Clinical Overview of Combination Therapy with Sitagliptin and Metformin
Pathophysiology of type 2 diabetes and mechanism of action of sitagliptin

Clinical data overview of sitagliptin: Monotherapy (PN021, 023, A201)

Complexities of getting patients to goal: a rationale for earlier combination therapy

Mechanism of action of the co-administration of sitagliptin plus metformin

Clinical data overview of combination therapy with sitagliptin and metformin
Major Pathophysiologic Defects in Type 2 Diabetes

Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels ↑ in response to a meal.

Concentrations of the active intact hormones are increased by JANUVIA™ (sitagliptin phosphate), thereby increasing and prolonging the actions of these hormones.

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.
Sitagliptin - Overview

- Provides potent and highly selective inhibition of the DPP-4 enzyme
- Fully reversible and competitive inhibitor
- DPP-4 inhibitor in development for the treatment of patients with type 2 diabetes, approved by the FDA on October 17 2006, and approved in EU on March 26 2007
- Approved in Korea on September 21 2007
Pharmacokinetics of Sitagliptin Supports Once-Daily Dosing

- With once-daily administration, *trough* (at 24 hrs) DPP-4 inhibition is ~ 80%
  - > 80% inhibition provides full enhancement of active incretin levels

- No effect of food on pharmacokinetics
- Well absorbed following oral dosing

- $T_{\text{max}}$ app 2 hours, $t_{1/2}$ app 12.4 hours at 100 mg dose
- Low protein binding, app 38%
- Primarily renal excretion as parent drug
  - Approximately 80% of a dose recovered as intact drug in urine

- No clinically important drug-drug interactions
  - No meaningful P450 system inhibition or activation
One Dose of Sitagliptin Inhibited Plasma DPP-4 Activity

OGTT=oral glucose tolerance test; AUC=area under the curve
Herman et al. J Clin Endocrinol Metab, November 2006, 91(11):4612–4619. PN005
A Single Dose of Sitagliptin Increased Active GLP-1 and GIP Over 24 Hours

Crossover study in patients with T2DM

Active GLP-1

OGTT 2 hrs (n=55)  
OGTT 24 hrs (n=19)

2-fold increase in active GLP-1  
p< 0.001 vs placebo

Active GIP

OGTT 2 hrs (n=55)  
OGTT 24 hrs (n=19)

2-fold increase in active GIP  
p< 0.001 vs placebo

Herman et al. J Clin Endocrinol Metab, November 2006, 91(11):4612–4619. PN005
A Single Dose of Sitagliptin Increased Insulin, Decreased Glucagon, and Reduced Glycemic Excursion After a glucose Load

Crossover Study in Patients with T2DM

**Insulin**

- Placebo
- Sitagliptin 25 mg
- Sitagliptin 200 mg

**Glucagon**

- p<0.05 for both dose comparisons to placebo for AUC

**Glucose**

- p<0.001 for both dose comparisons to placebo for AUC

Contents

- Pathophysiology of type 2 diabetes and mechanism of action of sitagliptin

- Clinical data overview of sitagliptin:
  - Monotherapy (PN021, PN023, A201, and PN040)

- Complexities of getting patients to goal: a rationale for earlier combination therapy

- Mechanism of action of the co-administration of sitagliptin plus metformin

- Clinical data overview of combination therapy with sitagliptin and metformin
Sitagliptin Consistently and Significantly Lowers A1C with Once-Daily Dosing in Monotherapy

\[ \Delta \text{change vs placebo}^* = \begin{array}{c}
-0.6\% \\
(p<0.001)
\end{array} \]

\[ -0.79\% \\
(p<0.001) \]

\[ -1.05\% \\
(p<0.001) \]

\*between group difference in LS means

Nonaka K et al; A201. Abstracts presented at: ADA 2006
Sitagliptin Provides Significant and Progressively Greater Reductions in A1C with Progressively Higher Baseline A1C

