# Welcome to Ipsen's first investor day



# Introduction

Jean-Luc Bélingard Chairman & CEO





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### **Objectives for today**

Where do we stand today?

- Update on our specialist care business
- Market dynamics

A growth story

- Update on US progress
- Focus on market opportunities

Where will Ipsen stand tomorrow?

- Update on pipeline
- Focus on key early and late stage assets

Ipsen viewed by Key Opinion Leaders

- Pr. Barnes
- Pr. Rosenfeld

Strong financials

- A strong balance sheet
- Financial objectives

# A profound change, in the making...

Jean-Luc Bélingard Chairman & CEO





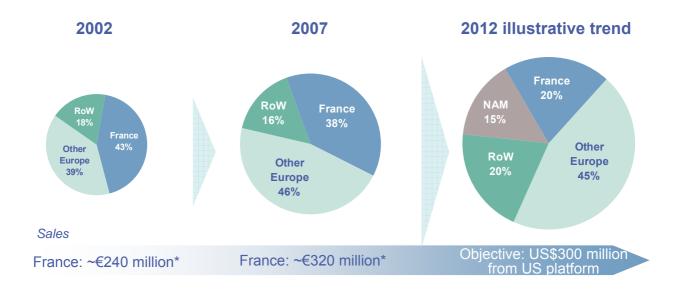
#### A renewed sales base



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### A renewed geographic footprint





resources



# An organisation fully aligned with the Group's strategy

Grow and globalize			Optimize returns		
ENDOCRINOLOGY ONCOLOGY	NEUROLOGY	HEMATOLOGY		PRIMARY CARE	
Portfolio Management Teams (cross-functional group of experts)					
			ear, aligned vision of the strategy across the company		
Arbitrate s	trategic choices	s within the Dis	eas	se Areas	
Strategic Product Planning Committee					
Review of external growth	Assessment of	FR&D projects		Arbitrage and allocation of	

Assessment of R&D projects

opportunities

<sup>\*</sup> Excludes sales of Ginkor Fort (€61 million in 2002, €37 million in 2007)



# An increasingly transactional model













































2003 - 2005

2006-2008



# **Organisation for today**

Jean-Luc Bélingard Chairman & CEO





# **Speakers**

Technologies	J-P Moreau, EVP - Chief Scientific Officer
Endocrinology	<ul> <li>Christophe Jean, EVP - Chief Operating Officer</li> <li>Mike Culler, Senior Director Discovery – Endocrinology</li> </ul>
Oncology	<ul> <li>Patrick Mérat, Chief Medical Officer, Senior VP Drug Development</li> <li>Emmanuelle Nuris, Director - Oncology Strategic Marketing</li> </ul>
Neurology	<ul> <li>Stéphane Thiroloix, EVP – Corporate Development</li> </ul>
Financials	Claire Giraut, EVP – Chief Financial Officer
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# Introduction to Ipsen's differentiating technologies

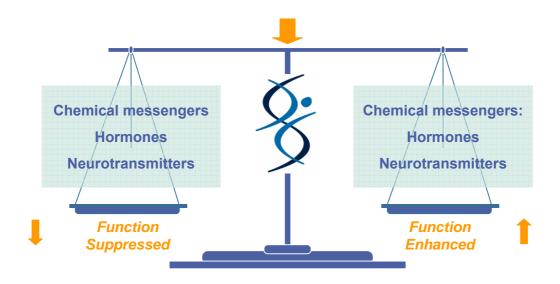
J-P. Moreau

**EVP - Chief Scientific Officer** 





#### The fundamentals: homeostasis

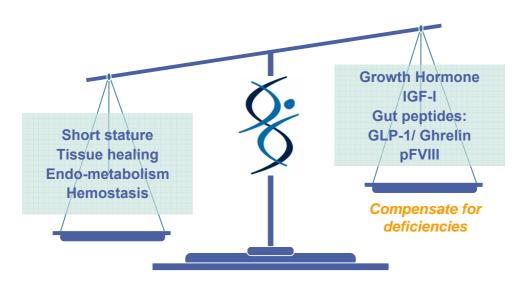


Therapeutic corollary :
Restore physiological levels, no more, no less





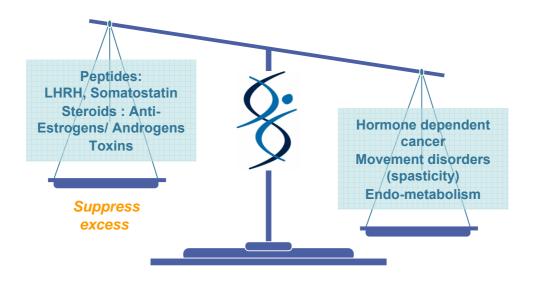
# Replacement therapies Engineered peptides proteins and steroids



Therapeutic corollary : Restore physiological levels, no more, no less



# **Depletion therapies Engineered peptides proteins and steroids**

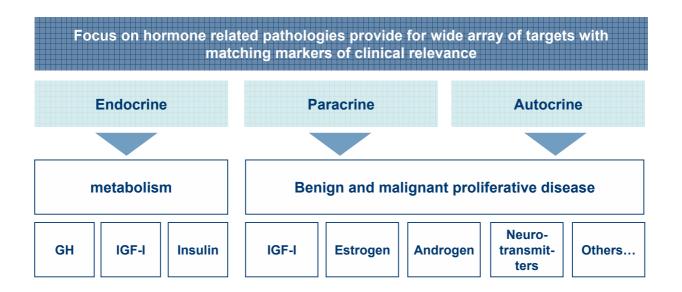


Therapeutic corollary : Restore physiological levels, no more, no less





# **Defining Ipsen's competitive edge in drug Discovery**





### Defining Ipsen's competitive edge in drug Discovery

Hormones provide well defined templates with matching targets both novel or validated

#### Resident know how based on the integration of basic discovery technologies

#### **Technologies**

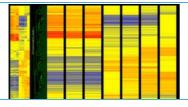
Target identification, validation and drugability based on clinical observations supported by ...omics technologies

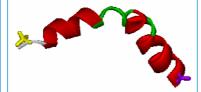
#### **Medicinal chemistry**

Steroids peptides, proteins engineering aiming at enhanced efficacy, potency, selectivity and safety over the endogenous hormone

#### **Delivery systems**

Emphasis on improved pharmacological properties, optimization of dosing regimen and improved patients compliance and convenience











### Defining Ipsen's competitive edge in drug Discovery

#### **Convergence of Technology Platforms**

Drugable Targets

Peptides, proteins, steroids engineering

Fully integrated production capabilities:

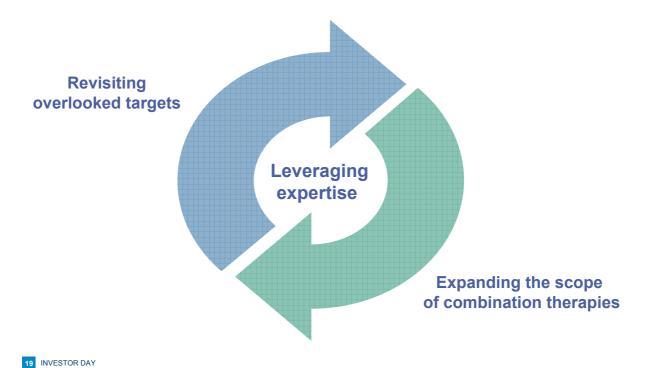
- Recombinant proteins (Cell culture)
- Peptide synthesis (Solid phase)
- Injectable formulation (Aseptic & sterile)

Optimal dosing regimen

Formulation Innovation parenteral Controlled release formulations



# **Defining Ipsen's competitive edge in drug Discovery**

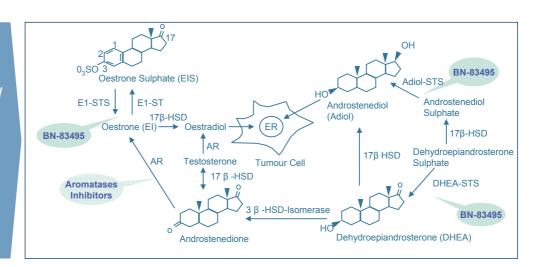




### Overlooked targets in steroids biosynthesis

Cancer / Gynecology / Urology :

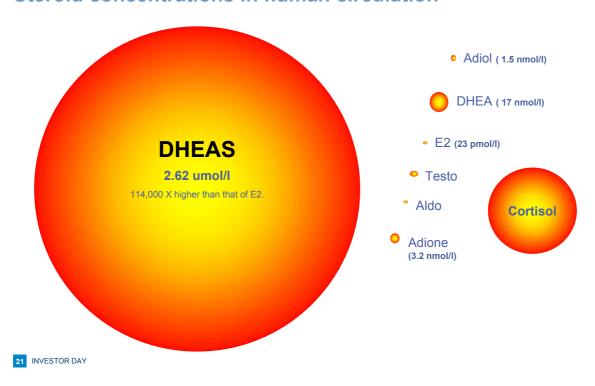
Breast
Prostate
Endometrium
Ovary



Sources of estrogenic substances



### Overlooked targets in steroids biosynthesis Steroid concentrations in human circulation





### Optimise BN-83495's development through Theranostics

The expression of the enzyme sulfatase has prognostic value in Breast Cancer\*



Determine if baseline STS level will influence BN-83495 clinical efficacy



Determine how STS expression evolve under BN-83495 treatment

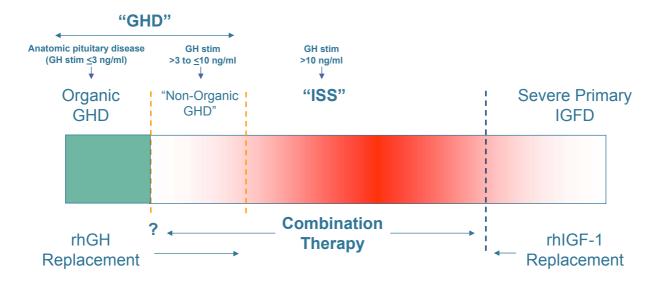




Potential development of a routine STS assay for patient therapy selection/ optimisation



# Expanding the scope of combination therapy GH + IGF-1 = Nutropin + Increlex in short stature indications



Combo therapy to address an unmet medical need in non-organic GHD





**Expanding the scope of combination therapy Addressing the idiopathic short stature through theranostics** 

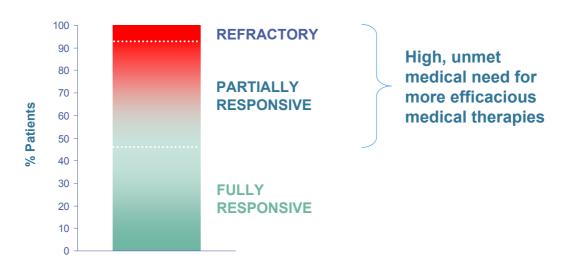




Toward a differentiated treatment franchise: IGF-1 +/- rhGH - based on specific molecular/ phenotypical etiologies that correlate with response

# FIPSEN Innovation for patient care

# **Expanding the scope of combination therapy BIM-23A760 > Somatostatin + Dopamine**

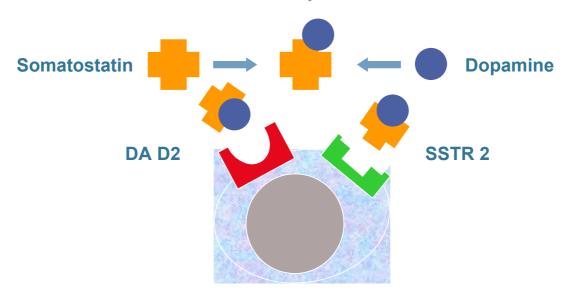


Lanreotide (Somatuline® - Ipsen) and Octreotide (Sandostatin - Novartis) are most effective on a subset of acromegaly patients





