SAVE THE DATE  APRIL 24-26, 2006  THE RITZ-CARLTON, BOSTON

THE GLOBAL THERAPEUTIC GROWTH STRATEGIES CONFERENCE
"...one of the three must attend annual industry meetings for senior executives."
Plenary Sessions

- **Beyond Debate: Pharma’s Innovation Bar and the Need for Uniquely Advantageous Therapeutics**
- **Will Can Pharma / Biotech Clear the Innovation Bar?**
- **Complex Therapies Redux: Therapeutic Vaccines, Cell and Gene Therapy – A New Game for New Players?**
- **Staring up the Face of the Mountain – Strategies for Launching into Uncharted Therapeutic Areas**
- **The Future of Cardiovascular Therapeutics: Is there Life Beyond Statins, and other Existential Issues**
- **Good, Better, Best: The Ethics of Improvement and Enhancement That Face the Pharma and Biotech Industries (Arthur L. Caplan, PhD, Keynote)**
- **Pharmacogenetics is Not Just for Targeted Therapies -- Making Intelligent Space for Chemotherapy in the 21st Century**
- **Not Your Father’s Drug Delivery: Novel Approaches to Novel Therapies**
- **Style or Substance: The Lifestyle Drug Continuum**
Speakers to Date

Karen Bernstein, PhD, Chairman & Editor-In-Chief, BioCentury
Alexis Borisy, AM, President & Chief Executive Officer, CombinatoRx
Arthur L. Caplan, PhD, Chair, Department of Medical Ethics, Director, Center for Bioethics, University of Pennsylvania School of Medicine (Keynote)
Michael D. Clayman, MD, VP, Lilly Research Laboratories, Eli Lilly
Bruce Cohen, President & CEO, Cellerant Therapeutics
David DeMarco, PhD, Formerly Vice President, Strategy & Corporate Development, Cambrex
Frederick Frank, Vice Chairman & Director, Lehman Brothers
Robert H. Glassman, MD, Managing Director, Healthcare Investment Banking, Merrill Lynch
Mitchell H. Gold, MD, President & Chief Executive Officer, Dendreon
James W. Harris, PhD, Founder and Chief Scientific Officer, Bioavailability Systems
Juergen Lasowski, Former VP, Head of Business Development & Strategy, US, sanofi-aventis
Brian Leyland-Jones, MD, Professor & Founding Chairman, Dept. of Oncology, McGill University
Clive A. Meanwell, MD, Chairman & CEO, The Medicines Company
Paul C. Nakagaki, PhD, Head, Pharma Research Strategy, Pharmaceuticals Div., Roche
Roger S. Newton, PhD, SVP, PGRD, Director, Esperion Therapeutics
Douglas E. Onsi, VP Business Development, Genzyme Genetics
Richard Pasternak, MD, VP, Clinical Research Cardiovascular/Atherosclerosis, Merck Research Laboratories
Jorge Plutzky, MD, Director, The Vascular Disease Prevention Prgm., Brigham and Women’s Hospital
Paul M. Ridker, MD, MPH, Cardiovascular Medicine, Department of Medicine, Brigham and Women’s Hospital
Mary C. Tanner, Partner, Life Sciences Partners, LLC
Thomas Tillett, President and CEO, RheoGene
Robert E. Ward, Executive Director Commercial Development, Biologics & Small Molecules, Schering-Plough
Obesity: Getting the Skinny on a Big Market

Defined Health

January 31, 2006
Obesity Insight Series – Tonight’s Discussion Topics

1. *Acomplia: Why the Buzz?*

2. Beyond the Buzz: The Risks and Rewards of the Pharmacologic Treatment of Obesity

3. Beyond *Acomplia*: The Obesity Pipeline
Acomplia: Why the Buzz?
In the U.S., there are over 120 million overweight adults, with 52 million considered obese!

**Figure 2. Age-adjusted* prevalence of overweight and obesity among U.S. adults, age 20-74 years**

*Age-adjusted by the direct method to the year 2000 U.S. Bureau of the Census estimates using the age groups 20-39, 40-59, and 60-74 years.
Obesity: A Growing Problem

Prevalence of Obesity in the U.S. has more than doubled over the past 20 years

Figure 1: Indexed Prevalence of Obesity, Overweight, and Healthy Weight among US Adults (1960-2002)

Source: National Health and Nutrition Examination Survey (NHANES)
Obesity: A Widespread Problem

Developed countries, including U.S. and Western Europe, and women, exhibit highest rates of Obesity, defined as body mass index (BMI) above 30

Figure 5: Prevalence of Adult Obesity by Sex and Country

Source: World Health Organization (WHO)
Obesity has Significant Consequences


No. of US Deaths in 2003 (000s)

CDC National Center for Health Statistics, NIH
Food selection and eating behaviour during weight maintenance intervention and 2-y follow-up in obese men.