Inclusion Criteria: 7%–10%

<table>
<thead>
<tr>
<th>Baseline A1c (%)</th>
<th>&lt;8%</th>
<th>8–9%</th>
<th>&gt;9%</th>
<th>18-week Study</th>
<th>24-week Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (%)</td>
<td>7.37</td>
<td>8.40</td>
<td>9.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in A1c (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.44</td>
<td>-0.57</td>
</tr>
<tr>
<td></td>
<td>N=96</td>
<td>N=70</td>
<td>N=27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reductions are placebo-subtracted
Sitagliptin Once Daily Significantly Improves Both Fasting and Post-meal Glucose In Monotherapy

**Fasting Glucose**

\[ \Delta \text{FPG}^* = -17.1 \text{ mg/dL (p<0.001)} \]

**Post-meal Glucose**

\[ \Delta \text{in 2-hr PPG}^* = -46.7 \text{ mg/dL (p<0.001)} \]

*LS mean difference from placebo after 24 weeks

Aschner P et al, PN021. Abstract presented at: American Diabetes Association; June 10, 2006; Washington, DC
Sitagliptin Improved Markers of Beta-Cell Function *In 24-Week Monotherapy Study*

**Proinsulin/insulin ratio**

- **Placebo**
  - Ratio (pmol/L / pmol/L)
  - Hatched = Baseline
  - Solid = Week 24

- **Sitagliptin 100 mg**
  - Ratio (pmol/L / pmol/L)
  - Hatched = Baseline
  - Solid = Week 24

\[ \Delta \text{from baseline vs pbo} = 0.078 \]

(95% CI -0.114, -0.023)

**HOMA-\(\beta\)**

- **Placebo**
  - Ratio (pmol/L / pmol/L)
  - Hatched = Baseline
  - Solid = Week 24

- **Sitagliptin 100 mg**
  - Ratio (pmol/L / pmol/L)
  - Hatched = Baseline
  - Solid = Week 24

\[ \Delta \text{from baseline vs pbo} = 13.2 \]

(95% CI 3.9, 21.9)

*P value for change from baseline compared to placebo

Sitagliptin Monotherapy in Asian Patients (PN040)

- A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of Sitagliptin Monotherapy in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control
AHA = antihyperglycemic agent; FPG = fasting plasma glucose; R = randomization; T2DM = type 2 diabetes mellitus.

### Study Design

#### Screening Period
- Patients with T2DM
- ≥18 years of age
- Not on AHA
- A1C ≥7.5% and ≤11%
- On AHA
- A1C ≥7% and ≤10%

#### Run-in Period
- Visit 1: Screening (Wk –9)
- Visit 2: Run-in (Start Wk –8)
- Visit 3: Wk –5
- Visit 4: Wk –2 (Start SB)
- Visit 5: Day 1 (Randomization)

#### Diet/Exercise Period
- Visit 6: Wk 6
- Visit 7: Wk 12
- Visit 8: Wk 18

#### Single-Blind Placebo
- A1C ≥7.5 and ≤11%
- FPG ≥130 mg/dL and ≤ 280 mg/dL

#### Double-Blind Treatment Period
- Sitagliptin 100 mg
- Pbo

#### Randomization (R)
- Visit 8: Wk 18

AHA = antihyperglycemic agent; FPG = fasting plasma glucose; R = randomization; T2DM = type 2 diabetes mellitus.
## Baseline Glycemic and Disease Characteristics Balanced Between Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sitagliptin (n=352)</th>
<th>Placebo (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>50.9 ± 9.3</td>
<td>50.9 ± 9.3</td>
</tr>
<tr>
<td>BMI (mean, kg/m²)</td>
<td>25.1 ± 3.4</td>
<td>24.9 ± 3.4</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.74 ± 1.01</td>
<td>8.75 ± 1.06</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>189.0 ± 44.0</td>
<td>181.6 ± 42.5</td>
</tr>
<tr>
<td>Fasting insulin (μIU/mL)</td>
<td>44.0</td>
<td>10.0 ± 8.4</td>
</tr>
<tr>
<td>Duration of Diabetes Mellitus (yrs)</td>
<td>9.7 ± 8.2</td>
<td>1.9 ± 1.6</td>
</tr>
<tr>
<td>HOMA Beta (%)</td>
<td>2.1 ± 1.7</td>
<td>32.0</td>
</tr>
<tr>
<td></td>
<td>33.0</td>
<td></td>
</tr>
</tbody>
</table>
Change from Baseline in HbA1c
Full-Analysis-Set Population