# Expanding the scope of combination therapies BIM-23A760 > Somatostatin + Dopamine

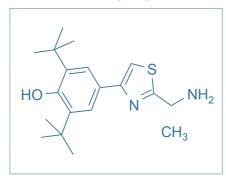


Clinical reports of enhanced GH suppression with combined somatostatin / dopamine therapy



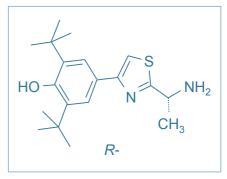
# **Expanding the scope of combination therapy to neurology: Movement disorders and neurodegenerative diseases**

BN-82451





**BN-83026** 



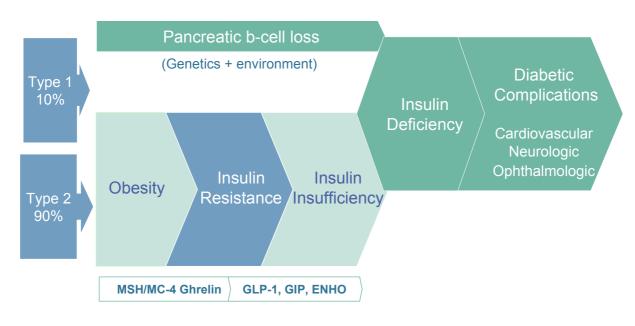
Mitochondria protective agents with mutiple pharmacophore through:

- -> Na + channel blocker (inhibition of excitotoxicity)
- -> Antioxidant
- > Anti-inflammatory (BN-82451 ≠ BN-83026)





# Leveraging expertise in endocrinology – metabolism Diabetes

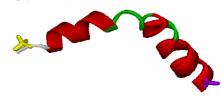




# Leveraging expertise in endocrinology - metabolism Taspoglutide

#### Once-a-week or twice-a-month injection

- Equal / greater potency compared to native compound
- Extended metabolic half-life, 22x more stable in plasma
- Complete retention of incretin properties
- Strong patent positions



#### Expected needle gauge

- (LAR) → 23G
- Taspoglutide Liquid SRF → 29G
   Insulin type needle for subcutaneous injection

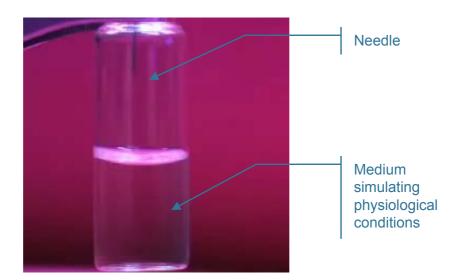
50 to 300 µl of highly concentrated aqueous solution devoid of excipient





## Leveraging expertise in endocrinology - metabolism Excipient free parenteral controlled delivery systems

In-situ Formation of Taspoglutide depot from Liquid Sustained Release Formulation





### **Ipsen's R&D in summary**

- Fundamental adherence to the medical concept of **restoring and sustaining homeostasis**
- Core expertise in drug discovery based on the rationale design of novel medicines inspired by endogenous human hormones
- Primary focus on the role of hormones in benign and malignant, degenerative and proliferative diseases
- Innovation for patient care : Conception of medicine through advanced, optimal dose, drug delivery systems
- Integrated knowledge based R&D with the versatility required to sustain Ipsen's strategy
- Strong partnerships with leading private and public academic institutions
- Dynamic portfolio optimization through a broad range of transactions: in/ out licensing, spin out, etc...



# **Endocrinology**

Christophe Jean

EVP - Chief Operating Officer



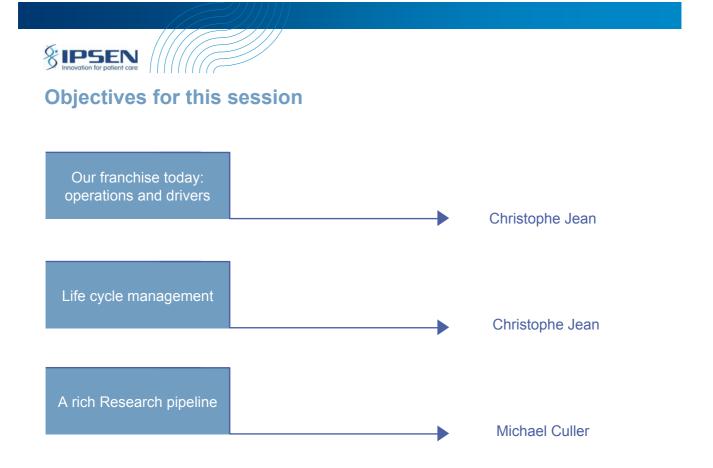


#### **Mission statement and ambitions**

# Building a global leadership in specialized endocrinology...



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# A global franchise outgrowing competition

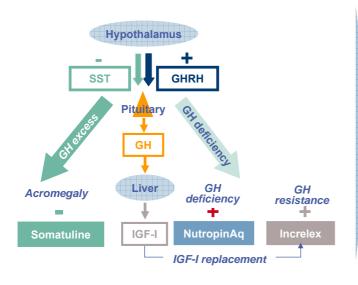
Christophe Jean

**EVP - Chief Operating Officer** 





# A unique focus on pituitary disorders and hormone dependent diseases



#### A strong franchise

- A range of products addressing today Short Stature, Acromegaly and NET
  - High morbi-mortality
  - · Debilitating pathologies
  - · High unmet medical needs
- Somatuline<sup>®</sup>, NutropinAq<sup>®</sup> and Increlex<sup>®</sup> contributed to ~15 % of 2007 Group sales, ie. ~ €130 million.
- A fast growing franchise: sales doubled in the past 3 years

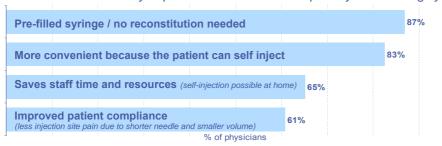




	Sandostatin LAR®	Somatuline® Autogel®
Administration	2.0 ml Intramuscular	0.3 ml – 0.5 ml Subcutaneous
Presentation	Powder vial + solvent filled syringe + 2 needles	Pre-filled syringe
Injection technique	10 steps needed to reconstitute	Ready to use Self administration*



For what reasons would you prescribe Somatuline® Depot to your acromegaly patients?\*\*



\* In selected countries







# Somatuline® Depot has significant growth potential

Intrinsic market growth

- Recent studies show prevalence of pituitary adenomas, including acromegaly (1 in 1,064) is 3-5 x higher than the prevalence reported in previous population based studies<sup>1,2</sup>
- NET incidence increased 5x in the past 30 years<sup>3</sup>

Differentiation

- Broad acceptance of efficacy by physicians
- Extended duration (6 to 8 weeks)
- Self injection (in Europe)
- Ready to use
- => Financial savings for patients and managed care

<sup>\*\*</sup> Study Sample: A total of 50 US endocrinologists completed a 30-minute online questionnaire between April 4 - 17, 2008
25 High Volume Endocrinologists: Endocrinologists who see 11 or more acromegaly patients in a year
25 Low Volume Endocrinologists: Endocrinologists who see between 5-10 acromegaly patients in a year







- Target audience : ~1,000 US paediatric endocrinologists
- Up to 20% of Rx come from new prescribers each month
- 2/3 of pediatric endocrinologists have prescribed Increlex®; 78% continued prescription

# Reimbursement success

- ~ 90% of private and public covered lives have formulary access
- 75% Increlex patients approved upon final decision (similar to GH)

#### Patient experience

- Sharp increase in patients on Increlex<sup>®</sup> initially GH-naïve to 60% in '08 from 30% in '07
- Dose increasing to appropriate targets, to 100 mcg/kg BID in '08 from 70 mcg/kg BID in '07
- Younger patients initiated with Increlex®, to average age at start of 10.0 years old in '08 from 11.5 years in '07

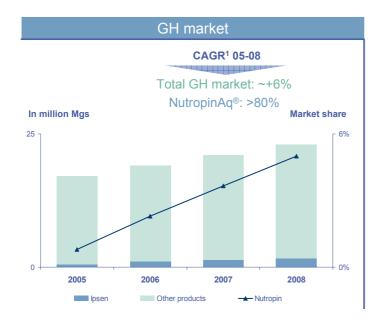


Sources: Internal data & US Increlex registry





### NutropinAq® in Ipsen territories is steadily gaining market share



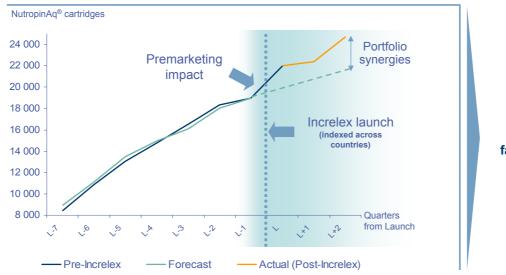
#### NutropinAq® attributes

- 1st liquid formulation launched WW
- A simple and user friendly pen
- An experienced post marketing surveillance database
- A dedicated experienced and professional team





# NutropinAq® + Increlex®: evidence of portfolio synergy



Up to 10% favorable impact

"Ipsen is the only company that can legitimately claim to treat all forms of growth failures through the spectrum of GH deficiency to GH resistance"

Pr. Martin Savage, St Bartholomew's Hospital, London



NOTE 1: UK, Germany, Sweden, France, Italy, Spain





### A competitive US endocrinology platform

Context

- A highly specialized market with strong KOL influence
- A limited target audience: 700 key customers on a total target of 1,000 and ~1,150 paediatric and adult endocrinologists respectively

**Assets** 

- Well established commercial organisation supported by strong managed care and medical affairs expertise
- Strong sales force targeting
- Properly sized and skilled sales force

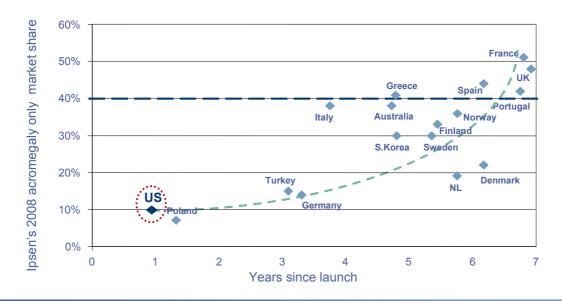
Results

- A significant proportion of adult endos are already prescribing Somatuline
- 75% of Increlex SMNs patients approved upon final decision
- Excellent coverage achieved in top 50 MSAs\* representing 80% of volume
- Competitive share of voice in key accounts: 13% for Increlex® vs. 9 to 19% for GH agents<sup>(1)</sup>





# Somatuline® Depot is poised to grow and gain market share



Somatuline® market share is directly correlated to its time on market

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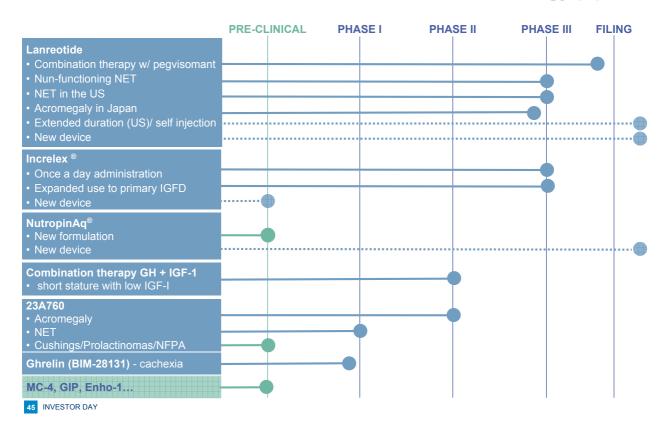
SOURCE: Strategix

