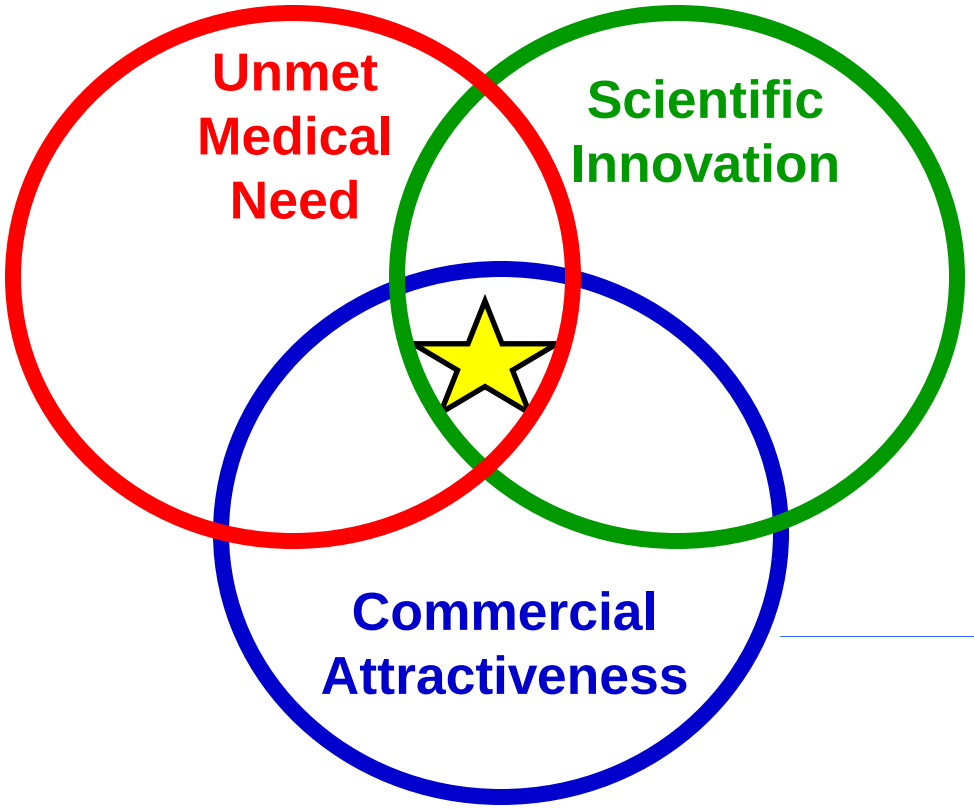
Positioning and Re-purposing of Drugs: Case Studies from BMS's Experience

