Third Quarter Results to September 30, 2011

Shire plc
October 28, 2011

Angus Russell
Chief Executive Officer

Graham Hetherington
Chief Financial Officer

Michael Cola
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SVP, Specialty Pharmaceuticals R&D

Shire

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

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

Statements included herein that are not historical facts are forward-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, the Company's results could be materially adversely affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of research, development, approval, reimbursement, manufacturing and commercialization of the Company's Specialty Pharmaceuticals, Human Genetic Therapies and Regenerative Medicine products, as well as the ability to secure new products for commercialization and/or development; government regulation of the Company's products; the Company's ability to manufacture its products in sufficient quantities to meet demand; the impact of competitive therapies on the Company's products; the Company's ability to register, maintain and enforce patents and other intellectual property rights relating to its products; the Company's ability to obtain and maintain government and other third-party reimbursement for its products; and other risks and uncertainties detailed from time to time in the Company's filings with the Securities and Exchange Commission.

Agenda

- **Q3 2011 Highlights** | Angus Russell
- **Financial Review** | Graham Hetherington
- **VYVANSE New Uses** | Jeff Jonas
- **Concluding remarks** | Angus Russell
- **Q & A** | All

Q3 2011 Highlights

Angus Russell
Chief Executive Officer

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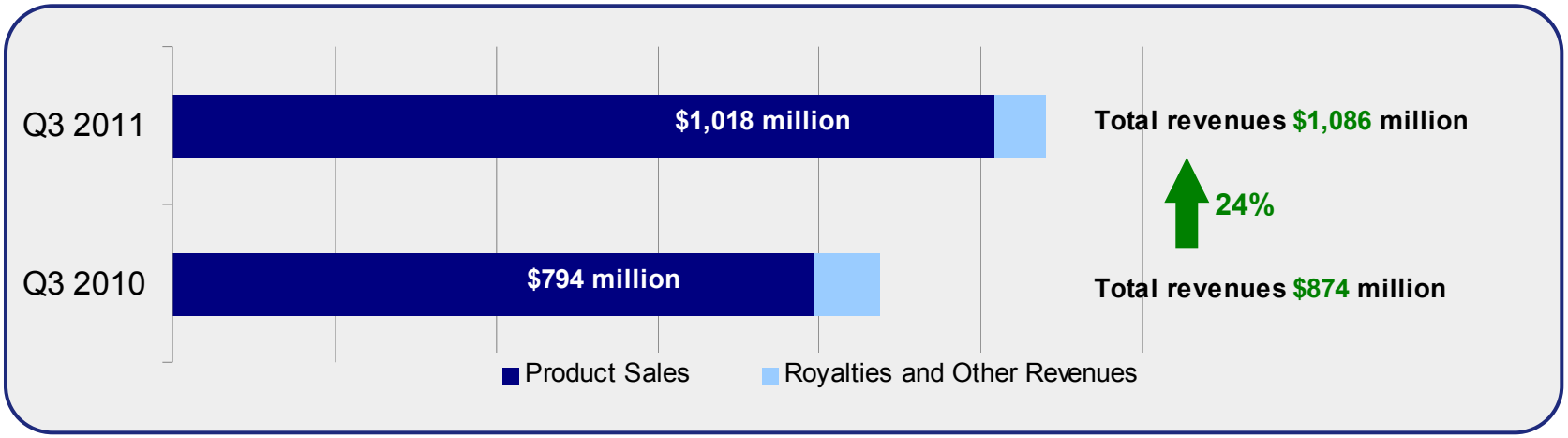
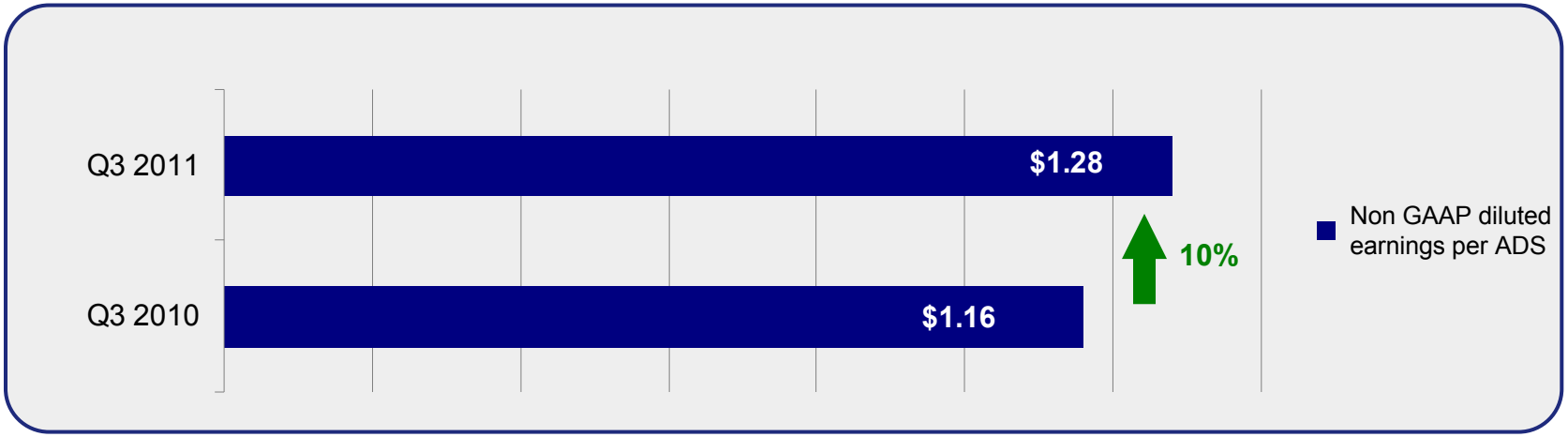
Balanced product portfolio continues to deliver strong revenue growth



Product sales ↑ **28%** to $1,018 million

Total revenues ↑ **24%** to $1,086 million

On track to deliver significant 2011 earnings growth



Q3 2011 Non GAAP diluted earnings per ADS: $1.28

Q3 2011 Non GAAP operating income ↑ 15% to $341 million

Specialty Pharma: Recent highlights

- ✓ Rx's increased 20% over Q3 2010; double the 10% quarterly total ADHD market growth; strong back to school season
- ✓ EU phase 3 pediatric trial data – consistent efficacy and safety profile to previous pivotal trials; Concerta reference arm included in design to compare to European standard of care; on track to file by year-end
- ✓ Potential Non-ADHD indications are progressing

- ✓ Rx's increased 9% over Q2 2011; 59% over Q3 2010
- ✓ Favorable increase in market share trends driven by new consumer marketing and adjunctive therapy with stimulant launch
- ✓ Enrolling EU pivotal phase 3 programs

- ✓ US Rx market share increased to 20.7%.
- ✓ FDA recently approved Lialda label change to add a maintenance of remission claim

