FDA Advisory Committee

June 13, 2007

ZIMULTI ® (rimonabant)

sanofi-aventis US

Presentation Agenda

Introduction	**Richard Gural, PhD**
Mechanism of Action	Ken Mackie, MD
Medical Need and Clinical Efficacy	Pierre Rosenzweig, MD
Clinical Safety	Paul Chew, MD
Risk MAP	Richard Gural, PhD
Benefit / Risk	Louis Aronne, MD

Basis for Development in Obesity (1)

- 1996 and 2007 FDA *Draft Guidance for the Clinical Evaluation of Weight-Control Drugs*
  - duration and size of phase 3 studies
    - one year of placebo-controlled exposure in 1500 patients
    - second year of open-label exposure in up to 500 patients
  - efficacy criteria
    - mean weight loss is 5% greater in drug vs. placebo-treated patients OR
    - proportion of patients losing 5% is greater in drug vs. placebo-treated group

Basis for Development in Obesity (2)

- 1996 and 2007 FDA *Draft Guidance for the Clinical Evaluation of Weight-Control Drugs*
  - patient population
    - BMI $\geq$ 30 kg/m^2 OR
    - > 27 kg/m^2 with comorbidities
      - hypertension
      - type 2 diabetes
      - dyslipidemia
- 1998/2000 NIH Clinical Guidelines on Overweight and Obesity
  - since obesity is a chronic disorder, the short-term use of drugs is not helpful

Efficacy Basis for Approval
Phase 3 Studies

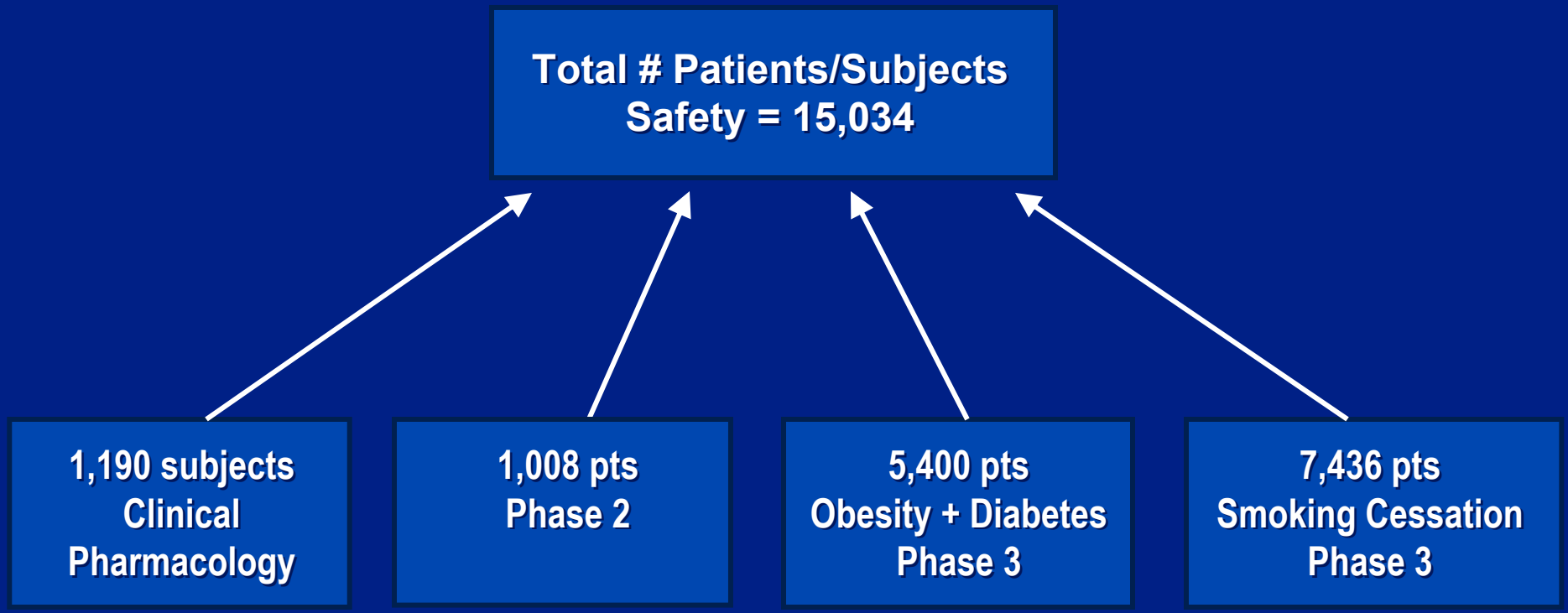
Obesity Program	Treatment Period
RIO-North America*	1 yr + 1 yr
RIO-Europe*	2 years
RIO-Lipids*	1 year
RIO-Diabetes*	1 year