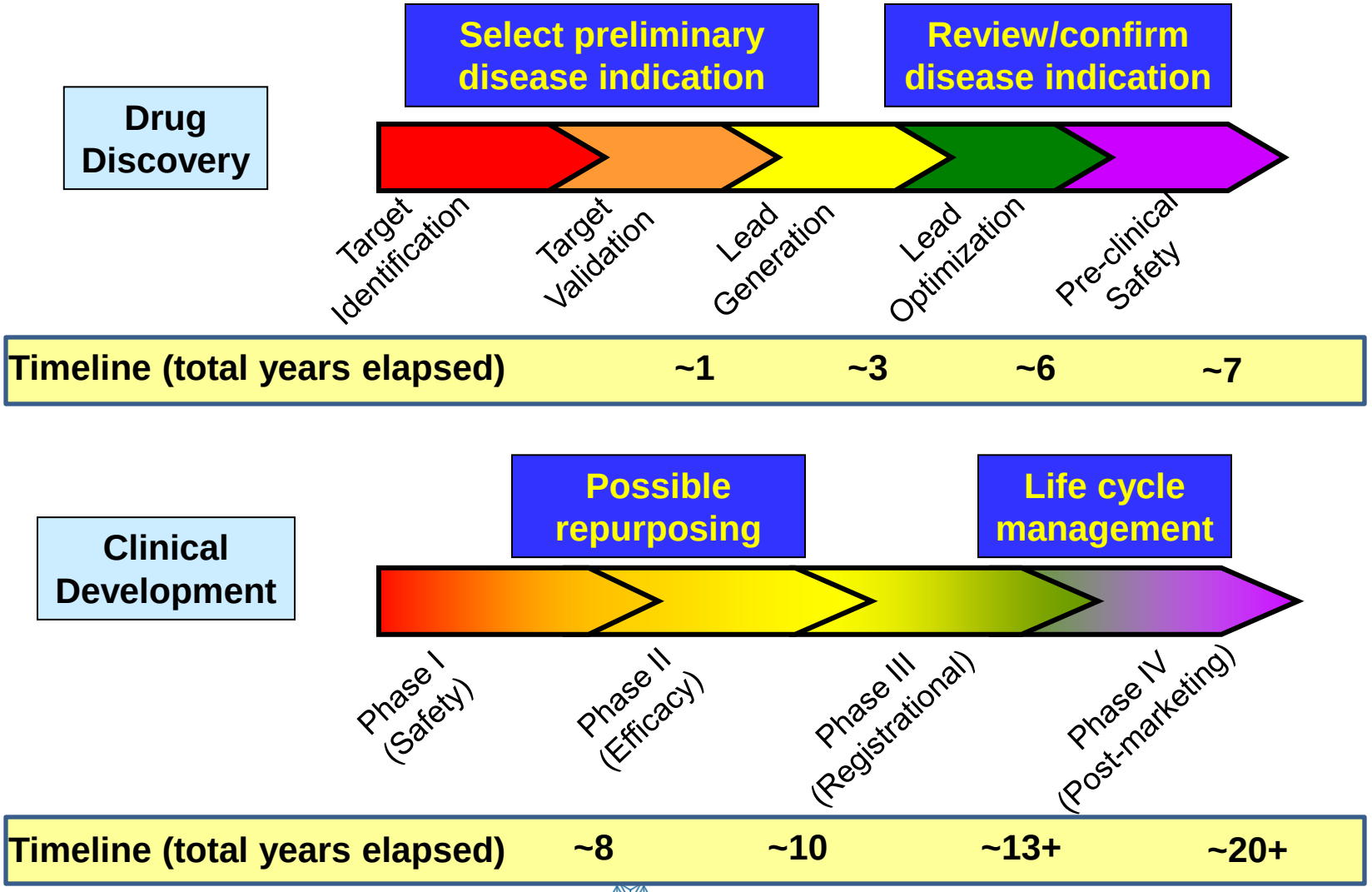
Simeon Taylor, MD, PhD
Vice President, Research & Scientific Affairs
Bristol-Myers Squibb

June 24, 2013

Translating scientific insights into novel therapies to address unmet medical need



Multiple opportunities to select disease indication during the life of an R&D program



Positioning/Repurposing: Key Learnings from BMS Experience

- **Value of academic:industry collaboration**
  - *Academia*: frequently provides innovative insight linking mechanism of action to disease indication
  - *Industry*: critical roles in late stage development, regulatory approval, manufacturing, and commercialization
- **Early decision-making**
  - Opportunity to optimize compound to target selected therapeutic indication
  - Preserves patent life
- **Reasons for repositioning/repurposing**
  - Lack of efficacy in 1st indication
    - May demonstrate efficacy in different indication
  - Safety concern in 1st indication
    - May have acceptable benefit:risk in disease with higher unmet medical need

Dasatinib: *abl* kinase inhibitor

Dasatinib: An Oncology drug derived from chemical leads from a program targeting *lck* (a *src*-family kinase)