* IMS NPA (National Prescription Audit) Sept 2011

HGT: Recent highlights

firazyr® icatibant	✓ Approved in the US with self-administration for acute attacks of Hereditary Angioedema in adults ✓ August US launch well received by patients, physicians and payers
REPLAGAL® agalsidase alfa	✓ Ex-US market share increased to 81%, driven by switch and new patients ✓ Continuing to meet high demand and monitoring closely to ensure supply continuity ✓ Commenced rolling BLA submission in US ✓ 40% growth in revenues vs Q3 2010
VPRIV® velaglucerase alfa for injection	✓ Sharp increase in demand created by Cerezyme shortage ✓ 31% growth in revenues vs Q3 2010
Lexington Manufacturing Facility	✓ VPRIV Process Validation Runs completed ✓ Initiating regulatory filings for VPRIV in November, with approval expected early in 2012 ✓ Approval of VPRIV also releases extra capacity for REPLAGAL

Regenerative Medicine: Recent highlights

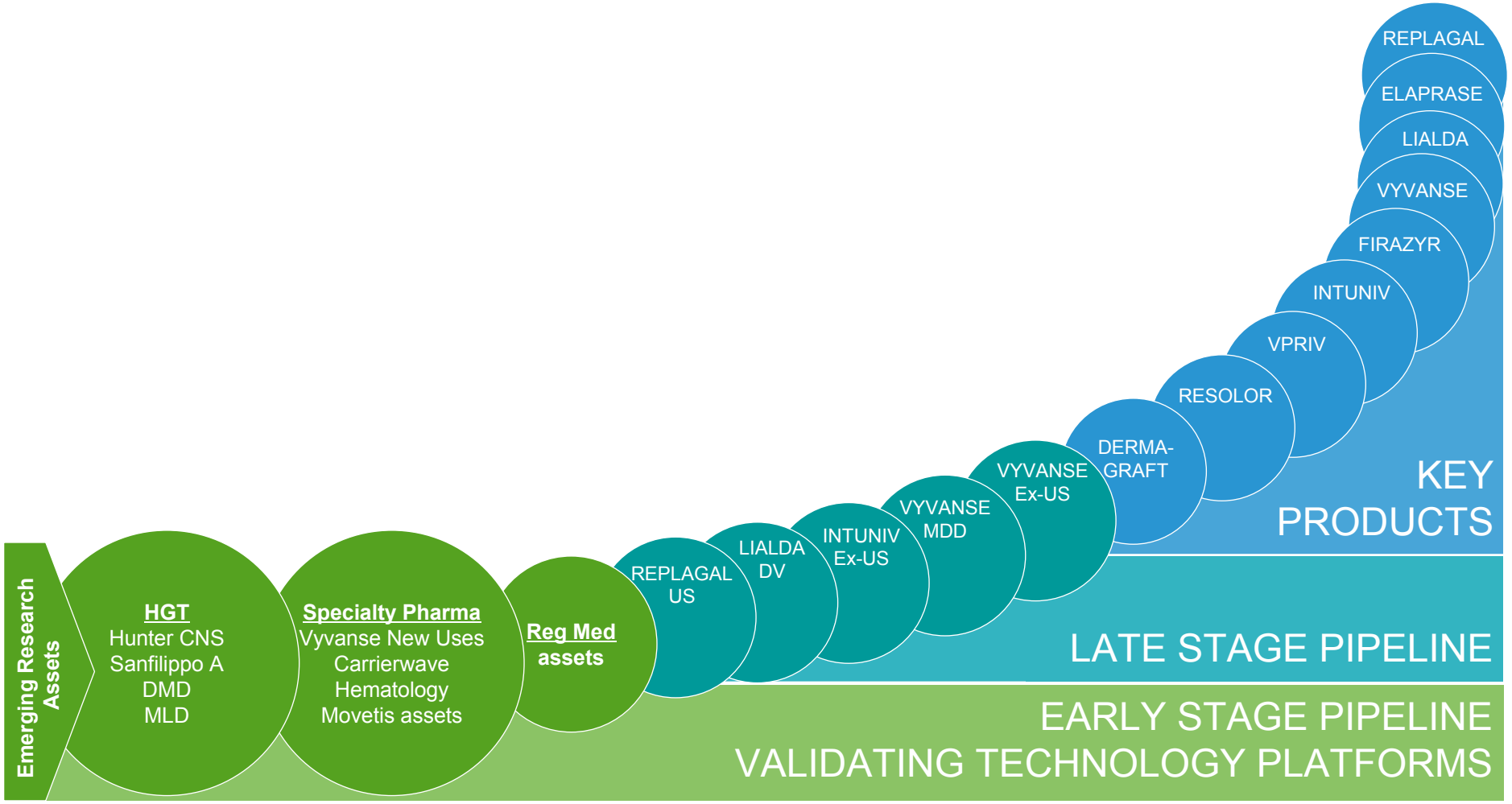
Dermagraft
Active Living Cells

- ✓ $50 million net sales in first full quarter as part of Shire
  - 27% increase vs Q3 2010*
  - Approximately 6% market share of addressable patient population
- ✓ Finalizing strategy for infrastructure necessary to increase manufacturing capacity
- ✓ Among U.S. residents ages 65 years and older, 10.9 million, or 26.9%, had diabetes in 2010**

* Shire acquired DERMAGRAFT through its acquisition of ABH on 28 June 2011

** Source: Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011

Investing to deliver growth now and into the future



Financial Review

Graham Hetherington
Chief Financial Officer

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2011 Q3 Performance summary

	Q3 2011 $m	Q3 2010 $m	Reported Growth	Like for Like Growth (1)
Product sales	1,018	794	+28%	+25%
Royalties and other revenues	68	80	-15%	-17%
Total revenues	1,086	874	+24%	+22%
EBITDA (2)	372	320	+16%	+15%
EBITDA % of product sales (2)(3)	30%	30%		
EPS - ADS (2)	$1.28	$1.16	+10%	
Cash generation (2)	296	271	+9%	

