New Therapies for Diabetes: Getting to the Heart of the Matter

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The contents of this presentation are not meant to be comprehensive, but to encourage a spirited dialogue. Feedback, comments and corrections are welcome.
Massive Epidemiology: Global prevalence of diabetes currently at 250M & expected to reach over 400M by 2030

IDF Regions and global projections for the number of people with diabetes (20-79 years), 2010-2030
Number of cases in US alone forecasted to double from 24M in 2009 to 44M in 2034

Projected distribution of newly diagnosed, undiagnosed and established cases of diabetes 2009 to 2034

Spending on diabetes and related complications projected to triple in the same period

Note: This model does not account for utilization of novel branded anti-diabetic agents in future. Expressed in 2007 dollars.

Current SOC for Type 2 Diabetes

Key Issues

♦ The standard of care for treatment of diabetes in the US has not changed meaningfully in over 15 years.
  • Entrenched first- and second-line add-on options are generic and inexpensive.
  • But there is still significant unmet need in glycemic control.
♦ Several branded drug classes have failed to gain sustained acceptance due to a variety of issues (tolerability, dosing, safety).
  • Newest classes of drugs approved, the incretin based therapies, made significant inroads into the 2nd and 3rd add-on positions. However, these drugs are yet to take a majority share in the market.
Several classes of anti-diabetics marketed, yet >60% of patients still have poor glycemic control

♦ Current drugs were approved based on their HbA1C reducing efficacy.
♦ But even with 7 different therapy classes and insulin analogs used in various combinations, **the majority of diabetics exhibit progressive worsening of glycemic control** (and end up with daily insulin).
♦ Diabetics continue to have significantly higher mortality, CV morbidity and microvascular complications as a consequence.

Schematic representation of current T2DM treatment paradigm

*OAD- oral anti-diabetic

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Diabetes Insight Briefing
Metformin is gold standard first-line therapy for T2DM due to robust HbA1c reduction without worsening other metabolic risk factors

- Metformin introduced in the US in 1994 and changed the SoC from solely insulin providing to increasing insulin sensitivity.
- First-line SoC hasn’t changed since then due to lack of compelling evidence that any other agent could do better.
No other anti-diabetic agent has come close to replacing metformin as first-line option

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Key Advantages</th>
<th>Key Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>• Extensive experience, low cost and high potency.</td>
<td>• Upper and/or lower GI side-effects in 10-15% of pts</td>
</tr>
<tr>
<td></td>
<td>• Relatively benign, no hypoglycemia as monotherapy, weight neutral,</td>
<td>• Contraindicated in patients with renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>favorable on lipids.</td>
<td>• Rare risk of lactic acidosis</td>
</tr>
<tr>
<td>Secretagogues</td>
<td>• Extensive experience, low cost and high potency.</td>
<td></td>
</tr>
<tr>
<td>SFUs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretagogues</td>
<td>• Rapid reduction of post-prandial hyperglycemia and potentially less</td>
<td>• Modest potency &amp; higher cost compared to SFUs</td>
</tr>
<tr>
<td>Glinides</td>
<td>risk of hypoglycemia.</td>
<td>• Risk of hypoglycemia still higher than other OADs</td>
</tr>
<tr>
<td>TZDs</td>
<td>• High potency and no hypoglycemia as monotherapy.</td>
<td>• Weight gain and edema</td>
</tr>
<tr>
<td></td>
<td>• Reduction in triglycerides (Actos) and increase in HDL</td>
<td>• Increased risk of congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>• Benefits demonstrated in large post-marketing studies</td>
<td>• Increased risk of fractures in women</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>• 2-4% weight loss</td>
<td>• SC injection</td>
</tr>
<tr>
<td></td>
<td>• Lack of severe hypoglycemia in combination with metformin</td>
<td>• Nausea in significant number of patients</td>
</tr>
<tr>
<td></td>
<td>• Potential for beta cell preservation</td>
<td>• Potential safety concerns such as risk of pancreatitis and cancer</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>• Once a day oral and well tolerated</td>
<td>• Modest efficacy</td>
</tr>
<tr>
<td></td>
<td>• Weight neutral and no risk of hypoglycemia</td>
<td></td>
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<tr>
<td></td>
<td>• Potential for beta cell preservation</td>
<td></td>
</tr>
<tr>
<td>ɑ-glucosidase</td>
<td>• No risk of hypoglycemia</td>
<td>• Modest efficacy</td>
</tr>
<tr>
<td>inhibitors</td>
<td>• Weight neutral</td>
<td>• Potentially severe GI tolerability issues (bloating, diarrhea and cramps)</td>
</tr>
</tbody>
</table>
Metformin – entrenched, effective and CHEAP!

♦ Even before going off-patent, *Glucophage* daily cost was $2 or less per day, cost now less than 50¢.

♦ If *Glucophage* were to be launched today at the price of Januvia, current US scripts of metformin alone would translate into a $12.6B market!
SFUs: No longer entrenched but also cheap

- SFUs now off patent, and were cheap by today’s standards of chronic daily branded therapy.
- Although SFU market share is declining due to increased awareness of hypoglycemia as a negative factor in long-term outcomes, SFUs still hold significant market share as second-line treatment option.
Need for improved glycemic controllers is clear