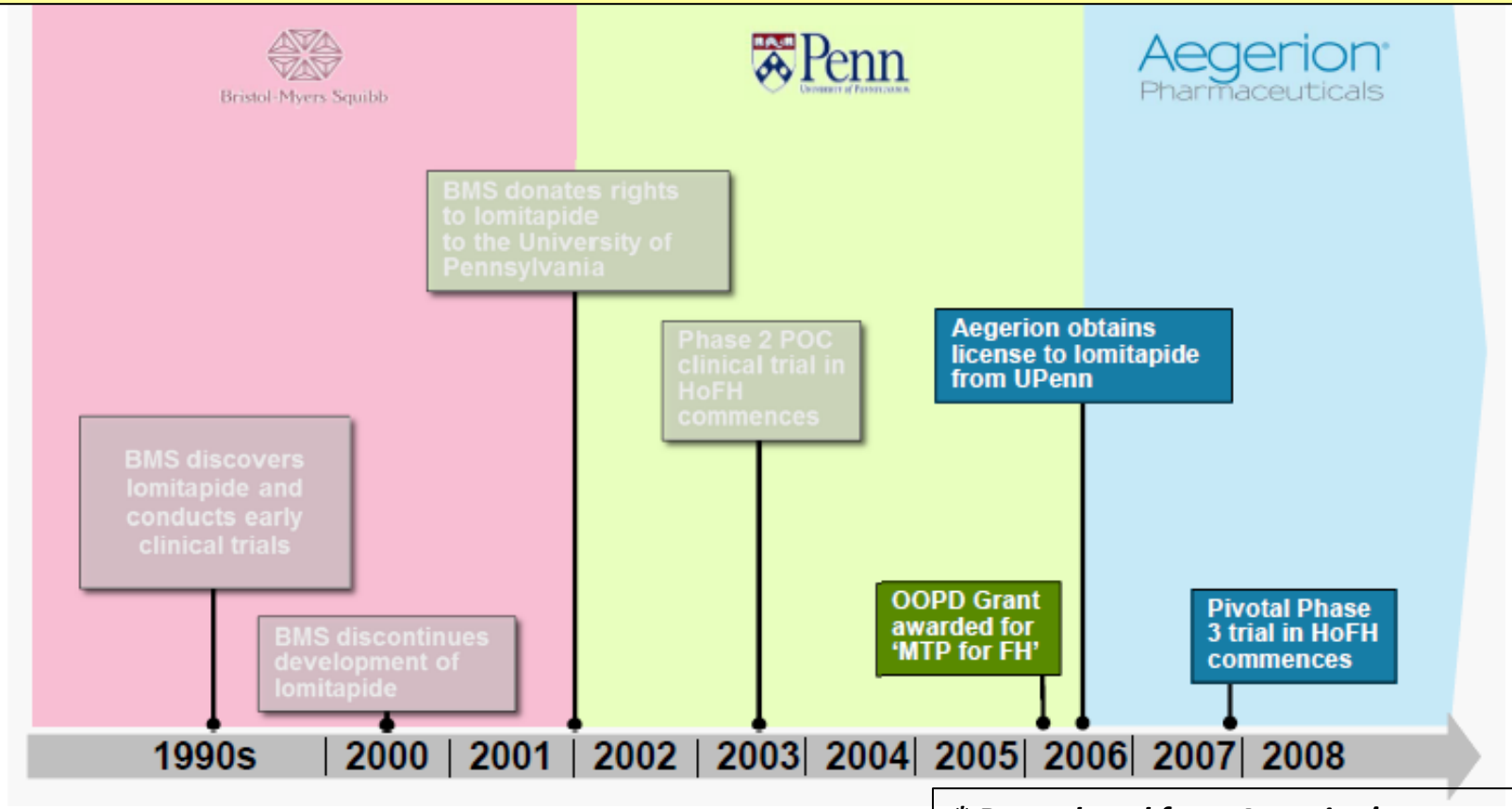
- **Lymphocyte-specific protein tyrosine kinase inhibitor program**
  - *lck*: a member of the *src* family of protein tyrosine kinases
    - Multiple publications in medicinal chemistry literature (2002-2004)
  - BMS's *lck* inhibitors also exhibited activity against other tyrosine kinases
- ***abl* inhibition: Suggested another potential therapeutic indication**
  - Demonstration that dasatinib was active against imatinib-resistant mutant forms of *BCR-ABL* (collaboration with Charles Sawyer's lab, UCLA)
    - N. P. Shah et al., *Science*, 305: 399, 2004
    - J. Das et al., *J. Med. Chem.*, 49: 6819, 2006
- **Efficacy in imatinib-resistant Philadelphia chromosome-positive leukemias**
  - FDA approval (June 28, 2006). Currently indicated in:
    - Newly diagnosed Ph^+ chronic myeloid leukemia (CML) in chronic phase
    - Chronic, accelerated, or myeloid or lymphoid blast phase Ph^+ CML with resistance or intolerance to prior therapy including imatinib
    - Ph^+ ALL with resistance or intolerance to prior therapy
  - M. Talpaz et al., N. Engl. J. Med., 15: 2531, 2006

Lomitapide: Microsomal transfer protein inhibitor

Lomitapide: History of Research & Development*

BMS scientists (John Wetterau , Richard Gregg *et al.*):