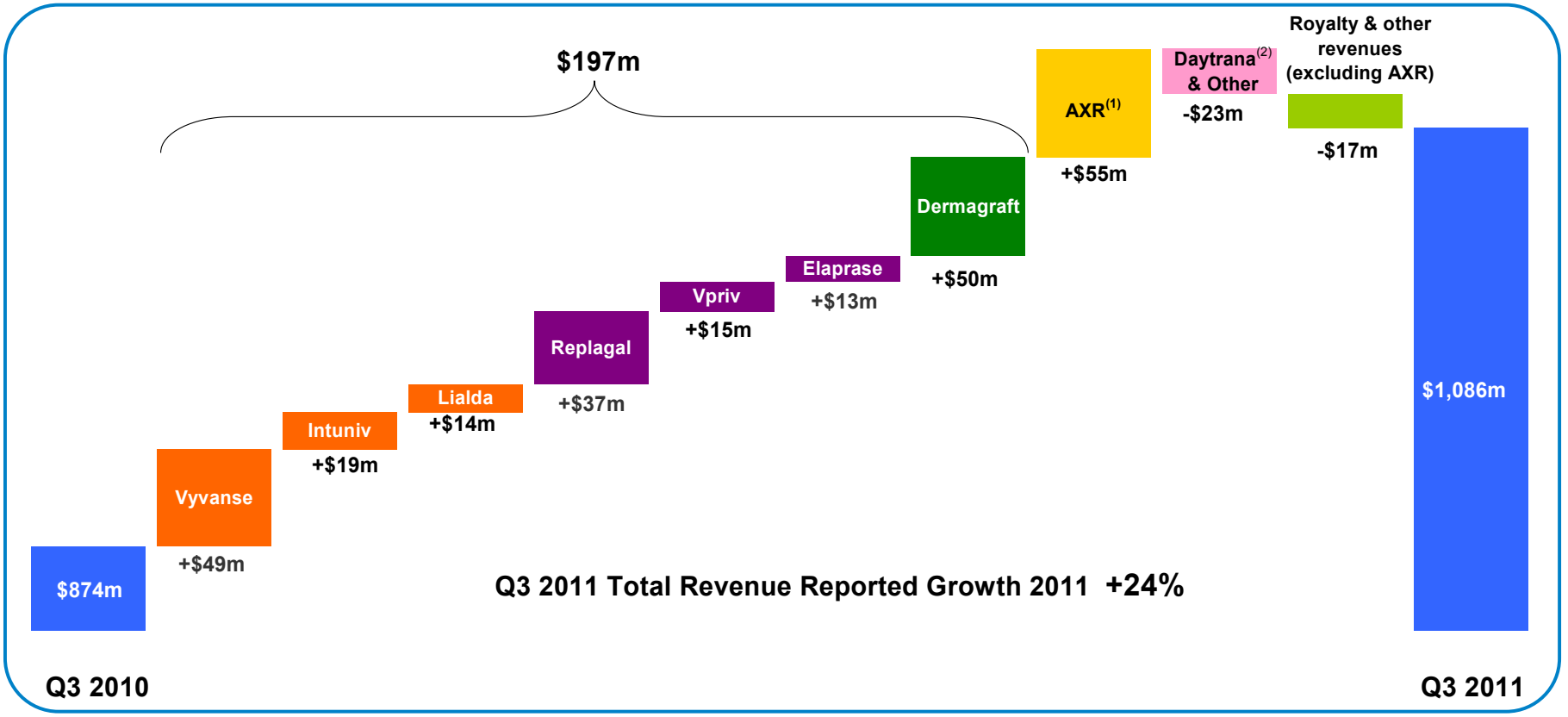
(1) 'Like for Like Growth' excludes movements in exchange rates by applying Q3 2010 exchange rates to Q3 2011 results.
(2) These are Non GAAP financial measures. See appendix for a list of items excluded from the US GAAP equivalent used to calculate these measures.
(3) Excluding royalties and other revenues

2011 Q3 Royalties

	Q3 2011 $m	Q3 2010 $m	Reported Change
ADDERALL XR	23	18	+27%
3TC and ZEFFIX	17	41	-57%
FOSRENOL	11	7	+56%
OTHER	12	11	+7%
Total Royalties	**63**	**77**	**-18%**

3TC & Zeffix affected by ongoing generic erosion and disagreement with GSK

Growth across portfolio drives $212m Total Revenues increase



(1) Product sales (+$50m) and royalties (+$5m)
(2) Daytrana was divested on October 1, 2010 and contributed $14.7m to Q3 2010 revenue

Operating leverage – Key Financial Ratios

Year on Year:	2011 YTD	2010 YTD
Product sales	+27%	+19%
R&D(1)	+25%	+11%
SG&A(1)	+23%	+11%

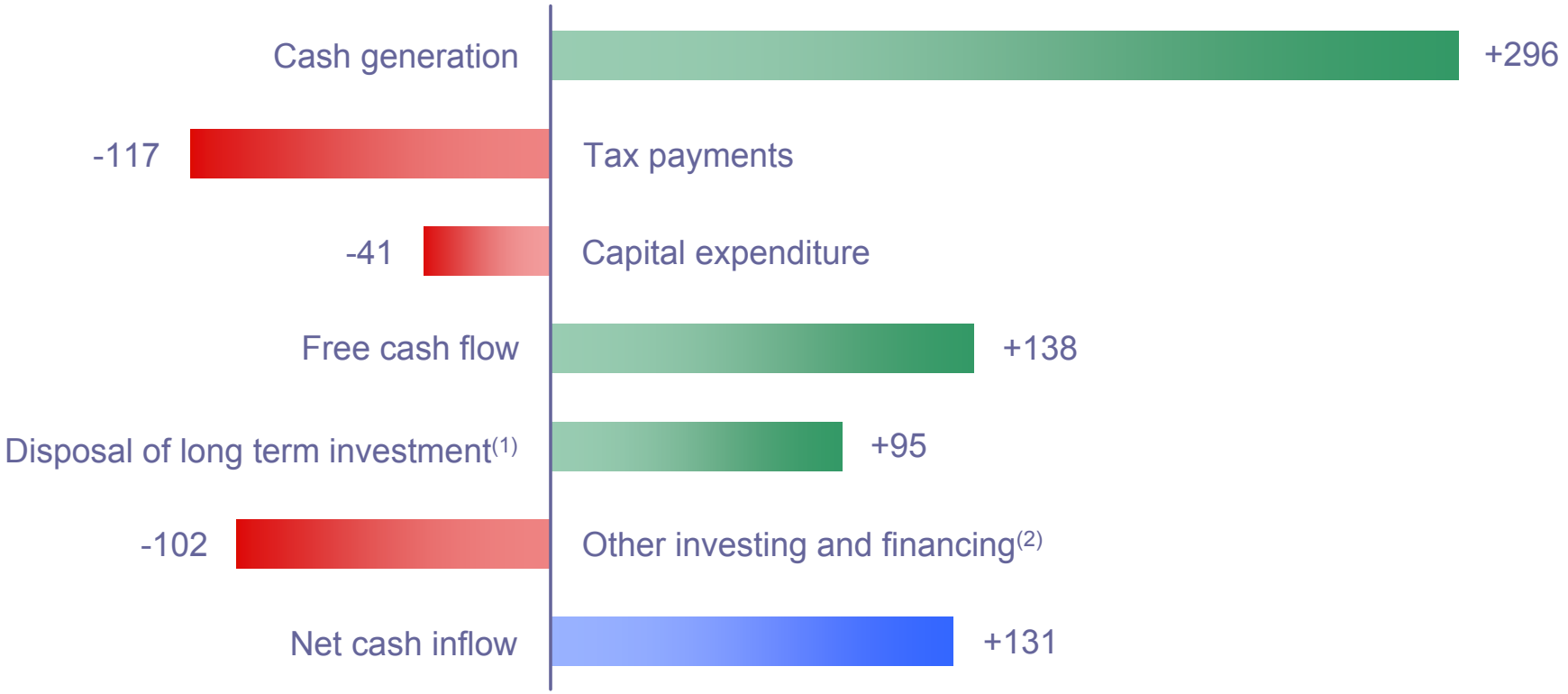
Ratios:

% of product sales		
Gross margin(1)	86%	87%
R&D(1)	18%	19%
SG&A(1)	39%	40%
EBITDA(1) (2)	29%	28%

(1) These are Non GAAP financial measures. See appendix for a list of items excluded from the US GAAP equivalents used to calculate these measures.
(2) Excluding royalties and other revenues.