- Weight gain and risk of hypoglycemia are common side-effects of older diabetes drugs and more recently the CV risk associated with TZDs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>HbA1c Reduction (percentage points)</th>
<th>LDL Cholesterol Change (mg/dL)</th>
<th>HDL Cholesterol Change (mg/dL)</th>
<th>Triglyceride Change (mg/dL)</th>
<th>Risk of Hypoglycemia (% of people)</th>
<th>Weight Change (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>▼ 1.3-1.8</td>
<td>♦</td>
<td>♦</td>
<td>▼ 10-20</td>
<td>10-22%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Glipizide</td>
<td>▼ 1.3-1.8</td>
<td>♦</td>
<td>♦</td>
<td>▼ 10-20</td>
<td>10-15%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>▼ 1.3-1.8</td>
<td>♦</td>
<td>♦</td>
<td>▼ 10-20</td>
<td>9-14%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Melformin</td>
<td>▼ 0.9-1.4</td>
<td>▲ 5-7</td>
<td>♦</td>
<td>▼ 15-25</td>
<td>0-7%</td>
<td>♦</td>
</tr>
<tr>
<td>Pioglitazone (Actos)</td>
<td>▼ 0.8-1.2</td>
<td>▲ 8-12</td>
<td>▲ 5</td>
<td>▼ 35-45</td>
<td>0-3%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>▼ 0.9-1.4</td>
<td>▲ 12-15</td>
<td>▲ 3</td>
<td>▼ 10-20</td>
<td>4-11%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Repaglinide (Prandin)</td>
<td>▼ 0.8-2.0</td>
<td>♦</td>
<td>♦</td>
<td>▼ 10-15</td>
<td>11-32%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Nateglinide (Starlix)</td>
<td>▼ 0.3-0.8</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>13%</td>
<td>IE</td>
</tr>
<tr>
<td>Acarbose (Precose)</td>
<td>▼ 0.6-0.9</td>
<td>♦</td>
<td>♦</td>
<td>▼ 10-15</td>
<td>0-5%</td>
<td>♦</td>
</tr>
<tr>
<td>Miglitol (Glyset)</td>
<td>▼ 0.4-0.9</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
</tr>
<tr>
<td>Sitagliptin (Januvia)</td>
<td>▼ 0.6-0.8</td>
<td>♦</td>
<td>♦</td>
<td>♦</td>
<td>Low</td>
<td>♦</td>
</tr>
</tbody>
</table>

Definitions: mg/dL = milligrams per deciliter of blood; HbA1c = hemoglobin A1c; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol. *Selected drugs and measures. For the complete table, see the full diabetes report at www.ConsumerReportsHealth.org/BestBuyDrugs.
New incretin-based agents have had success taking share from TZDs & SFUs

- Safety concerns with SFUs (hypoglycemia, weight gain) and Avandia (CV) have borne well for the newer drugs like Januvia (DPP-IV inhibitor) and Byetta (GLP-1 analog).

- DPP-IV inhibitors are weight neutral and do not cause hypoglycemia.
- GLP-1s have the added benefit of weight loss.

Growth of GLP-1s and DPP-IV inhibitors is coming at the expense of SFU’s and TZD’s; SFU and TZD use is expected to decline, based on concerns about hypoglycemia (SFU's) and weight gain (and other TZD side effects such as heart failure and fracture risk).
Key Issues:

♦ There is agreement that new diabetes treatments are needed and there is still significant unmet need.

• Good news is that a new wave of innovation has produced attractive new classes of glycemic controllers, which are likely to be safe, convenient and not marred by weight gain (and some even promise weight loss).

♦ But, introduction of new branded agents will come with a huge increase in per patient drug costs in the context of massive increases in disease prevalence -- a treatment cost implosion.

• In addition to cost, polypharmacy concerns means some classes of drugs will need to replace others.
Significant therapeutic class innovation anticipated this decade

2 years
- GLP-1 analogs
- DPP-IV inhibitors
- SGLT2 inhibitors
- IL-1 antagonist
- 11 β HSD1 inhibitors

5 – 7 years
- Selective PPAR Agonists
- DGAT1 inhibitor
- RAGE antagonist
- GPR 119 agonists
- GPR40 agonist

7-10 years
- Glucokinase Stimulants
- Other peptide hormone MOAs
- NPY-Y2 agonist
- FGF-21 agonist
- Peptides Islet Neogenesis
- AMPK stimulants
- Glycogen Phosphorylase inhibitor
- HSD1 inhibitors
Key issue for pipeline classes: where will they fit in diabetes algorithm?

♦ With the first spot taken and second spot more or less taken by SFUs or Januvia, achieving large patient share is going to be challenging for novel anti-diabetic agents poised to enter the type II diabetes market.

- 20% patients on 1 agent*
- 40% patients on 2 agents, 10% patients on 2+ agents
- 30% Insulin + combinations

Novel anti-diabetics will need to compete in these spaces

*OAD- oral anti-diabetic
Metformin not likely to cede first-line position so all new classes will compete for first add-on position. Second add-on drugs may still achieve commercial success, but revenue forecasts plunge for third add-ons as this is at the limit of patient and payer tolerance and majority of patients requiring 3 drugs should likely be on insulin.
Replacement of SFU in second-line with a branded agent will increase cost of therapy by 1200%!

WW Sales of Sulfonylurea Agents (2000-2014e) ($USD billions)

Increase in treatment cost based on cost of DPP-IV inhibitor in place of SFU therapy

Red Book; DH analysis
Diabetes drugs are predicted to be largest category driving spending growth (at almost 2x the rate of cancer drugs!)

- Rapid growth in epidemiology, increased use of new oral and injectable agents and limited first-time generic introductions are contributing to the increase in diabetes drug costs.

Top Therapeutic Classes Contributing to Projected Drug Trend (2010-2012)

- Therapeutic classes that are likely to drive the majority of spending growth between 2010 and 2012.
- Data are expressed as a percentage of the total projected increase in plan ingredient cost.
What will be the expected pay back for the new high cost of better glycemic control?

♦ Evidence from large randomized trials suggests microvascular complications will be reduced.
  - Nephropathy and CKD present reasonable opportunity for pharmacoeconomic justification of increased Rx treatment cost.

♦ Evidence from large randomized trials suggests macrovascular complications will not be reduced.
  - Lack of link between improved glycemic control and reduction of CVD, greatly weakens pharmacoeconomic argument as CVD drives majority of diabetes cost.
Tight glycemic control has some impact on microvascular but not macrovascular complications.

### Impact of Intensive Therapy in Type 2 Diabetes: Summary of Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>Macrovascular</th>
<th>Mortality</th>
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<tr>
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<td>←</td>
<td>←</td>
<td>←*</td>
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<td>ACCORD</td>
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<td>ADVANCE</td>
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<td>VADT</td>
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*Initial Trial: Light Gray, Long Term Follow-up: Dark Gray*
But the greater unmet need in diabetes is associated CVD

♦ People with diabetes mellitus have a 2–8-fold excess in cardiovascular mortality than people without diabetes.