- **Cloned microsomal transfer protein (MTP) cDNA (1992),**
- **Identified MTP as disease gene for abetalipoproteinemia (1996)**
- **Demonstrated efficacy of MTP inhibitor in rabbit model for familial hypercholesterolemia (1998).**

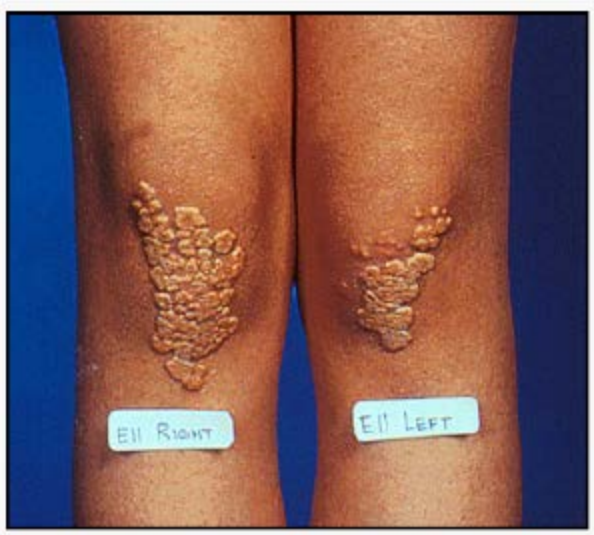


Bristol-Myers Squibb

**** Reproduced from Aegerion's presentation at FDA Advisory Committee***

Homozygous familial hypercholesterolemia (FH): High unmet medical need

Patient: 28 year old female



- **LDL cholesterol = 780 mg/dL**
- **Cutaneous xanthomas beginning at age 3**
- **Obstructive coronary artery disease and CABG at age 12**

Cardiovascular Consequences of Markedly Elevated LDL-C

- Patients with HoFH typically develop cardiovascular disease before the age of 20[1]
  - Coronary artery disease
  - Myocardial infarction
  - Severe aortic stenosis
  - Heart failure
  - Stroke
  - Sudden death
- Even with currently existing therapies, the mean age of death is 33 years[2]

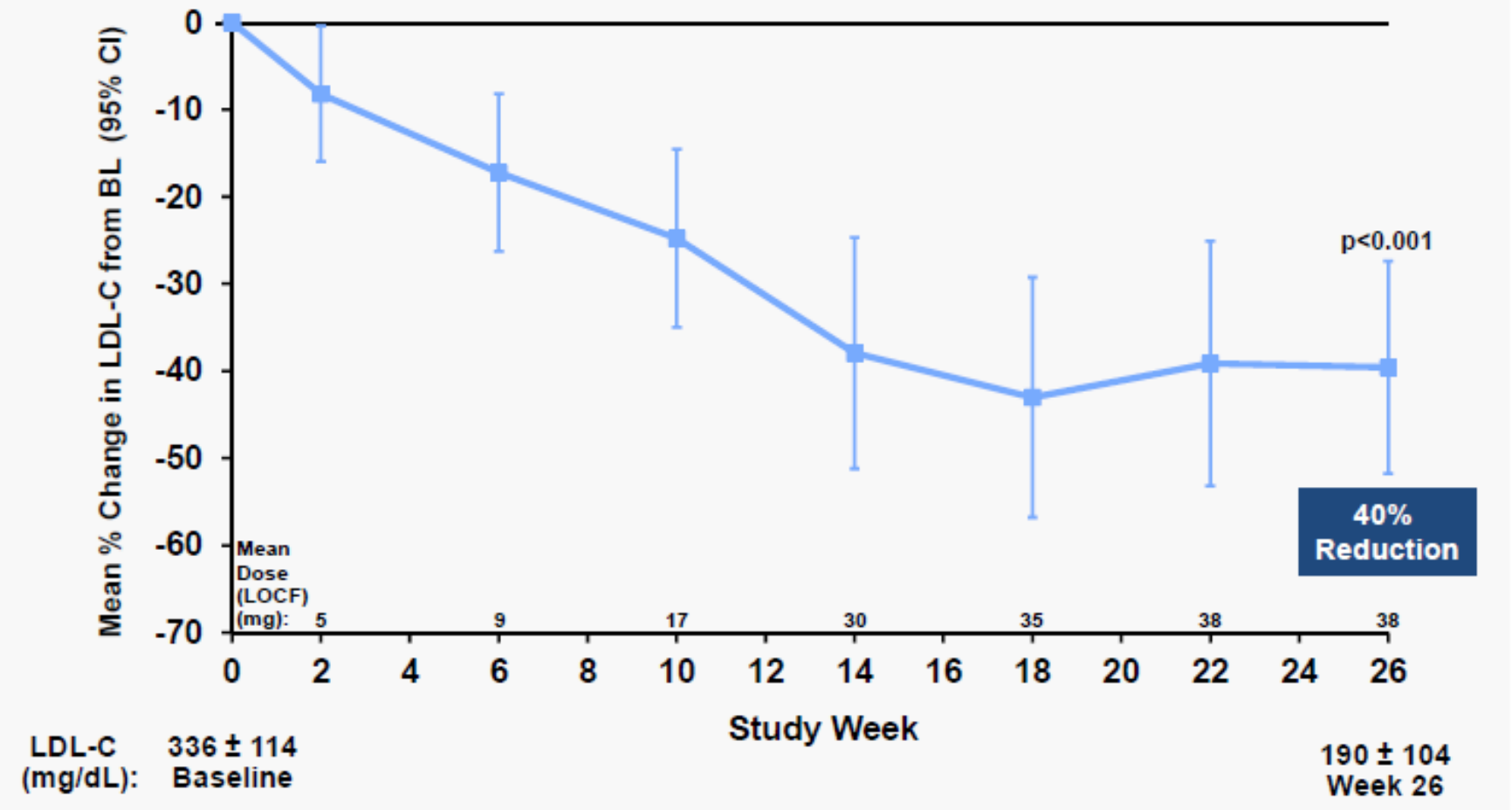
1. Goldstein, J. L., H. H. Hobbs, et al. (2001). *The Metabolic and Molecular Basis of Inherited Disease*.
2. Raal J, et al. *Circulation*. (2011).