Diabetes Program	Treatment Period
RIO-Diabetes*	1 year
SERENADE*	6 months

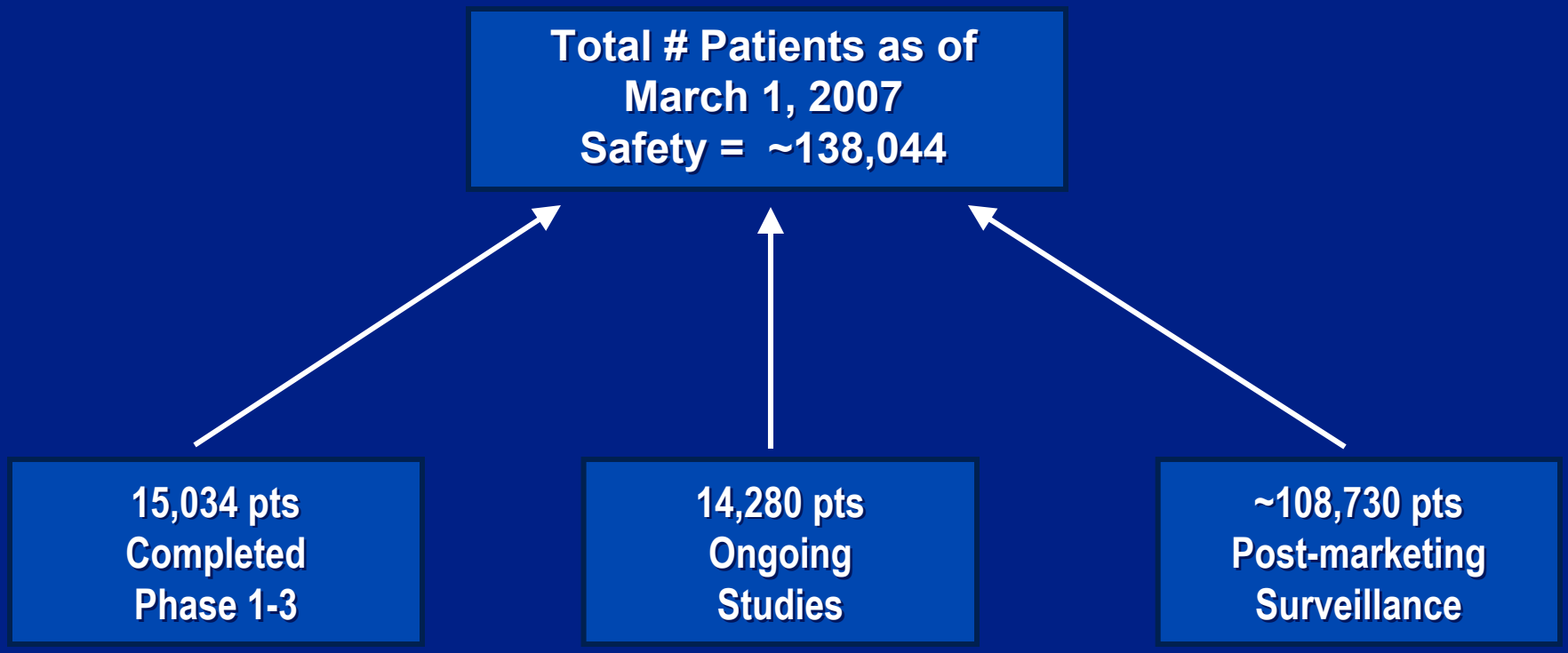
* Publication

Rimonabant Safety Population Completed Phase 1 to Phase 3 Studies

- 7,447 patients at 20 mg QD from 1 day to 2 years



Rimonabant Safety Population



Ongoing Clinical Development Program

Study Number	Study Title	Number of Subjects Enrolled
EFC5823	ADAGIO-Lipids – treatment of atherogenic dyslipidemia in abdominally obese patients.	799
EFC5826	CRESCENDO – reduction in the risk of major cardiovascular events in abdominally obese patients with clustering risk factors	8269/17000
EFC5827	STRADIVARIUS – inhibition of athersclerosis progression assessed by intravascular ultrasounds in overweight patients with clustering risk factors	838
EFC5828	AUDITOR – inhibition of atherosclerosis progression assessed by carotid artery intima-media thickness in overweight patients with additional risk factors	660
PMC0172	VICTORIA – effect on the amount and the activity of visceral fat in abdominally obese patients with metabolic syndrome	229
EFC5593	ARPEGGIO – effect on glycemic control in type 2 diabetic patients inadequately controlled with insulin	366
EFC5107	RAPSODI – prevention of type 2 diabetes in patients with prediabetic status	2397
EFC6001	RIO ASIA – weight-reducing effect and safety in obese patients with or without comorbidities	642
	TOTAL	**14200**

ZIMULTI® (rimonabant)

- Selective and neutral antagonist of the cannabinoid-1 (CB_1) receptor
- Tablet
- 20 mg once daily

Rimonabant Pharmacokinetics

- Metabolized by CYP3A and amidohydrolases
  - potent inhibitors of CYP3A increase rimonabant exposure up to 2.7 fold
- Terminal half-life 16 days
  - steady state accumulation of 3.3 fold in 25 days
- No effect of rimonabant on CYP enzymes

Global Regulatory Status

- Approved in 37 countries and marketed in 18
- Marketing Application submitted in EU – April 2005
- Approved via Centralized Procedure – June 2006
- Approved EU Indication:
  - an adjunct to diet and exercise for the treatment of obese patients (BMI $\geq$ 30 kg/m^2), or overweight patients (BMI > 27 kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidemia
- EU Risk Management Plan (EU-RMP)
  - initial version – June 2006

US Regulatory History