~65% of deaths are due to CV disease

Coronary heart disease deaths ↑2- to 4-fold

Heart failure ↑2- to 5-fold

Cardiovascular complications of T2DM

Stroke risk ↑2- to 4-fold

T2DM = type 2 diabetes mellitus

Bell DSH. Diabetes Care. 2003; 26: 2433-41
Centers for Disease Control (CDC). www.cdc.gov
CVD complications generates greatest % cost of chronic diabetes management

♦ Much of the morbidity and cost of diabetes management is attributable to long-term, diabetes-related complications, particularly cardiovascular disease (CVD).
Will massive increase in Rx costs for T2D be accepted without big payoff in CVD event reduction?

♦ Payers will demand glycemic controllers be associated with either additional metabolic benefits capable of translating into reduced CVD (e.g., weight loss, triglyceride reduction, increase in HDL, BP reductions, etc).
♦ **Best case:** payers accept surrogate markers.
♦ **Worst case:** morbidity and mortality reduction studies required for even initial acceptance.
In Summary

- **Multiple innovative treatment options** in development for near & mid-term.
- **Improved therapies** will be welcomed by patients.
  - Global disease burden of T2D is enormous.
  - Dysglycemia associated with T2D remains poorly controlled.
- **However, in addition to the increased clinical development cost and regulatory risk** associated with diabetes drug development **commercial rewards for pharma tempered** by several emerging barriers.
  - Limits of polypharmacy will make the important first add-on position behind metformin highly competitive (between classes and intra-class).
  - Costs of new branded drugs represent dramatic increase over current SoC (generic and inexpensive).
  - Pharmacoeconomic justification & payer acceptance in regards to the various therapeutic classes; weak argument without impact on CVD (greatest cost driver).
In today’s T2DM market, late-in-class minimally differentiated products face a steeper uphill climb

**Januvia & Onglyza WW Sales ($M)**
First 5 Quarters Post-Launch of Each Product

Increasing commercial risk has dampened enthusiasm for 3rd or 4th in class agents of even successful classes of drugs

Phenomix Announces Positive Results from a Phase 3 Study of Dutogliptin in Type 2 Diabetes Mellitus

April 20, 2010

Phenomix Corporation today announced positive top-line results from a six-month Phase 3 study comparing dutogliptin 400mg and 200mg once daily as monotherapy versus placebo for the treatment of patients with Type 2 diabetes mellitus. Dutogliptin is Phenomix's internally-discovered dipeptidyl peptidase-4 (DPP-4) inhibitor.

In this study, patients with moderately elevated baseline hemoglobin A1c (HbA1c) levels (mean: 8.19%) treated with dutogliptin showed statistically significant reductions of HbA1c versus placebo at week 24, the primary endpoint of the study. Reductions in HbA1c corrected for placebo effects were 0.59% for the 400mg dose (p <0.0001) and 0.28% for the 200mg dose (p <0.0138). The results are similar to published data from trials evaluating other DPP-4 inhibitor classes.

Statistical significance was observed at the 400mg dose for all secondary endpoints, which included change from baseline in fasting and peak postprandial plasma glucose, change from baseline in glucose AUC (0-2 hours) after a standard test meal, and percentage of subjects reaching treatment goal of HbA1c of less than 7.0%

In this monotherapy Phase 3 study, dutogliptin was well tolerated. The percentages of subjects reporting adverse events, discontinuing due to adverse events and reporting serious adverse events were similar in the dutogliptin and placebo groups. The table below lists the adverse events reported with a frequency of greater than or equal to 2% in any treatment group.

“We are very pleased with the results of this successful Phase 3 trial with dutogliptin. These results suggest that dutogliptin will provide clinically important glycemic control with potential improvements in tolerability in patients with Type 2 diabetes,” said Laura K. Shawver, Ph.D., CEO of Phenomix.

Forest Laboratories today announced its decision to terminate its collaboration with Phenomix for the development and commercialization of dutogliptin for business reasons. “We are disappointed that on the heels of such positive Phase 3 data that we will not be moving forward with our collaboration with Forest. We expect to be talking to new prospective partners soon,” added Dr. Shawver.

Even an FDA approval for a first in class agent . . .

Cycloset (bromocriptine) was approved by the FDA in May 2009 for the treatment of type 2 diabetes. VeroScience completed the required Phase IIIb trial cardiovascular safety study in 3070 patients with type 2 diabetes.

"Cycloset represents a new treatment paradigm for Type 2 diabetes." said Richard Scranton M.D., M.P.H., Chief Medical Officer, VeroScience.
May prove insufficient without meaningful clinical and commercial relevance

Diabetes drug gets FDA nod, but who'll sell it?
May 7, 2009 — 12:21pm ET | By Tracy Staton

These days, diabetes is where it's at. There's so much activity in the diabetes business, it's tough to keep track. Eli Lilly and Amylin—have they submitted their app for once-weekly Byetta? What's up with that AstraZeneca/Bristol-Myers Squibb treatment Onglyza? And what about Victoza (liraglutide)? (The answers are Yes, Still awaiting FDA, respectively.)

Beating an FDA drug that doesn't beat a drug that doesn't beat a Parkinson's drug that doesn't beat sugar, in that order. It's unlikely, it says.

Cycloset approved in May 2009 was launched in the US in November 2010.

S2 Therapeutics and VeroScience granted Santarus exclusive rights to manufacture and commercialize bromocriptine in the US. Under the terms of the agreement Santarus will pay $US5 million upfront to S2 and VeroScience in addition to future royalty payments. S2 and VeroScience remain responsible for all third party royalties and FDA post-approval requirements.

http://www.theheart.org/article/1065123.do
What does this mean for companies developing novel anti-diabetic agents?

For Biotech Companies

♦ Traditionally the challenge had been to move to the proof-of-concept (PoC) point for their approach (demonstrating that the agent induced meaningful reductions in hyperglycemia) to drive value inflection.