Bristol-Myers Squibb

**** Reproduced from Aegerion's presentation at FDA Advisory Committee***

Lomitapide: LDL-C reduced by 40% at 26 weeks*

Phase 3: ITT with LOCF (N=29)



** Reproduced from Aegerion's presentation at FDA Advisory Committee*

Bristol-Myers Squibb

Metreleptin: Treatment for leptin-deficient states

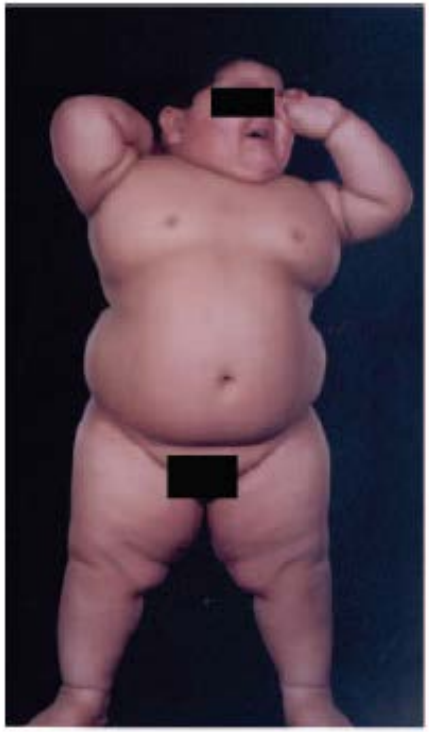
Cloning of mouse ob gene: Identification of leptin, a hormone secreted by adipose tissue

+/+ **ob/ob**

- **ob/ob mouse: homozygous loss-of-function mutations in the leptin gene**
- **Loss of "feedback" from adipose tissue to brain**
  - **Increased appetite and increased food intake**
  - **Increased body weight (and other associated phenotypic features)**