# **Life Cycle Management initiatives:** Significant scope for expansion



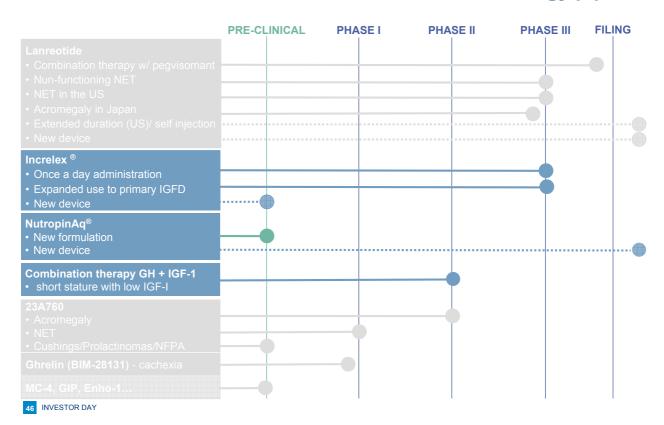


### A rich endocrinology pipeline





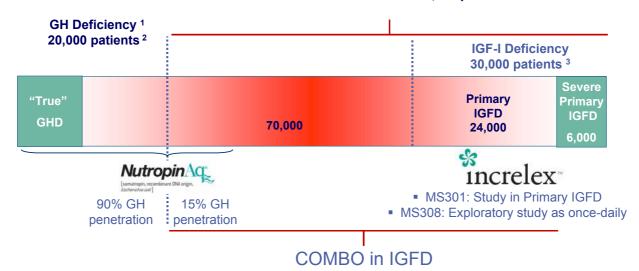
# A rich endocrinology pipeline





### Ipsen is redefining the treatment of short stature

#### Non-GH Deficient Short Stature: 100,000 patients in the US



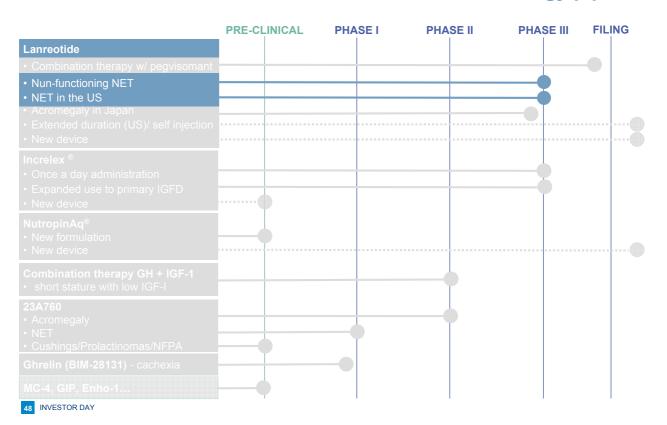
- MS316: Ph.II dose titration studyrecruitment to be completed by Q2 '09
  - Ph.II study in GH Deficient children to start by end '09

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1) Includes TS, SGA, CRI, PWS 2) Approximate number seen by Ped Endos; Finkelstein et. Al. 3) NCGS Analysis

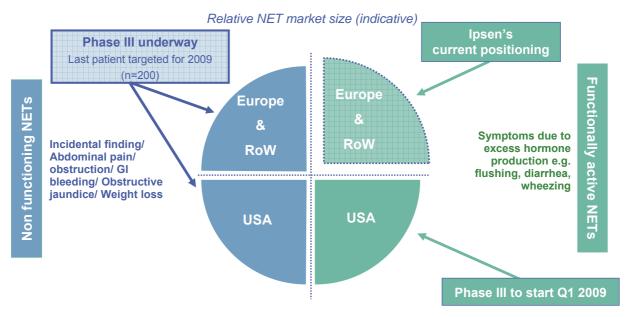


## A rich endocrinology pipeline





# Somatuline® offers significant life cycle growth opportunities



Significant scope for expansion



# A new wave of best-in-class compounds for tomorrow

Michael Culler, Ph.D.
Senior Director, Endocrinology Research





# Ipsen's endocrinology discovery focuses on 2 main areas

#### 1 2 **Pituitary Disorders Metabolic Disease** Adenomas Hyposecretion Wasting Excess Acromegaly • GH deficiency Obesity -Diabetes • Cushing's • IGF1 deficiency -CV disease • NFPA • Hyperprolactinemia

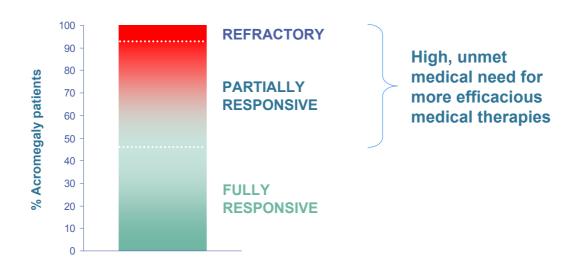
51 INVESTOR DAY



Pituitary Disorders		Metabolic Disease		
		<ul><li>Wasting</li></ul>	<ul><li>Excess</li><li>Obesity</li><li>Diabetes</li></ul>	
BIM-23A760	BIM-23A760			
Secretion	Proliferation			



# The efficacy of current clinical Somatostatin analogs in acromegaly still requires improvement



Lanreotide and Octreotide are most effective on a subset of acromegaly patients





# **Clinical reports of combination of Somatostatin and Dopamine show enhanced GH suppression**

A comparison of octreotide, bromocriptine, or a combination of both drugs in acromegaly

Flogstad et al, JCEM, 79:461-465, 1994

Acute effects of octreotide, cabergoline and a combination

Acute effects of octreotide, cabergoline and a combination of both drugs on GH secretion in acromegalic patients

Minniti et al., Clin Ter 148:691-607, 1997

Efficacy of combined treatment with lanreotide and —cabergoline in selected therapy-resistant acromegalic patients

Marzullo et al., Pituitary 1:115 - 120, 1999

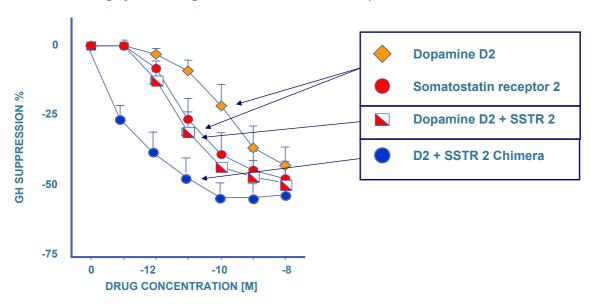
Treatment of Chinese acromegaly with a combination of bromocriptine and octreotide.

Li et al., Aust NZ J Med 30:457-61, 2000



# Enhanced GH-suppressing activity with chimeric Somatostatin receptor 2 – Dopamine D2 molecule

Human Acromegaly-Producing Adenoma Cells - ex vivo experiment





A. Saveanu, P. Jaquet / M. Culler U. Mediterranee / Ipsen



# We have identified the optimal Somatostatin-Dopamine chimera

BIM-23A760 - Activity ratios

<u>hSSTR Subtype Ki (nM)</u>

1 2 3 4 5
843 0.03 160 >1000 42

<u>Dopamine D2 Ki (nM)</u>

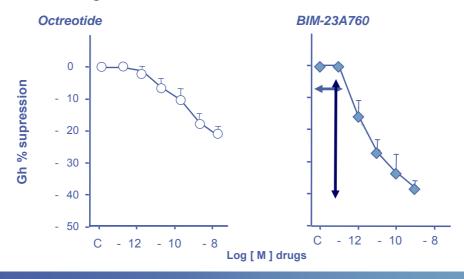
16 nM

Best activity ratio: Potent SSTR2 and DAD2, with moderate SSTR5



# BIM-23A760 show enhanced potency and efficacy in SST-resistant acromegalic tumors

SST-Resistant Acromegalic Tumors (1)



A potential best-in-class

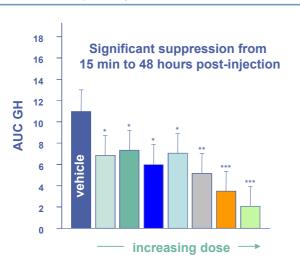


NOTE 1: Saveanu, Jaquet (ICNE - U. Mediterranée) / Culler (Ipsen,

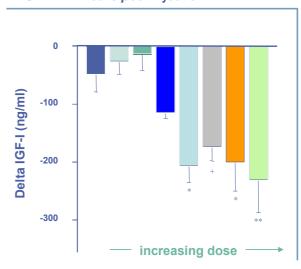


# BIM-23A760 induces significant, dose-related suppression of GH and IGF-I in normal primates...

GH - 2 hours post injection



IGF-I - 24 hours post injection

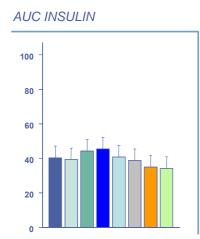


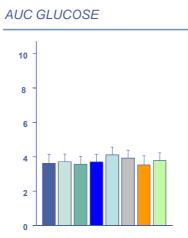
Similar dose-related effect on prolactin

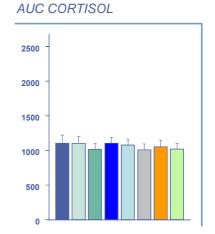




# ... with no effect on insulin, glucose or cortisol





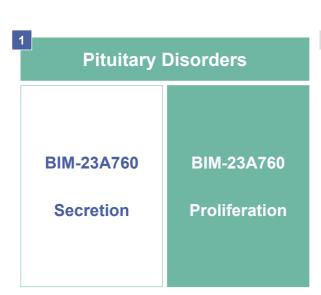


No effect observed at any time or dose through 72 hours post-injection



1 Hour Post Injection n=4 Cynomolgus monkeys - 2 male, 2 female

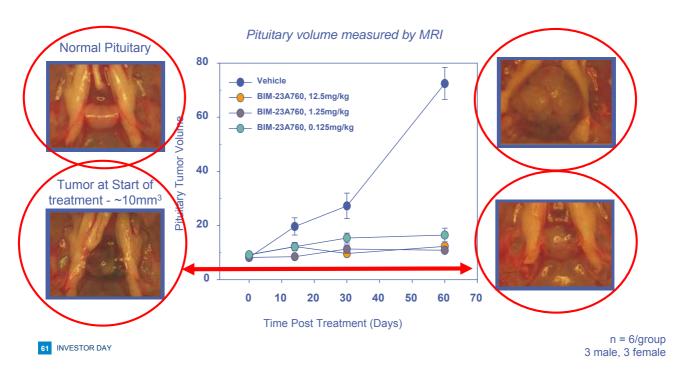








# BIM-23A760 suppresses non-functioning intermediate lobe pituitary tumor growth in vivo





### BIM-23A760 may offer unique therapeutic advantages

#### Acromegaly

- Increased efficacy, lower dose
- Effective monotherapy for greater percentage of acromegalics
- Multi-hormone suppression GH and Prolactin
- Greater and more consistent tumor shrinkage?
- Decreased potential for pancreatic/glycemic side effects

#### **Beyond Acromegaly**

- NETs expressing both SST and DA receptors
  - Prolactinomas
  - ACTH-Secreting Adenomas (Cushings)
  - Gastroenteropancreatic Tumors (GETs)
  - · Non-Functioning Pituitary Adenomas

# Progress of clinical development

- Encouraging phase 1 data, safety profile, prolactin reduction
- Final results expected in Q1 09



Pituitary Disorders

Metabolic Disease

Wasting

Excess
Obesity
Diabetes
CV
disease



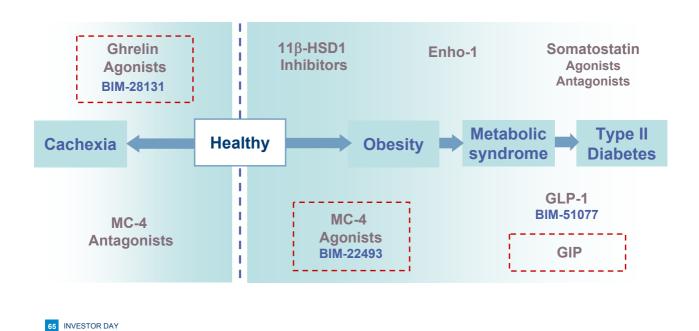


# Metabolic disease - A paradigm with bidirectional problems





# Peptide based therapeutics for metabolic disease Multiple targets – Multiple options









### BIM-28131 - A key pathway for feeding and nutrient utilization

#### **Target**

#### Ghrelin agonist

Increase weight and GI motility, with good safety in humans

#### Best-in-class

- Targets full spectrum of ghrelin activity: GHS1a plus additional pathways
- ty
- Greater efficacy for increasing weight and gastric motility