♦ However, it is now actually equally or more important to prove that its approach provides a **clinically and commercially relevant value proposition in the evolving diabetes treatment paradigm that makes the program attractive to potential partners. In other words, demonstration of Proof of Relevance (PoR).**

♦ Given the high cost of Phase III diabetes drug development, the vast majority of early stage biotechs will need to prioritize development toward elucidation of PoR, **even at very early development stages**, over traditional push to PoC.

For Pharma Companies

♦ **Evaluation of early Proof of Relevance (PoR)** of both internal and in-licensing opportunities is crucial to avoid costly regulatory and commercial failure at a later stage.
What is PoR in the evolving diabetes landscape?

**Limited Opportunity**

**Addressed Needs**
(newer classes of approved drugs)
- Drug induced weight gain
- Risk of severe hypoglycemia
- CV Safety
- Tolerability
- Convenience

**Unmet Needs in Diabetes**

**Continued Unmet Need**
(opportunity to demonstrate PoR)
- Weight loss
- Metabolic syndrome
- Chronic inflammation
- Progressive beta cell failure
- Ultimately leading to long term CV complications

- While presently, outcomes trials for cardiovascular safety are de rigueur for approval in type 2 diabetes, there is no regulatory requirement to demonstrate cardiovascular benefit.

- Considering the high cost and risk that would be associated with running outcome trials powered to demonstrate cardiovascular benefit, **companies may increasingly rely upon indicative surrogates for macrovascular benefit, such as weight loss and improvement in lipids and blood pressure to communicate the clinical and commercial value of agents in development.**
Weight Loss As A Surrogate For PoR
Obesity is number one co-morbidity in T2DM patients that has a definite link to CVD

Diabetes KOL: “With all other things being equal, minor improvements in lipids and blood pressure are good to have, but are not as important as weight loss. Weight loss is one of the most important unmet needs in oral anti-diabetic agents. Apart from injectable GLP-1 agonists, no drugs address this need.”

> 66% of persons with diabetes are obese

> 50% of persons with diabetes have concomitant hypertension and dyslipidemia

No drug approved in more than a decade. Available therapeutic options don’t work too well.

Multiple drugs inducing generic options available for hypertension and dyslipidemia.

137,745 managed-care enrollees (Kaiser Permanente)
While FDA recognizes need for diabetics to lose weight..

This month, FDA approved expanded use of the gastric band for obese adults who have a BMI of 30 to 40 kg/m² and 1 additional obesity-related co-morbid condition, such as diabetes or hypertension.

*Previously, the gastric surgery was indicated only for patients with a BMI >35 kg/m² and at least two additional risk factors or >40 kg/m² in those without any other conditions.*
Its tough stance on obesity drugs is a huge opportunity for anti-diabetic agents that induce even modest weight loss.

Bariatric docs disappointed in latest setback: Another antiobesity drug fails to make FDA cut

FEBRUARY 14, 2011 | Michael O’Riordan

Denver, CO - The American Society of Bariatric Physicians (ASBP) is publicly questioning the recent US Food and Drug Administration decision to not approve the diet drug Contrave, saying the nonapproval handicap of another antiobesity drug in the market because this was the third drug the FDA has turned down.

Dr Larry Richardson, president of ASBP, expressed concerns with Contrave for treating obesity drugs, including hypertension.

As reported earlier by manufacturer, Orexigen, the potential cardiovascular benefits of the drug, The nonapproval came from the Metabolic Drugs Advisory Committee gave the drug the "likely benefits of the risk." Despite a majority of concerns about blood-pressure and heart-rate changes going in the wrong direction. Committee members spent considerable time discussing the finding that the only patients in the placebo-controlled studies whose blood pressure improved were those who managed to lose at least 10% of their original weight—a minority of patients in the trials—and even then the blood-pressure improvements were nominal.
Current T2DM deal landscape is indicative of a push towards mechanisms that induce weight loss

- Pharma interest is particularly high on agents that induce weight loss via the established marker GLP-1.

Note: majority of the other novel MOAs are weight neutral or induce some weight loss.
GLP-1 analogues are an exciting class of drugs that induce weight loss, but require daily injections.

Emergence of long-acting versions is anticipated to enhance market penetration, but need for oral agents that induce weight loss will remain.

**Potential Cardiovascular Benefits of GLP-1 Analogs**

- Promote weight loss\(^a\)
- Lower triglyceride level and raise HDL level,\(^b\) lower blood pressure\(^c\)
- Improve endothelial dysfunction,\(^d\) reduce levels of C-reactive protein and other inflammatory markers\(^e\)

**Why don’t we have an oral GLP-1 agonist?**

Unlike GPCRs for which oral small molecule agents have been successfully developed such as the opioid receptors which belong to GPCR family A, GLP-1 receptor belongs to GPCR family B which require large ligands with spatially separated points of contact (peptides) which are not easy to be made orally bioavailable.

Given the established metabolic benefits with GLP-1 agonists and lack of late stage oral GLP-1 analogues in the pipeline, oral agents that work by novel mechanisms to induce GLP-1 make a great PoR argument!
Examples for GLP-1 stimulation as surrogate marker for PoR: Oral Islet GPCR Agonists

♦ Islet GPCRs activated by lipids have received considerable interest in the last few years. This family of receptors includes the closely related GPR40, GPR41 and GPR43 as well as GPR119 and GPR120.

♦ Among the islet GPCRs, GPR119 agonists are the most advanced in clinic.

♦ In addition to pancreatic islets, GPR119 is also expressed on enteroendocrine cells in the intestine where it is thought to play a role in controlling the release of GLP-1 and GIP in response to nutrient ingestion.

Value proposition

♦ The ability to directly modulate both GLP-1 secretion and insulin secretion through the same receptor.
Islet GPCRs in development for T2DM

**Novelty**
- Several islet GPCRs are involved in the regulation of islet hormone secretion and are therefore potential targets for the treatment of islet dysfunction — the key defect in type 2 diabetes.
- These therapies could offer effect of GLP-1 analogues with an oral dosing.

