# 10 Highly Innovative Compounds in Attractive Market Segments

| | Phase | First in class | Gold standard potential | Large market potential |
|---|---|---|---|---|
| Zoledronic acid (osteoporosis) | III | | ✓ | ✓ |
| AAE581 (osteoporosis) | II | ✓ | | ✓ |
| PTK787 (cancer) | III | ✓[1] | | |
| ICL670 (iron overload) | III | ✓ | ✓ | |
| FTY720 (transplantation) | III | ✓ | ✓ | ✓ |
| LB[illegible]0 (hepatitis B) | III | | ✓ | |
| LAF237 (type 2 diabetes) | II | ✓ | ✓ | ✓ |
| SPP100 (hypertension) | II | ✓ | | ✓ |
| TCH346 (neurodegeneration) | II | ✓ | | ✓ |
| QAB149 (asthma, COPD[2]) | II | | ✓ | ✓ |

[1] First oral VEGF inhibitor
[2] Chronic Obstructive Pulmonary Disease

GP product | Specialty product



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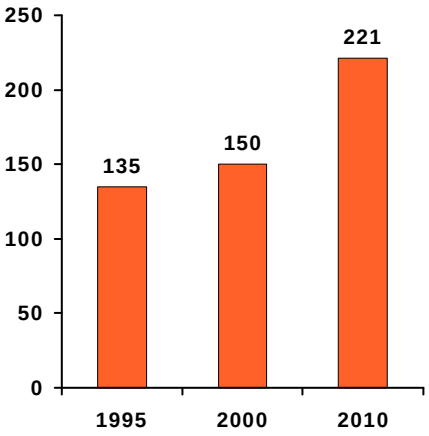
# Diabetes Prevalence Is Increasing Rapidly

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

Source: Data Monitor 2002, International Diabetes Federation



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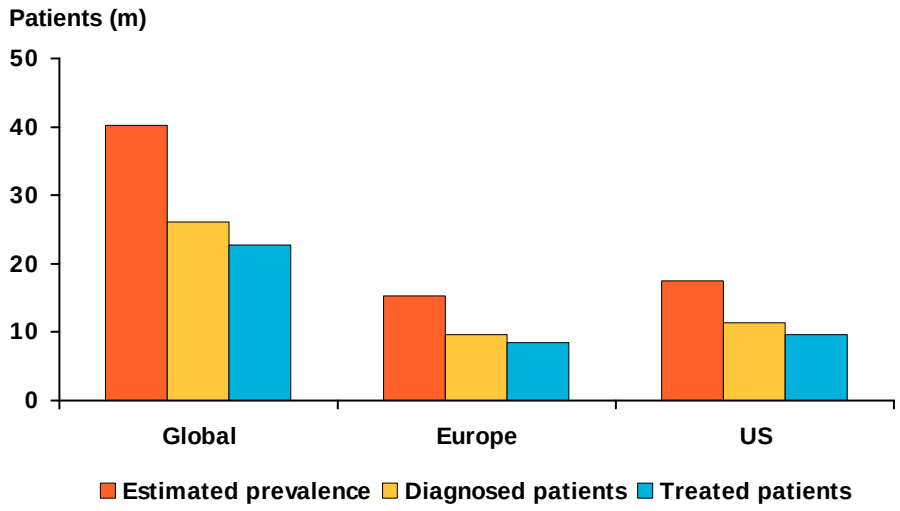
## A Significant Proportion of Diabetes Patients Are not Diagnosed or Treated




Source: Datamonitor, IMS, published data



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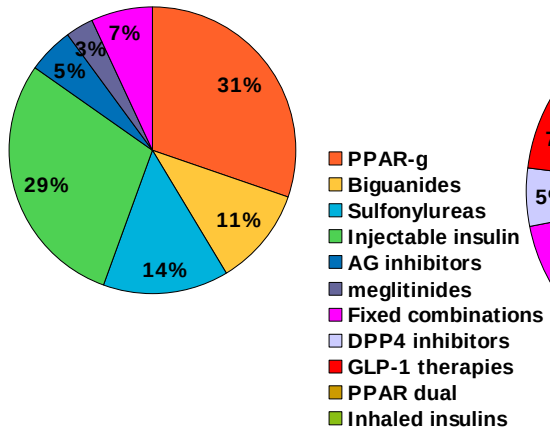
## New Drug Classes Will Contribute to the Type II Diabetes Market Growth

