

# **Onglyza™ (saxagliptin): Major Adverse Cardiovascular Events Bristol-Myers Squibb Company (BMS)**

**NDA 22,350**

## **Endocrinologic and Metabolic Drugs Advisory Committee Meeting**

**Silver Spring, Maryland**

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# Overview

- **Introduction to saxagliptin**
- **Clinical Development Program**
- **Phase 3 Study Design**
- **Demographics**
- **Disposition**
- **Duration of Exposure**
- **MACE Analysis**
- **Summary**

# Saxagliptin: Background

- **Onglyza® (saxagliptin) is an oral dipeptidyl peptidase 4 (DPP-4) inhibitor.**
- **Bristol-Myers Squibb is seeking an indication for saxagliptin as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.**

# **Saxagliptin: DPP-4**

- **DPP-4 is the enzyme responsible for inactivation of GLP-1 and GIP, the incretin hormones.**
- **In response to an enteral glucose challenge, the incretins are gut hormones that regulate post-prandial glucose excursion in a glucose-dependent manner.**

# Incretins

- **Incretins regulate post-prandial glucose excursion by:**
  - **Increasing insulin secretion**
  - **Decreasing glucagon release**
- **Because effect is glucose-dependent, hypoglycemia is minimized**

# DPP-4 Inhibitors

- **Januvia™ (sitagliptin) is currently the only FDA-approved DPP-4 inhibitor.**



# **Clinical Development Program: Overview**

- **The Phase 2b/3 program included in the NDA is comprised of 8 studies:**
  - 6 Core Phase 3 studies (24 weeks)**
  - Phase 2b dose-finding study (12 weeks)**
  - Phase 3 mechanism of action study (12 weeks)**

# Core Phase 3 Studies

- Comprised of short-term (ST) and long-term (LT) periods
- At the time of NDA submission, LT periods were ongoing.
- Data from the LT periods were included in the NDA and the 120-Day Safety Update.



# Core Phase 3 Studies: Study Design

Screening



Placebo Lead-in Period (1-4 weeks)



Short-term, Double-blind, Placebo- or  
Active-controlled Treatment Period (24 weeks)



Long-term, Double-blind Period (12 months minimum)

# Entering LT Period

- **Subjects entered the LT period by:**
  - **completing the 24 week ST period without requiring rescue**
  - **requiring rescue during the 24 week ST period and entering LT**

# LT Period

- **For rescued subjects, randomized treatment remained double-blind into the LT period in addition to open-label rescue.**
- **LT period not voluntary**

# **Core Phase 3 Studies: Drug Dosage**

- **Three doses of saxagliptin used:**
  - **2.5 mg**
  - **5 mg (proposed marketing dose)**
  - **10 mg**

# Core Phase 3 Studies

## **Monotherapy Studies**

**CV181011, CV181038**

## **Add-on Combination Studies**

**CV181014, CV181013, CV181040**

## **Initial Combination with Metformin Study**

**CV181039**



# **Core Phase 3 Studies: Efficacy Endpoint**

- **Primary Efficacy Endpoint: change in hemoglobin A1c from baseline to Week 24**

# Rescue criteria

ST Period	LT Period
<ul style="list-style-type: none"><li>•Based on fasting plasma glucose (FPG)</li><li>•Cut-off values ranged from FPG&gt;200 to FPG&gt;240</li></ul>	<ul style="list-style-type: none"><li>•Based on HbA1c</li><li>•Cut-off values ranged from HbA1c&gt;7.0% to HbA1c&gt;8.0%</li></ul>

# Open Label Rescue Treatment

Study	Rescue Treatment
Monotherapy	Metformin 500 mg
Add-on to Met	Pioglitazone 15 mg
Add-on to SU	Metformin 500 mg
Add-on to TZD	Metformin 500 mg
Initial Combination with Metformin	Pioglitazone 15 mg



# Baseline Demographics

- Include:
  - Age
  - DM Duration
  - History of CAD
  - Previous DM treatment
- Important in interpreting Forest plots
  - Define cardiovascular risk of population
  - Presenting unpooled data

# Demographics: Monotherapy Studies

Demographic	11	38
Age (yrs.) Mean (SD)	53 (11)	55 (10)
DM Duration (yrs.) Mean (SD)	3 (3)	2 (3)
History of CAD	5%	13%
Previous DM treatment	2.5%	5%

# Demographics:

## Initial Combination with Metformin Study

Demographic	39 Met
Age (yrs.) Mean (SD)	52 (11)
Duration of DM (yrs.) Mean (SD)	1.7 (3.1)
History of CAD	8%
Previous DM treatment	2%

# Demographics:

## Add-on Combination Studies

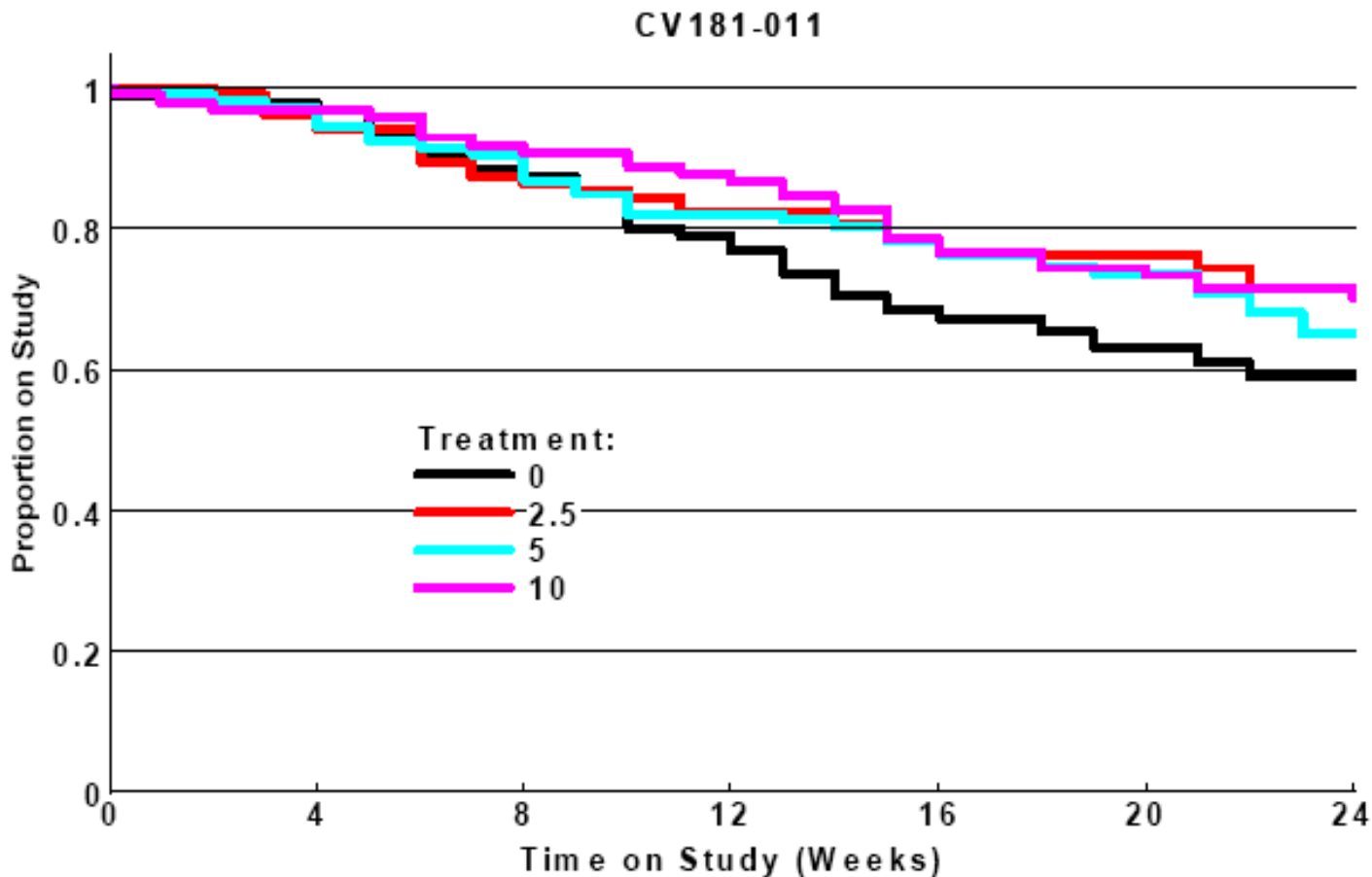
Demographic	14Met	40SU	13TZD
Age (yrs.) Mean (SD)	55 (10)	55 (10)	54 (10)
DM Duration (yrs.) Mean (SD)	6.5 (5)	6.9 (6)	5 (5)
History of CAD	3%	3%	4%
Previous DM treatment	100%	100%	100%