# Peptide selectivity and safety over small molecules

- Potent anti-inflammatory action
- Greater safety : no hyperglycemia or CV toxicity

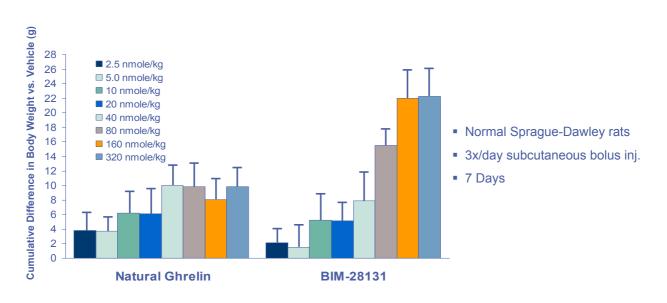
# Market opportunity

- Cachexias
- GI motility disorders





### BIM-28131 - Superior pharmacologic profile to natural Ghrelin

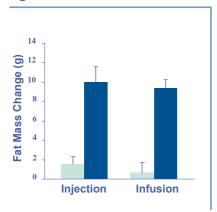


Enhanced body weight gain vs. natural ghrelin

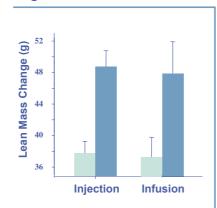


#### BIM-28131 - Increases both fat and lean mass

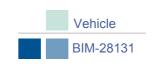
8g FAT increase



10g LEAN increase



- Rodents
- 50 nmole/ kg/day
- bolus sc (tid)
- continuous sc infusion (osmotic pump)
- 14 days



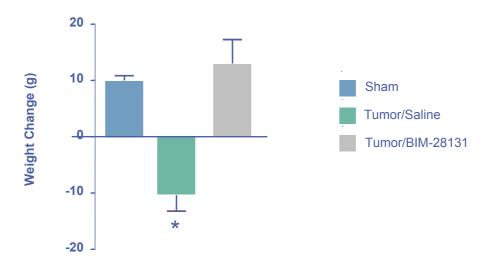
✓ Equivalent efficacy with SC infusion → compatible with sustained-release delivery

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# BIM-28131 - Demonstrated efficacy in multiple cachexia models

Cachexia: Lobund-Wistar Rat Model of Prostate Cancer

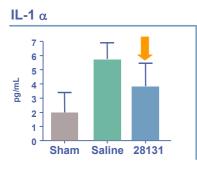


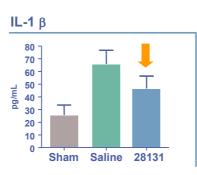
Efficacy also demonstrated in models of cardiac and renal cachexia

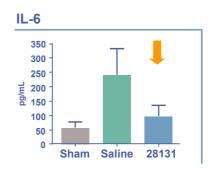


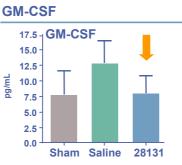
### BIM-28131 - Potent anti-inflammatory activity to address underlying cause of cachexia

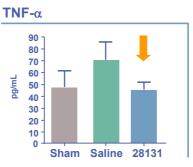
Rat model of renal failure















### **BIM-28131 - Summary**

### Efficacy

- Highly Efficacious in Promoting Weight Gain
  - Both muscle & fat mass
- Superior Pharmacologic Profile to Natural Ghrelin
- Demonstrated Efficacy
  - · Cachexia from multiple causes
  - · Potent anti-inflammatory action
  - · Potent GI pro-kinetic agent

Time frame

• First administration to man – Early 2009

BIM-28131 is compatible with sustained release delivery



2 **Metabolic Disease** BIM-22493 Obesity





# BIM-22493 - In a nutshell



# Target MC4 Agonist

- MC4 is is central node for regulating appetite and energy balance
  - · Validated by human genetic defects

### Best-in-Class

Peptide safety advantages over small-molecule MC4 agonists

- Increased receptor selectivity versus small-molecule compounds
- Decreased potential for random side effects
- Selective for MC4:

ED50: MC1 = 6nM; MC3 = 5nM; MC4 = 0.3nM; MC5 = 1600nM

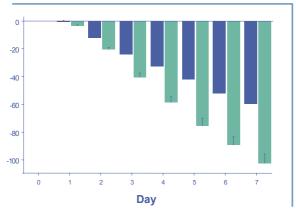
# **Market Opportunity**

- Obesity
- Diabetes
- Other metabolic diseases

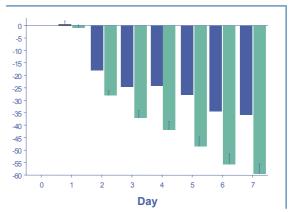


# BIM-22493 - Reduces weight in rats

# Cumulative Difference in Food Intake vs. Controls (g)



Cumulative Difference in Body Weight vs. Controls (g)



Obese Zucker Rats

# No nausea or observed behavioral changes in multiple species



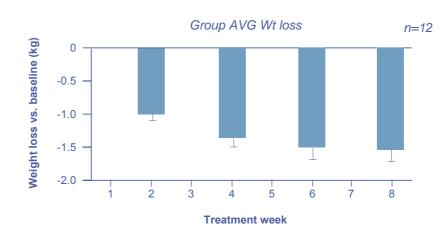
50nmole/kg/day sc infusion
500nmole/kg/day sc infusion



# BIM-23493-induced weight loss in obese, insulin-resistant Rhesus monkeys



Obese Rhesus Monkey (DEXA scan)



- \* ~ 13% Body weight loss
- \* Loss of fat mass, not lean mass
- \* Reversal of insulin resistance
- \* Normalization of basal insulin



# **BIM-22493 - Summary**

# Established mechanism

MC4 is central node for weight regulation

# **Demonstrated efficacy**

- · Suppresses food intake, decreases body weight
- Improves insulin sensitivity
- · Improves lipid profile
- Efficacy in both diet-induced and genetic rodent models of obesity, as well as dogs and primates

### Side effects

No evidence of nausea or behavioral effects







# Pituitary Disorders Metabolic Disease Wasting Excess Diabetes GIP

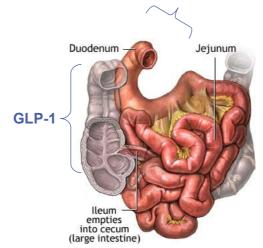


# Two major incretins - 50 to 70% of insulin response to meal

### **Characteristics**

- Released in response to meal
- Enhances insulin only when glucose elevated
- Low risk of hypoglycemia
- Beta cell protective/restorative
- No GI motility effect no nausea

Glucose- Dependent Insulinotropic Polypeptide (GIP)



- K-Cells
  - Duodenum
- 42 amino acids
- DPPIV inactivation





# **Ipsen's GIP program**

Scope of research

- Large library of human GIP analogs designed and synthesized
  - · variety of structures
  - · differing physiochemical properties
  - differing PK profiles, formulation potential
  - · unique position in IP landscape

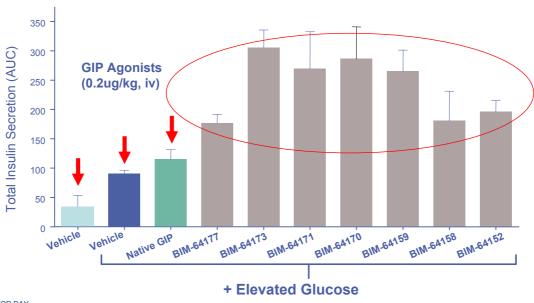
**Progress** 

- Screened for human GIP receptor binding/ activation
- Demonstration of enhanced plasma stability
- Controlled release formulation feasibility established
- Selected compounds tested in in vivo incretin model



# **Examples of enhanced GIP glucoincretin activity with lpsen analogs**

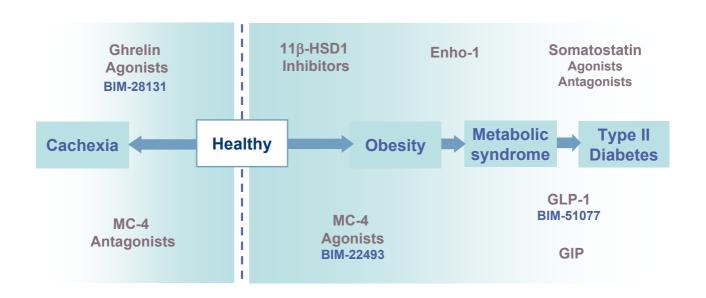
In Vivo Results in Glucoincretin Model - Normal Rats







# Peptide based therapeutics for metabolic disease Multiple targets – Multiple options



# Conclusion





# A unique global player in a highly specialized market

A global player in paediatric and adult endocrinology...

 Ipsen is becoming a truly global player in the highly specialized endocrinology market, paediatric and adult

... with a well balanced R&D portfolio

 The development portfolio is well balanced between short term/ low risk projects (GH/IGF-I Combo) and long term/ higher risk projects (BIM23A760)

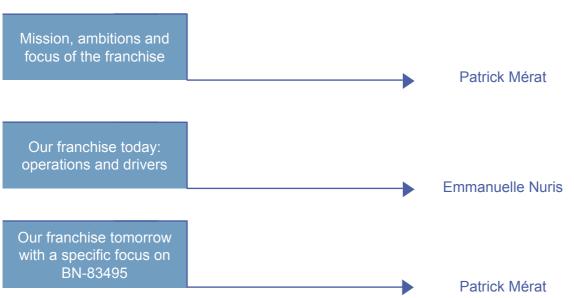
# **Oncology**

Patrick Mérat MD.

Senior Vice President, Drug Development Chief Medical Officer







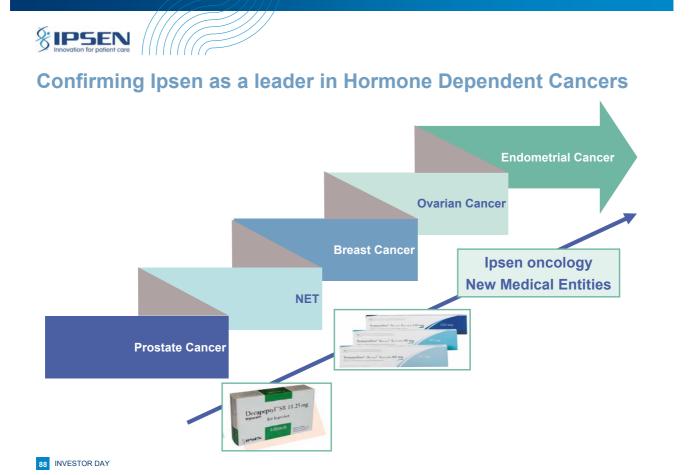


# Mission statement and ambitions

# Leveraging a successful and expanding uro-oncology franchise today ...

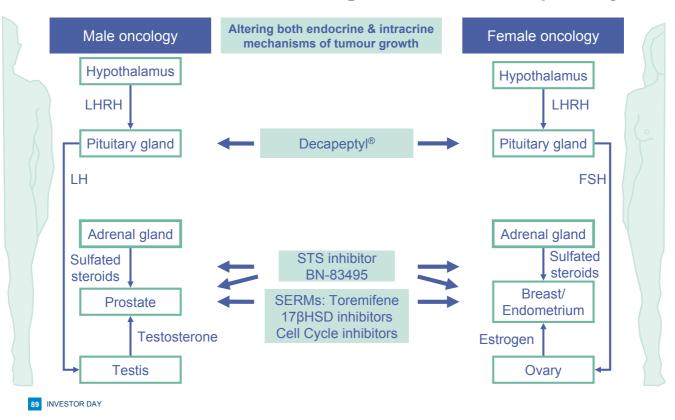
...confirming Ipsen as a leader in therapy of hormone dependent tumours