**Estimated launch**
- First agent could be launched in 6-8 years.

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<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Phase</th>
<th>MOA</th>
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<tr>
<td>PSN821</td>
<td>Prosidion</td>
<td>II</td>
<td>G-Protein Coupled Receptor 119</td>
<td>T2DM</td>
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<tr>
<td>MBX 2982</td>
<td>Metabolex</td>
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<td>G-Protein Coupled Receptor 119</td>
<td>T2DM</td>
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<tr>
<td>APD 597</td>
<td>Ortho-McNeil-Janssen, Arena</td>
<td>I</td>
<td>G-Protein Coupled Receptor 119</td>
<td>T2DM</td>
</tr>
</tbody>
</table>

DH secondary research
Metabolex’s GPR119 agonist partnered after completion of Phase I

**Metabolex / sanofi-aventis**
- **Compound:** MBX-2982
- **Mechanism:** GPR119 Agonist
- **Indication:** Type 2 diabetes
- **Stage at Deal:** Phase I completed (Phase II enrolling)
- **Upfront Payment:** undisclosed
- **Total Potential Deal:** $375 M
- **Clinical Trial History at Deal:**
  - Preclinical - demonstrated dual MOA - stimulates insulin secretion from beta cells and GLP-1 secretion from intestines.
  - Phase I - clinically meaningful glucose reductions in healthy volunteers and subjects with impaired glucose tolerance.

**PoR**
- Oral agent that increases GLP-1 levels. Potential for weight loss and improved islet health currently only offered by injectable GLP-1 agonists.
- Unique dual MOA of stimulating insulin as well GLP-1 in a glucose dependent manner.

Clinicaltrials.gov; Thomson Reuters; company website; Defined Health analysis.
Examples for GLP-1 stimulation as surrogate marker for PoR: TGR5 agonist

♦ TGR5, a member of the GPCR superfamily which is highly expressed in the gall bladder and intestine with lower levels of expression in brown adipose tissue and liver. Bile acids have been implicated as endogenous TGR5 agonists.

♦ In the intestine, TGR5 is expressed in enteroendocrine L cells, which secrete the potent glucose-lowering incretin hormone glucagon-like peptide-1 (GLP-1).

♦ Recently it was shown that bile acid-induced activation of TGR5 results in intestinal secretion of GLP-1 and that enhanced TGR5 signaling improves postprandial glucose tolerance in diet-induced obese mice.

♦ In addition to its role in stimulating GLP-1 secretion TGR5 is also implicated in energy homeostasis in brown adipose tissue.
TGR5 agonists in development for T2DM

**Novelty**

- Novel MOA that is involved in the regulation of energy metabolism and stimulate GLP-1 secretion in the intestine with oral dosing.

**Estimated launch**

- First agent could be launched in 8-10 years.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Phase</th>
<th>MOA</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>XL 475</td>
<td>Exelxis</td>
<td>Preclinical</td>
<td>TGR5 agonist</td>
<td>Metabolic disorders</td>
</tr>
<tr>
<td>Research program</td>
<td>Intercept</td>
<td>Preclinical</td>
<td>TGR5 agonist</td>
<td>Metabolic disorders</td>
</tr>
</tbody>
</table>

DH secondary research
Exelixis intestinal selective TGR5 agonist partnered at preclinical stage

**Exelixis/ BMS**
- **Compound:** TGR5 program (XL-475 lead)
- **Mechanism:** TGR5Agonist
- **Indication:** Type 2 diabetes
- **Stage at Deal:** Preclinical
- **Upfront Payment:** $60M (for 2 programs)
- **Total Potential Deal:** $250 M
- **Preclinical/ Clinical History at Deal:**
  - Preclinical- Designed to selectively target the TGR5 receptors in the intestine without significant systemic exposure. Increased GLP-1 levels in multiple species.
  - In preclinical models of type 2 diabetes, XL475 is highly effective in lowering blood glucose, improving glucose tolerance, improving plasma and hepatic lipid levels, and reducing hepatic steatosis.

**PoR**
- Oral agent that increases GLP-1 levels. Potential for weight loss and improved islet health currently only offered by injectable GLP-1 agonists.
Examples for GLP-1 stimulation as surrogate marker for PoR: GLP/ GIP dual agonists

- Marcadia Biotech is developing dual GLP-1/GIP agonists.
- GIP and GLP-1 are the two major incretin hormones in humans. Like GLP-1 receptor agonists, Marcadia’s dual agonists cause direct receptor activation, but uniquely cause simultaneous activation of both the GLP-1 and GIP receptors with a single peptide.
- Marcadia’s lead compound, MAR701, is a first in class dual GLP-1/GIP agonist which is initially being developed for the treatment of diabetes with once-weekly dosing.
- Preclinical testing by Marcadia of MAR701 demonstrated significant reductions in blood glucose levels and body weight.
Roche acquired Marcadia late last year for close to $537M

**Roche / Marcadia**

- **Compound:** Lead program MAR701
- **Mechanism:** GLP-1/GIP dual agonists and GLP-1/glucagon receptor modulators
- **Indication:** Type 2 diabetes and obesity
- **Stage at Deal:** Phase I Initiated
- **Acquisition:** $537M
- **Preclinical/ Clinical History at Deal:**
  - In preclinical studies, MAR 701 showed simultaneous activation of GLP-1 and GIP receptors that produced additive efficacy with no apparent adverse events. During preclinical testing, MAR 701 demonstrated significant reduction of blood glucose levels and body weight.
  - In preclinical diet induced obese mice model, Marcadia’s dual GLP-1 agonist/glucagon receptor modulator normalized adiposity and glucose tolerance when dosed once weekly.

**PoR**

- Highly significant weight loss and normalization of glucose tolerance in preclinical models when dosed as once weekly injection.
Examples for GLP-1 stimulation as surrogate marker for PoR: SGLT1/ SGLT2 dual agonist

- There are 10 publicly disclosed SGLT programs in clinical development.
- Based on available data (from 3 agents), the efficacy and safety risks seem to be similar across the class. The increased risk of genitourinary infections appears to be a class effect.
- While there exist certain pharmacokinetic differences among the inhibitors, so far this has not translated into clinical differentiation.
- Even if the SGLT2 class ultimately performs well, given the number of SGLT2 inhibitors in clinical development, there is a challenge for late entrants in the hands of Biotech such as Lexicon’s LX4211 (Phase II) unless clinical differentiation is explored early.
Examples for GLP-1 stimulation as surrogate marker for PoR: SGLT1/ SGLT2 dual agonist

♦ LX4211 is a small molecule SGLT inhibitor being developed by Lexicon Pharmaceuticals.