Global 2004 sales[1] USD 11.3 bn

Global 2009 sales[1] USD 18.2 bn




[1] Internal forecast, top 7 countries

Peroxizome proliferator activated receptor (PPAR), α-glucoosidase (AG), Dipeptidyl peptidase (DPP), Glucagon-like peptide (GLP)



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## Current Treatments for Type 2 Diabetes Have Limitations

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

| | Sulfonyl-ureas | Insulin | Metformin | Acarbose | Thiazolidi-nediones |
|---|---|---|---|---|---|
| Hypoglycemia | ■ | ■ | | | |
| GI side effects | | | ■ | ■ | |
| Lactic acidosis | | | ■ | | |
| Weight gain | ■ | ■ | | | ■ |
| Edema | | | | | ■ |
| Need LFT monitoring | | | | | ■ |
| Restricted populations | | | ■ | | ■ |
| Poor responder rate | | | | | ■ |



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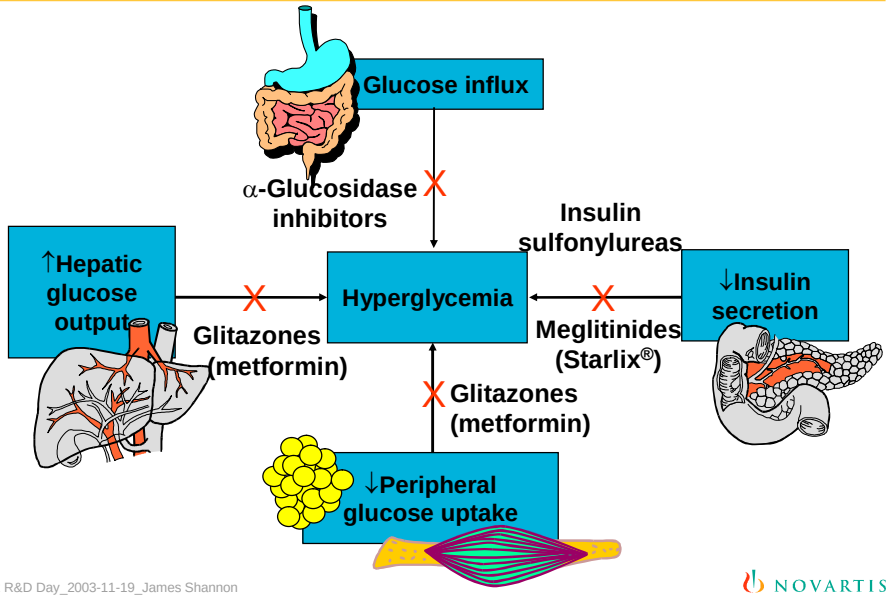
## Current Therapies for Diabetes Do Not Address All Deranged Pathways