# A strategy of multi-targeted agents focusing on core hormonal pathways



# A successful and expanding uro-oncology franchise...

**Emmanuelle Nuris** 

Oncology Corporate Strategic Marketing Director





# Decapeptyl®: Ipsen's largest product

### A 20 years growth story...

- Marketed in over 60 countries (Ex-US, incl. Europe, China...)
- Indications:
  - Prostate Cancer (more than 70% of sales)
  - Gynaecology
  - Precocious puberty
  - IV/F
- Daily, 1 month formulation & 3 month formulations
  - Patents run off in mid 2010
- No generics of GnRH analogs anticipated
  - Only look-a-likes (1 launched in Germany)
  - Look-a-likes of triptorelin 1&3 in preclinical stage

### ... and still poised to grow

- 6 month formulation filed in Europe
- A growing market:
  - Growing population
  - Earlier diagnosis
- More room to grow in some emerging countries long with market maturity
- More room to grow in some key mature markets through market share gain



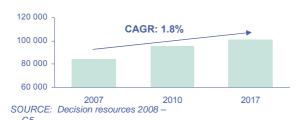


# Multiple growth drivers contribute to market expansion

# Aging population and early diagnosis increase incidence



Drug treatable Stage III, IV & biochemical recurrence population



SOURCE: IMS - MAT June 2008

# GnRH analogs is a growing market

Expansion of reimbursement

• Emerging countries' growth





# Decapeptyl® 3 months formulation: a competitive product profile

# Formulation and efficacy

- Marketed 1 month (1M) and 3 month (3M) formulations
- Maintenance of castrate testosterone levels at 3M in 98% of patients<sup>1</sup>
- At 3M, 91% decrease of PSA levels, showing tumor control

# Local tolerance/ convenience

- IM route of administration, good local tolerance
- Injection not visible for the patient

# Storage and reconstitution

- Stored at room temperature
- 5 steps reconstitution
- Safety needle system

### Competitor 1

### Competitor 2

### Competitor 3

# Formulation and efficacy

- Various formulations across territories:
   1M formulation = 3,75mg or 7,5mg and 3M formulation = 11,25mg or 22,5mg
- Increased survival rate at 9 months in triptorelin group vs competitor 1<sup>2</sup>
- Conservation between 2 4° = needs to be warmed up before reconstitution
- Manual reconstitution to obtain SR
- Risk of nodules, abscess
- Ready to use implant
- Very large needle : need of local anesthesia

### 93 INVESTOR DAY

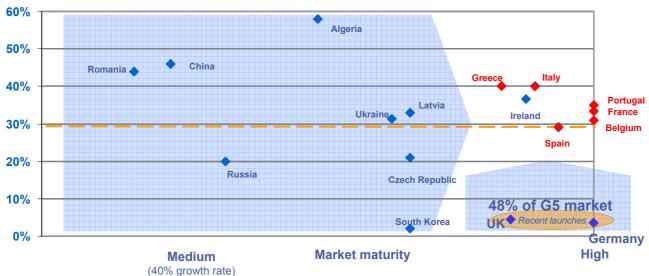
SOURCE: French SmPC

REFERENCE . 1: Teillac, Horm Res,2004, 252-58 2: Heyns, BJU Int, 2003, 226-231



# Decapeptyl®: strong positions, and poised to grow

# **Current market share**



94 INVESTOR DAY



# 6 month formulations: addressing both patients' needs and physicians' expectations

# Increased comfort for patients

- Prostate Cancer is being treated as a chronic disease
- Less injections means less anxiety and pain for the patient
- Less injection also means more flexibility for active patients

# Better alignment with medical practice

- In many developed countries, when treated, Prostate Cancer patients are more and more seen every 6 months by their doctor
- Compliance increases with convenience

6 month formulation fits with current urology practice and patient therapeutic management





# Decapeptyl® 6 month formulation: a more differentiated product profile

### Efficacy

- Comparable efficacy to 1 and 3 months formulation
  - · Castration levels (testosterone)
  - Disease control (PSA)

# Local **Tolerance**

Limited local side effects (6.7% of patients )

# Storage and reconstitution

Formulation/

Efficacy

- Storage at room temperature (no need to heat up before reconstitution)
- 5 Steps to reconstitute, change needle, and inject IM route

### 6 month competitor 1

### 80% of patients castrated after 6M <sup>2</sup>

# Testosterone to be tested every 6M\* 1

### Formation of Nodules or abscess <sup>1</sup>

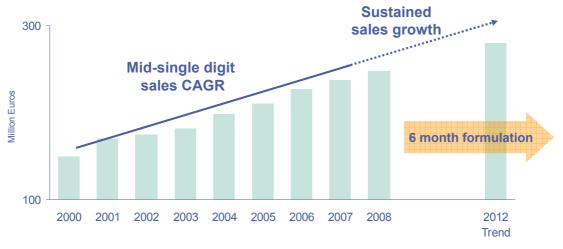
### 6 month competitor 2

- Slow release formulation dependent on manual 60 mixture<sup>1</sup> step
- Storage at 2-4°: need to heat up for reconstitution 1



# Decapeptyl®: a steady revenue growth for the long term





Capitalizing on its leading positions and 6 month formulation, Decapeptyl® will benefit from an untapped reservoir of growth

97 INVESTOR DAY

SOURCE: Ipsen



# Toremifene citrate: a companion product for Decapeptyl®

Action of ADT\*, standard of care for the treatment of advanced Prostate Cancer

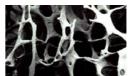
- ADT leads to a specific secondary osteoporosis and increases the fracture risk
- ADT induces other specific side effects like gynaecomastia, metabolic changes...

Pivotal phase III ADT clinical trial with toremifene citrate 80mg results

- 50% risk reduction in incidence of ADT-induced osteoporosis-related vertebral fractures (p<0.05)</li>
- Significant increases in bone mineral density (each skeletal site demonstrating p<0.0001)</li>
- Favourable effects on lipid profile, gynaecomastia
- Favorable safety profile



Normal bone



Bone structure of patient with ADT induced Osteoporosis

# A leader in the therapy of hormone-dependent tumours

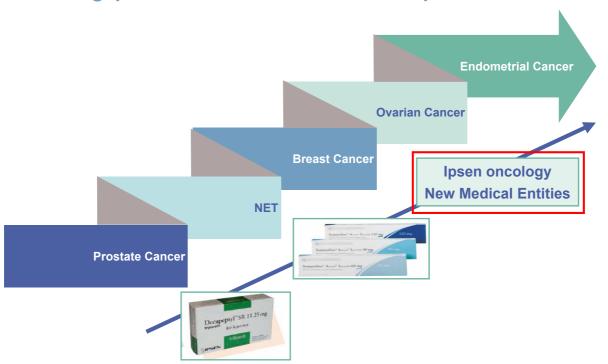
Patrick Mérat MD.

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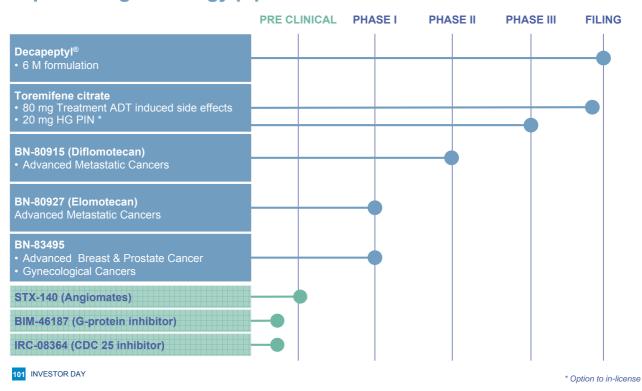
**Confirming Ipsen as a leader in Hormone Dependent Cancers** 





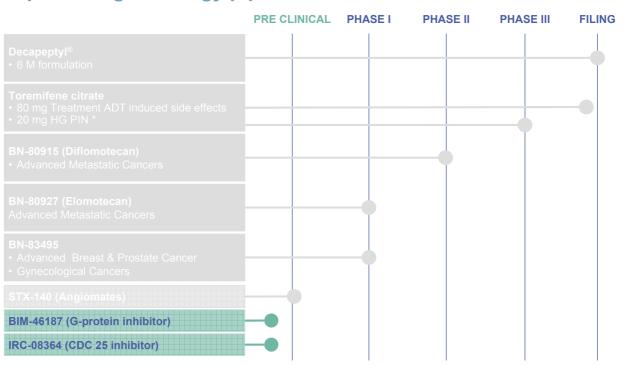


# A promising Oncology pipeline





# **A promising Oncology pipeline**





# Promising early stage candidates...

**CDC25** inhibitor

A first-in-class irreversible cell cycle inhibitor of all 3 isoforms of CDC25

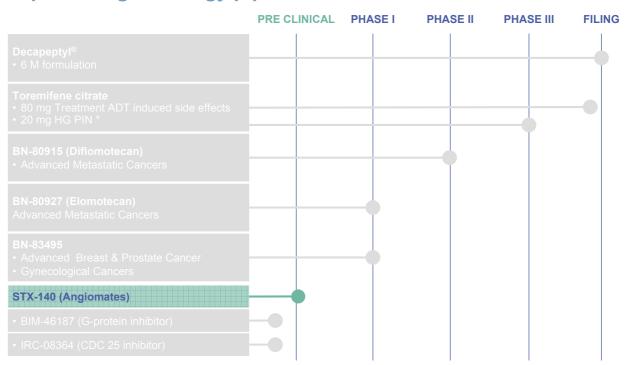
**G** Protein inhibitor

A first-in-class anti-cancer agent with pain relief activity



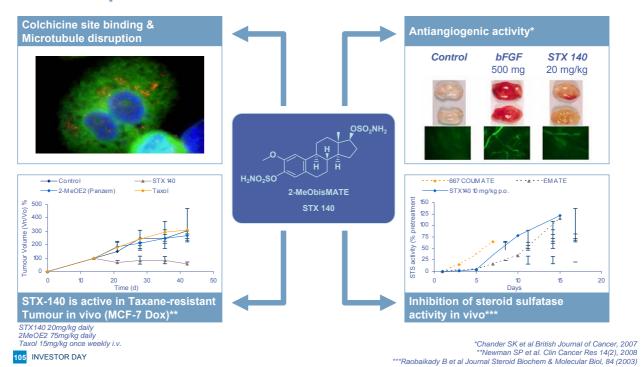


# A promising Oncology pipeline



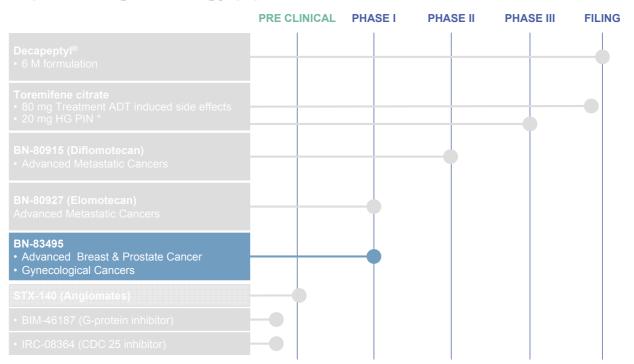


# Angiomates (STX-140): new orally-active anticancer agents with multiple mechanisms of action



PSEN Innovation for patient care

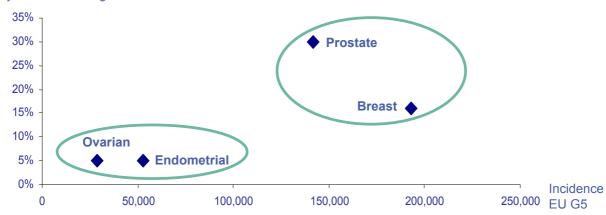
# **A promising Oncology pipeline**





# Moving up to higher prevalence diseases and higher unmet medical needs





Ipsen New Medical Entities: multi targeted agents aiming at large markets as well as niche indications with large unmet medical needs