LS Mean Change from Baseline

Week
0 6 12 18

Sitagliptin 100 mg
Placebo

-1.03%
<table>
<thead>
<tr>
<th>Country</th>
<th>Group</th>
<th>Placebo Subtracted % A1c change</th>
<th>Placebo Subtracted mg/dL FPG</th>
<th>Placebo Subtracted mg/dL PPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Sita (n=119)</td>
<td>-1.36</td>
<td>-38.8</td>
<td>-49.8</td>
</tr>
<tr>
<td></td>
<td>Plbo (n=59)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>Sita (n=158)</td>
<td>-0.68</td>
<td>-18.2</td>
<td>-49.9</td>
</tr>
<tr>
<td></td>
<td>Plbo (n=79)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td>Sita (n=62)</td>
<td>-1.37</td>
<td>-54.5</td>
<td>-90.6</td>
</tr>
<tr>
<td></td>
<td>Plbo (n=31)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HbA1c Reduction in Korean Diabetes Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo Subtracted mg/dL FPG</th>
<th>Placebo Subtracted mg/dL PPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sita (n=62)</td>
<td>-54.5</td>
<td>-90.6</td>
</tr>
<tr>
<td>Plbo (n=31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sitagliptin vs. placebo = -1.37%
Summary
(PN040: Sitagliptin Monotherapy in Asian patients)

- Sitagliptin demonstrated strong glycemic efficacy compared to placebo, as measured by HbA1c, FPG and PPG

- Sitagliptin was overall well tolerated

- No hypoglycemia

- For adverse experiences within GI system organ class, a higher incidence was observed with Sitagliptin
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- Clinical data overview of combination therapy with sitagliptin and metformin
ADA and IDF Guidelines:
Treatment Goals for HbA$_{1c}$, FPG, and PPG

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Level</th>
<th>ADA Goal</th>
<th>IDF Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG, mg/dl (mmol/L)</td>
<td>&lt;110 (&lt;6.1)</td>
<td>90–130 (5.0–7.2)</td>
<td>&lt;100 (&lt;5.5)</td>
</tr>
<tr>
<td>PPG, mg/dl (mmol/L)</td>
<td>&lt;140 (&lt;7.8)</td>
<td>&lt;180 (&lt;10.0)</td>
<td>&lt;140 (&lt;7.8)</td>
</tr>
<tr>
<td>HbA$_{1c}$</td>
<td>4%–6%</td>
<td>&lt;7%*</td>
<td>&lt;6.5%</td>
</tr>
</tbody>
</table>

*Reference to a nondiabetic range of 4.0% to 6.0% using a DCCT-based assay.
ADA=American Diabetes Association; IDF=International Diabetes Federation.
Societies Recommend Earlier Intervention to Help Attain Glycaemic Control

- **2006 Consensus statement from the ADA and EASD**
  - “Our consensus is that an HbA$_{1c}$ of $\geq 7$ should serve as a call to action to initiate or change therapy…”
  - “If lifestyle intervention and maximal tolerated dose of metformin fail to achieve or sustain glycaemic goals, another medication should be added within 2–3 months of the initiation of therapy or at any time when HbA$_{1c}$ goal is not achieved”

- **2005 Global Guideline by IDF**
  - “Begin with metformin unless evidence or risk of renal impairment, titrating the dose over early weeks to minimise discontinuation due to gastro-intestinal intolerance”
  - “Step up doses, and add other glucose-lowering drugs, at frequent intervals until blood glucose control is at target levels”

EASD=European Association for the Study of Diabetes.
HbA$_1$c Levels Above ADA/EASD Target Goals Have Not Triggered Timely Therapy Modifications$^a$