# Disposition For ST Period

- **Across all Core Phase 3 studies, 74% of subjects completed the ST period.**
- **Majority of drop-outs due to rescue**
- **Examples:**
  - **Monotherapy**
  - **Add-on Combination Studies**

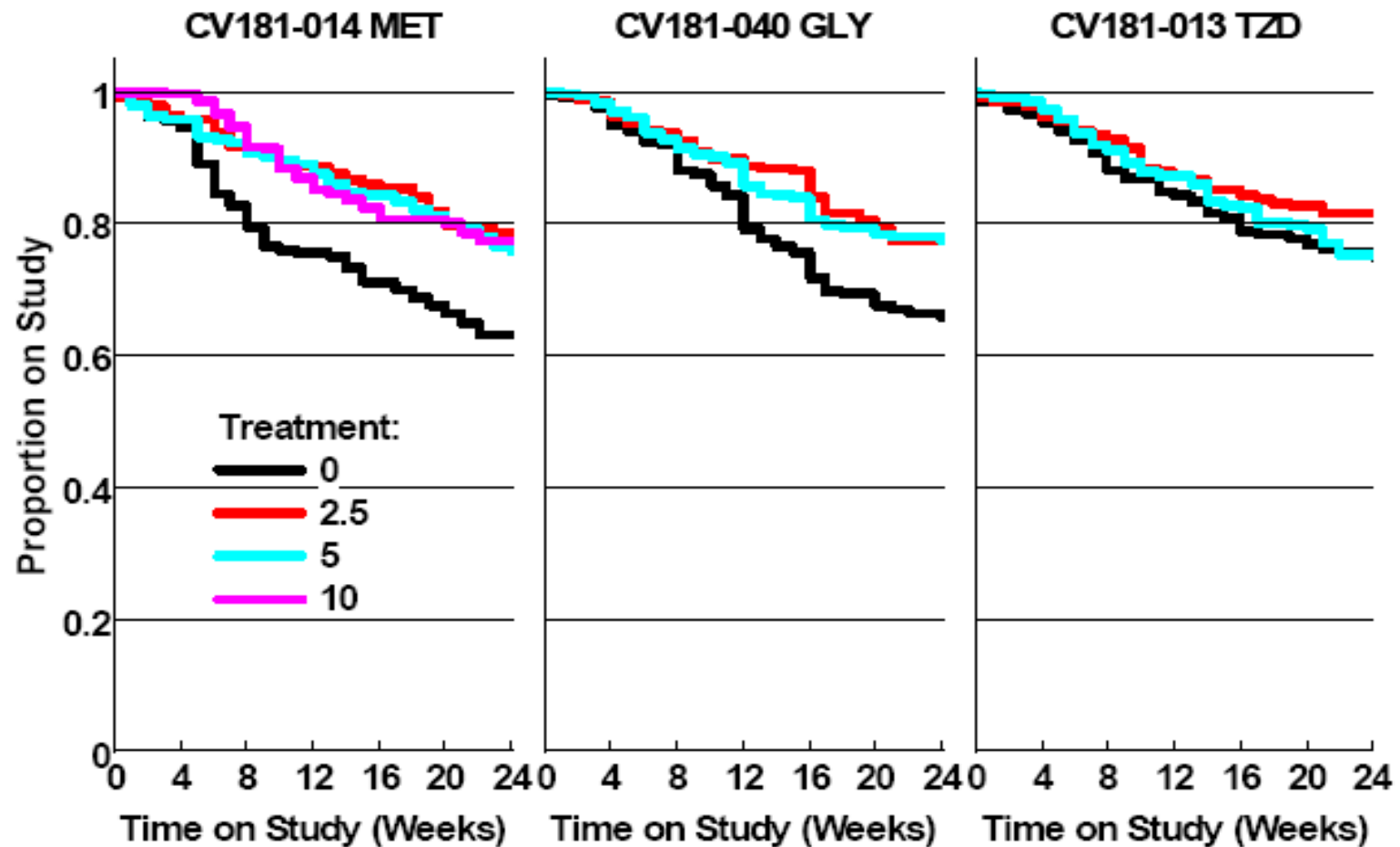
# ST Patient Disposition

## Monotherapy Study CV181-011



# Patient Disposition

## Add-on Combination Studies



# Disposition in LT Periods

- **Proportion of randomized subjects entering LT period: 78%-90%**
- **As of the 120-Day Safety Update, proportion of subjects who continue in:**
  - **Monotherapy: 50-58%**
  - **Add-on Combination: 29-77%**
  - **ICM: 66-77%**



