### 10 Highly Innovative Compounds in Attractive Market Segments

<table>
<thead>
<tr>
<th>Compound</th>
<th>Phase</th>
<th>First in class</th>
<th>Gold standard potential</th>
<th>Large market potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid (osteoporosis)</td>
<td>III</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>AAE581 (osteoporosis)</td>
<td>II</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>PTK787 (cancer)</td>
<td>III</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ICL670 (iron overload)</td>
<td>III</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FTY720 (transplantation)</td>
<td>III</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>LDT600 (hepatitis B)</td>
<td>III</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>LAF237 (type 2 diabetes)</td>
<td>II</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>SPP100 (hypertension)</td>
<td>II</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>TCH346 (neurodegeneration)</td>
<td>II</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>QAB149 (asthma, COPD)</td>
<td>II</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

1. First oral VEGF inhibitor  
2. Chronic Obstructive Pulmonary Disease  

*GP product*  
*Specialty product*

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### Diabetes Prevalence Is Increasing Rapidly

**People with diabetes (m)**

- The prevalence of diabetes is increasing rapidly due to:
  - Aging populations
  - Unhealthy diets
  - Obesity
  - Sedentary lifestyles
- More aggressive treatment guidelines
- Few recent innovations in anti-diabetic therapies
- Recently introduced drugs have potential tolerability concerns

![](chart.png)

Source: Data Monitor 2002, International Diabetes Federation
A Significant Proportion of Diabetes Patients Are not Diagnosed or Treated

Patients (m)

- Estimated prevalence
- Diagnosed patients
- Treated patients

Source: Datamonitor, IMS, published data

New Drug Classes Will Contribute to the Type II Diabetes Market Growth

Global 2004 sales\(^1\) USD 11.3 bn

- PPAR-g: 31%
- Biguanides: 29%
- Sulfonylureas: 14%
- Injectable insulin: 11%
- AG inhibitors: 5%
- meglitinides: 7%
- Fixed combinations: 8%
- DPP4 inhibitors: 5%
- GLP-1 therapies: 23%
- PPAR dual: 6%

Global 2009 sales\(^1\) USD 18.2 bn

- PPAR-g: 23%
- Biguanides: 8%
- Sulfonylureas: 5%
- Injectable insulin: 9%
- AG inhibitors: 22%
- meglitinides: 7%
- Fixed combinations: 5%
- DPP4 inhibitors: 3%
- GLP-1 therapies: 23%
- PPAR dual: 10%
- Inhaled insulins: 8%

\(^1\) Internal forecast, top 7 countries

Peroxisome proliferator activated receptor (PPAR), α-glucoosidase (AG), Dipeptidyl peptidase (DPP), Glucagon-like peptide (GLP)
Current Treatments for Type 2 Diabetes Have Limitations

Despite limitations, recently introduced drugs have taken 20% of market segment share

<table>
<thead>
<tr>
<th></th>
<th>Sulfonylureas</th>
<th>Insulin</th>
<th>Metformin</th>
<th>Acarbose</th>
<th>Thiazolidinediones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GI side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need LFT monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricted populations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor responder rate</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Current Therapies for Diabetes Do Not Address All Deranged Pathways

[Diagram showing glucose metabolism and drug actions]
GLP-1 Offers New Mechanism with Potential Multiple Effects

Intestine:
- Slows gastric emptying
- Promotes satiety

Liver:
- Inhibits glucagon secretion and hepatic glucose production

Pancreas:
- Augments glucose-induced insulin secretion
- Increases insulin biosynthesis
- Promotes beta-cell differentiation

Adipose tissue and muscle:
- Improves glucose uptake

Glucose influx
- Hyperglycemia
- Insulin secretion
- Peripheral glucose uptake

Stimulation of intestinal production of GLP-1
- Short half-life limits this approach

Administration of exogenous GLP-1
- Must be given in injectable, nasal or buccal formulations
- Short half-life limits the approach

Receptor agonists of GLP-1
- Injectable formulation
- High level of nausea

Alternative Approaches to GLP-1-Based Therapies Have Limitations
LAF237 Augments GLP-1 Levels by Inhibiting DPP4 Activity

Mixed meal
Intestinal GLP-1 release

GLP-1 Active

DPP4

GLP-1 Inactive

Rapid inactivation (>80% of pool)

Excreted by kidneys

Intestinal GLP-1 release

GLP-1 actions

Source: Deacon et al. Diabetes 1995;44:1126

Phase I Study Demonstrates Increase in Active GLP-1 with LAF237

Active GLP-1 (pmol)