2011 Q3 Cash flow

Millions of USD



(1) Shire received these shares in Vertex Pharmaceuticals Inc. as partial consideration for its investment in ViroChem Pharma Inc. following that company being acquired by Vertex.

(2) Other investing and financing includes repayment of the RCF ($30M) and purchase of shares by ESOT ($63M).

Note: Shire has a revolving 5 year credit facility of $1.2bn signed in November 2010 which remained undrawn at September 30, 2011.

Shire 2011 outlook

Full year 2011 dynamics	Direction versus FY 2010	
Product sales	↑	Benefiting from continued product sales growth and Dermagraft sales
Royalties	↓	Total royalties & other revenue down ~17%
Total Revenues	↑	H2 growth aligned with 22% seen in H1
Gross margins	≈	Marginal dilution from ABH; full year in line with 2010
R&D and SG&A	↑	Growth of 20% (5% due to ABH)
Tax rate	≈	22-24% tax rate
Reported EPS-ADS	↑	Significant earnings growth

Venvanse (Vyvanse) EU

Overview of Study 325 Data

Dr. Jeffrey Jonas
SVP, Specialty Pharmaceuticals R&D

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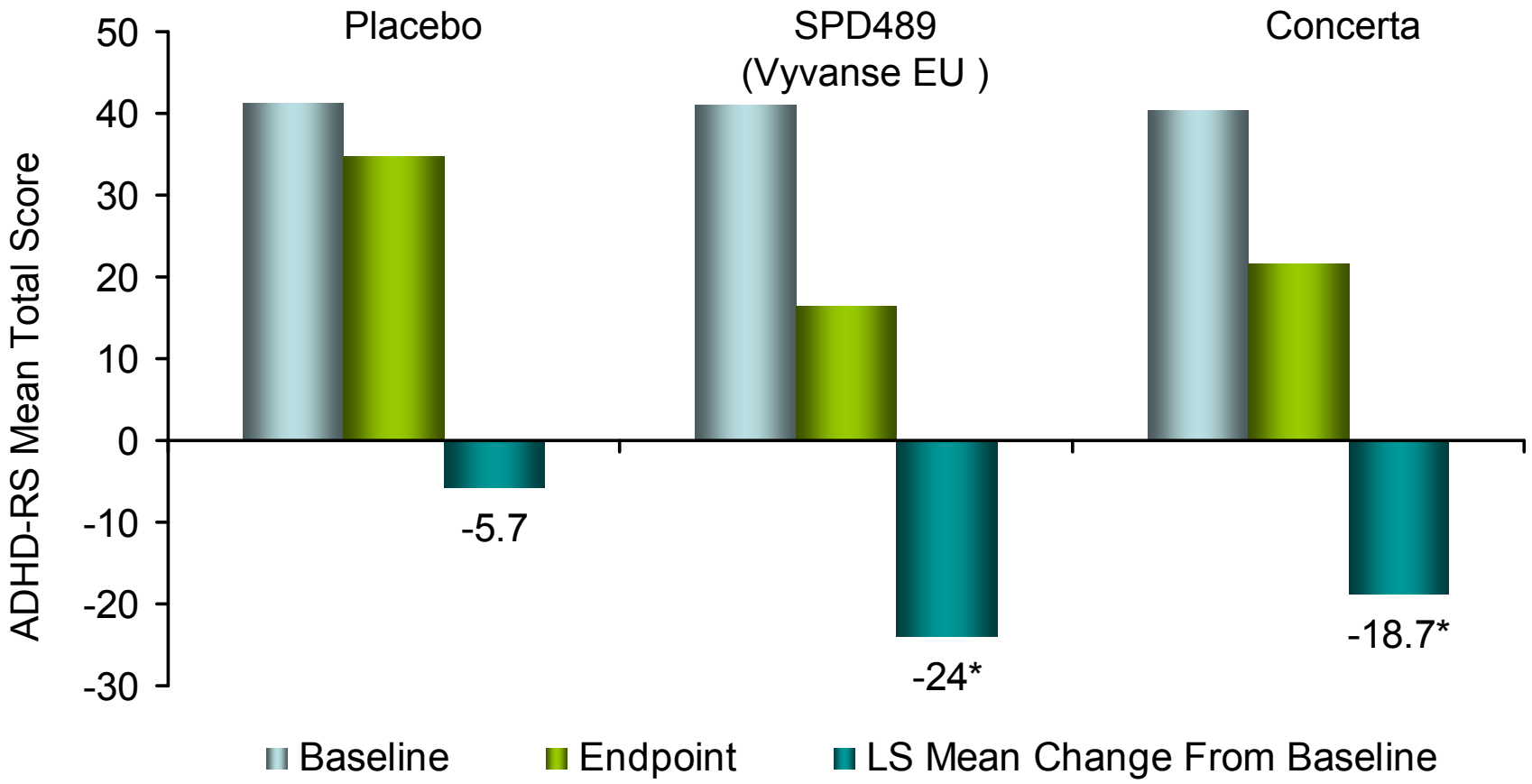
Venvanse (Vyvanse) EU

- EU filing – on target for Q4 2011
- Opportunity to grow market and treatment rates
- Ph 3 Study SPD489-325 (including methylphenidate as a reference arm)
  - Double blinded placebo and active-controlled study in children and adolescents aged 6-17 with ADHD
  - Conducted at 48 sites across Europe; approximately 200 patients completed trial
  - Showed that Vyvanse demonstrated robust efficacy on all key endpoints
  - Safety profile consistent with the known effects of amphetamine treatment and previous Vyvanse trials
- Ph 3 Study 317 (including Strattera comparator): ongoing

SPD489-325 Mean Change from Baseline in ADHD-RS-IV Total Score



**P*<0.001
FAS=full analysis set (n=332)

VYVANSE® New Uses Update

This communication describes investigational studies which evaluate the potential use of VYVANSE in treating non-ADHD conditions. These data are presented to inform the medical and financial communities about Shire development programs. No conclusions can be drawn regarding the safety or efficacy of VYVANSE in any of these other conditions without additional studies and review by regulatory authorities. VYVANSE is approved only for the treatment of Attention Deficit Hyperactivity Disorder. Shire does not recommend the use of its products in any way other than as described in the Prescribing Information.

