Management of Diabetes: Beyond the Insulin and Incretin Pathways

Moderator:
- Michael C. Rice – Senior Consultant, Defined Health

Panelists:
- Cord Dohrmann – CSO and Board Member, Evotec
- Olle Korsgren – Professor, Cell Therapeutics, Department of Immunology, Genetics and Pathology, Rudbeck Laboratory, Uppsala University Hospital
- Tomas Landh – Innovation Sourcing VP, Senior Principal Scientist, Novo Nordisk
- Matthias Urmann – Associate VP, Diabetes External Innovation, Sanofi
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Diabetes Has Been Among the Most Consistent Growth Drivers in the Pharmaceutical Market, Fueled by Demographics and Innovation

Obesity has a CAGR of 28% between 2016-2020

CVD yielded double-digit growth since the 1980s

Historical Sales Growth CAGR (2005-2015)

Bubble size correlates to 2015 WW TA Sales
The Diabetes Market Is Steadily Growing – Nearing Parity With The Eroding CV Market

Total Worldwide CVD & Metabolics Therapeutic Category Sales, 2004-2020

EvaluatePharma

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Leading Diabetes Franchises Built on Insulins – Newer Players Entering With OADs

♦ In 2020, Novo Nordisk, Sanofi, Lilly, Merck, AstraZeneca and J&J will dominate a projected $53B market, driven by growth of insulins, GLP-1s and OAD.

♦ SGLT-2s are the latest oral anti-diabetic entrant and significant growth is expected (CAGR 44%), likely at the expense of DPP-4’s. JNJ’s Invokana (approved March 2013) had first to market advantage and AZN’s Farxiga offers limited differentiation. Lilly/BI’s Jardiance was approved late 2014 and may become market leader as the only antidiabetic agent that has shown CV benefit.

♦ T1D is a small, but stable component of the diabetes market.
Higher Regulatory/Commercial Hurdles and Threats from Genericization and Biosimilars Are Tempering Growth in Coming Years

- *Lantus* (insulin glargine) for type I and type II diabetes, with sales of EUR8.7 billion in the EU5 and the U.S. in the year to September 2015. *Lantus* lost exclusivity in the EU in 2015.

*Exhibit 1: EU5+U.S. Sales of Key Biologics Scheduled to Lose Patent Protection in 2015–2020*

Source: IMS Health, MIDAS, Dec 2015
Many Studies Aiming to Introduce New Drug Classes Proving CV Outcomes Improvement – Largely Enrolling High Risk Diabetics

Timeline of Anticipated Launches Late Stage CV & Diabetes Drugs With Outcomes Data*

CV agents
- Statin/CAI
- DPP-IV
- Niacin
- GLP-1
- SGLT2
- CETP
- Lp-PLA₂
- PPAR
- ApoB 100
- MTP
- PCSK9
- Omega-3

T2DM agents
- Onglyza
  - US Launch
- Victoza
  - US Launch
- Tanzeum
  - US Launch
- Invokana
  - US Launch
- Nesina
  - US Launch
- Januvia
  - US Launch
- Dapagliflozin
  - US Launch
- Jardiance
  - US Launch
- Victoza
  - LEADER Trial

*HoFH launches based on surrogate only

Defined Health, EvaluatePharma, *HoFH launches based on surrogate only

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Dearth of Metabolic Agents in Both Preclinical and Clinical Development Compared to Other TAs

**Pipeline by Therapeutic Category**

- CVD
- Diabetes
- Obesity
- CNS
- Genito-Urinary
- Musculo-skeletal
- Oncology
- Respiratory
- Anti-infectives
- Others

**Diabetes Pipeline By Mechanism**

- DPPIV inhibitor
- Gluconeogenesis
- Insulin Analogs
- AMPK Activators
- GLP-1
- TK Modulators
- SGLT-2 inhibitor
- GPCR Agonists
- GR modulators
- Hydrolase inhibitors

Late stage mostly, next-in-class agents and LCM
Low Deal Activity in Diabetes, Obesity Deters Further Investment into Innovative Early Stage Programs

Number of Deals From 2012 to 2015 by Therapeutic Area

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Commercial & Regulatory Risk More Challenging Than Scientific Risk?
Transforming Diabetes: Three Potential Overlapping Strategies

(3) New modalities and regenerative medicine
- Cell therapies: Islet cell transplantation / Devices / Nanoparticles
- Immunotherapy: Treg, CAR T-Cell, Dendritic Cell Vaccine
- RNA (ASOs, siRNA inhibition/miRNA, mRNA augmentation)

(2) Focus on high unmet need sub-populations
- Type 1 Diabetes
  - LADA, IDDM1 variants, other subsets
- Genetically or Biomarker defined populations
  - MODY, Hyperinsulinemia
- Gestational Diabetes

(1) Bring an oncology-like development model
- Genetically/Scientifically driven R&D, Targeted Therapies
- Initial launch for advanced/refractory disease patient subsets
- Subsequent label expansion to earlier lines of therapy and broader patient segments with post-marketing studies.
T2DM Example: The newest drug class in the treatment of type 2 diabetes, SGLT2 inhibitors (gliflozins)

- Gene mutations in SGLT2 were found in people with a *benign familial renal glucosuria*.
- >90% of the glucose filtered by the kidney is reabsorbed by SGLT-2 in the early convoluted segment of the proximal tubules.
- Inhibition of SGLT2 blocks reabsorption of glucose in the kidney and represents the first insulin-independent glucose lowering agent.
- Phlorizin first isolated in 1835 and was subsequently found to be potent but rather non-selective inhibitor of both SGLT-1 and SGLT-2 proteins.
- Canagliflozin was the first SGLT2 inhibitor that was approved by the FDA, it was accepted in March 2013. Dapagliflozin and empagliflozin were accepted in 2014.
- SGLT2 inhibition lowers HbA1c, has favorable body weight benefits and has shown improved CV outcomes when.

