancing toward clinical development

# Questions and answers

All