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VYVANSE® New Uses Update

Investigation of dopamine-norepinephrine modulation in

- ✓ Major Depressive Disorder (MDD)
- ✓ Excessive Daytime Sleepiness (EDS)
- ✓ Negative Symptoms in Schizophrenia (NSS)
- ✓ Binge Eating Disorder (BED)

Dr. Jeffrey Jonas
SVP, Specialty Pharmaceuticals R&D

Shire

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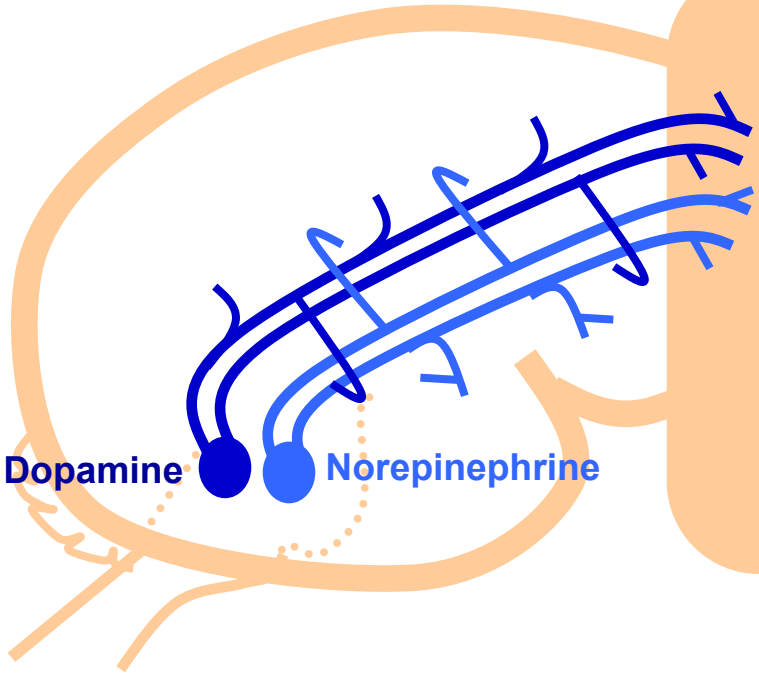
VYVANSE NEW USES

Dopamine (DA) and norepinephrine (NE) dysregulation is implicated in many neuropsychiatric disorders

As VYVANSE impacts DA and NE transmission, therapeutic effects may be seen in symptomatic disorders involving these neural pathways



- MOOD
- COGNITION
- INTEREST
- INHIBITION
- ENERGY
- MOTIVATION
- WAKEFULNESS

- ADHD
- Major Depression
- Excessive Daytime Sleepiness
- Schizophrenia
- Binge Eating

Kessler RC et al. *Am J Psychiatry* 2006;163:716-723; Atlfas et al. *BMC Psychiatry* 2002;2:9; Hudson et al. *Biol Psychiatry* 2007;61:348-358; Ross et al. *Schiz. Res* 2006;88:90-95; Wingo et al. *J Clin Psychiatry*, 2007, 68:11:1776-1784; Walters et. al. *J Clin Sleep Med*, 2008, 4:6:591-600; Dunlop & Nemeroff *Arch Gen Psych* (2007); 64:327-37.

VYVANSE NEW USES

Augmentation of first-line anti-depressants for inadequately responsive MDD

- **Placebo-controlled Phase 2 trial in 'all comers' showed clinically meaningful improvement in depressive symptoms (MADRS) and disability (SDS)**
  - 'All comers' reflects all patients, regardless of which residual symptoms are prominent (e.g., sadness, anxiety, energy, concentration)
- **Phase 3 program enrolling globally: 3 controlled, short-term trials and 1 open-label long-term trial**
  - Enrollment ~ 24 months, Treatment: 4 to 12 months, depending on trial
  - Final submission expected to include ~1,500 subjects
- **Additional Phase 2 trial in MDD patients near or at remission with persistent cognitive impairment using patient-centric approach**
  - Approximately 20 to 30% of MDD patients have persistent cognitive problems despite improvement in core depressive symptoms
  - Exploring potential innovative pathway for development and pharmacoeconomic benefit in targeted patients, given the disability associated with persistent cognitive impairment

MADRS=Montgomery-Åsberg Depression Rating Scale; SDS=Sheehan Disability Scale; Iverson et al, *J Aff Disord* (2011); Hasselbalch et al, *J Aff Disord* (2010): 134 (1-2): 20-31.

VYVANSE Study 205

Examined persistent cognitive impairment in MDD in patients near or at remission

- **Double-blind, placebo-controlled study (27 sites, 18 to 55 year old subjects)**
  - Subjects had no greater than mild depressive symptoms (MADRS total score ≤ 18) and continued to exhibit significant executive function impairments (≥ 1 standard deviation from normal)
- **Cognitive impairment examined with subjective and objective measures**
  - Neuropsychological battery including memory, attention, executive function, speed

Treatment Phase
9 week double-blind (following 2 week screening)

- **Randomization to placebo or VYVANSE augmentation of any background SSRI (1:1) of at least 8 weeks duration**
- **Weekly blinded assessments; Placebo (n=72), VYVANSE (n=71)**
- **143 enrolled, 119 completed (83.2%) study; Mean MADRS total baseline = 12.3**
- **Optimised dose [20 to 70 mg/d] first 6 weeks, maintained for 3 additional weeks; Mean daily VYVANSE dose = 53 mg**

Measures included
- Cognitive-based behavioral ratings and computerized neuropsychological battery
- Depressive and anxiety symptoms
- Quality of Life, Productivity, Sexual Functioning
- Suicidal thinking, Vital signs, Adverse events, Laboratories, Electrocardiograms

MADRS=Montgomery-Åsberg Depression Rating Scale; Roth et al, BRIEF-A Professional Manual, PAR 2005; SPD489-205 Data Tables 1.1.1; 1.2.2. 1.2.3; 4.1; 4.4.4; 4.4.3; 4.7.1

VYVANSE Study 205

Clinically significant improvement in subjective and objective cognitive endpoints

- **Significant improvement in self-rated and caregiver-rated subjective measures (BRIEF-A)**
  - Global Executive Composite T-score (mean change v. placebo; both $p<0.001$)
- **No new or emerging safety findings in this MDD subpopulation**
- **Full data to be presented at American College of Neuropsychopharmacology on December 5th, 2011**

205 Primary endpoint was self-rated BRIEF-A comparison at Week 9, VYVANSE versus placebo. MADRS=Montgomery-Åsberg Depression Rating Scale; BRIEF-A=Behavioral Rating Inventory of Executive Functioning-Adult Version; Roth et al, BRIEF-A Professional Manual, PAR 2005; Data Table 3.1.1.3; 3.2.3.1

VYVANSE NEW USES

Other programs

Indication	Status
Excessive Daytime Sleepiness	• Completing health authority interactions regarding potential for comparative labeling to enable optimal commercial positioning
Negative Symptoms in Schizophrenia	• Positive health authority and global thought leader response to current data set • Given tolerability in previous trial (highest VYVANSE doses), exploring risk-benefit profile of a higher dose range prior to initiating Phase 3 to enable optimal clinical use • Will determine clinical pathway 1H12
Binge Eating Disorder	• Phase 2 trial enrolment completed • Expected data availability 1H12

Concluding remarks

Angus Russell
Chief Executive Officer

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

Strategy continues to deliver

Balanced product portfolio delivers over $1 billion of sales for the quarter

Investing in promising pipeline opportunities

Delivering valuable and innovative treatments to meet the changing healthcare environment

Helping patients lead better lives

Questions and Answers

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APPENDIX

Non GAAP measures

- This presentation contains financial measures not prepared in accordance with US GAAP.
- These Non GAAP financial measures are used by Shire's management to make operating decisions because they facilitate internal comparisons of Shire's performance to historical results and to competitors' results. They should not be considered in isolation from, as substitutes for, or superior to financial measures prepared in accordance with US GAAP.
- The following items are excluded from these non-GAAP financial measures:

Amortization and asset impairments:

- Intangible asset amortization and impairment charges; and
- Other than temporary impairment of investments.