- **Metformin monotherapy (n=513 episodes)**
- **Sulfonylurea monotherapy (n=3394 episodes)**

<table>
<thead>
<tr>
<th>First HbA$_1$c on Treatment</th>
<th>Best HbA$_1$c on Treatment</th>
<th>Last HbA$_1$c before Switch or Addition$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA goal</td>
<td>ADA goal</td>
<td>ADA goal</td>
</tr>
<tr>
<td>EASD goal</td>
<td>EASD goal</td>
<td>EASD goal</td>
</tr>
<tr>
<td>Metformin monotherapy</td>
<td>Sulfonylurea monotherapy</td>
<td></td>
</tr>
<tr>
<td>8.2</td>
<td>7.6</td>
<td>8.8</td>
</tr>
<tr>
<td>7.7</td>
<td>7.1</td>
<td>9.1</td>
</tr>
</tbody>
</table>

$^a$US Physicians; 1994–2002

$^b$Mean number of months that elapsed until a new or additional treatment was started.

$^c$Monotherapy switched to another agent or additional agent added.


ADA=American Diabetes Association.

EASD=European Association for the Study of Diabetes.
Traditional Type 2 Diabetes Management: A “Treat-to-Fail Approach”

Published Conceptual Approach

OAD=oral anti-hyperglycaemic drug.
Less than 50% of Adults With Type 2 Diabetes Have Achieved HbA$_{1c}$ Goals

US Population

UKPDF=United Kingdom Prospective Diabetes Study.
Data adjusted for age, sex, and ethnic group, expressed for white men aged 50–54 years at diagnosis and with mean duration of diabetes of 10 years.
Major Targeted Sites of Oral Drug Classes

DPP-4=dipeptidyl peptidase 4; TZDs=thiazolidinediones.
Mechanisms of Action of Major Oral Monotherapies Are Unable to Address the 3 Core Defects in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Mechanisms of Action</th>
<th>Oral Monotherapies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SUs</td>
</tr>
<tr>
<td>Improves insulin secretion</td>
<td>✓</td>
</tr>
<tr>
<td>Improves insulin resistance</td>
<td></td>
</tr>
<tr>
<td>Lowers hepatic glucose production</td>
<td></td>
</tr>
</tbody>
</table>

SUs=sulfonylureas; TZD=thiazolidinediones; DPP-4=dipeptidyl peptidase 4.
Earlier Use of Combination Therapy May Improve Treating to Target Compared With Conventional Therapy

Published Conceptual Approach

- **Mean HbA1c of patients**
- **OAD=oral anti-hyperglycaemic drug.**
Percentage of patients with type 2 diabetes getting to glycaemic goal is far from optimal.

Current conventional treatment paradigm has been characterised by ‘treatment to failure’ rather than ‘treatment to success’

- Physicians see adverse events and adherence as the main barriers to earlier use of current combination therapy regimens.

Revised/proactive treatment paradigm for type 2 diabetes, involving earlier use of combination therapy, is urgently needed to be more effective in reaching and maintaining HbA$_{1c}$ goals.

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- Clinical data overview of combination therapy with sitagliptin and metformin (PN024)
The Combination of Sitagliptin and Metformin Addresses the 3 Core Defects of Type 2 Diabetes in a Complementary Manner

Sitagliptin improves markers of β-cell function and increases insulin synthesis and release

Sitagliptin indirectly reduces HGO through suppression of glucagon from α cells

Metformin acts as an insulin sensitiser (liver>muscle/fat)

Metformin significantly decreases HGO by directly targeting the liver to decrease gluconeogenesis and glycogenolysis

β-Cell Dysfunction

Insulin Resistance

Hepatic Glucose Overproduction

HGO=hepatic glucose overproduction.
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- Clinical data overview of combination therapy with sitagliptin and metformin (PN024)
HbA$_{1c}$ With Sitagliptin or Glipizide as Add-on Combination With Metformin: Comparable Efficacy

LSM change from baseline (for both groups): –0.7%

Achieved primary hypothesis of non-inferiority to sulfonylurea

Sulfonylurea$^a$ + metformin (n=411)
Sitagliptin$^b$ + metformin (n=382)

Adapted from Nauck MA, Meininger G, Sheng D, et al, for the Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007;9:194–205 with permission from Blackwell Publishing Ltd., Boston, MA.