Borg P, Fogelholm M, Kukkonen-Harjula K.

UKK Institute for Health Promotion Research, Tampere, Finland. patrik.borg@helsinki.fi

OBJECTIVE: The aim was to assess long-term changes in food consumption and eating behaviour during and 2 y after dietary counselling in weight-reduced obese men. DESIGN: Observational study from a randomised controlled trial. SETTING: Outpatient clinic of a research institute. SUBJECTS: A total of 36 subjects with complete data on food intake during the study. Subjects were obese (mean body mass index (BMI) 32.8 kg/m2) men aged 35-50 y, recruited by media advertising. INTERVENTIONS: Dietary counselling was included in 2 months weight reduction with very-low-energy-diet and in 6 months weight maintenance programme, which also included physical activity counseling. This was followed by a 23 months unsupervised follow-up with yearly assessments. Food intake was assessed six times during the study by 4-day food records. Eating behaviour was assessed by Three-Factor Eating Questionnaire (TFEQ). RESULTS: Increased consumption of low-fat cheese, low-fat margarine, vegetables and high-fibre bread, and decreased consumption of sugar, sausage, high-fat cheese, high-fat margarine, fat products and sweets were observed during dietary counseling. Most of these changes returned later to prestudy consumption level. The relapse in dietary changes was partly associated with scoring low in restraint and high in disinhibition and hunger. CONCLUSION: In obese men, long-term maintenance of dietary changes was difficult. New ways to ease self-monitoring and increase self-efficacy might be necessary to improve maintenance of dietary changes.
Prior drug launches have been characterized by very rapid initial growth, then a long-term plateau or decline in sales.
Massive potential treatment population

+ Few realistic treatment options

+ Safe, effective oral agent

= 1 BIG FAT blockbuster!
Acomplia: Pharma Blockbuster Potential?

With Acomplia, Pharma finally again has a potential megabrand to promote to PCP, however, blockbuster potential will depend on product labeling and reimbursement.

Acomplia WW Sales Forecast (US$ Millions)

<table>
<thead>
<tr>
<th>WW Sales (US$ Millions)</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
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<tr>
<td>$0</td>
<td>$191</td>
<td>$604</td>
<td>$1,027</td>
<td>$1,484</td>
<td>$1,886</td>
<td></td>
</tr>
</tbody>
</table>

© Defined Health, 2006
Behind the Buzz:
A New Blockbuster is Big News!

Trend in Annual Number of Pharma Blockbusters (> $1B Annual Sales)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001A</td>
<td>51</td>
</tr>
<tr>
<td>2002A</td>
<td>69</td>
</tr>
<tr>
<td>2003A</td>
<td>74</td>
</tr>
<tr>
<td>2004E-2008E</td>
<td>30</td>
</tr>
</tbody>
</table>

Decision Resources, Parexel; DH analysis

© Defined Health, 2006
## “Could Have Been” PCP Blockbusters

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Launch Year</th>
<th>Year Withdrawn</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propulsid (J&amp;J)</td>
<td>1993</td>
<td>2000</td>
<td>Fatal cardiac arrhythmias</td>
</tr>
<tr>
<td>Posicor (Roche)</td>
<td>1997</td>
<td>1998</td>
<td>DDI with Zocor/Mevacor; CHF</td>
</tr>
<tr>
<td>Rezulin (Pfizer)</td>
<td>1997</td>
<td>2000</td>
<td>Liver toxicity</td>
</tr>
<tr>
<td>Baycol (Bayer)</td>
<td>1998</td>
<td>2001</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Seldane (Aventis)</td>
<td>1985</td>
<td>1997</td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Pondimin (Wyeth)</td>
<td>1996</td>
<td>1997</td>
<td>Aortic/mitral valve damage</td>
</tr>
<tr>
<td>Redux (Wyeth)</td>
<td>1996</td>
<td>1997</td>
<td>Aortic/mitral valve damage</td>
</tr>
<tr>
<td>Vioxx (Merck)</td>
<td>1999</td>
<td>2004</td>
<td>MI</td>
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</table>

Company Reports, USFDA; DH analysis
## PCP Blockbusters: The Extinct & The Endangered