♦ The company has positioned LX4211 as a differentiated agent that has been designed to target both SGLT2 (present in kidneys) and SGLT1 (present in kidney, gut and other tissues; known to play a role in glucose absorption in the gut).

♦ While the prospect of dual inhibition is interesting, it is clear that in order to succeed, the agent would need to demonstrate clinical differentiation as opposed to purely mechanistic differentiation over the more advanced SGLT2 inhibitors.

♦ Lexicon demonstrated what could be conceived as ‘PoR’ with its Phase II study demonstrating increased GLP-1 stimulation hypothesized to occur due to SGLT1 inhibition in the intestine in addition to SGLT2 inhibition.
Lexicon study recently showed that LX4211 increases levels of GLP-1 and PYY in addition to SGLT2 inhibition

♦ In a short clinical study (15 days, 3 doses) performed to compare a new tablet formulation with an oral liquid formulation, Lexicon measured GLP-1 and PYY (important mediators of glycemic and appetite control known to be unregulated via inhibition of SGLT1 in the gut). Positive results were published indicating that LX4211 rapidly lowered blood sugar and increased GLP-1 and PYY after a single dose.

♦ This trial is particularly interesting as a PoR strategy since it established both the dual mechanism and its clinical relevance in diabetics. Although the company did not report the extent of increase in GLP-1 levels, the activation of GLP-1 in addition to SGLT2 inhibition implied potential for improved glycemic efficacy and weight loss, thus supporting a potential superior clinical profile vs. pure SGLT2 inhibitors.

Lexicon shares soar after GLP-1 increase reported in a new clinical study.

DH analysis; company website; Yahoo finance
Reduction of Inflammation as a Surrogate for PoR
 Diabetes as an inflammatory disease-link between diabetes and CVD

✧ Components of the immune system are altered in obesity and type II diabetes, with the most apparent changes occurring in adipose tissue, the liver, pancreatic islets, the vasculature and circulating leukocytes.

✧ These immunological changes include altered levels of specific cytokines and chemokines, changes in the number and activation state of various leukocyte populations and increased apoptosis and tissue fibrosis.

✧ Together, these changes suggest that inflammation participates in the pathogenesis of T2D.

✧ Preliminary results from clinical trials with salicylates and interleukin-1 antagonists support this notion and have opened the door for immunomodulatory strategies for the treatment of type II diabetes that simultaneously lower blood glucose levels and potentially reduce the severity and prevalence of the associated complications of this disease.

Development of Inflammation in Type II Diabetes

Development of inflammation in type 2 diabetes. Excessive levels of nutrients, including glucose and free fatty acids, will stress the pancreatic islets and insulin-sensitive tissues such as adipose tissue (and the liver and muscle, not shown), leading to the local production and release of cytokines and chemokines. These factors include interleukin-1β (IL-1β), tumour necrosis factor (TNF), CC-chemokine ligand 2 (CCL2), CCL3 and CXC-chemokine ligand 8 (CXCL8). Furthermore, production of IL-1 receptor antagonist (IL-1RA) by β-cells is decreased. As a result, immune cells will be recruited and contribute to tissue inflammation. The release of cytokines and chemokines from the adipose tissues into the circulation promotes inflammation in other tissues, including the islets.
Inflammatory mechanisms in diabetes: role of cytokine IL-1

Role of inflammatory cytokines in diabetes and CVD

Pro-inflammatory cytokines in insulin resistance and atherogenesis

- Increasing adiposity activates inflammatory responses in fat and liver, with associated increases in production of cytokines and chemokines.
- Immune cells, including monocytes and macrophages are recruited and/or activated, and together these cause local insulin resistance.
- Portal delivery of abdominal fat-derived cytokines and lipids contributes to hepatic inflammation, insulin resistance and atherogenesis.

Pro-inflammatory cytokine IL-1 in beta cell destruction

- Beta cells producing interleukin-1β have been observed in pancreatic sections obtained from patients with type 2 diabetes
- IL-1 is hypothesized to be secreted as a result of glucotoxicity on beta cells and is a proposed mediator of islet cell apoptosis.

Completed and ongoing clinical trials of broad anti-inflammatory approaches

Clinical studies using anti-inflammatory approaches to treat type 2 diabetes or pre-diabetes

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
<th>Trial Phase</th>
<th>Number of subjects</th>
<th>Treatment duration (weeks)</th>
<th>Main findings</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1 receptor blockade</td>
<td>Anakinra (Kinere; Angen/Biovitrum)</td>
<td>II</td>
<td>69</td>
<td>13</td>
<td>↓ Glycated haemoglobin, ↓ CRP, ↑ insulin production</td>
<td>25</td>
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<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salasate</td>
<td>II</td>
<td>20</td>
<td>4</td>
<td>↓ FBG, ↓ CRP, ↑ insulin sensitivity, ↑ adiponectin</td>
<td>107</td>
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<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salasate</td>
<td>II</td>
<td>16</td>
<td>2–4</td>
<td>↓ FBG, ↓ FFA, ↓ triglycerides, ↓ CRP, ↑ adiponectin</td>
<td>143</td>
</tr>
<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salasate</td>
<td>II</td>
<td>40</td>
<td>1</td>
<td>↓ FBG, ↑ insulin</td>
<td>144</td>
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<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salasate</td>
<td>IIb</td>
<td>104</td>
<td>12</td>
<td>↓ Glycated haemoglobin, ↓ FBG, ↓ triglycerides, ↑ adiponectin</td>
<td>28</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>XOMA 052 (Xoma)</td>
<td>I</td>
<td>98</td>
<td>Single injection</td>
<td>↓ Glycated haemoglobin, ↓ CRP, ↑ insulin production</td>
<td>27</td>
</tr>
<tr>
<td>IL-1 receptor blockade</td>
<td>Anakinra (Kinere; Angen/Biovitrum)</td>
<td>II</td>
<td>12</td>
<td>4</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT00928876*</td>
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<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
<td>II</td>
<td>231</td>
<td>Unknown</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT00605475*</td>
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<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
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<td>48</td>
<td>Ongoing</td>
<td>NCT00995930*</td>
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<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
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<td>232</td>
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<td>Ongoing, closed for recruitment</td>
<td>NCT01068860*</td>
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<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
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<td>IKKβ–NF-κB inhibition</td>
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<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salasate</td>
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<td>Ongoing, closed for recruitment</td>
<td>NCT00330733*</td>
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<td>IL-1β-specific antibody</td>
<td>XOMA 052 (Xoma)</td>
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<td>325</td>
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<tr>
<td>IL-1β-specific antibody</td>
<td>XOMA 052 (Xoma)</td>
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<td>NCT01144975*</td>
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<tr>
<td>IL-1β-specific antibody</td>
<td>LY2189102 (Lilly)</td>
<td>II</td>
<td>80</td>
<td>12</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT00942188*</td>
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<td>IL-1β-specific vaccine</td>
<td>CYT013-IL1bQb (Cytos Biotech)</td>
<td>I</td>
<td>32</td>
<td>Unknown</td>
<td>Ongoing</td>
<td>NCT00924105*</td>
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</tbody>
</table>