BN-83495 is potentially a company transforming product



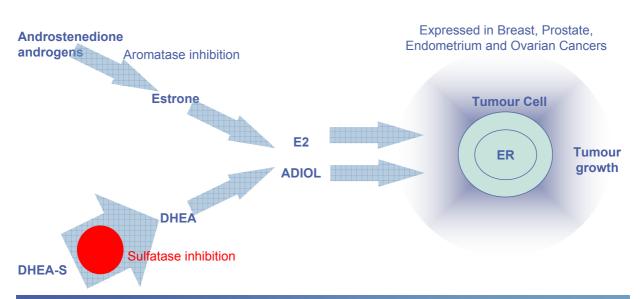
SOURCE: deVita (2008), Datamonitor

BN-83495



# Rationale for Sulfatase inhibitor development

Inhibition of Androstenediol synthesis from DHEA-S



Adiol can bind to oestrogen receptor and stimulate tumour growth (90% Adiol derived from DHEA-S in post-menopausal women)

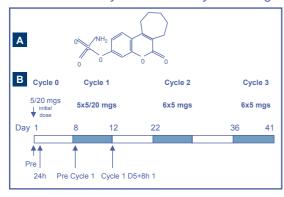


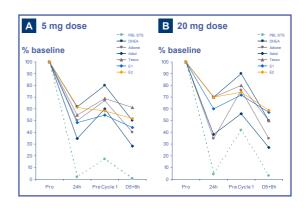


# First clinical study in Breast Cancer patients

STS inhibition leads to significant reduction in circulating steroids and induces clinical benefit\*\*

First clinical study CR UK \* - Daily x 5 dosing





Next step: confirmation of the results in Metastatic Breast Cancer and exploration of the full range of hormonal dependent tumours



\* SOURCE: Stanway, S. J. et al. Clin Cancer Res 2006;12:1585-1592

\*\* 3 patients with stable disease >6M

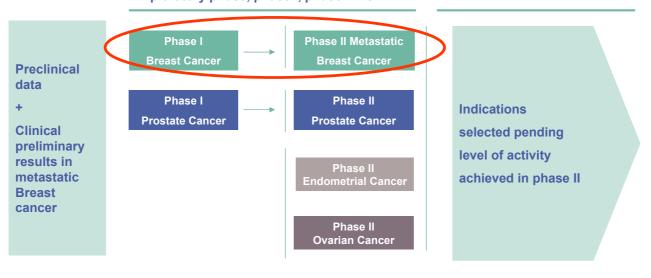
BN-83495



# BN-83495: exploring the full potential of STS inhibition in hormone-dependent tumours

Exploratory phase, phase I, phase II POC

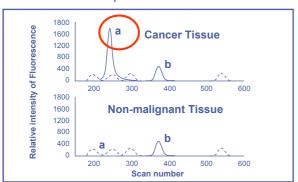
Confirmatory/registration phase III



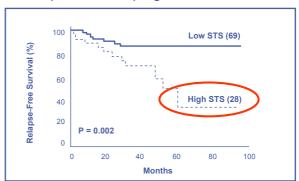


# **BN-83495** in Breast Cancer: STS expression is an independent predictor of recurrence in BCa

STS is overexpressed in BCa tissue\*



STS expression has prognostic value in BCa\*\*



### Second phase I clinical trial:

A Phase I Dose Escalation Study to Determine the Optimal Biological Dose of BN-83495 - an Oral Steroid Sulfatase Inhibitor - in Postmenopausal Women with Oestrogen-Receptor Positive Breast Cancer whose Disease Progressed after Prior Therapy for Locally Advanced/Metastatic Disease

### **Expected first results in Q1 2009**



\*Utsumi T. et al. JSBMB 73, 141, 2000 \*\*Utsumi T.et al. Cancer Research, 59 (2):377-81 1999

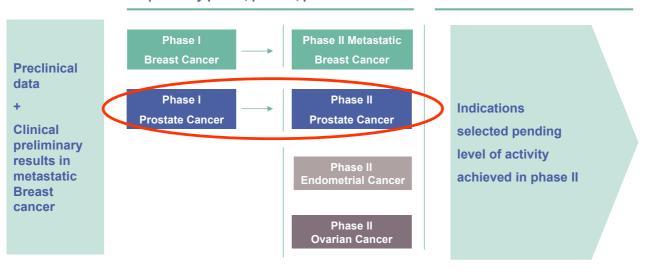
BN-83495



# BN-83495: exploring the full potential of STS inhibition in hormone-dependent tumours

**Exploratory phase, phase I, phase II POC** 

Confirmatory/registration phase III



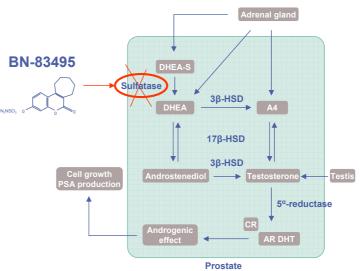


# **BN-83495** in Prostate Cancer

# Prostate is a major peripheral tissue in which STS produces biologically active androgens



Expected first results in Q3/Q4 2009



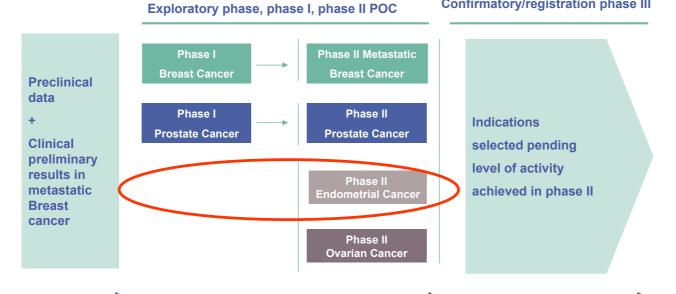
113 INVESTOR DAY

BN-83495



# BN-83495: exploring the full potential of STS inhibition in hormone-dependent tumours

# Exploratory phase phase I phase II POC Confirmatory/registration phase III





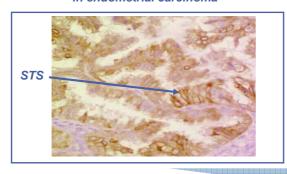
# **BN-83495** in Endometrial Cancer

**Endometrial Cancer** is the most common gynecologic malignancy

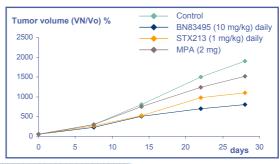
MPA\* is the reference hormonal treatment in patients with advanced disease

Targeting steroidconverting enzymespecific activities seems a promising hormonal treatment strategy

STS is expressed in endometrial carcinoma\*\*



BN-83495 is more active than MPA in an endometrial carcinoma in vivo model\*\*\*



# Phase II PO clinical trial in Endometrial Cancer to be initiated in 2009

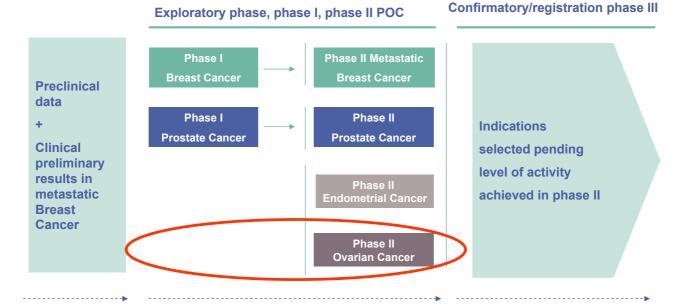
115 INVESTOR DAY

\* Medroxyprogesterone acetate \*\* Utsunomiya, H. et al. Clin Cancer Res 2004 \*\*\* Foster A. and al. Endocrinology 2008

BN-83495



# BN-83495: exploring the full potential of STS inhibition in hormone-dependent tumours

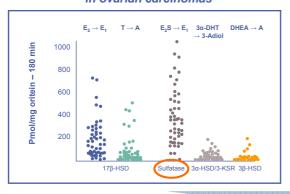




# **BN-83495** in Ovarian Cancer

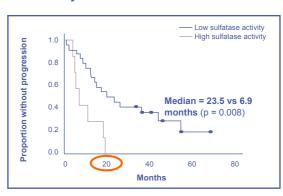
Ovarian Cancer is the leading cause of death from gynecological malignancies

Steroid-converting enzyme-specific activities in ovarian carcinomas\*



Targeting steroid-converting enzyme-specific activities in ovarian carcinomas seems a promising hormonal treatment strategy

STS activity is related to disease-free survival\*



# Phase II PO clinical trial in ovarian carcinoma to be initiated in 2009

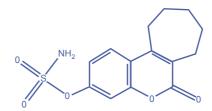


\*Chura JC et al. Mol Cell Endocrinology, in press

BN-83495



# BN-83495 in a nutshell: a new mechanism of action and potential therapeutic breakthrough



Tricyclic coumarin sulfamate

### Irreversible Oral steroid sulfatase (STS) inhibitor

Preclinical data supporting correlation between STS inhibition and tumour suppression in **Endocrine Cancers** 

Early clinical POC in metastatic Breast Cancer

POC trial in HR Prostate Cancer commenced Jan. 2009

POC trials in **Gynecological Cancers** to commence in 2009

Strong patent platform position & available back-up

# Conclusion

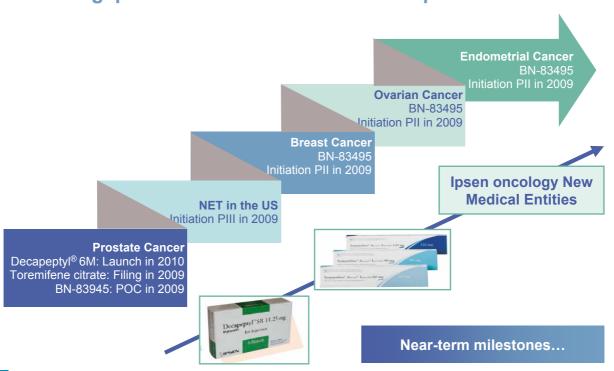
Patrick Mérat MD.

Senior Vice President, Drug Development Chief Medical Officer





# **Confirming Ipsen as a leader in Hormone Dependent Cancers**

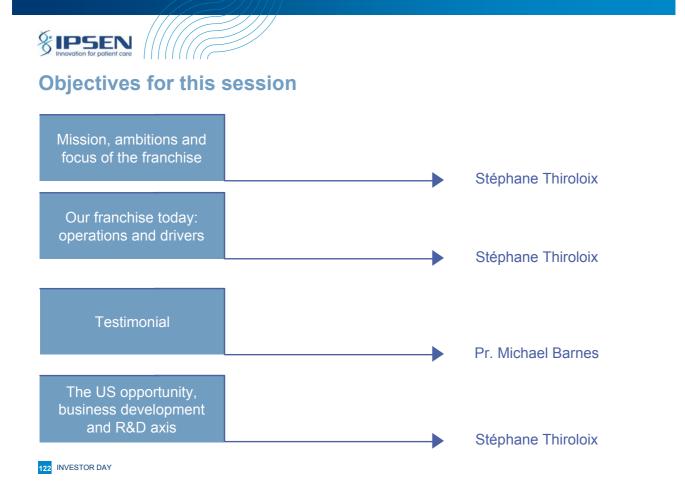


# **Neurology**

Stéphane Thiroloix

**EVP - Corporate Development** 







# Mission statement and ambitions

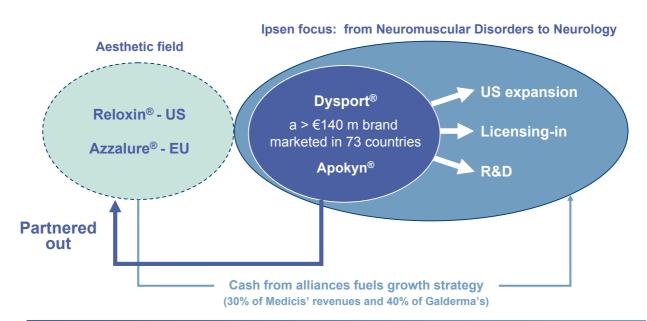
# From a regional Neuromuscular specialty...