Acquisitions and integration activities:

- Upfront payments and milestones in respect of in-licensed and acquired products;
- Costs associated with acquisitions, including transaction costs, and fair value adjustments on contingent consideration and acquired inventory;
- Costs associated with the integration of companies; and
- Non-controlling interest in consolidated variable interest entities.

Divestments, re-organizations and discontinued operations:

- Gains and losses on the sale of non-core assets;
- Costs associated with restructuring and re-organization activities;
- Termination costs; and
- Income / (losses) from discontinued operations.

2011 Portfolio Strength and Diversity – Q3 Product Sales

	Q3 2011 $m	Q3 2010 $m	Reported Growth	Like for Like Growth[1]
VYVANSE	200	151	+32%	+32%
ADDERALL XR	150	100	+50%	+50%
REPLAGAL	129	92	+40%	+31%
ELAPRASE	110	97	+13%	+7%
LIALDA / MEZAVANT	90	76	+18%	+17%
VPRIV	65	50	+31%	+27%
INTUNIV	56	37	+50%	+50%
PENTASA	56	57	-2%	-2%
DERMAGRAFT	50	-	n/a	n/a
FOSRENOL	41	45	-10%	-14%
FIRAZYR	7	3	+148%	+129%
RESOLOR	2	-	n/a	n/a
OTHER	62	86[2]	-25%	-29%
PRODUCT SALES	**1,018**	**794**	**+28%**	**+25%**

(1) 'Like for Like Growth' excludes movements in exchange rates by applying 2010 exchange rates to 2011 results.
(2) 2010 'Other' includes DAYTRANA sales of $14.7m.

2011 Emerging Shape of Shire Income Statement

	2010 Q1	2010 Q2	2010 Q3	2010 Q4	2010 FY	2011 Q1	2011 Q2	2011 Q3	FY 2011 Dynamics Direction v. FY 10	Commentary
Total Product Sales	$718m	$764m	$794m	$852m	$3,128m	$889m	$993m	$1,018m	↑	Benefiting from continued product sales growth and Dermagraft sales
versus prior year [1]	*-9%*	*+37%*	*+24%*	*+21%*	+16%	+24%	+30%	+28%		
Royalties & Other revenues	$98m	$85m	$80m	$80m	$343m	$83m	$70m	$68m	↓	Total royalties & other revenue ~ 17%
versus prior year	+58%	+19%	+24%	-31%	+9%	-15%	-18%	-15%		
Total Revenues	$816m	$849m	$874m	$932m	$3,471m	$972m	$1,063m	$1,086m	↑	H2 growth aligned with 22% seen in H1
versus prior year [1]	*-5%*	*+35%*	*+24%*	*+14%*	+15%	+19%	+25%	+24%		
Gross Margin [2] [3]	87%	86%	87%	86%	87%	87%	87%	86%	≈	Marginal dilution from ABH; full year in line with 2010
R&D [3]	$127m	$144m	$149m	$178m	$598m	$173m	$171m	$180m		
versus prior year	+$10m	+$26m	+$5m	+$34m	+$75m	+$46m	+$27m	+$31m	↑	Growth of 20% (5% due to ABH)
SG&A [3]	$309m	$304m	$302m	$373m	$1,288m	$352m	$388m	$389m		
versus prior year	+$38m	+$19m	+$35m	+$58m	+$150m	+$43m	+$84m	+$87m		
Tax Rate [3]	26%	25%	24%	16%	23%	22%	23%	24%	≈	22-24% tax rate

(1) 2010 Product sales growth compared to 2009 product sales on a “normalized Medicaid rebate” basis.
(2) Gross margin calculated as a percentage of product sales.
(3) These are Non GAAP financial measures. See appendix for a list of items excluded from the US GAAP equivalents used to calculate these measures.

2011 Q3 Non GAAP cash flow measures

Non GAAP cash generation reconciliation	Q3 2011 $m	Q3 2010 $m
Net cash provided by operating activities	**179**	142
Tax and interest payments, net	**117**	84
Payment for acquired and in-licensed products	-	45
Non GAAP cash generation[(1)]	**296**	271

Non GAAP free cash flow reconciliation	Q3 2011 $m	Q3 2010 $m
Net cash provided by operating activities	**179**	142
Capital expenditure	**(41)**	(54)
Non GAAP free cash flow[(2)]	**138**	88

(1) Non GAAP cash generation represents net cash provided by operating activities, excluding upfront and milestone payments for in-licensed and acquired products, tax and interest payments

(2) Non GAAP free cash flow represents net cash provided by operating activities, excluding upfront and milestone payments for in-licensed and acquired products, but including capital expenditure in the normal course of business

Non GAAP net debt

	Sep, 30 2011 $m	Dec, 31 2010 $m
Cash and cash equivalents	276	550
Restricted cash	21	27
Convertible bonds	(1,100)	(1,100)
Building finance obligation	(8)	(8)
Net debt	**(811)**	**(531)**

Current pipeline

Preclinical and earlier	Phase 1	Phase 2	Phase 3	Registration
HGT 1110 MLD	**Guanfacine Carrier Wave**	**VYVANSE** NSS/EDS/BED	**VYVANSE (EU)** ADHD	**DERMAGRAFT (Canada)** DFU
Undisclosed Programs	**Carrier Wave for Pain**	**SPD 557 (M0003)** rGERD	**INTUNIV (EU)** ADHD	**INTUNIV (Canada)** ADHD
	HGT 1410 Sanfilippo A(1)	**SPD 556 (M0002)** Ascites	**VYVANSE** MDD	**REPLAGAL (US)** Fabry Disease
	HGT 2310 Hunter CNS(1)	**HGT 4510** DMD(2)	**LIALDA** Diverticular Disease	
		SPD 535 Platelet Reducing	**XAGRID (Japan)** Essential Thrombocythaemia	

ERT
DMD
Early Research

ADHD/CNS
GI
Hematology
Regenerative Medicine
Pain

Note
(1) HGT 1410 and HGT 2310 are currently in Phase 1/2 clinical trials
(2) Currently on clinical hold