Invocana Website,
CV Example: Scientific Transformation of PCSK9 mAbs Not Limited to Targeting Micro Populations

http://sitn.hms.harvard.edu/flash/2015/a-potential-new-weapon-against-heart-disease-pcsk9-inhibitors/
# Nucleic Acid Technologies in The Continuum of Biologic Therapeutics Platforms

## Therapeutic Interventions

### Small Molecule Modulators
- Immune Modulators
- SMIs
- Chaperones
- Substrate Reduction
- Transcription / Translation enhancers
- Epigenetics

### Protein Augmentation
- Plasma/tissue derived proteins
- Recombinant Proteins
  - Clotting factors
  - Cytokines
  - Hormones
  - Growth factors
- Enzyme Replacement

### Antibodies
- Plasma derived Polyclonal IgGs
- Monoclonal antibodies
- mAB fragments
- Scaffolds
- Intrabodies

### Nucleic Acids
- Antisense
- mRNA
- RNAi /siRNA
- miRNA
- Toll modulators
- Aptamers
- Ribozyme
- Exon skipping

### Gene Correction & Augmentation
- Viral vectors
  - Retro/
  - Lentiviral
  - AdV
  - AAV
- Non-viral
  - Plasmids/
  - Fragments
- Gene editing with
  - Meganucleases
  - Zinc Fingers
  - TALENS
  - CRISPR/Cas9

### Cell Therapy / Regen Med
- Autologous and allogeneic BMT/Cell therapy
- Other cell sources: e.g. ES, iPS
- Devices
  - Encapsulation
  - Scaffolds
  - Implants
  - Micro-organs
  - Aphaeresis

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Role of The Immune System May Go Beyond T1D – Evidence Suggests Role in Obesity-related Insulin Resistance as Well

Autoimmunity in Type I Diabetes

Autoimmunity in Type II Diabetes?

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# Pharma Doing Early Stage Deals to Enrich Diabetes Pipelines

<table>
<thead>
<tr>
<th>Alliance</th>
<th>Type</th>
<th>Area (Phase)</th>
<th>Upfront (Mlns)</th>
<th>Total (Mlns)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi/Evotec (Aug 7 2015)</td>
<td>strategic Collaboration</td>
<td>Field of diabetes</td>
<td>€3.0</td>
<td>€300 Development and</td>
<td>• Risk-shared transaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>commercial milestones</td>
<td>• Development of beta cell replacement therapy</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>plus royalties</td>
<td>• Discovery and development of beta cell modulating drugs</td>
</tr>
<tr>
<td>AstraZeneca/Moderna (March 2013)</td>
<td>Strategic Collaboration</td>
<td>Messenger RNA therapeutics for the treatment of serious cardiovascular, metabolic, and renal diseases and cancer</td>
<td>$240.0</td>
<td>$420.0 Three technical milestone payments</td>
<td>• AstraZeneca will have exclusive access to select a target of its choice in cardiometabolic diseases over a period of five years for subsequent development of messenger RNA</td>
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<td>• AZ will lead the development and commercialization of therapeutics resulting from the agreement.</td>
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<td></td>
<td>• Moderna will be responsible for designing and manufacturing the messenger RNA against selected targets</td>
</tr>
<tr>
<td>Novo Nordisk/Ablynx</td>
<td>global exclusive collaboration and licensing agreement</td>
<td>Discover and develop novel multi-specific Nanobody® drug candidates for an undisclosed disease area.</td>
<td>€9.0 Upfront</td>
<td>up to €377</td>
<td>• Milestone payments of up to €182 million per program plus tiered royalties on the annual net sales</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>€5m and €4m in research funding</td>
<td></td>
<td>• Novo Nordisk will be responsible for the development, manufacturing and commercialization</td>
</tr>
</tbody>
</table>
Appendix
T2DM is a Challenging Health Problem in the 21st Century - It is One of the Most Common Non-Communicable Diseases Globally

- Global prevalence of diabetes 382M & expected to reach 592M by 2035
  - Diabetes increasing in all parts of the world yet nearly 50% of people globally undiagnosed

  Top 10 countries/territories of number of people with diabetes (20-79 years), 2013

<table>
<thead>
<tr>
<th>Country</th>
<th>2013</th>
<th>2035</th>
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<tbody>
<tr>
<td>China</td>
<td>90.4</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>65.1</td>
<td></td>
</tr>
<tr>
<td>USA</td>
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<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>Russian Federation</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>7.2</td>
<td></td>
</tr>
</tbody>
</table>

- Over $200 Billion (USD) Global Healthcare Expenditure Due To Diabetes.
  - Large disparity in healthcare spending on diabetes between regions and countries
  - Only 20% of global healthcare expenditures due to diabetes were made in low- and middle-income countries, where 80% of people with diabetes live

International Diabetes Federation Diabetes Atlas Sixth Edition

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Continued Strong Growth in Diabetes Market Fueled by Demographics and Innovation

**Worldwide Pharmaceutical Sales by Therapy Area, 2004-2020**

Sales expected to grow by $176B to an estimated $754B by 2020

- CV
- Diabetes
- Obesity
- Other
- Endocrinology
- CNS
- Genito-Urinary
- Musculo-skeletal
- Oncology
- Respiratory
- Systematic
- Anti-infectives
- Other

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