### NOTABLE PATENT EXPIRATIONS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Paxil</td>
<td>Allegra</td>
<td>Zoloft</td>
<td>Zocor</td>
<td>Norvasc</td>
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<tr>
<td>Cipro</td>
<td>Celexa</td>
<td>Zithromax</td>
<td>Pravachol</td>
<td>Fosamax</td>
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<tr>
<td>Flovent</td>
<td>Duragesic</td>
<td>Biaxin</td>
<td>Neupogen*</td>
<td>Risperdal</td>
</tr>
<tr>
<td>Flonase</td>
<td>Diflucan</td>
<td>Zofran</td>
<td>Ambien</td>
<td>Effexor</td>
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<tr>
<td>Accupril</td>
<td>Paraplatin</td>
<td>Rocephin</td>
<td>Actos</td>
<td>Seroquel</td>
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<td>Ortho-Novum</td>
<td>Epogen*</td>
<td>Zoladex</td>
<td>Mevalotin</td>
<td>Zyrtec</td>
</tr>
<tr>
<td>Serzone</td>
<td></td>
<td>Aredia</td>
<td>Lamisil</td>
<td>Toprol XL</td>
</tr>
<tr>
<td>Lotensin</td>
<td></td>
<td></td>
<td>Pulmicort</td>
<td></td>
</tr>
</tbody>
</table>

*Assumes no generics

EvaluatePharma; Defined Health estimates

- [ ] = PCP Drug
- [ ] = Specialty Drug

© Defined Health, 2006
## PCP Blockbusters: The Failed “Replacement Crops”

<table>
<thead>
<tr>
<th>Company</th>
<th>Oral GP IIb/IIIa</th>
<th>ACE/NEP Inhibitors</th>
<th>Endothelin A/B Antagonists</th>
<th>NK1 (Depression)</th>
<th>Dual-acting PPARs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>Failed (Ph III)</td>
<td>Active (Ph II)</td>
<td></td>
<td>Failed (Ph II)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[Searle]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSK</td>
<td>Failed (Ph III)</td>
<td>Active (Ph II)</td>
<td>Mixed Results (Ph II)</td>
<td></td>
<td>Active (Ph II)</td>
</tr>
<tr>
<td>Merck</td>
<td></td>
<td>Active (Ph II)</td>
<td>Failed (Ph III)</td>
<td>Failed (Ph III)</td>
<td></td>
</tr>
<tr>
<td>AZ</td>
<td>Failed (Ph III)</td>
<td></td>
<td></td>
<td></td>
<td>Active (Ph III)</td>
</tr>
<tr>
<td>BMS</td>
<td>Active (Ph III)</td>
<td>Failed (Ph III)</td>
<td></td>
<td></td>
<td>Active (Ph III)</td>
</tr>
<tr>
<td>J&amp;J</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aventis</td>
<td>Failed (Ph II)</td>
<td></td>
<td>Failed (Ph II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[RPR]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td></td>
<td></td>
<td></td>
<td>Failed (Ph II)</td>
<td></td>
</tr>
<tr>
<td>Lilly</td>
<td></td>
<td>Active (Ph III)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche</td>
<td>Failed (Ph II &amp; III)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acomplia: Why the Buzz?

- Huge potential PCP market
- “One size fits all,” old-style blockbuster
- First one of this type since *Viagra* in 1997 (excluding withdrawals)
Blockbuster Party Time?
1. **Acomplia**: Why the Buzz?

2. **Beyond the Buzz: The Risks and Rewards of the Pharmacologic Treatment of Obesity**

3. Beyond **Acomplia**: The Obesity Pipeline
Obesity Drug Development: Framing the Risk

- Acceptance of adverse events in Pharma therapy

**Tolerance for Adverse Events**

- High
- Low

**Increasing Morbidity - Imminent Mortality**

- Metastatic Disease
- Neurodegenerative Disease
- Inflamm. Disease
- CVD
- ED
- OAB
- Pain
- Insomnia
- Obesity?
Redux: Framing the Risk

• Interneuron licensed exclusive rights to dexfenfluramine to treat abnormal carbohydrate craving and/or obesity in the United States from Servier in 1990.

• Servier marketed dexfenfluramine in 65 countries outside the United States and reported in 1996 that the drug had been taken by more than ten million individuals.

• In November 1992, Interneuron granted American Home Products exclusive rights to market dexfenfluramine in the United States in exchange for royalties on product sales and milestone-related cash payments and equity investments, while retaining co-promotion and certain manufacturing rights.

• In May 1993, Interneuron submitted a NDA to the FDA for dexfenfluramine for the treatment of obesity. The NDA included 19 double-blind, placebo-controlled clinical studies involving over 4,000 patients, conducted in the United States and several foreign countries by Interneuron and others.
Redux Result: Risk Trumps Reward!