Trials with tumour necrosis factor (TNF) antagonists are not listed owing to the lack of effects in patients with type 2 diabetes. CRP: C-reactive protein; FBG, fasting blood glucose; FFA, free fatty acid; IKKβ, IκB kinase-β; IL-1, interleukin-1; NF-κB, nuclear factor-κB. *ClinicalTrials.gov Identifier.
Several IL-1 antagonists currently in the pipeline

**Novelty**
- Encouraged by early clinical data generated from human trial of Anakira and Xoma-052 (both IL-1 antibodies) showing impact of HbA1c reduction and CRP level reduction, several other IL-1 antagonists.

**Impact on future treatment algorithm**
- Current challenge for IL-1 and other costly injectable monoclonal antibody approaches in type II diabetes is lack of surrogates to measure CV and beta cell preserving benefits via reduction of inflammation.
- Ultimately if IL-1 antagonists do demonstrate a reduction in CV risk in type II diabetics and succeed in once a month or less dosing, these agents would have significant market potential despite being expensive injectables.

**Estimated launch**
- 5-10 years time frame

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Phase</th>
<th>MOA</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>canakinumab</td>
<td>Novartis</td>
<td>II/III</td>
<td>IL-1β mAb</td>
<td>T2DM</td>
</tr>
<tr>
<td>LY 2189102</td>
<td>Lilly</td>
<td>II</td>
<td>IL-1β antibody</td>
<td>T2DM</td>
</tr>
<tr>
<td>CYT013</td>
<td>Cytos Biotech</td>
<td>I/IIa</td>
<td>IL-1β vaccine</td>
<td>T2DM</td>
</tr>
<tr>
<td>XOMA 052</td>
<td>XOMA</td>
<td>II (RA), I (T2DM)</td>
<td>IL-1 beta antagonist</td>
<td>P1 – T2DM, P2 – RA</td>
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<td>VRS 826</td>
<td>Versartis</td>
<td>PC</td>
<td>IL-1ra-rPEG</td>
<td>T2D, RA</td>
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<tr>
<td>APG 101.10</td>
<td>Allostera</td>
<td>PC</td>
<td>IL-1 antagonist</td>
<td>T2D, Gout, RA</td>
</tr>
</tbody>
</table>

DH secondary research
However, challenge is lack of established inflammatory markers for CV risk in diabetics.

♦ Among the continuously evolving landscape of CV risk markers, C-reactive protein (CRP) is one of the most established and preferred markers (owing to ease of assaying and reliability) to assess generalized inflammation levels.

♦ Multiple small to mid size studies have found a correlation between CRP levels and intermediate endpoints for cardiovascular disease (such as Intima Media thickness (IMT), Flow Mediated Dilatation (FMD) or arterial stiffness) in diabetics.

♦ In the Women's Health Study, in this subset of about 15,000 women, there is a stepwise relationship as we stack the components of the metabolic syndrome in terms of the CRP at the outset of the study.

♦ However, whether such markers could be used to guide therapy in diabetics is still an open question which needs to be answered via clinical testing.
While CRP is an established marker for presence of inflammation, so far no proof exists for using it to guide therapy.

Recently, XOMA announced mixed interim results from the ongoing six month Phase 2a trial of XOMA-052 (IL-1 antagonist) treatment for Type 2 diabetes. The exploratory trial was designed to focus on overall safety and pharmacokinetics.

Additionally, measures of biological activity including C-reactive protein (CRP) and hemoglobin A1c (HbA1c) were looked at. Interim results indicate 50% reduction in CRP but, no impact on HbA1c.

Last month Xoma announced a $505 M pact with Servier for its IL-1 antagonist.
Novel oral anti-inflammatory mechanisms in development: Alpha7 neuronal nicotinic receptor modulator

- TC-6987 is a selective modulator of the alpha7 neuronal nicotinic receptor being developed by Targacept Inc.

- A number of preclinical studies have confirmed the therapeutic potential of targeting alpha7 nicotinic acetylcholine receptor-mediated anti-inflammatory effects through modulation of pro-inflammatory cytokines.

- The company reports that TC-6987 demonstrated a potent anti-inflammatory response in a variety of preclinical studies conducted by Targacept, including models of asthma and diabetes, and was generally well tolerated in Phase I clinical trials.

- Most recently, Targacept has initiated exploratory Phase II trials with TC-6987 in type 2 diabetes and asthma.
  - The Phase II diabetes trial expects to enroll 120 patients in a randomized, double blind study testing TC-6987 vs., placebo.
  - The primary efficacy endpoint will be the change in fasting plasma glucose (FPG) from Baseline (Day 1) at Week 4.
  - Secondary efficacy endpoints include measuring of glycemic and lipid parameters.
  - In addition Targacept has included an exploratory endpoint measuring inflammation markers: Change from Baseline at Week 4 in 46 human inflammatory biomarkers in plasma and after the ex vivo LPS challenge using Rules-Based Medicine’s Multi-Analyte Panel (MAP) technology.