Study 325

The poster can be accessed through the following link: www.shirecongressposters.com/686144

4.10

Efficacy and safety of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder: a phase 3, randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled, dose-optimized study in Europe

David R Coghill,[1] Tobias Banaschewski,[2] Michel L Lecendreux,[3] César A Soutullo,[4] Mats Johnson,[5] Colleen S Anderson,[6] Richard Civil,[6] C Nicholas Higgins,[6] Andrew Lyne,[7] Liza A Squires[6]

[1]Division of Neuroscience, Ninewells Hospital, Dundee, UK; [2]Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany; [3]Pediatric Sleep Center, CHU Hospital Robert-Debré, Paris, France; [4]Child and Adolescent Psychiatry Unit, Department of Psychiatry and Medical Psychology, University Clinic of Navarra, Pamplona, Spain; [5]Child Neuropsychiatry Unit, Queen Silvia Children's Hospital, Gothenburg, Sweden; [6]Shire Development Inc., Wayne, PA, USA; [7]Shire Pharmaceutical Development Ltd, Basingstoke, UK

BACKGROUND

- Stimulant medication is commonly used to treat attention-deficit/hyperactivity disorder (ADHD).
- Lisdexamfetamine dimesylate (LDX) is the first long-acting, prodrug stimulant.
- Following oral administration, the therapeutically inactive molecule of LDX is converted to the active metabolite, d-amphetamine, primarily in the blood.
- The therapeutic benefits of LDX are ongoing at 13 hours in children and 14 hours in adults. Rates of interpatient and intrapatient variability in key pharmacokinetic measures are low.[1]
- In pivotal phase 3 trials conducted outside of Europe, LDX was effective in treating the core symptoms of ADHD in children[2] and adolescents,[3] with safety and tolerability profiles generally consistent with those of other central nervous system stimulant medications.
- LDX is indicated for the treatment of ADHD in the USA, Canada and Brazil, but is not yet licensed in Europe.
- This phase 3 study will provide additional data in European patients to support the regulatory submission of LDX in Europe as a treatment for children and adolescents with ADHD, and the continuation into adulthood for adolescents who have shown clear benefits from treatment.

OBJECTIVE

- To evaluate the efficacy and safety of LDX when administered as a daily morning dose, compared with placebo, over the course of 7 weeks in children and adolescents with ADHD of at least moderate severity.

METHODS

Study design

- Randomized, double-blind, parallel-group, placebo- and active-controlled study comprising three phases: dose optimization (≤ 4 weeks); dose maintenance (≥ 3 weeks); and post-treatment washout (1 week).
- A reference arm of osmotic-release oral system methylphenidate (OROS-MPH) was included to establish assay sensitivity.
- Patients were randomized equally to receive a once-daily, morning dose of LDX 30 mg, OROS-MPH 18 mg or placebo. During weeks 1–4, the daily dose of active drug was optimized to LDX 30, 50 or 70 mg or to OROS-MPH 18, 36 or 54 mg until an 'acceptable response' was achieved, defined as a composite of:
  - ≥ 30% reduction from baseline in ADHD Rating Scale version IV (ADHD-RS-IV) total score
  - Clinical Global Impressions-Global Improvement (CGI-I) score of 1 or 2
  - absence of intolerable side effects.
- Weekly assessments of safety and efficacy were conducted, with reference to baseline.

Study population

- Children and adolescents (6–17 years old) diagnosed with ADHD of at least moderate severity (baseline ADHD-RS-IV total score ≥ 28) were enrolled at 48 sites across Europe.
- Exclusion criteria included, but were not limited to: previous failure to respond to an adequate course of OROS-MPH; significant symptoms resulting from a current controlled or uncontrolled comorbid psychiatric diagnosis; symptoms or a condition that may have contraindicated LDX or OROS-MPH treatment; history of serious cardiac abnormalities; and hypersensitivity, intolerance or non-response to amphetamine or methylphenidate.

Study measures

- *Primary efficacy measure:* change from baseline in the investigator-rated ADHD-RS-IV total score at endpoint (defined as last on-therapy, post-randomization treatment visit, up to day 49, at which a valid ADHD-RS-IV total score was observed).
- *Key secondary efficacy measure:* improvement in the CGI-I scale ('improved' = CGI-I ≤ 2; 'not improved' = all remaining levels).
- *Safety* assessments included treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms (ECGs), laboratory and physical investigations, and psychiatric rating scales.

RESULTS

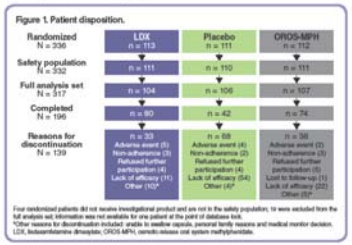
Patient disposition and demographics

- Of the 336 patients randomized, 332 received at least one dose of investigational product (safety population), 317 were included in the full analysis set (FAS, used for comparative efficacy assessments) and 196 completed the study (Figure 1).
- At baseline, all groups were balanced for age, sex, race, weight and ADHD-RS-IV and CGI-I scores (Table 1).

Efficacy

- Mean ADHD-RS-IV total scores at baseline and endpoint, and least-squares (LS) mean changes from baseline in ADHD-RS-IV total scores, are shown in Figure 2 (FAS).
- The difference between active agents (optimized dose) and placebo in LS mean change from baseline in ADHD-RS-IV total score (95% confidence interval [CI]) was −18.6 (−21.5, −15.7) for LDX ($p < 0.001$) and −13.0 (−15.9, −10.2) for OROS-MPH ($p < 0.001$).
- The effect size based on this difference in the LS mean change from baseline was 1.80 for LDX and 1.26 for OROS-MPH.
- Improved CGI-I at endpoint was seen in 78% of patients receiving LDX, 14% receiving placebo and 61% receiving OROS-MPH (FAS). The percentage of patients categorized as 'improved' was higher in the LDX and OROS-MPH groups than in the placebo group at every on-treatment visit (Figure 3).

Figure 1. Patient disposition.



Four randomized patients did not receive investigational product and are not in the safety population; 19 were excluded from the full analysis set; information was not available for one patient at the point of database lock.
*Other reasons for discontinuation included: unable to swallow capsule, personal family reasons and medical monitor decision.
LDX, lisdexamfetamine dimesylate; OROS-MPH, osmotic-release oral system methylphenidate.