- NDA 21-888 (obesity + type 2 diabetes) submitted April 2005; approvable letter – February 2006
- Complete response submitted October 2006
  - response included:
    - updated safety data for completed and ongoing studies
    - review of all neurological and psychiatric events
    - proposed risk management plan
- Agreed to 3 month extension for review – February 2007
- Submitted SERENADE study in T2D – February 2007
- Advisory Committee Meeting – June13, 2007
- PDUFA Action Letter Date – July 26, 2007

Proposed Indications

as an adjunct to diet and exercise for the treatment of overweight patients with BMI > 27 kg/m^2 and at least one other cardiovascular risk factor, or for the treatment of obese patients with a BMI ≥ 30 kg/m^2.

in combination with metformin or a sulfonylurea to improve glycemic control and reduce weight in patients with type 2 diabetes and a BMI > 27 kg/m^2 when diet and exercise plus a single agent do not result in adequate control.

Who is the Appropriate Patient?

- NOT Everyone
- Appropriate
  - patients with a BMI > 27 kg/m^2 with at least one cardiovascular risk factor or a BMI ≥ 30 kg/m^2
  - chronic indication intended for long-term use
- Not Appropriate
  - past history of depressive disorders and/or suicidality or patients with a diagnosis of depressive disorders or current anti-depressant therapy
  - treatment with anti-epileptic therapy

Consultants

Mechanism of Action

Ken Mackie, MD – Indiana University

Endocrinology

Louis Aronne, MD – Medical College of Cornell University

George Bray, MD – Pennington Biomedical Research Ctr

Michael Jensen, MD – Mayo Clinic

Donna Ryan, MD – Pennington Biomedical Research Ctr

Internal Medicine

Patrick Moriarty, MD – University of Kansas Medical Center

Consultants

Psychiatry

Robert Anthenelli, MD – University of Cincinnati College of Medicine

Bassalingappa Hungund, PhD – New York State Psychiatric Institute

Ranga Krishnan – Duke University Hospital

J. John Mann, MD – New York State Psychiatric Institute

Consultants

Neurology

Walter Bradley, MD – University of Miami

Richard Mattson, MD – Yale University

Dan Mikol, M.D., PhD – University of Michigan Medical Center

Maral Mouradian, MD – Robert Wood Johnston University Hospital

Epidemiology

Judith Jones, M.D., PhD – The Degge Group

Biostatistics

Gary Koch, PhD – University of North Carolina