Pharmaceutical Executive, The American Lawyer
(http://www.law.com/jsp/tal/PubArticleTAL.jsp?id=1109128224002); Evaluate Pharma

DH Insight Briefing – Obesity
February, 2005 – pg. 27
© Defined Health, 2006
Trial Lawyers Love Drugs for “Trivial” Conditions!

Tort Lawyer Roulette

Spin the wheel! If debilitating side effects and toxicities land on a drug, YOU COULD BE A BIG WINNER!
After the initial rebound from the “Fen-Phen” withdrawal, growth in total Obesity prescriptions is on a slow steady decline, further illustrating ongoing issues with marketed products.
The other reason for Xenical’s disappointing uptake is the high level of gastrointestinal (GI) side-effects.

"For healthy people who are trying to lose weight, even for cosmetic reasons, it didn't seem like there was much risk," Dr. Wood said, "except what I would call the underwear risk."
The Disease of Obesity: Framing the Risk

Reimbursement

In the case of Xenical we clearly saw that good data on cardiovascular co-morbidities alone is not sufficient to achieve wide reimbursement, even if certain language is reflected in the drug’s label. To secure reimbursement, we believe cardiovascular data needs to translate into strong, specific label claims beyond weight loss.

We have conducted an in-depth research project that involved discussion with key opinion leaders and industry sources, as well as a comprehensive review of the literature. We have concluded that based on the RIO data, an Acomplia label beyond weight loss (and smoking cessation) seems extremely unlikely, which most probably would prevent broad reimbursement.

---

**Figure 1. Potential Indications for Acomplia Beyond Weight Loss**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Our Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>? Metabolic Syndrome</td>
<td>- No precedent</td>
</tr>
<tr>
<td></td>
<td>- Multiple definitions of the syndrome, so diagnosis is unclear</td>
</tr>
<tr>
<td></td>
<td>- FDA position on a May 2004 workshop was not endorsing the concept</td>
</tr>
<tr>
<td>? Prevention of Diabetes</td>
<td>- No data for Acomplia</td>
</tr>
<tr>
<td></td>
<td>- Drugs with data (Xenical, Alliace, Metformin, e.c) did not get a prevention claim (so no precedence)</td>
</tr>
<tr>
<td></td>
<td>- Diagnosis of ‘at risk population’ is unclear</td>
</tr>
<tr>
<td>? Insulin Resistance</td>
<td>- Cannot be measured for diagnosis and therapy monitoring in a primary care setting</td>
</tr>
<tr>
<td>? Treatment of Diabetes</td>
<td>- Only one clinical trial – further work prior to filing in this indication will be required</td>
</tr>
</tbody>
</table>
Over the next five years, WW Obesity market is projected to grow to $2.3B, driven solely by CB-1 antagonist Acomplia.

*Other includes Phentermine (Novartis), Ionamin (UCB), sibutramine (Eisai KES514) and CB-1 antagonist SR 147778 (Sanofi-Aventis). EvaluatePharma; DH analysis.
Is OTC Xenical a bigger opportunity than Acomplia?

<table>
<thead>
<tr>
<th>Product</th>
<th>Range of Peak Year WW Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenical OTC^</td>
<td>$2-5 B!</td>
</tr>
<tr>
<td>Acomplia*</td>
<td>$0.4-0.9 B</td>
</tr>
</tbody>
</table>

^Based on prediction of 5-6 million US customers spending $16 to $33 per week  
*Obesity-only label

Bear Stearns (Acomplia), GSK Report to FDA Advisory Committee (Xenical)
Drug Treatment of Obesity: Elucidating the Reward

- Whom to treat?
- When to treat?
- How to treat?
- How do we measure success?

### Classification of Overweight and Obesity by BMI, Waist Circumference and Associated Disease Risk*

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Obesity Class</th>
<th>Disease Risk* Relative to Normal Weight and Waist Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>—</td>
</tr>
<tr>
<td>Normal†</td>
<td>18.5 – 24.9</td>
<td>—</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0 – 34.9</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>35.0 – 39.9</td>
<td>Very High</td>
</tr>
<tr>
<td>Extreme Obesity</td>
<td>≥40</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Disease risk for type 2 diabetes, hypertension, and CVD.
† Increased waist circumference can also be a marker for increased risk even in persons of normal weight.