# Exposure

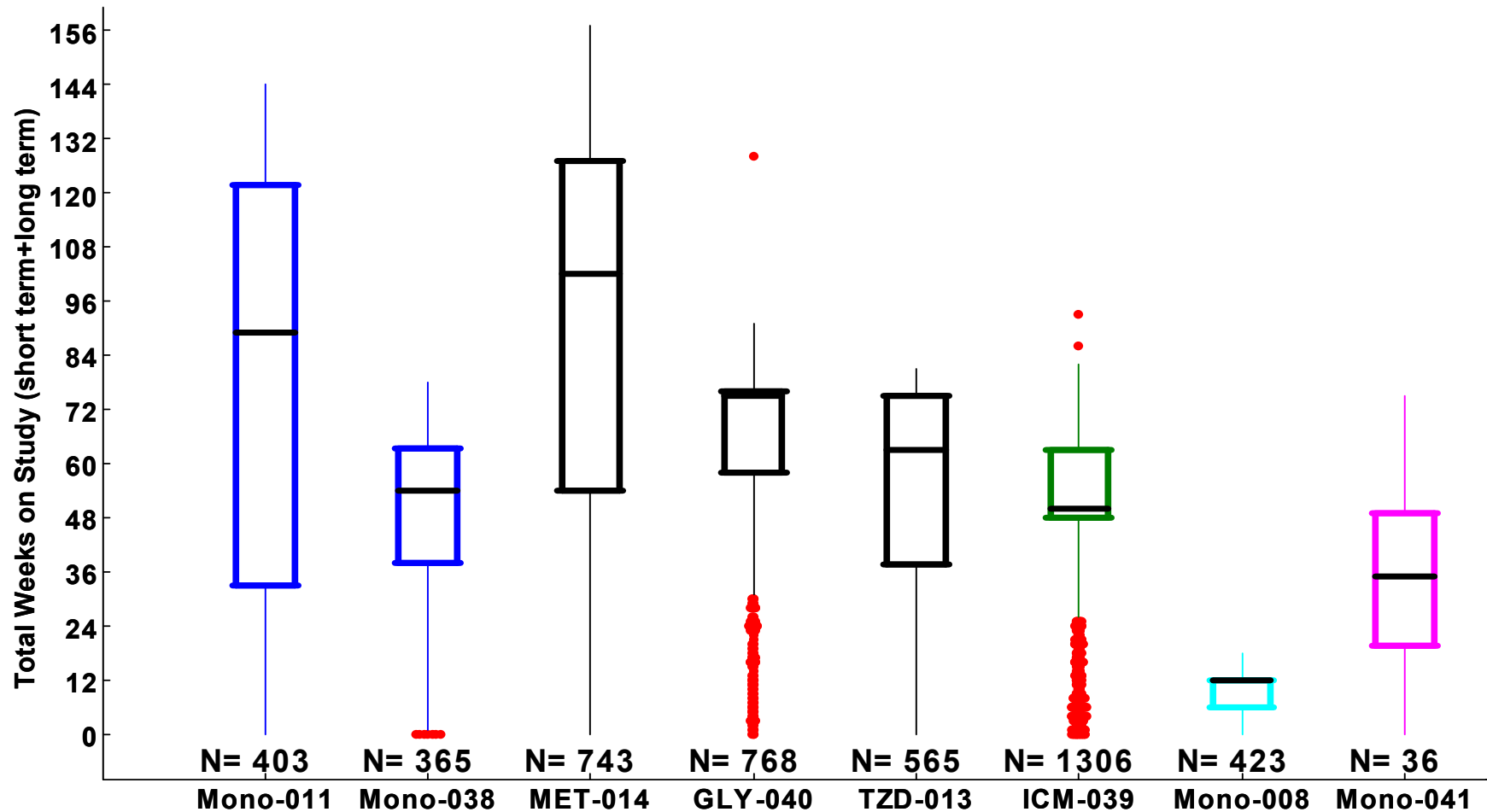
- **Important for Forest plots**
- **Analyses performed by FDA and the Applicant were based on exposures from the ST + LT periods.**
  - **includes rescued subjects**
  - **includes data from the 120-day Safety Update**

# **Exposure: Saxagliptin-treated Subjects**

	<b>NDA</b>	<b>Safety Update</b>
<b>N <math>\geq</math>24 Weeks</b>	<b>2642</b>	<b>2655</b>
<b>N <math>\geq</math>52 Weeks</b>	<b>1080</b>	<b>1937</b>

# Total Duration of Exposure ST+LT

## Includes Safety Update Data



# **MACE: Analysis Populations**

- **Database for MACE analyses requested composed of 8 Phase 2b/3 Studies**
- **Seven of eight are placebo-controlled -ICM (39) contained active and placebo comparisons**

# **MACE: Analysis Populations**

- **Analyses requested by FDA were performed of the following:**
  - 1) Short-term (ST), 24-week periods**
  - 2) Short-term (ST) plus long-term (LT) periods (120-day Safety Update database)**

# **MACE: Analysis Endpoints**

## **Intent:**

- 1) Broad: Capture all possible strokes and myocardial infarctions**
- 2) Specific: Include terms which, when chosen by the Investigator, were likely to represent true myocardial infarction or stroke**

# **MACE: Analysis Populations**

**Two endpoints were chosen when evaluating these study periods:**

- 1) Broad SMQ MACE**
- 2) Custom MACE**

**+ Cardiovascular deaths**

# Broad SMQ MACE: Definition

- **Composite endpoint that included:**
  - **all cardiovascular deaths**
  - **all preferred terms in the Standardized MedDRA Queries (SMQ) for:**
    - » **“Myocardial Infarction”**
    - » **“Central Nervous System Hemorrhages and Cerebrovascular Accidents”**



# **Custom MACE: Defined**

- **A subset of “Broad SMQ MACE”**
- **Developed by collaboration and consensus of 3 FDA reviewers**

# **Custom MACE: Defined**

- **Selected terms which:**
  - **Seemed highly likely to represent events that would truly be a myocardial infarction or stroke**
  - **Represented events which were acute and atherosclerotic in mechanism**

# Preferred Terms for MACE

## Analyses: Examples

	Broad	Custom
<b>Myocardial Infarction Terms</b>		
<b>Acute MI</b>	✓	✓
<b>Blood CPK Increased</b>	✓	
<b>Stroke Terms</b>		
<b>CVA</b>	✓	✓
<b>Paralysis</b>	✓	

# Incidence: Custom MACE

**Custom MACE: Total Subjects with an Event for the ST and ST + LT Periods**

	<b>Comparator</b>  <b>N=1251</b>	<b>Saxa</b> <b>2.5 mg</b> <b>N=937</b>	<b>Saxa</b> <b>5 mg</b> <b>N=1269</b>	<b>Saxa</b> <b>10 mg</b> <b>N=1000</b>
<b>ST</b>	<b>7 (0.6%)</b>	<b>1 (0.1%)</b>	<b>1 (&lt;0.1%)</b>	<b>2 (0.2%)</b>
<b>ST + LT</b>	<b>17 (1.4%)</b>	<b>6 (0.6%)</b>	<b>6 (0.5%)</b>	<b>11(1.1%)</b>

# Analysis Results:

## Custom MACE

**Custom MACE: Total Subjects with an Event (%) for the ST and ST + LT Periods**

	<b>Comparator</b>	<b>All Saxagliptin</b>
	<b>N=1251</b>	<b>N=3356</b>
<b>ST</b>	<b>7 (0.6%)</b>	<b>4 (0.1%)</b>
<b>ST + LT</b>	<b>17 (1.4%)</b>	<b>23 (0.7%)</b>