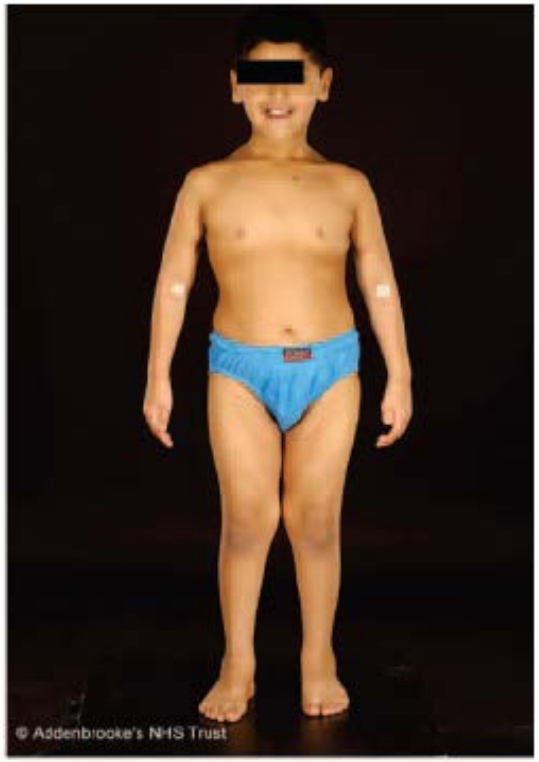
Y Zhang *et al* (1994) *Nature*, 372: 425-432

Metreleptin Rx: Dramatic weight loss reported in leptin-deficient child



weight = 40kg, age 3yrs

BEFORE LEPTIN

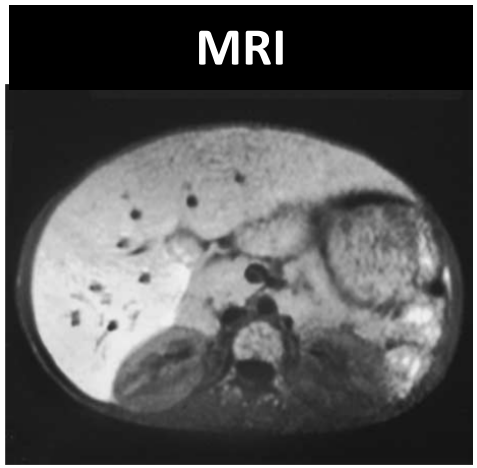


weight = 29kg, age 6yrs

AFTER LEPTIN

IS Farooqi *et al* (1999) *N Engl J Med*, **341**: 879-884
IS Farooqi & S O'Rahilly (2006) *Endocrine Reviews*, **27**: 710-718

Lipodystrophy: Heterogeneous collection of syndromes associated with paucity of fat (lipoatrophy)

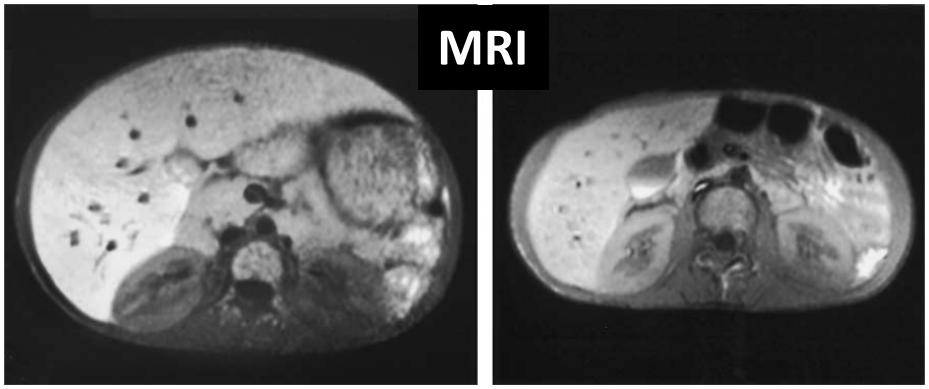


- **Generalized lipodystrophy (most severe metabolic abnormalities: hypertriglyceridemia; insulin resistance/diabetes; low plasma leptin)**
  - Congenital (genetic)
  - Acquired (often associated with autoimmune diseases)
- **Partial lipodystrophy (similar metabolic abnormalities; possibly somewhat less severe)**
  - Congenital (genetic)
  - Acquired