DH Insight Briefing – Obesity
February, 2005 – pg. 35
© Defined Health, 2006
BMI may not tell the whole story

**EAT AND RUN** Why we’re so fat. by STEVEN SHAPIN

What counts as overweight? In the United States, as in other countries, the body mass index is the officially approved way of deciding whether or not you’re too heavy. Leith, who curiously makes no mention of the medical issues associated with obesity, never seems to have worked out his own B.M.I. Had he done so, the answer would have been 32. (To calculate your B.M.I., divide your weight in pounds by the square of your height in inches, and then multiply the result by 703.) The C.D.C. tells you that a B.M.I. over 30 means you’re “obese,” while values between 25 and 29.9 mean you’re “overweight.” Still, the B.M.I. net catches some surprising fish. At six-six and a playing weight of two hundred and sixteen pounds, Michael Jordan was “overweight” (with a B.M.I. of 25); and, on the Boston Red Sox, Manny Ramirez and David (Big Papi) Ortiz are “overweight” (27.1 and 28, respectively), while the pitcher David Wells is “obese” (31.2), though that won’t come as a shock to Red Sox Nation. (Yankees fans should not feel too smug: both Jaret Wright and Hideki Matsui, at 29.5, are a Fenway Frank short of obesity.) The B.M.I. doesn’t tell you the percentage of body fat you’re carrying or how your fat is distributed, and it hasn’t got much to do with how you feel or whether you’re repulsive to potential sex partners. What it’s meant to do is provide a rough-and-ready index of a population’s health risks.

*The New Yorker*
Drug Treatment of Obesity: Realizing the Reward

Acomplia

Obesity BMI >=30, <40

Morbid Obesity BMI >=40

Risk Factors

Type II Diabetes (IGT), Hypertension, Hyperlipidemia, CVD, etc.

Many Other Treatment Options

- Obesity
- Diabetes
- Dyslipidemia
- Hypertension

Higher BMI associated with hypertension and high total cholesterol

Midlife Body Mass Index and Hospitalization and Mortality in Older Age

Lijing L. Yan, PhD, MPH; Martha L. Daviglus, MD, PhD; Kiang Liu, PhD; Jeremiah Stamler, MD; Renwei Wang, MD, MS; Amber Pirzada, MD; Daniel B. Garside, BS; Alan R. Dyer, PhD; Linda Van Horn, PhD, RD; Youlian Liao, MD; James F. Fries, MD; Philip Greenland, MD

Mean follow-up was 32 years.

Participants were 17,643 men and women aged 31 through 64 years…

...as well as for those with 1 or more risk factors, those who are obese in middle age have a higher risk of hospitalization and mortality from CHD, cardiovascular disease, and diabetes in older age than those who are normal weight.
Acomplia’s Challenge: “The Virtuoso” vs. “The One Man Band”

vs.

© Defined Health, 2006
No “Virtuosos” Can Do This

The New York Obesity Research Center, St. Luke’s – Roosevelt Hospital Center
Acomplia vs. Competitive Products for Weight Loss and Beyond

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results</th>
<th>Compared to what</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (lbs.)</td>
<td>-15.2 (+/- 13.4)</td>
<td>-13.4 (Xenical)</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>-15.8% (+/- 38.0)</td>
<td>-50% (Tricor - fenofibrate)</td>
</tr>
<tr>
<td>HDL Cholesterol (%)</td>
<td>+23.4% (+/- 22.0)</td>
<td>+25% (Niaspan)</td>
</tr>
<tr>
<td>Fasting Insulin (uU/ml)</td>
<td>-1.7 (+/- 12.4)</td>
<td>-5.3 (Metformin)</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>-3.6 (+/- 22.0)</td>
<td>-6.2 (Lisinopril)</td>
</tr>
</tbody>
</table>

Lisinopril: J Clin Hypertens 2004 Sep;6(9):485-93
Xenical trial discontinuation rate was 8% vs. 13% for Acomplia. Discontinuation rate for drugs that treat obesity co-morbidities are generally much lower than for either weight-loss drug, despite the fact the patients receive a cosmetic benefit from the latter.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acomplia</td>
<td>7.7%</td>
<td>13.6%</td>
</tr>
<tr>
<td>Xenical</td>
<td>5.0%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Meridia</td>
<td>7.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Zocor</td>
<td>5.1%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Lipitor</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Lescol</td>
<td>-</td>
<td>3.9%</td>
</tr>
<tr>
<td>Actos</td>
<td>2.8%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Avandia</td>
<td>7.80%</td>
<td>8.20%</td>
</tr>
<tr>
<td>Zestri*</td>
<td>-</td>
<td>5.70%</td>
</tr>
<tr>
<td>Diovan</td>
<td>2.00%</td>
<td>2.30%</td>
</tr>
</tbody>
</table>

* In hypertension.
Source: Pooled RIO-LIPIDS, RIO-NA and RIO-EUROPE studies (Acomplia); FDA advisory committee meeting slides (Avandia); US prescribing information (all others).
However, the US market alone could reach $2.3 B, if a diabetes claim for Acomplia proves successful.