Company website and information provided by company
Specific pathways of vascular inflammation in diabetics

- Atherosclerosis is the major causal factor for these cardiovascular events in diabetics.
- Atherosclerosis is an inflammation driven process. Several observations point to the presence of an exaggerated inflammatory component in the diabetic atherosclerotic plaque.
- Among the proposed mechanisms involved at the level of the intima, RAGE and the ubiquitin–protease system seem to be potential links between diabetes and the inflammatory processes of atherosclerosis.

**AGE-RAGE pathway**

- AGE in ECM (collagen)
- Soluble AGE
- AGE receptors
- Macrophages
- ENHANCED PERMEABILITY PROLIFERATION FIBROBLASTS AND SMC SYNTHESIS ECM PROCOAGULANT EFFECTS (reduction in thrombomodulin activity, increase in tissue factor)
- SECRETION OF IL1 SECRETION OF TNF alpha

**Ubiquitin-proteosome pathway**

- Postprandial hyperglycemia, diabetes, oxidative stress
- CYTOPLASM
- Proinflammatory cytokines, adhesion molecules
- ENDO THELIAL DYSFUNCTION
- ENDO THELIAL ACTIVATION
- COMPLICATED RuptURE

Cardiovascular Diabetology 2007
There is increasing evidence that advanced glycation end products (AGEs) play a pivotal role in atherosclerosis, in particular in diabetes.

AGE accumulation is a measure of cumulative metabolic and oxidative stress, and may so represent the "metabolic memory".

Furthermore, increased AGE accumulation is closely related to the development of cardiovascular complications in diabetes.

A variety of interventions against AGE accumulation, predominantly tested in preclinical contexts, appear to show beneficial effects on the development/progression of diabetic complications.

Findings from current clinical trials, including feasibility studies, may further help in determining the relevance of AGE assessment in diabetes.

Table 3: Future clinical perspective of advanced glycation endproducts

<table>
<thead>
<tr>
<th>Clinical trials with various anti-AGE interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility studies in daily clinical practise:</td>
</tr>
<tr>
<td>- metabolic control (e.g. HbA1c vs AGEs)</td>
</tr>
<tr>
<td>- tailoring treatment</td>
</tr>
<tr>
<td>- risk analysis of interventions (e.g. surgery)</td>
</tr>
<tr>
<td>Role of AGEs in subjects with impaired (fasting) glucose tolerance</td>
</tr>
<tr>
<td>Identifying the &quot;vulnerable patient&quot; at risk for cardiovascular disease in e.g. primary care</td>
</tr>
</tbody>
</table>
Emerging data indicate AGE-RAGE both as a marker for vascular inflammation and as a target for therapy.

**DPPIV inhibitor Vildagliptin blocks vascular injury in thoracic aorta of diabetic rats by suppressing advanced glycation end product-receptor axis.**

Pharmacol Res. 2011 Feb 11.

Matsui T, Nishino Y, Takeuchi M, Yamagishi SI.

Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume, Japan.

**Abstract**

Vildagliptin is a stable inhibitor of dipeptidyl peptidase-IV, a responsible enzyme that mainly inactivates glucagon-like peptide-1, and now one of the widely used agents for the treatment of diabetes. However, effects of vildagliptin on vascular injury in diabetes are largely unknown. Since advanced glycation end products (AGEs) and their receptor RAGE axis are reported to contribute to vascular complications in diabetes, we investigated here whether vildagliptin inhibits vascular damage in thoracic aorta of diabetic rats. OLETF and control LETO rats at 22 weeks old were given vehicle or 3 mg/kg of vildagliptin for another 12 weeks. Vildagliptin treatment decreased fasting plasma glucose and heart rate in OLETF rats. Compared with control LETO rats, levels of AGEs, RAGE mRNA and protein, an oxidative stress marker, 8-hydroxydeoxyguanosine, two membrane components of NADPH oxidase, p22 and gp91phox mRNAs, and phospho-NF-κB p65 in thoracic aorta were significantly enhanced in OLETF rats, all of which were inhibited by the treatment with vildagliptin. Vildagliptin significantly reduced both mRNA and protein levels of monocyte chemoattractant protein-1, vascular cell adhesion molecule-1 and plasminogen activator inhibitor-1 in thoracic aorta of OLETF rats. Enhanced expression of transforming growth factor-β in the aorta of diabetic rats was also suppressed by vildagliptin. Our present data suggest that vildagliptin could play a protective role against vascular injury in diabetes partly by attenuating the deleterious effects of AGEs-RAGE-oxidative stress axis.

AGE accumulation is a measure of cumulative metabolic and oxidative stress, and may so represent the "metabolic memory". In addition, a variety of interventions against AGE accumulation, predominantly tested in preclinical contexts, appear to show beneficial effects on the development/progression of diabetic complications.
In Conclusion

♦ While ‘improved glycemic control’ remains the recognized marker for demonstration of PoC in type 2 diabetes, emerging commercial issues may render it insufficient to gain significant share in the increasingly competitive type 2 diabetes market.

♦ Hence, demonstration of clinical and commercial relevance, in other words proof of relevance, ‘PoR’, in type 2 diabetes would need to focus on the remaining unmet need via demonstration of additional cardiometabolic benefits.

♦ Clinically meaningful weight loss via an established mechanism such as GLP-1 agonism appears to be currently one of the most attractive indicative surrogates available to demonstrate PoR in type 2 diabetes.

♦ With the growing understanding of the inflammatory and beta cell destructive mechanisms in play in type 2 diabetes, in the future surrogates to measure benefit of anti-inflammatory and beta cell preserving targets may be established.
See us at these upcoming EBD conferences:

<table>
<thead>
<tr>
<th>Conference</th>
<th>Dates</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIO-Europe Spring 2011</td>
<td>March 14–16, 2011</td>
<td>Milan, Italy</td>
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<tr>
<td>BioPharm America 2011</td>
<td>September 7-9, 2011</td>
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