$^a$Specifically glipizide ≤20 mg/day;
$^b$Sitagliptin 100 mg/day with metformin (≥1500 mg/day).
Per-protocol population; LSM=least squares mean. SE=standard error.
Greater Reductions in HbA\textsubscript{1c} Associated With Higher Baseline HbA\textsubscript{1c} – 52-Week Post Hoc Analysis

<table>
<thead>
<tr>
<th>Baseline HbA\textsubscript{1c} Category</th>
<th>Mean Change From Baseline in HbA\textsubscript{1c}, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7%</td>
<td>-0.1, -0.3</td>
</tr>
<tr>
<td>≥7 to &lt;8%</td>
<td>-0.6, -0.5</td>
</tr>
<tr>
<td>≥8 to &lt;9%</td>
<td>-1.1, -1.1</td>
</tr>
<tr>
<td>≥9%</td>
<td>-1.8, -1.7</td>
</tr>
</tbody>
</table>

- Sulfonlurea\textsuperscript{a} plus metformin
- Sitagliptin\textsuperscript{b} plus metformin

\textsuperscript{a}Specifically glipizide ≤20 mg/day.

\textsuperscript{b}Sitagliptin 100 mg/day with metformin (≥1500 mg/day); Per-protocol population. Add-on sitagliptin with metformin vs sulfonylurea with metformin study.

Sitagliptin With Metformin Provided Weight Reduction (vs Weight Gain) and a Much Lower Incidence of Hypoglycaemia

Least squares mean change over time\textsuperscript{c}

\begin{itemize}
  \item Sulfonylurea\textsuperscript{a} plus metformin (n=416)
  \item Sitagliptin\textsuperscript{b} plus metformin (n=389)
\end{itemize}

\textbf{Hypoglycaemia\textsuperscript{c}}

\begin{itemize}
  \item Sulfonylurea\textsuperscript{a} plus metformin (n=584)
  \item Sitagliptin\textsuperscript{b} plus metformin (n=588)
\end{itemize}

- \(\Delta\) between groups = –2.5 kg
- \(P<0.001\)
- 32% vs 5%
- \(P<0.001\)


\textsuperscript{a}Specifically glipizide \(\leq 20\) mg/day;
\textsuperscript{b}Sitagliptin (100 mg/day) with metformin (\(\geq 1500\) mg/day);
\textsuperscript{c}All-patients-as-treated population.
Summary: Sitagliptin or Glipizide as Add-on Combination With Metformin

Efficacy profile

- Comparable efficacy in lowering HbA₁c
- Both provided greater HbA₁c reductions in patients with the highest baseline HbA₁c

Safety profile

- Both were generally well tolerated
- Adverse event profiles (ie, serious and GI-related adverse events, those leading to discontinuation) were similar, with the exception of hypoglycaemia
  - Significantly lower incidence of hypoglycaemic episodes associated with sitagliptin with metformin
- Body weight significantly decreased for sitagliptin with metformin, but increased for glipizide with metformin

Summary

- Insulin resistance, \(\beta\)-cell dysfunction, and elevated hepatic glucose production are the 3 core pathophysiologies of type 2 diabetes

- Incretins positively affect glucose homeostasis by physiologically helping to regulate
  - Insulin secretion from \(\beta\) cells in a glucose-dependent manner
  - Glucagon secretion in a glucose-dependent manner

- Getting patients to goal may be enhanced by targeting all 3 core defects and hyperglycaemia in the fasting and post-prandial states

Summary (Continued)

- Sitagliptin and metformin have complementary mechanisms of action that address all 3 core defects of type 2 diabetes
- Sitagliptin as add-on combination with metformin provided HbA1c reductions comparable to adding an SU
  - With less hypoglycemia
  - With weight loss

Thank You!