Bear Stearns; DH analysis
DH Insight Briefing – Obesity
February, 2005 – pg. 45

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Maximizing the Reward: The Statin Analog

Story of Statins is one of multiple pharma blockbusters

Statin Launches and Growth

EvaluatePharma; DH analysis

DH Insight Briefing – Obesity
February, 2005 – pg. 46
Maximizing the Reward: The Statin Analog

As compared to Dyslipidemia, diagnosis and treatment of Obesity faces more challenges

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Treatment</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>High</td>
<td>• New Class of Drugs</td>
<td>• Lab analysis (HDL / LDL)</td>
<td>• Efficacy clearly established</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unmet Need is clear</td>
<td></td>
<td>• We know LDL/HDL impact was quantified</td>
</tr>
<tr>
<td>Obesity</td>
<td>Very high</td>
<td>• New Class of Drugs</td>
<td>• Visible onset / BMI</td>
<td>• Widely reimbursed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unmet need is clear</td>
<td></td>
<td>• Chronic therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Efficacy debatable (minimal % weight loss)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Studies/data have shown contradictory results</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Significant reimbursement challenges</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Given these challenges, may be shorter-term therapy</td>
</tr>
</tbody>
</table>
Maximizing the Reward: The Statin Analog

*Lipitor leveraged clinical success of competitive compounds within the class*

- **1987:** Framingham on Cholesterol
- **1994:** West of Scotland (6595 pts): ACM -22%
- **1995:** 4S (4444 pts) ACM -30%

**Randomized Trial of Cholesterol Lowering in 4444 Patients with Coronary Heart Disease:** the Scandinavian Simvastatin Survival Study (4S)

**Landmark Study:** Pravastatin rapidly reduces risk of Heart Attacks and Saves Lives of People with High Cholesterol with no previous history of heart attacks

**EvaluatePharma**

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- Whom to treat?
- When to treat?
- How to treat?
- How do we measure success?
Determine lipoprotein levels—obtain complete lipoprotein profile after 9-12 hour fast.

Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent).

Determine presence of major risk factors (other than LDL).

If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk.

Consider adding drug therapy if LDL exceeds levels shown in Step 5 table.

Identify metabolic syndrome and treat, if present, after 3 months of therapeutic lifestyle changes (TLC).

Treat elevated triglycerides.

**National Cholesterol Education Program (NCEP) ATP III Guidelines “At-A-Glance.”**

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
<th>Step 6</th>
<th>Step 7</th>
<th>Step 8</th>
<th>Step 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine lipoprotein levels—obtain complete lipoprotein profile after 9-12 hour fast.</td>
<td>Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent).</td>
<td>Determine presence of major risk factors (other than LDL).</td>
<td>If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk.</td>
<td>Determine risk category.</td>
<td>Initiate therapeutic lifestyle changes (TLC) if LDL is above goal.</td>
<td>Consider adding drug therapy if LDL exceeds levels shown in Step 5 table.</td>
<td>Identify metabolic syndrome and treat, if present, after 3 months of therapeutic lifestyle changes (TLC).</td>
<td>Treat elevated triglycerides.</td>
</tr>
</tbody>
</table>

*NH, NHLBI
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A Guide to Selecting Treatment: NIH Guidelines*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BMI Category 25–26.9</th>
<th>BMI Category 27–29.9</th>
<th>BMI Category 30–34.9</th>
<th>BMI Category 35–39.9</th>
<th>BMI Category ≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, physical activity, behavior therapy</td>
<td>Yes with comorbidities</td>
<td>Yes with comorbidities</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>-</td>
<td>-</td>
<td>Yes with comorbidities</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Weight loss surgery</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes with comorbidities</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Yes alone indicates that the treatment is indicated regardless of the presence or absence of comorbidities. The solid arrow signifies the point at which therapy is initiated.

The New York Obesity Research Center, St. Luke’s – Roosevelt Hospital Center

*The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity In Adults. NIH/NHLBI/NAASO; October 2000. NIH publication No. 00-4084.*
Pharmacologic and Surgical Management of Obesity in Primary Care: A Clinical Practice Guideline from the American College of Physicians

Multiple failures needed before using drug therapy

Figure. Algorithm for managing obesity.