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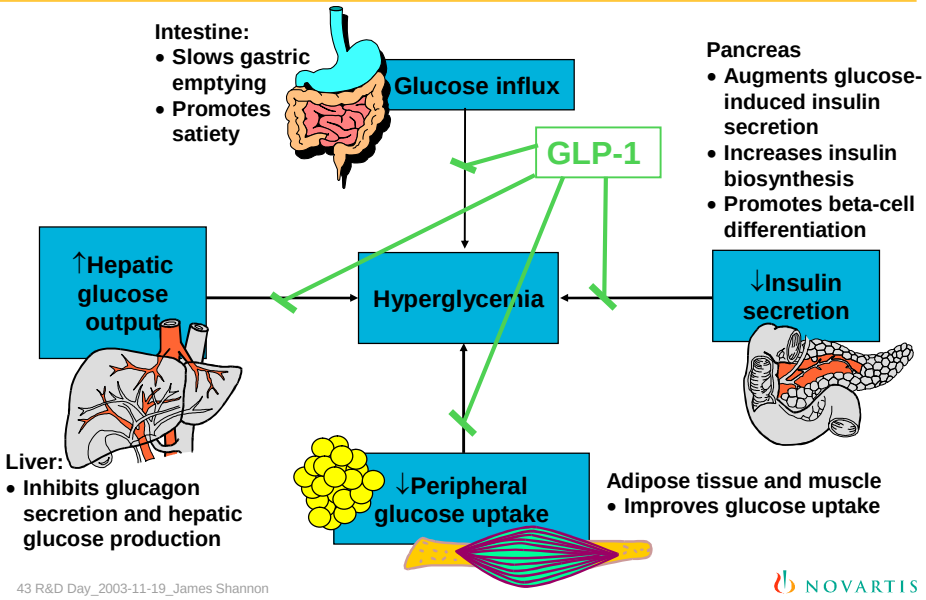
## GLP-1 Offers New Mechanism with Potential Multiple Effects



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## Alternative Approaches to GLP-1-Based Therapies Have Limitations

- 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



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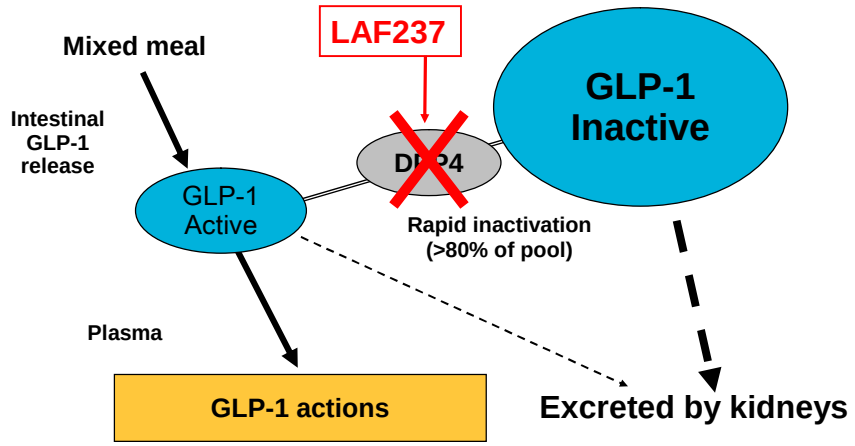
## LAF237 Augments GLP-1 Levels by Inhibiting DPP4 Activity




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



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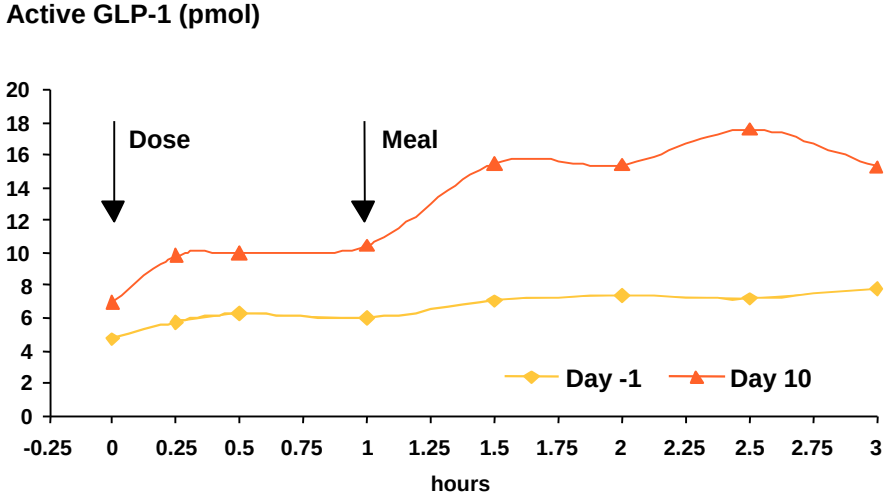
## Phase I Study Demonstrates Increase in Active GLP-1 with LAF237