# Analysis Results:

## Custom MACE Events by SOC

### ST Period

System-Organ-Class	Comparator	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg
Cardiac Disorders	5 (0.4%)	0	0	1 (0.1%)
General Disorders	1 (<0.1%)	0	0	0
Nervous System Disorders	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	1 (0.1%)

# Custom MACE Events under Cardiac Disorders SOC for ST Period

	Comparator	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg
Acute MI	1 (<0.1%)	0	0	0
Cardiac Failure	1 (<0.1%)	0	0	0
Cardiogenic Shock	1 (<0.1%)	0	0	0
Myocardial Infarction	3 (0.2%)	0	0	1 (0.1%)

# Custom MACE Events under Nervous System Disorders SOC for ST Period

	Comparator	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg
CVA	1 (<0.1%)	1 (0.1%)	1 (<0.1%)	0
Hemorrhagic Stroke	0	0	0	1 (0.1%)



# Analysis Results: Broad (SMQ) MACE

**Broad MACE: Total Subjects with an Event for the ST and ST + LT Periods**

	<b>Comparator</b> <b>N=1251</b>	<b>Saxa</b> <b>2.5 mg</b> <b>N=937</b>	<b>Saxa</b> <b>5 mg</b> <b>N=1269</b>	<b>Saxa</b> <b>10 mg</b> <b>N=1000</b>
<b>ST</b>	<b>25 (2.0%)</b>	<b>16 (1.7%)</b>	<b>18 (1.4%)</b>	<b>19 (1.9%)</b>
<b>ST + LT</b>	<b>41 (3.3%)</b>	<b>28 (3.0%)</b>	<b>37 (2.9%)</b>	<b>30 (3.0%)</b>

# Analysis Results:

## Broad (SMQ) MACE

**Broad MACE: Total Subjects with an Event for the ST and ST + LT Periods**

	<b>Comparator</b>	<b>All Saxagliptin</b>
	<b>N=1251</b>	<b>N=3356</b>
<b>ST</b>	<b>25 (2.0%)</b>	<b>58 (1.7%)</b>
<b>ST + LT</b>	<b>41 (3.2%)</b>	<b>100 (3.0%)</b>

# Analysis Results:

## Broad MACE Events by SOC for ST Period

System-Organ-Class	Comparator	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg
Cardiac Disorders	5 (0.4%)	0	0	1 (0.1%)
General Disorders	1 (<0.1%)	0	0	0
<b>Investigations</b>	<b>14 (1.1%)</b>	<b>14 (1.5%)</b>	<b>17 (1.3%)</b>	<b>16 (1.6%)</b>
Nervous System Disorders	5 (0.4%)	1 (<0.1%)	1 (<0.1%)	2 (0.2%)
Vascular Disorders	0	1 (0.1%)	0	1 (0.1%)



# Broad SMQ MACE Events under Investigations for ST + LT Periods

	Comparator	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg
<b>Blood CPK Increased</b>	<b>19 (1.5%)</b>	<b>19 (2.0%)</b>	<b>28 (2.2%)</b>	<b>17 (1.7%)</b>
<b>EKG ST Segment Abnormal</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.1%)</b>	<b>0</b>
<b>Blood CPK-MB Increased</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.1%)</b>

# **Results of MACE Analyses**

**Issues to Consider  
Statistical Methods**

**Overview**

**SMQ MACE**

**Custom MACE**

**Subgroups**



# Considerations for MACE Analyses

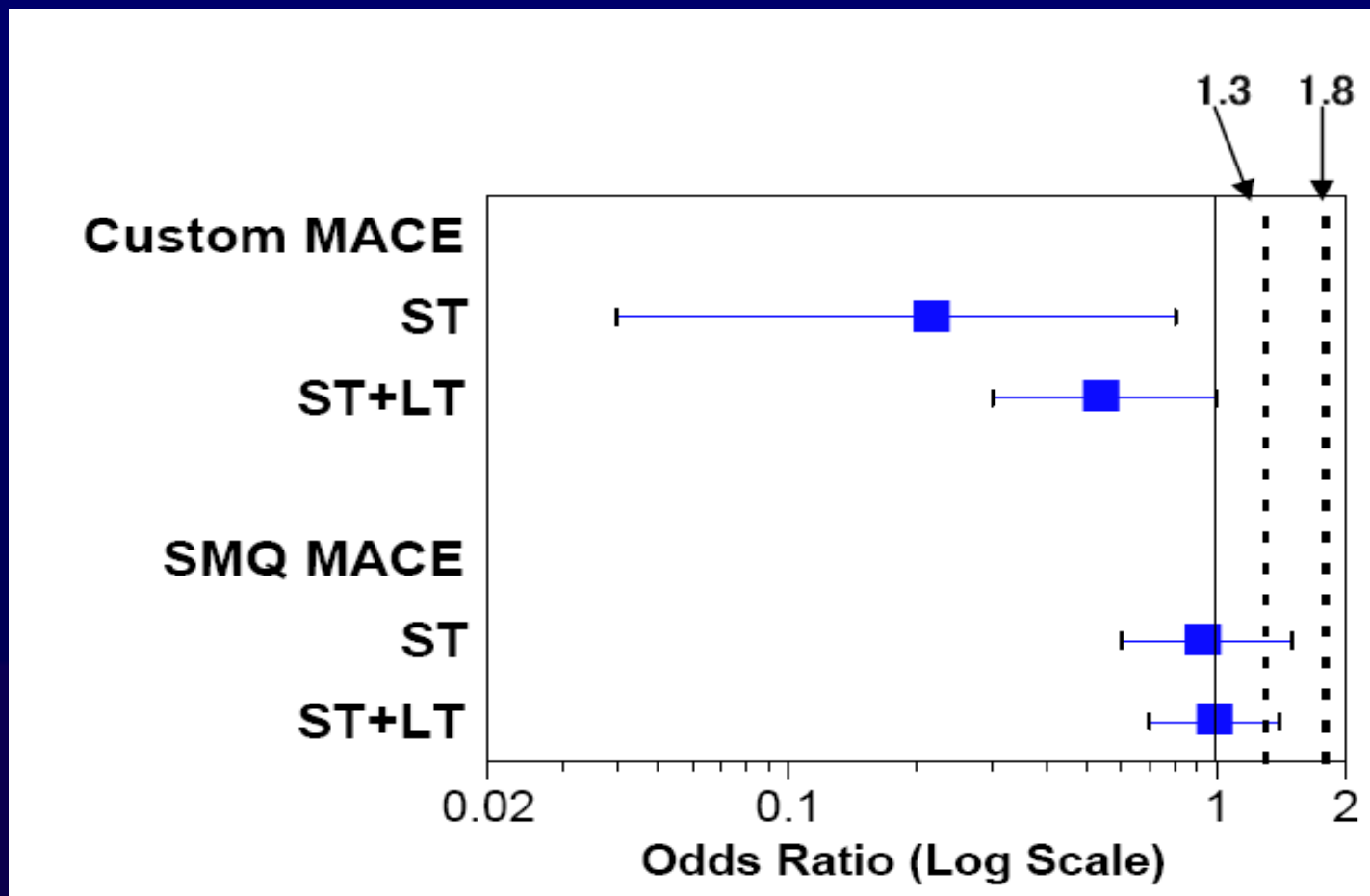
- **Two MACE Endpoints**
  - SMQ (Broad) vs. Custom (Narrow)
- **Two Time Periods**
  - Short-term
    - Double-blind, no rescue
  - Short-term + Long-term
    - Double-blind
    - Open label rescue medication for ~1/3 pts
- **Multiple Statistical Methods**
  - Rare events