BMI = body mass index. *References 13–15. †U.S. Preventive Services Task Force recommendations (11, 12). ‡Assess side effects and efficacy; no data are available past 12 months except for orlistat.
Obesity Insight Series – Tonight’s Discussion Topics

1. **Acomplia**: Why the Buzz?
2. Beyond the Buzz: The Risks and Rewards of the Pharmacologic Treatment of Obesity

3. **Beyond Acomplia**:
   
   **The Obesity Pipeline**
Obesity pipeline is predominately early-stage, with increased focus on GPCRs.

IDdb; DH analysis

Obesity Pipeline / Overall

~80% Discovery-Stage

GPCRs (n=102)
All Others (n=100)
Research is looking beyond CB-1 to many other GPCR mechanisms for appetite suppression
Drugs in Development Target Two Primary Locations: Central & Peripheral
Central Targets

Hypothalamus

- **Bupropion** (GSK) Phase II
  - Catecholamine Re-uptake inhibitor

- **Apd 356** (Arena) Phase II
  - 5-HT2C agonist

- **Axokine** (Regeneron)
  - Discontinued
  - CNTF/gp130 agonist

- **Peptide YY3-36** (Nastech) Phase II
  - Peptide Y agonist

- **AC 162352** (Amylin)
  - Phase I
  - Peptide Y Agonist

- **S2367** (Shionogi) Phase I
  - Neuropeptide Y antagonist

- **Urocortin 2** (Neurocrine Biosciences) Phase II
  - GNRH receptor antagonist

- **AMG 076** (Amgen) Phase I
  - Melanocortin receptor antagonist

- **MCHR program** (GSK) Phase I
  - Melanocortin receptor antagonist

- **SR 147778** (Sanofi) Phase II
  - CB receptor antagonist

- **SLV 319** (Solvay/BMS) Phase I
  - CB receptor antagonist

- **AVE 1625** (Sanofi) Phase I
  - CB receptor antagonist

- **CP 945598** (Pfizer) Phase I
  - CB receptor antagonist

- **Para Ventricular Hypothalamus/VentroMedial Hypothalamus**

  - **AgRP-NPY**
  - **POMC/CART**
  - **BDNF**
  - **MC4R**

- **Higher CNS Regions**

  - **Axokine** (Regeneron)

  - **Peptide YY3-36** (Nastech) Phase II

  - **Peptide Y agonist**

- **Lateral Hypothalamus**

  - **Ghrelin Vaccine (Cytos)** Phase I
    - Ab depletion of ghrelin

- **Orexin**

  - **MCH**

- **Higher CNS Regions**

  - **S2367** (Shionogi) Phase I

  - **Neuropeptide Y antagonist**


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Peripheral Targets

- **Advanced Obesity Drug 9604** (Metabolic Pharmaceuticals) Phase II
  Growth hormone fragment

- **N 5984** (Kyorin Pharmaceuticals) Phase II
  $B_3$ Adrenoreceptor agonist

- **Obesity Candidate** (Merck) Phase II
  $B_3$ Adrenoreceptor agonist

- **HMR 1426** (Sanofi) Phase II
  Reduces gastric emptying - unknown mechanism

- **PTP inhibitors** (Serono) Phase I
  Increase insulin sensitivity

- **Cetilistat** (Alizyme) Phase II
  Blocks intestinal lipase

- **GT 389255** (Peptimmune/Genzyme) Phase I
  Blocks intestinal lipase

ADIS R&D Insight; DH analysis

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Focus on GPCRs Coupled With Learning From Previous Difficulties Creates an Agent With Potential

- Arena’s serotonin mimetic discriminates among the various serotonin receptors (unlike previous agents, e.g. dexfenfluramine from Wyeth), showing 100 fold preference for 5H₂c over 5HT₂b and 15 fold preference over 5HT₂a. It is believed that activation of the 5HT₂b receptor is an important contributor to the valvular defects seen with earlier compounds, while activation of 5HT₂a is associated with broad central nervous system effects.

- **APD 356 is effective**: results from a recently released phase IIb study demonstrate dose-dependent weight loss, with 8 lbs shed in 3 months at the highest dose (10 mg- twice a day). This was a relatively large study: 3 doses of APD356 were investigated in close to 500 individuals.

- Absence of structural abnormalities in the heart after acute treatment has been reported (one month exposure, echochardiograms at 90 days). The drug appeared to be well-tolerated from a psychiatric standpoint.

- This study did not include any diet or exercise regimen, raising the possibility that larger benefits may be achieved with incorporation of these measures.
Investors Are Betting Big on a Potentially Safer Redux

**Arena raises $164.8 million** in a bumped-up follow-on through the sale of 9.8 million shares at $16.90. The company proposed to sell 8.5 million shares last week, when its stock price was $15.74.