Dose
Meal

Day -1
Day 10

hours

Source: Deacon et al. Diabetes 1995;44:1126
In Phase IIA Study in Diabetic Patients LAF237 Elevates Active GLP-1 After Meals

Change in GLP-1 from baseline (hr x pmol/L)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>n=19</td>
<td></td>
</tr>
<tr>
<td>LAF237 100 mg</td>
<td>n=20</td>
<td></td>
</tr>
<tr>
<td>LAF237 200 mg</td>
<td>n=20</td>
<td></td>
</tr>
</tbody>
</table>

\(^* *\) *p < 0.001 vs placebo
\(^1\) Area under the curve calculated over 4 hours after the meal

LAF237 – Comprehensive Phase IIb Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Doses</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2203</td>
<td>12-week dose finding</td>
<td>Placebo 25 mg bid, 25, 50, 100 mg od(^1)</td>
<td>Drug-naïve patients HbA1c(^2): 6.8-10%</td>
</tr>
<tr>
<td>2204</td>
<td>12-week add-on to metformin</td>
<td>Metformin + placebo or + 50 or 100 mg od</td>
<td>Non-responders to metformin HbA1c: 7-9%</td>
</tr>
<tr>
<td>2205</td>
<td>12-week ‘wide baseline’ study</td>
<td>Placebo 25 mg bid(^3)</td>
<td>Drug-naïve patients HbA1c: 6.8-11%</td>
</tr>
</tbody>
</table>

\(^1\) Once daily
\(^2\) Glycosylated Hemoglobin A
\(^3\) Twice daily
LAF237 Leads to Dose-Dependent Reductions in HbA1c\(^1\) in Mild Diabetics

Change in HbA1c (%) from mean baseline of 7.7% at 12 weeks

\[
\begin{array}{cccccc}
\text{Placebo} & 25 \text{ mg od} & 25 \text{ mg bid} & 50 \text{ mg od} & 100 \text{ mg od} \\
\text{n=44} & \text{n=38} & \text{n=38} & \text{n=40} & \text{n=46} \\
-0.20 & -0.30 & -0.46 & -0.56 & -0.68 \\
p < 0.05 & p < 0.05 & & & \\
\end{array}
\]

\(^1\) Glycosylated Haemoglobin A

Source: Study 2203 per protocol analyses

HbA1c Reductions Are Greater in Patients with a Higher Baseline

Change in HbA1c (%)

\[
\begin{array}{ccc}
\text{HbA1c subgroup} & 7\% - 8.5\% & 8\% - 9.5\% \\
\text{Mean baseline A1c} & 7.5\% & 8.5\% \\
\text{n=9} & \text{n=35} & \text{n=11} & \text{n=24} \\
-0.7\% & -0.7\% & -1.2\% \text{ Placebo subtracted} \\
\end{array}
\]

Source: Study 2205

Source: Study 2203 per protocol analyses
LAF237 Lowers HbA1c When Added to Maximally Tolerated Doses of Metformin

Change in HbA1c (%) from mean baseline of 7.8% at 12 weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>50 mg OD</th>
<th>100 mg OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>50</td>
<td>53</td>
<td>12</td>
</tr>
<tr>
<td>Change in HbA1c (%)</td>
<td>0.09</td>
<td>-0.56</td>
<td>-0.82</td>
</tr>
</tbody>
</table>

p < 0.05

Source: Study 2204

LAF237 Monotherapy Suggested to Be As Effective¹ As Exenatide in Combination with Metformin

HbA1c (%)

- 12 weeks LAF monotherapy: 8.5 (-1.0%)
- 26 weeks combination:
  - Baseline: 8.2
  - Post-treatment: 7.3 (-0.9%)

¹ Not head-to-head studies
Source: Novartis Study 2205, Amylin/Lilly Press Release 6 Aug 03
**LAF237**  
**Phase II Data Reveal a Very Competitive Profile**

- Once-daily dosing providing 24-hour effect on HbA1c
- Good safety and tolerability profile
  - No increase in nausea or vomiting
  - Low incidence of symptoms of hypoglycemia
  - No changes in liver enzymes
  - No increased creatinine phosphokinase (CPK)
  - No significant change in body weight
  - No edema

**LAF237 Phase III program**

- Phase III to start in Q1 2004
  - Aggressive program to support monotherapy and combination therapy indication
  - Robust program to evaluate mechanisms of action of LAF237 and improvement in beta cell function
  - Long-term durability trial
  - Wide range of HbA1c population
  - Evaluating insulin combination and looking at further reductions in HbA1c as well as reduction in insulin dose
  - Doses up to 100 mg once daily
- First results due by Q3 2005
- Submission planned for 2006