# Statistical Methods for Estimates Stratified on Study

- **Risk Difference**
  - Mantel-Haenszel estimate based on fixed effects model
- **Incidence Rate Ratio**
  - Exact procedure based on BMS Poisson model
- **Odds Ratio**
  - Exact test of 2x2 contingency tables
  - Forest plots include Mantel-Haenszel estimate with continuity correction

# Overall MACE Results

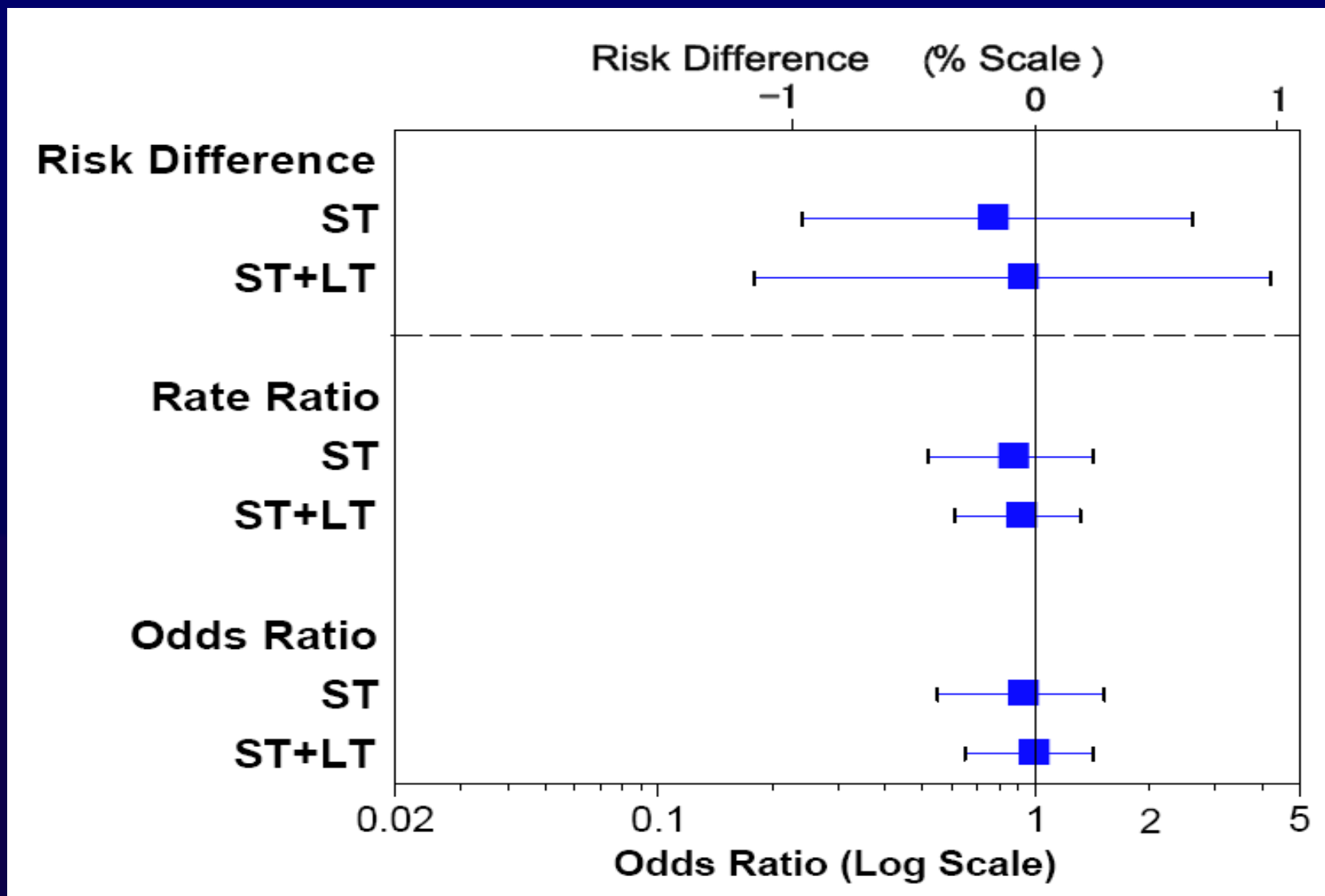
## Common Odds Ratios (95% CI) Stratified by Study