...to a global Neurology Franchise





# A specific therapeutic focus



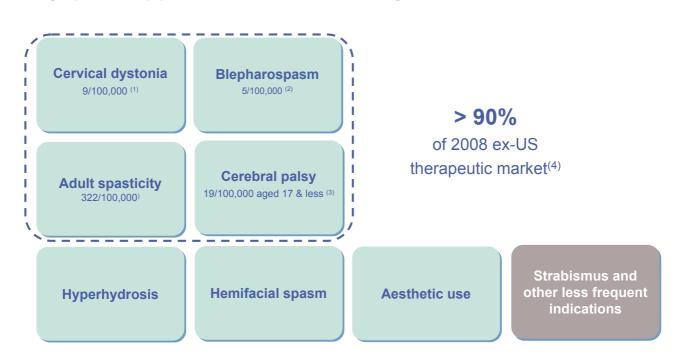
Dysport®: the cornerstone of a Neurology franchise

# A strong neuromuscular specialty franchise



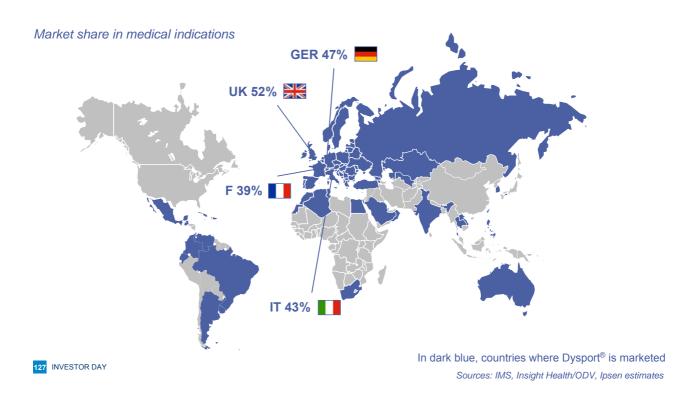


# Dysport®: approved ex-US in most key indications





# Dysport®: launched in 1991, approved in 73 countries





# **Dysport®: strong brand, strong positions**

# High patient exposure 640,000 patient/ year Calculate the US Under regulatory review in the US No additional clinical data requested Fast growth ~17% sales CAGR ex-US 2002- 9M 2008 State-of-the art Manufacturing cGMP compliant with FDA

# **Professor Michael P. Barnes**

# Professor of Neurological Rehabilitation, Newcastle University

Founder and former President of the World Federation for Neuro Rehabilitation

Former President of the British Society of Rehabilitation Medicine

Former Chairman of the Royal College of Physicians of London Joint Specialty Committee for Rehabilitation Medicine.

Chairman of the UK Acquired Brain Injury Forum

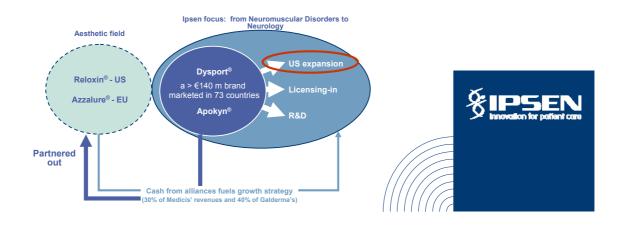
Lawrence Poole Prize, University of Edinburgh

Hon. Member of Japanese Association of Rehabilitation Medicine



# From a regional neuromuscular specialty...

# ...to a global Neurology Franchise





# **Update on Dysport® BLA (cervical dystonia)**

FDA confirmed approval of Dysport® manufacturing process

FDA issued a Complete Response Letter

No additional clinical data requested

Update of
Pharmacovigilance
Safety Update Report\*

REMS and labeling finalization

Targeting mid-2009 approval

Market access and launch plan in progress



\* (BoNT...CFR 314.50 (d)(5)(iv)(b))



# Update on Reloxin® BLA (glabellar lines)

Ipsen granted Medicis the rights to develop, distribute and market Reloxin in the USA, Canada and Japan

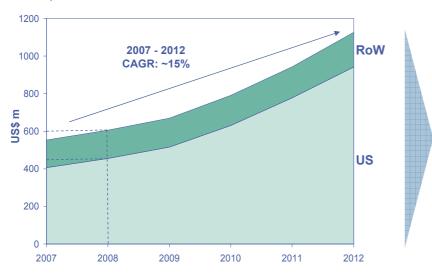
FDA confirmed approval of Reloxin® manufacturing process

FDA extended PDUFA action date to April 13th No additional clinical or safety data requested



# The Botulinum toxin therapeutic market is expanding fast, driven by US dynamics

Therapeutic use of botulinum toxin - World market



US is the largest market for toxin therapeutic use

Cervical dystonia represents 60% of the 2008E US therapeutic market ie. ~US\$280 million

US anticipated continued double digit growth rate

133 INVESTOR DAY

Source: Global Markets for Botulinum Toxin 2009 Millennium Research Group - November 2008



# Dysport®'s US value proposition

A valuable treatment alternative for physicians, patients and payers

A dedicated and specific focus on therapeutic use

**Extensive support**programs will help
physicians use Dysport
safely and effectively

Apokyn<sup>®</sup> & Dysport<sup>®</sup>

Operational synergy and enhanced specialty profile with physicians



# Ipsen Pharma Inc. is rightly sized to benefit from the Dysport® opportunity

A strong commercial team that will leverage the Apokyn® network and approach

- 34 Sales Representatives, experienced in marketing an injectable product
- Established relationships with key Neurology thought leaders
- Ability to leverage existing Apokyn support programs
  - Existing call panel covers ~75% of Movement Disorder Specialist
  - Sufficient capacity to add Physical Medicine & Rehab physicians while maintaining reach and frequency goals

Experienced

Managed Care team

- Highly experienced staff, specialized in injectable products
- Specific expertise in coverage, coding and reimbursement strategies
- Leverage established relationships with key payers of endocrinology franchise

Well positioned to cover the target physician population





# A good track record at catching-up market shares...

Market share in medical indications



Russia
Botox launched in '94, now 56% market share

Dysport®:

Launched 5 years later, now 44% market share

South Korea

Botox launched in '95, now has 40% market share

Dysport®:

Launched 4 years later, now 23% market share



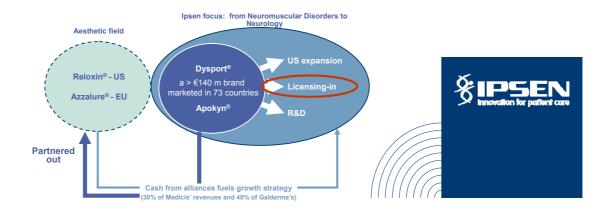
Botox launched in '90, now has 40% market share

Dysport®:

Launched 10 years later, now 51% market share

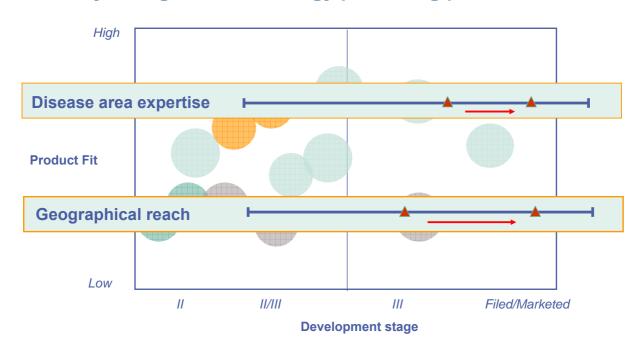
# From a regional neuromuscular specialty...

# ...to a global Neurology Franchise



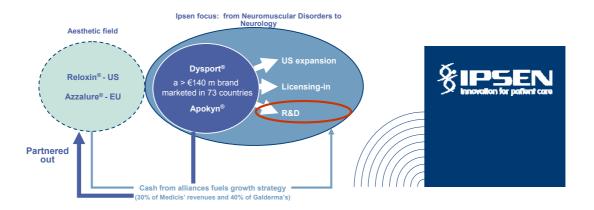


# US entry changes our neurology partnering profile



# From a regional neuromuscular specialty...

# ...to a global Neurology Franchise





# **Discovery in Neurology: 3 long term axes**

- Investigate and evaluate novel methodologies (substitute cellular models, pharmacology, method of administration..) and potential new (indications) formulations for Dysport®
  - Research on new toxins with a modulated duration or oriented to a specific indication
    - Evaluate new therapeutic approaches in targeted areas of movement disorders

# Conclusion

Stéphane Thiroloix

**EVP - Corporate Development** 





# Dysport® in the US: a step further toward a global neurology franchise

- 1. Dysport®: a proven track record and field proven product
- 2. A true global product
- 3. A unique focus on medical use
- 4. Focus on US opportunity strong positioning with well prepared launch
  - · Sound value proposition: the medical treatment alternative
  - · Targeted and appropriate sales force
  - · Managed care experience
- 5. Building up a neurology franchise leveraging the business development capability
- 6. Intense efforts in the discovery area



# OBI-1

Michel Dahan

**Programme Director** 





# An agent targeting both acquired and congenital hemophilia

# Congenital hemophilia A with inhibitors to human FVIII

- Affects 1:4000 male births
- The development of neutralizing antibodies (inhibitors) to hFVIII following replacement therapy is a major complication
- Inhibitors develop in about 28% of severe patients and in between 3% to 13% of mild and moderate hemophilia A patients
- Patients no longer respond to hFVIII therapy

## **Acquired hemophilia**

Acquired factor VIII inhibitor

- Affects 1 to 2 individuals in 1,000,000, predominantly in older individuals
- A small proportion of younger patients may develop the disease, predominantly postpartum women
- Clinical manifestation is more severe and anatomically diverse than in congenital hemophilia A
- A mortality rate approaching 20%. Bleeding is often spontaneous or in response to minimal trauma

pFVIII is a promising treatment to stop bleeds in patients with inhibitors to hFVIII



### **Current and past treatment options**

hFVIII replacement therapy

hFVIII is the preferred treatment when inhibitor levels are low

Bypassing therapy

- Activated rFVIIa
- Activated prothrombin complex concentrate (aPCC)

Plasma derived porcine FVIII (Hyate:C)

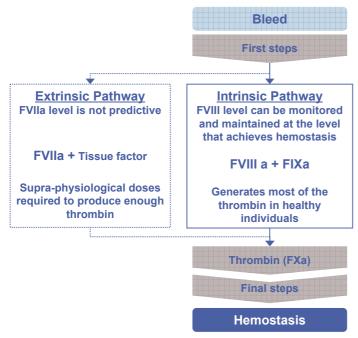
- Hyate:C was an important treatment option
- Same procoagulant activity as hFVIII
- Effective in treating and preventing bleeding episodes
- Lower cross reactivity to anti-hFVIII antibodies

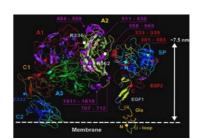
pFVIII allows to reach measurable FVIII activity even in the presence of anti-hFVIII inhibitor levels