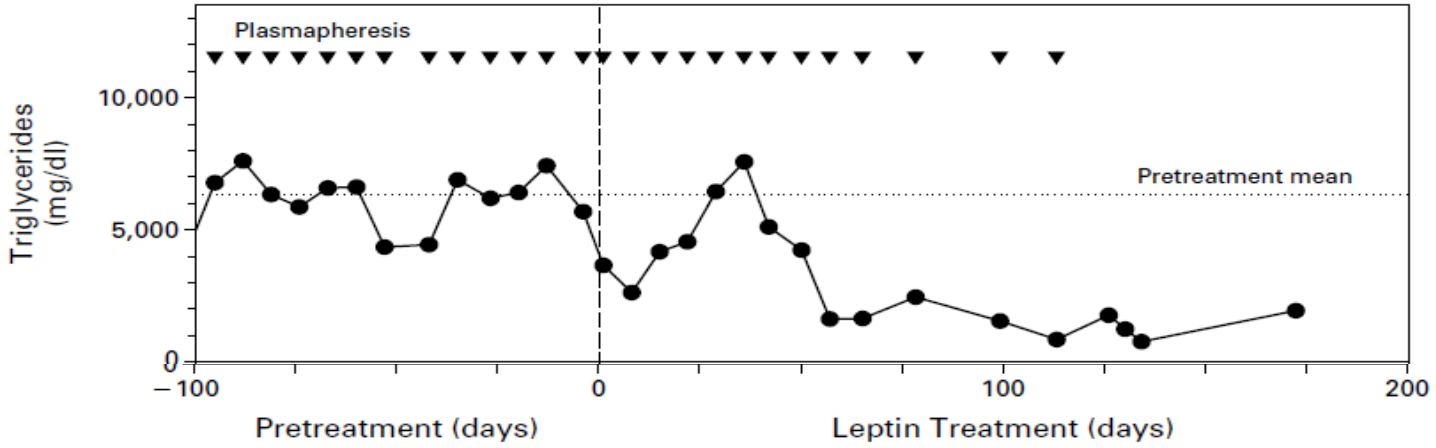
Bristol-Myers Squibb

EA Oral *et al* (2002) *N Engl J Med*, **346**: 570-578

Metreleptin therapy in lipodystrophy: a leptin-deficient state (NIDDK, Univ. Texas Southwestern)



Baseline **Post-leptin**



Biological Licensing Application (BLA) currently under review at FDA.

Bristol-Myers Squibb

EA Oral *et al* (2002) *N Engl J Med*, **346**: 570-578

Summary & Conclusions

“It takes a village to develop a drug….”

	Dasatinib
Pioneering research into mechanisms of disease	CML (Philadelphia chromsome; abl) (Univ. Penn., Fox-Chase, UCLA, M.D. Anderson, OHSU)
Drug Discovery	BMS
Initial Clinical Indication	lck inhibitor; RA
Selection of Ultimate Clinical Indication(s)	Ph^+ CML (UCLA; BMS)
Phase 3 Development , Regulatory Filing, and Commercialization	BMS

“It takes a village to develop a drug….”

	Dasatinib	**Lomitapide**
Pioneering research into mechanisms of disease	CML (Philadelphia chromsome; abl) (Univ. Penn., Fox-Chase, UCLA, M.D. Anderson, OHSU)	**Abetalipoproteinemia (Cornell, BMS)**
Drug Discovery	BMS	**BMS**
Initial Clinical Indication	lck inhibitor; RA	**Dyslipidemia (BMS)**
Selection of Ultimate Clinical Indication(s)	Ph^+ CML (UCLA; BMS)	**Homozygous familial hypercholesterolemia (Univ. Pennsylvania, FDA funding)**
Phase 3 Development , Regulatory Filing, and Commercialization	BMS	**Aegerion**

“It takes a village to develop a drug….”

	Dasatinib	Lomitapide	**Metreleptin**
Pioneering research into mechanisms of disease	CML (Philadelphia chromsome; abl) (Univ. Penn., Fox-Chase, UCLA, M.D. Anderson, OHSU)	Abetalipoproteinemia (Cornell, BMS)	**ob/ob mouse (Rockefeller Univ)**
Drug Discovery	BMS	BMS	**Amgen**
Initial Clinical Indication	lck inhibitor; RA	Dyslipidemia (BMS)	**Obesity (Amgen, Amylin)**
Selection of Ultimate Clinical Indication(s)	Ph^+ CML (UCLA; BMS)	Homozygous familial hypercholesterolemia (Univ. Pennsylvania, FDA funding)	**Lipodystrophy syndromes (NIDDK, UTSW, Amgen)**
Phase 3 Development , Regulatory Filing, and Commercialization	BMS	Aegerion	**NIDDK (Clinical) Amylin (BMS/AZ)**