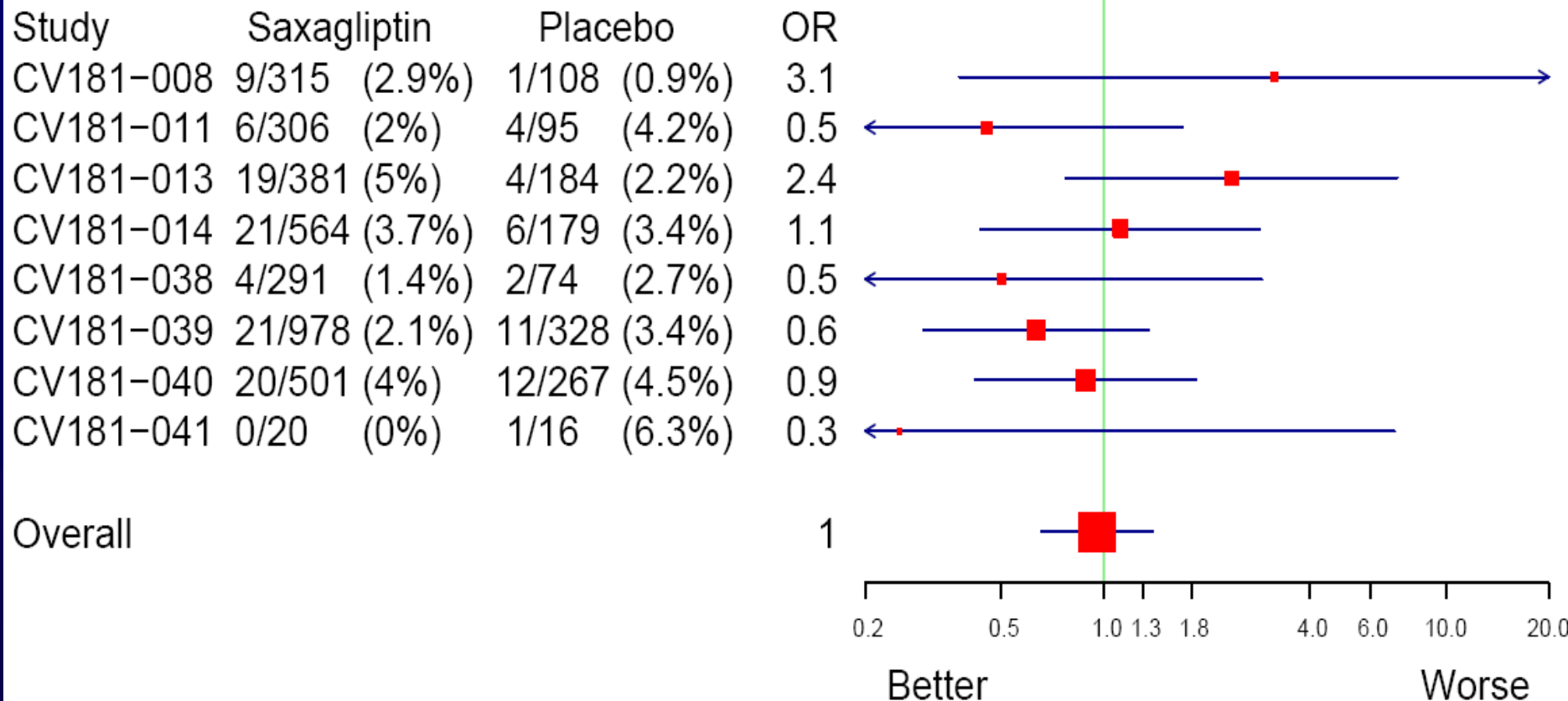
# Broad SMQ MACE Results of 3 Analyses

24-week short-term period (ST) & short-term plus long-term (ST+LT)