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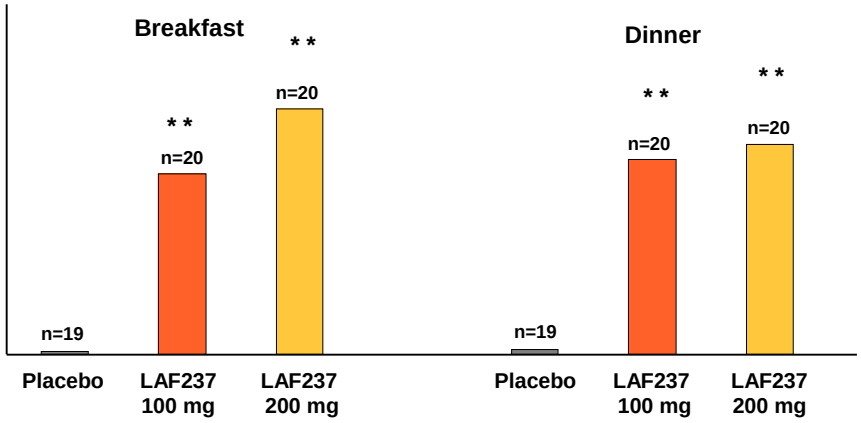
## In Phase IIA Study in Diabetic Patients LAF237 Elevates Active GLP-1 After Meals

**Change in GLP-1 from baseline**
**(hr x pmol/L)[1]**




* * p < 0.001 vs placebo
[1] Area under the curve calculated over 4 hours after the meal



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## LAF237 – Comprehensive Phase IIb Program

| Study | Description | Doses | Inclusion criteria |
|---|---|---|---|
| 2203 | 12-week dose finding | Placebo<br>25 mg bid, 25, 50, 100 mg od[1] | Drug-naïve patients<br>HbA1c[2]: 6.8-10% |
| 2204 | 12-week add-on to metformin | Metformin<br>+ placebo or<br>+ 50 or 100 mg od | Non-responders to metformin<br>HbA1c: 7-9% |
| 2205 | 12-week 'wide baseline' study | Placebo<br>25 mg bid[3] | Drug-naïve patients<br>HbA1c: 6.8-11% |

[1] Once daily
[2] Glycosylated Hemoglobin A
[3] Twice daily



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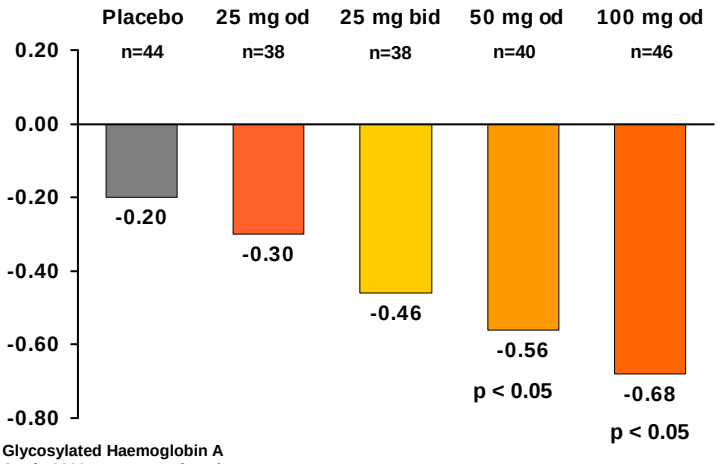
## LAF237 Leads to Dose-Dependent Reductions in HbA1c[1] in Mild Diabetics