Table 1. Key demographics and baseline characteristics (safety population)

Characteristic	LDX (n = 111)	Placebo (n = 110)	OROS-MPH (n = 111)	Total (n = 332)
Age, years, mean (SD)	10.9 (2.9)	11.0 (2.8)	10.9 (2.6)	10.9 (2.8)
Sex				
Male, n (%)	87 (78.4)	91 (82.7)	90 (81.1)	268 (80.7)
Female, n (%)	24 (21.6)	19 (17.3)	21 (18.9)	64 (19.3)
Race				
White, n (%)	107 (96.4)	108 (98.2)	107 (96.4)	322 (97.0)
Non-white, n (%)	4 (3.6)	2 (1.8)	4 (3.6)	10 (3.0)
Weight, kg, mean (SD)	44.6 (17.4)	42.6 (13.9)	43.1 (14.9)	43.4 (15.5)
BMI, kg/m², mean (SD)	19.3 (3.7)	19.0 (3.3)	19.1 (3.2)	19.1 (3.4)
Baseline ADHD-RS-IV total score,* mean (SD)	41.0 (7.3)	41.2 (7.2)	40.4 (6.8)	40.9 (7.1)
Baseline CGI severity rating,* mean (SD)	5.0 (0.8)	4.9 (0.8)	5.0 (0.8)	5.0 (0.8)

*Five patients had no baseline ADHD-RS-IV total score and no CGI severity rating.
ADHD-RS-IV, ADHD Rating Scale version IV; BMI, body mass index; CGI, Clinical Global Impressions; LDX, lisdexamfetamine dimesylate; OROS-MPH, osmotic-release oral system methylphenidate; SD, standard deviation.

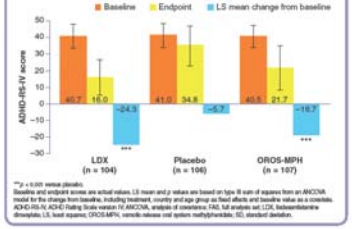
Safety

- TEAEs were reported by 80/111 (72%), 63/110 (57%) and 72/111 (65%) of patients receiving LDX, placebo and OROS-MPH, respectively (Table 2, safety population).
- The most common TEAEs reported by patients receiving LDX are listed in Table 2.
- Mean changes in vital signs and ECG parameters were modest and consistent with the known profile of LDX (Table 3); ECG changes were not clinically significant.

CONCLUSIONS

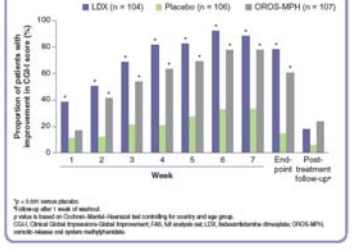
- A once-daily optimized morning dose of LDX was effective in children and adolescents with ADHD of at least moderate severity.
- LDX was generally well tolerated and displayed a safety profile consistent with the known effects of long-acting stimulant use and the results from previous LDX trials.
- LDX has the potential to be an important additional treatment option for the management of children and adolescents with ADHD in Europe.

Figure 2. ADHD-RS-IV mean total scores at baseline and endpoint (± SD), and LS mean changes from baseline (FAS, n = 317).



**p < 0.001 versus placebo.
Baseline and endpoint scores are actual values. LS mean and p values are based on type III sum of squares from an ANCOVA model for the change from baseline, including treatment, country and age group as fixed effects and baseline value as a covariate.
ADHD-RS-IV, ADHD Rating Scale version IV; ANCOVA, analysis of covariance; FAS, full analysis set; LDX, lisdexamfetamine dimesylate; LS, least squares; OROS-MPH, osmotic-release oral system methylphenidate; SD, standard deviation.

Figure 3. Proportion of patients with improvement in CGI-I scores at each on-treatment visit (FAS, n = 317).



†p < 0.001 versus placebo.
*Follow-up after 1 week of washout.
p value is based on Cochran–Mantel–Haenszel test controlling for country and age group.
CGI-I, Clinical Global Impressions-Global Improvement; FAS, full analysis set; LDX, lisdexamfetamine dimesylate; OROS-MPH, osmotic-release oral system methylphenidate.

Table 2. Summary of TEAEs reported by ≥ 5% of patients in any one active treatment group (safety population)

TEAE, n (%)	LDX (n = 111)	Placebo (n = 110)	OROS-MPH (n = 111)
Any TEAE	80 (72.1)	63 (57.3)	72 (64.9)
Decreased appetite	28 (25.2)	3 (2.7)	17 (15.3)
Headache	16 (14.4)	22 (20.0)	22 (19.8)
Insomnia	16 (14.4)	0	9 (8.1)
Weight decreased	15 (13.5)	0	5 (4.5)
Nausea	12 (10.8)	3 (2.7)	8 (7.2)
Anorexia	12 (10.8)	2 (1.8)	6 (5.4)
Nasopharyngitis	8 (7.2)	8 (7.3)	14 (12.6)
Abdominal pain (upper)	8 (7.2)	6 (5.5)	9 (8.1)
Abdominal pain	6 (5.4)	6 (5.5)	4 (3.6)
Sleep disorder	6 (5.4)	1 (0.9)	2 (1.8)
Cough	3 (2.7)	0	8 (7.2)
Initial insomnia	3 (2.7)	1 (0.9)	7 (6.3)

LDX, lisdexamfetamine dimesylate; OROS-MPH, osmotic-release oral system methylphenidate; TEAE, treatment-emergent adverse event.

Table 3. Summary of vital signs, weight and electrocardiogram parameters (change from baseline, safety population)

	LDX (n = 111)	Placebo (n = 110)	OROS-MPH (n = 111)
Systolic blood pressure, mmHg			
Baseline, mean (SD)	107.4 (10.4)	107.8 (10.4)	107.1 (9.9)
Endpoint, mean change (SD)	+1.0 (9.8)	+1.0 (9.8)	+0.3 (11.1)
Diastolic blood pressure, mmHg			
Baseline, mean (SD)	68.3 (9.9)	66.1 (9.1)	65.0 (9.5)
Endpoint, mean change (SD)	+0.2 (9.6)	+1.2 (8.7)	+1.7 (9.9)
Pulse, bpm			
Baseline, mean (SD)	75.0 (11.7)	77.5 (11.5)	76.6 (10.2)
Endpoint, mean change (SD)	+5.5 (13.2)	−0.6 (10.6)	+3.4 (13.2)
Weight, kg			
Baseline, mean (SD)	45.0 (17.5)	43.1 (14.0)	43.8 (15.1)
Endpoint, mean change (SD)	−2.1 (2.0)	+0.7 (1.0)	−1.3 (1.4)
Heart rate, bpm			
Baseline, mean (SD)	74.6 (12.1)	77.2 (10.3)	75.9 (10.2)
Endpoint, mean change (SD)	+5.7 (15.3)	−1.1 (9.6)	+5.0 (12.8)
QTcF interval, ms			
Baseline, mean (SD)	376.9 (16.4)	377.9 (17.4)	375.9 (16.4)
Endpoint, mean change (SD)	+0.3 (15.6)	+2.0 (13.6)	+0.2 (15.9)

bpm, beats per minute; LDX, lisdexamfetamine dimesylate; QTcF, QT interval corrected using Fridericia's formula; OROS-MPH, osmotic-release oral system methylphenidate; SD, standard deviation.

REFERENCES

1. Goodman DW. *P T* 2010;35:273–87.
2. Biederman J *et al. Clin Ther* 2007;29:450–63.
3. Findling RL *et al. J Am Acad Child Adolesc Psychiatry* 2011;50:395–405.

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