# FVIII plays a key role in the "hemostasis cascade" activating the intrinsic pathway

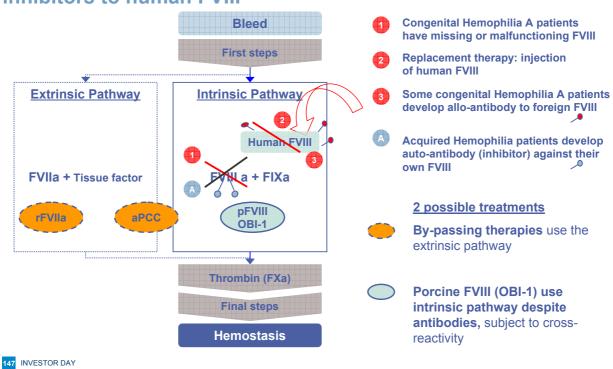




FVIII Structure Model – complex with FIX



# Porcine FVIII activates the intrinsic pathway in patients with inhibitors to human FVIII





As a recombinant porcine FVIII OBI-1 leverages a clear competitive advantage over by-passing therapies based on differentiated attributes

#### **OBI-1...**

...activates the primary coagulation pathway

10 to 11 hours half-life

...is a recombinant product

No risk of contamination from blood infectious or viral agents

...allows to reach measurable FVIII activity

Lower cross reactivity to anti-hFVIII antibodies

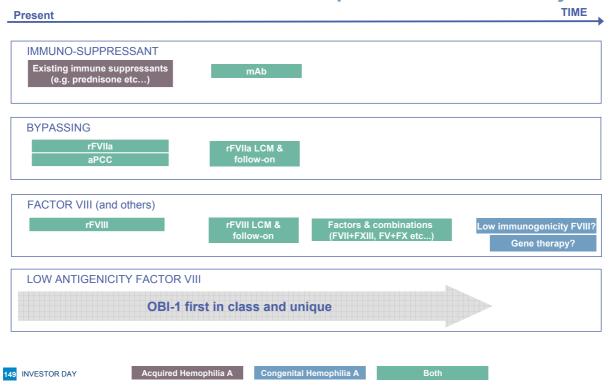
... eliminates plasmaderived side effects

Much purer than plasma-derived pFVIII

Phase 3 aims at providing a clear dosing schedule based on measurable FVIII levels



# OBI-1 will be first-in-class and unique for the next 5 to 10 years





# Now preparing for phase 3...

2 prospective clinical trials, in liaison with Medical Community & Regulatory Agencies

Study in patients with acquired factor VIII inhibitor (acquired hemophilia)

Treatment of all acute bleeding episodes

Study in patients with congenital hemophilia A and inhibitors to hFVIII

Treatment of life or limb threatening bleeding episodes

Both will be of similar design

Open label, non comparative prospective studies, with about 40 patients in each study

Standards setting: first ever prospective trial in acquired hemophilia

Protocols finalization and pre-phase 3 CMC consultations with regulatory agencies to be completed in H1 2009



# A highly specialized hospital product addressing unmet need

First biologics to conclude Phase 2 resulting from strategic biotechnology platform

Patent protection until 2023 in Europe and US

World-wide commercialization rights

Lean commercial infrastructure

A commercial potential in excess of US\$200 million

Fourth specialty therapeutic focus in Haematology



# **Financials**

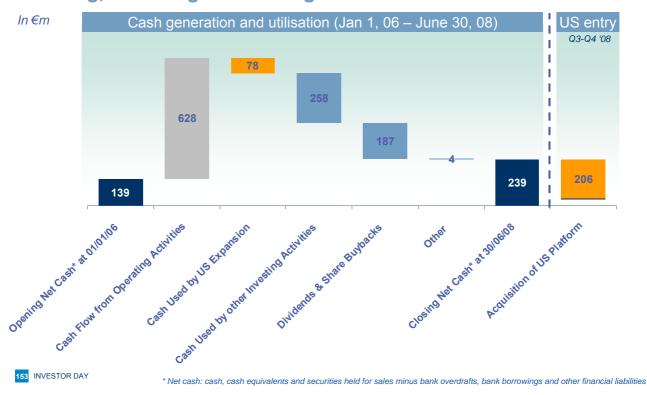
Claire Giraut

**EVP - Chief Financial Officer** 



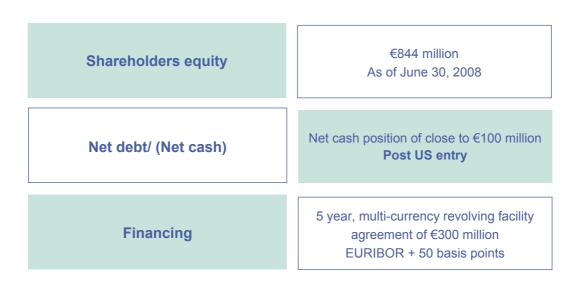


### A strong, recurring cash flow generation





# After its US acquisitions, Ipsen remains cash positive, with a sound financial structure





### 2009 objectives

Sales growth

12.0 to 14.0%\*

**Operating margin** 

Around 15% (in % of sales)

Operating margin objective set before taking into account:

- any restructuring costs, acquisition related one-off items or purchase accounting impacts and;
- the potential impacts of the dispute with Bayer on a royalty revenue stream

While the Group is currently finalising the analysis of the potential impacts of difficult macroeconomic conditions on its future performance, it remains confident in its ability to achieve its future financial objectives and, given its growth prospects, to significantly outpace the average pharmaceutical industry growth rate



\* Compared to a stand alone 2008



# Confidence in our long term objectives

US Endocrinology platform

. . . .

Sales in excess of \$250 million

US Neurology platform

2012

Sales in excess of \$50 million

WW hematology (OBI-1)

At peak

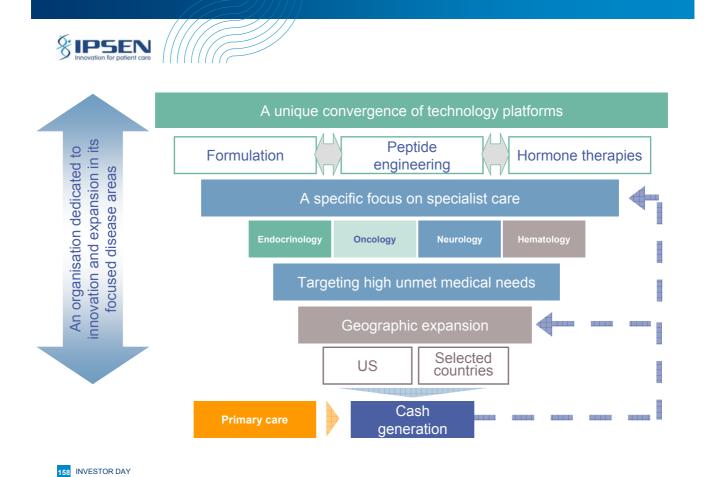
Sales in excess of \$200 million

A US platform generating close to \$1 billion by the end of the next decade

# Conclusion

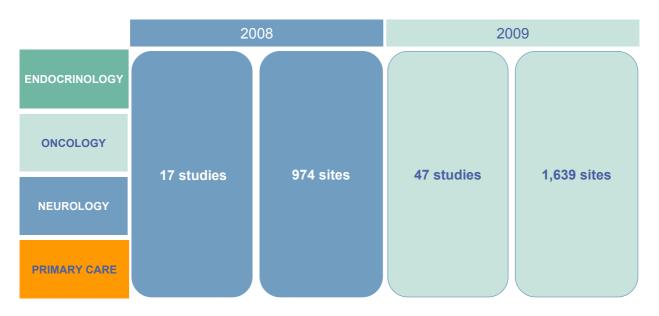
Jean-Luc Bélingard Chairman & CEO







# In 2009, Ipsen will accelerate its clinical activity in drug development







# You will hear from us in the months to come...

		Decapeptyl® 6 Months Approval	
	BIM-23A760 Phase II initiation	Toremifene Citrate 80 mg European filing	Adenuric® Partnership(s) and launches
	OBI-1 Phase III initiation	Azzalure® EMEA approval	Primary care products In-licensing deal(s)
BN-83495 Phase I results Breast / Prostate	BN-83495 Phase II initiation prostate/gynecology	Reloxin® FDA approval	Reloxin® Launch by Medicis
BIM-28131 Phase I initiation	Somatuline® Depot US NET Phase III initiation	Dysport® FDA approval	Dysport® Launch
Phase I	Phase II/ III	Regulatory	Launch



# "A ROADMAP FOR PERSONALIZED MANAGEMENT OF GROWTH DISORDERS"

# Presentation by Pr. Rosenfeld during Lunch

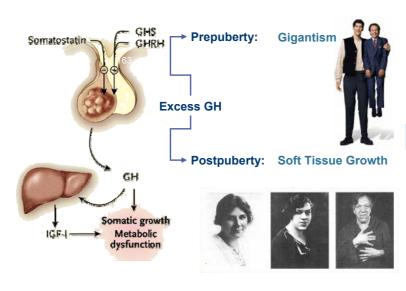


**Appendix 1: Endocrinology** 





### **Acromegaly**



#### **Medical Considerations**

- Significant morbidity and mortality 1,2
- 2.5 to 5 times excess mortality<sup>1</sup>
- 5-10 years less life expectancy <sup>2</sup>
- GH/ IGF-I control normalizes mortality 3,4

#### Prevalence

- Prevalence: 60 per 1 million
- 50% receive drug therapy
- North America: ~ 15,000 patients
- Europe: ~ 15,000 patients



Orme SM et al. JCEM 83: 2730-4, 1998
 Clayton RN et al. J Endocrinol (Suppl 1): S23-9, 1997
 Abosch A et al. JCEM 83: 3411-8, 1998
 Swearingen B et al. JCEM 83: 3419-26, 1998



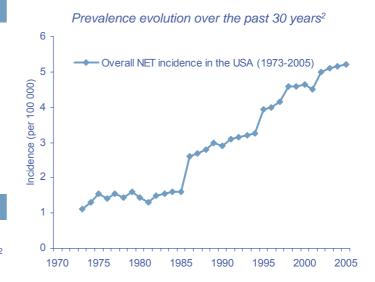
### **Neuroendocrine Tumours**

#### **Medical Considerations**

- Arise from cells with both neuronal and endocrine origins<sup>1</sup>
- Can arise from almost any organ, most commonly GI tract and pancreas, endocrine organs, lung
- 5 years of survival for carcinoid tumours in 60% of case<sup>3</sup>
- Second NIH top priority funding

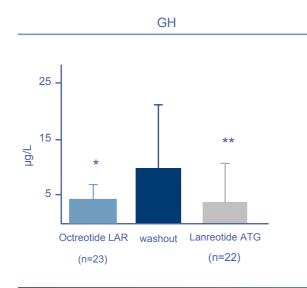
#### Incidence & Prevalence

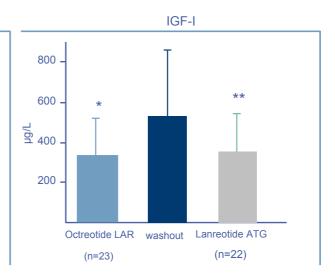
- 2.5 to 5 new cases per 100,000
- Prevalence increased 5x in last 3 decades<sup>2</sup>
- Usually slow-growing tumours<sup>1</sup>





# Somatuline®: A proven track record of efficacy¹ in Acromegaly





In approximately half of patients, Somatuline® Autogel® 120 mg may be administered every 6 to 8 weeks, instead of every 4 weeks, with similar efficacy

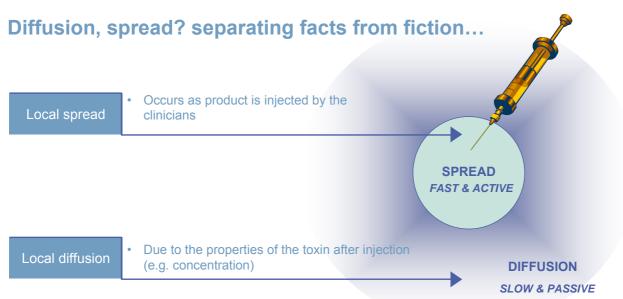
165 INVESTOR DAY

1. : Ronchi, Clin Endo, 2007

# **Appendix 2: Neurology**







The spread/ diffusion effects are similar between the different type A toxins