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




[1] Glycosylated Haemoglobin A
Source: Study 2203 per protocol analyses



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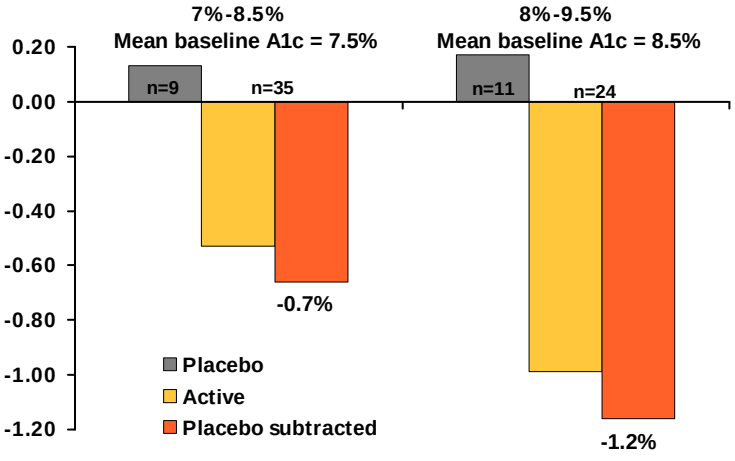
## HbA1c Reductions Are Greater in Patients with a Higher Baseline

**Change in HbA1c (%)** **HbA1c subgroup**




Source: Study 2205



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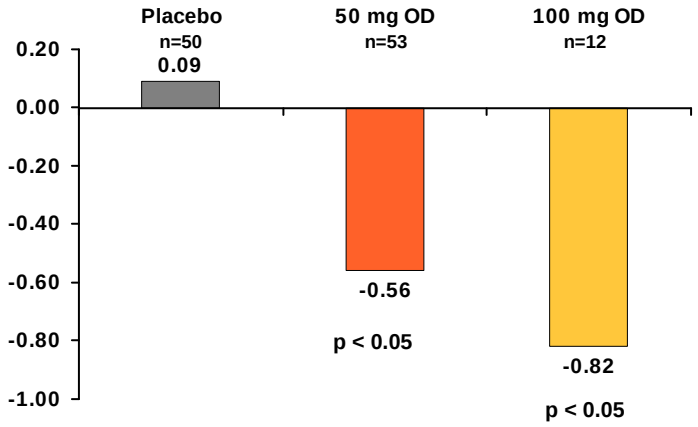
## LAF237 Lowers HbA1c When Added to Maximally Tolerated Doses of Metformin

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




Source: Study 2204



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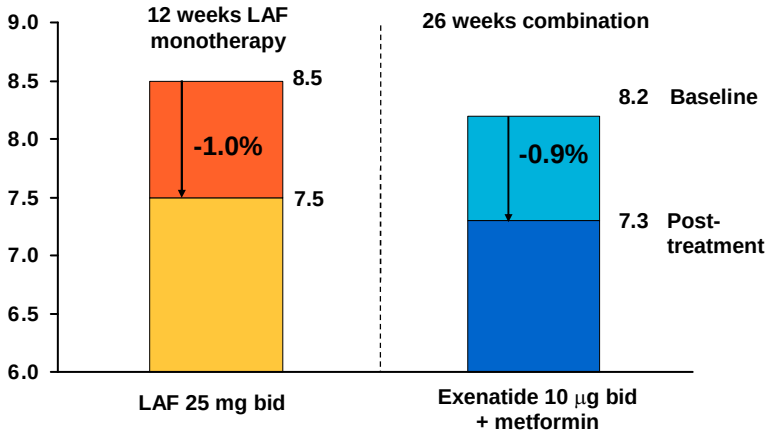
## LAF237 Monotherapy Suggested to Be As Effective[1] As Exenatide in Combination with Metformin

**HbA1c (%)**




[1] Not head-to-head studies

Source: Novartis Study 2205, Amylin/Lilly Press Release 6 Aug 03



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## LAF237
## Phase II Data Reveal a Very Competitive Profile

- Once-daily dosing providing 24-hour effect on HbA1c
- Good safety and tolerabilty 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



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## 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



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