# Forest Plot of Broad SMQ MACE

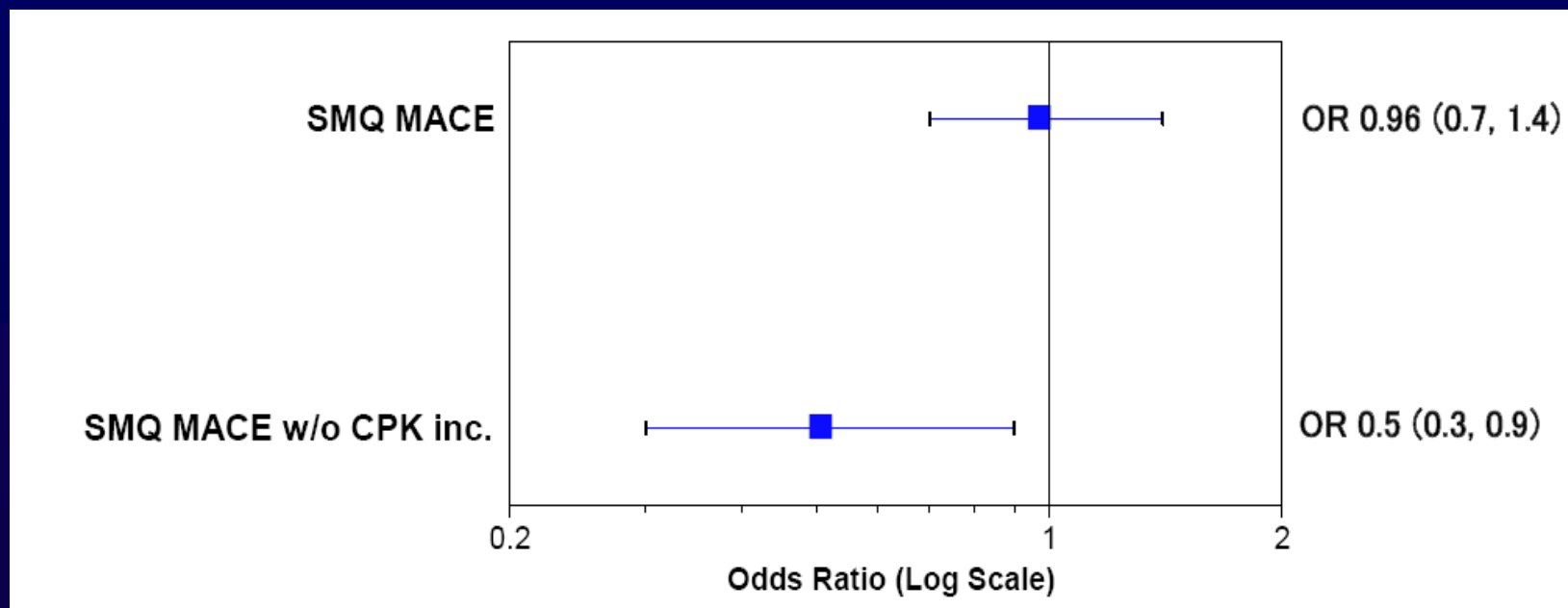
## Odds Ratios ST+LT



# Broad SMQ MACE Results

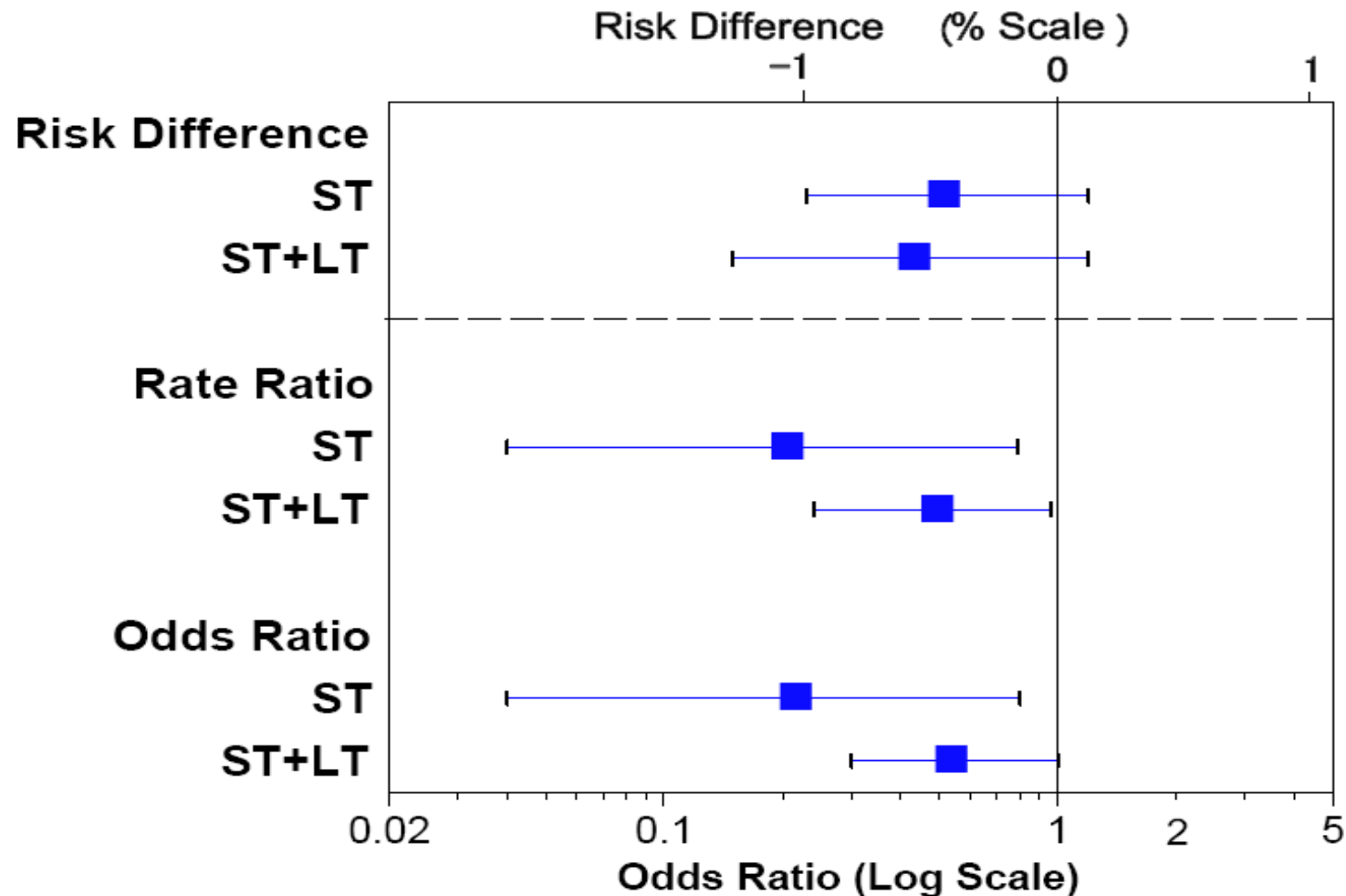
Common Odds Ratios (95% CI) Stratified by Study

- 50 of 58 SMQ events for saxagliptin and 14 of 25 SMQ events for comparator were recorded as “blood creatine phosphokinase (CPK) increased”
- Exclusion of preferred term for CPK increase from analysis produces results similar to Custom MACE