ARNA's APD356 has completed a Phase IIb trial to treat obesity. The serotonin (5-HT$_{2C}$) receptor agonist is expected to enter Phase III testing this year. On Friday, ARNA was up $0.36 to $17.33.

*BioCentury Today 1/27/06*
Metabolic Pharmaceuticals: AOD 9604 Utilizes a Distinct Mechanism

• AOD 9604 is an orally active fragment of human growth hormone. Since growth hormone receptors are found on a wide range of cell types, the precise mechanism of how it reduces weight is unclear. However, it is known that growth hormone can stimulate fat cell metabolism, so AOD 9604 is likely to work at peripheral sites to reduce fat cell mass. Consistent with this idea, it activates fat cells directly *in vitro*.

• Significantly, this fragment of growth hormone does not appear to induce systemic side effects, such as non-specific growth or alterations in insulin sensitivity. The drug is well-tolerated, though long term studies have yet to be performed.

• Despite being a polypeptide, it is orally active in all animals examined.

• In a Phase II study of 300 patients, AOD 9604 produced a 6 lb. weight loss in three months. Interestingly, the greatest weight loss was observed with the smallest dose (1 mg.), suggesting a complicated dose-response relationship.
Alizyme Concentrates on Gastrointestinal Physiology: Cetilistat is Their Lead Candidate for Obese Diabetics

- Cetilistat inhibits intestinal lipases and thus reduces fat absorption in the same manner as *Xenical*.
- Cetilistat is similar in potency at reducing weight to Xenical but appears to reduce the intensity of unpleasant side effects. A press release states that the prevalence of adverse gastrointestinal events “was up to 90% lower, compared to that reported for other drugs of this class.” In addition, this phase II trial (over 600 patients) reported a minor reduction in the number of patients discontinuing treatment due to side effects for *Cetilstat* (12%) vs. *Xenical* (18%).
- Similar to other agents in this class, cetilistat reduced HbA1c levels and improved cholesterol levels.

*Adis R&D Insight, IDdb, www.alizyme.com*
Nastech’s Peptide Y Agent Recently Began Phase II

- Nastech partnered with Merck to develop nasally delivered Peptide Y3-36 in 2004. This neurohormone is produced in the gut following meals and signals satiety.
- Acute administration has demonstrated that Peptide Y3-36 is generally well-tolerated. Side effects observed included nausea, headache and dizziness but frequency decreased as the trial progressed.
- The half-life of Peptide Y3-36 is brief: $T_{1/2} = 1$ hour. This feature will likely make the timing of administration an important determinant of effectiveness.
- Preliminary studies have examined Peptide Y3-36 in a short term setting. Reports of appetite and food intake were reduced one day after a post lunchtime administration. The most effective dose of Peptide Y3-36 reduced caloric consumption by 15% (mean) in 12 overweight patients. A second phase I trial achieved 1.3 lb reduction in six days in 15 obese patients.

Adis R&D Insight, IDdb, www.nastech.com
In the U.S., growth in bariatric procedures, such as gastric bypass and gastric banding, has spiked over the past five years, to an estimated 0.17 million in 2005. However, this represents only 2% of an eligible patient population. As less-invasive procedures advance, the surgical alternative to drug therapy may become more attractive.

**US Trend in Bariatric Surgery to Treat Obesity**

GES / VSM: Gastric Electrical Stimulation / Vagal Smart Modulation

JP Morgan Chase; DH analysis

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Buzz Kill – Reality Check

• Even with a significant pipeline investment, and promising mechanisms, there are a number of factors that confound assessment of the true market potential for new anti-Obesity drugs, including:
  – Physicians’ and patients’ lingering concerns with anti-Obesity drug safety after the withdrawal of Wyeth’s *Redux* implicated in the “Fen-Phen” debacle.
  – Stigma around currently marketed products that are burdened by safety issues and unseemly side effects.
  – Reimbursement challenges associated with Managed Care’s perception that anti-Obesity agents are largely lifestyle drugs.
    • Tendency to only reimburse morbidly obese patients or obese patients with significant co-morbidities or high rate of complications.
  – Based on clinical study data, relatively modest weight loss that can actually be achieved, and diminishing rates of weight loss over time.
  – Poor physician acceptance and patient compliance.
  – Absence of well-vetted and established treatment guidelines for obesity.
Bon Appetit!
SAVE THE DATE APRIL 24-26, 2006 THE RITZ-CARLTON, BOSTON

THE THERAPEUTIC INSIGHT 2006

THE GLOBAL THERAPEUTIC GROWTH STRATEGIES CONFERENCE
"...one of the three must attend annual industry meetings for senior executives."