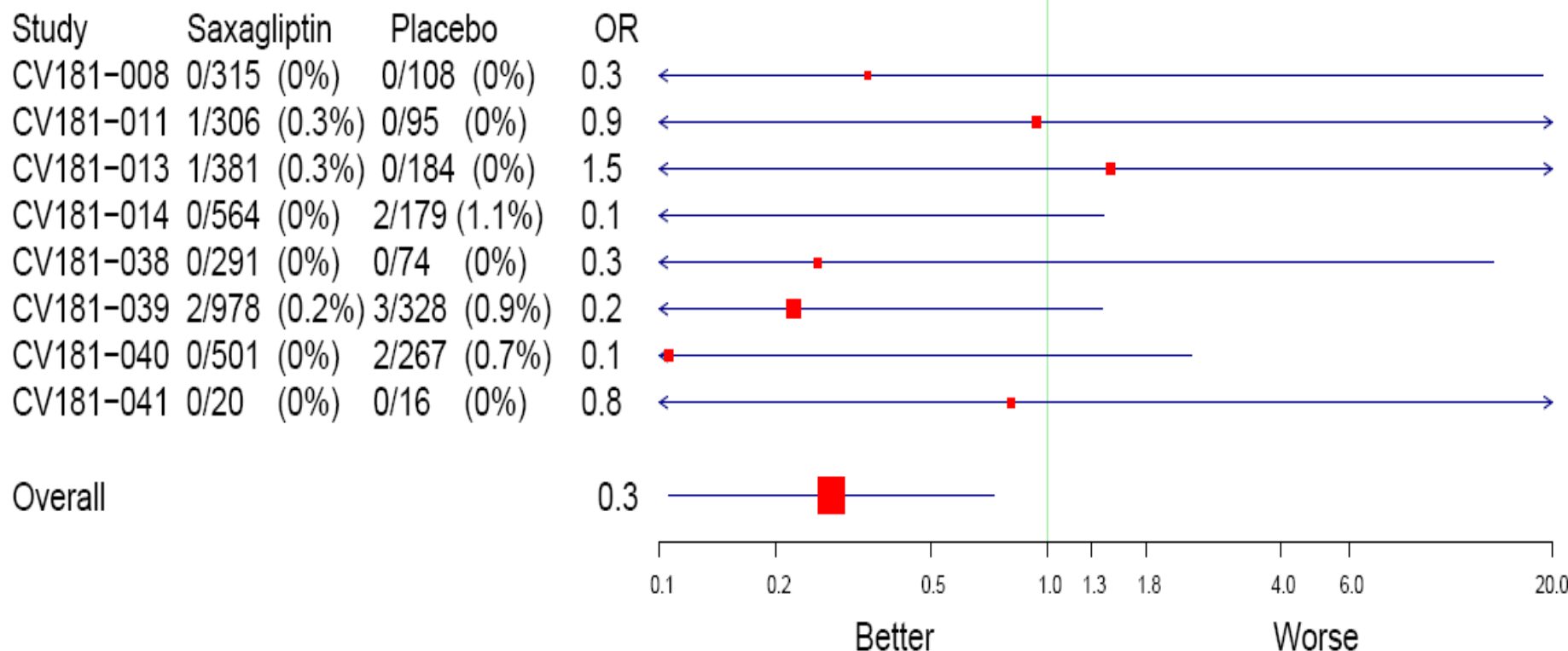


# Custom MACE Results of 3 Analyses

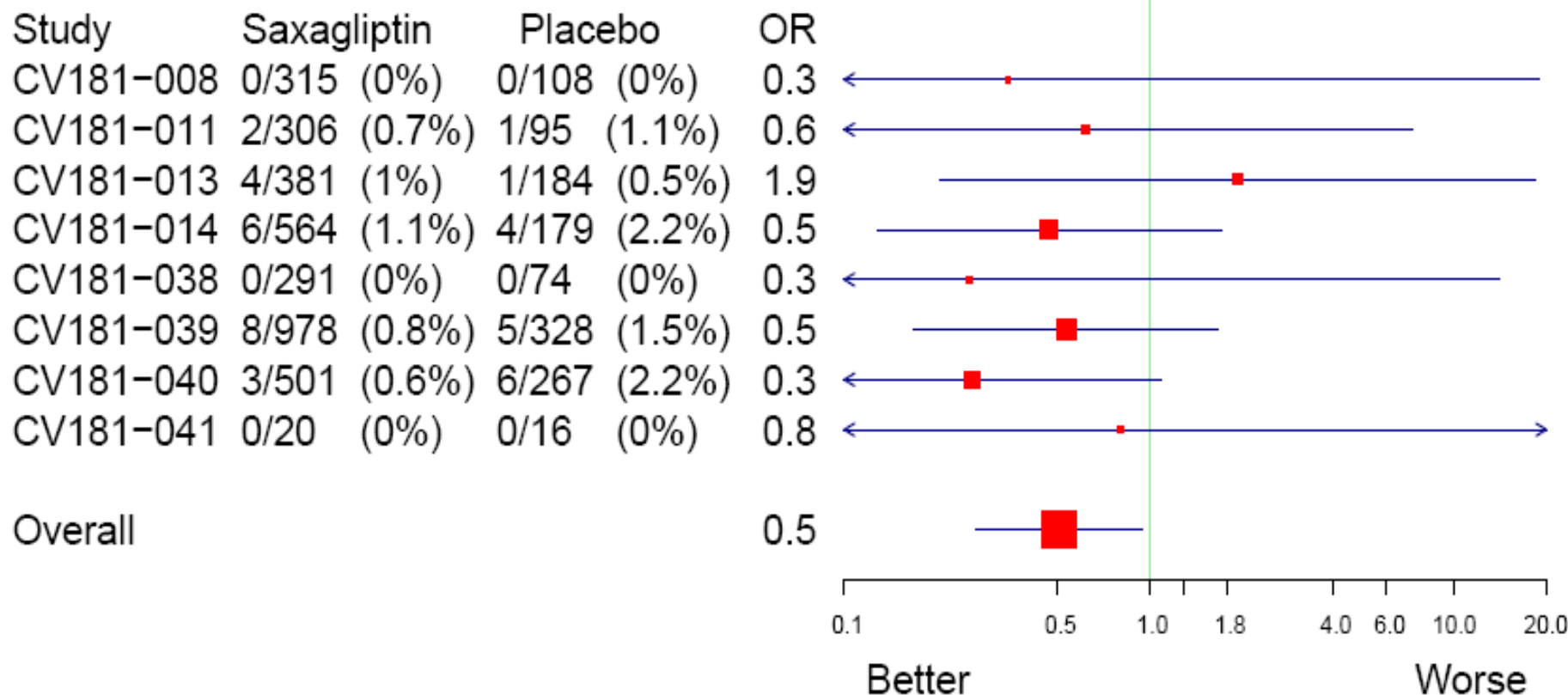
24-week short-term period (ST) & short-term plus long-term (ST+LT)



# Forest Plot of Custom Mace Odds Ratios ST



# Forest Plot of Custom Mace Odds Ratios ST+LT



# **Study CV181013**

## **Custom MACE Events by Background TZD (ST+LT)**

	<b>PLA</b>	<b>SAXA 2.5</b>	<b>SAXA 5.0</b>
<b>Background PIO</b>	<b>0/108</b>	<b>2/102</b>	<b>0/108</b>
<b>Background ROSI</b>	<b>1/76</b>	<b>1/93</b>	<b>1/78</b>

# Custom MACE ST+LT

## Subgroup Results for Type of Study, Sex and Age

Monotherapy N=1225 Control 0.3%

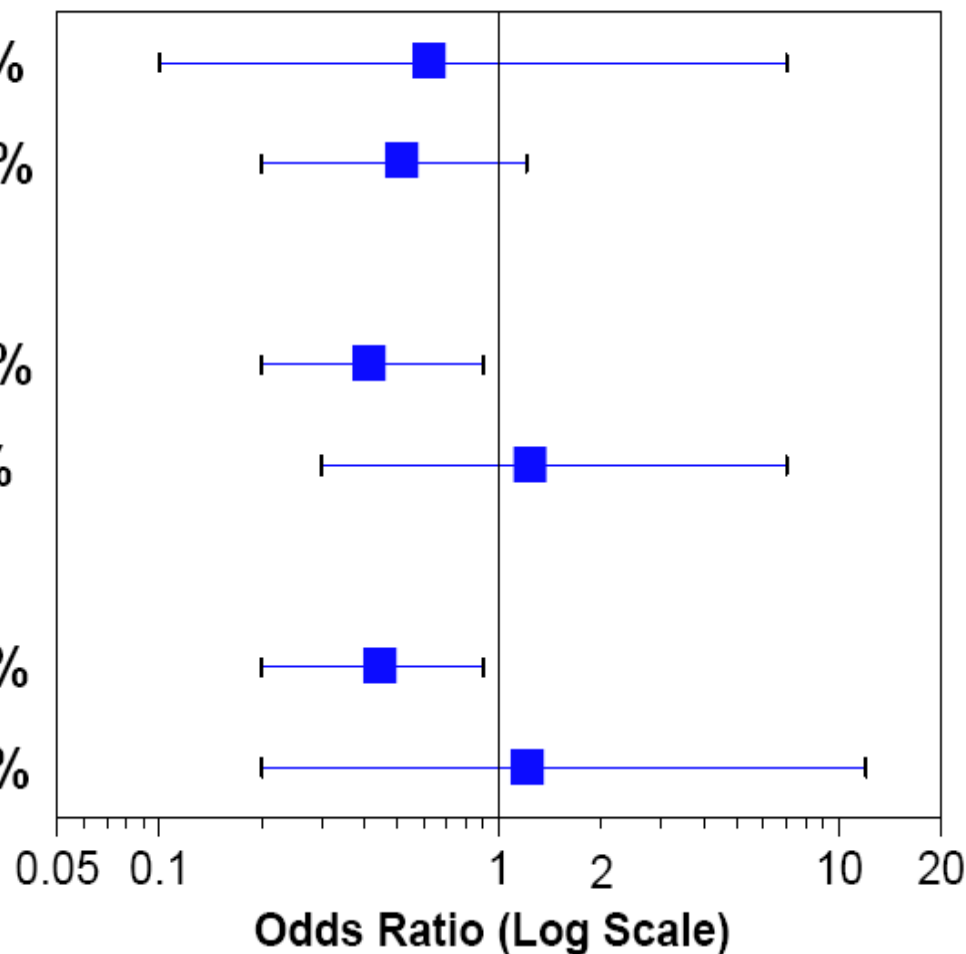
Add-on N=2076 Control 1.8%

Male N=2279 Control 2.3%

Female N=2328 Control 0.5%

<65 years N=3908 Control 1.4%

65 or older N=699 Control 1.0%





# MACE: Summary

	<b>Saxagliptin N=3356</b>	<b>Comparator N=1251</b>	<b>Common Odds Ratio Stratified on Study (95% CI)</b>
<b>BMS MACE ST + LT</b>	<b>17 (0.5%)</b>	<b>12 (1.0%)</b>	<b>0.5 (0.2, 1.2)</b>
<b>Custom MACE ST</b>	<b>4 (0.1%)</b>	<b>7 (0.6%)</b>	<b>0.21 (0.04, 0.8)</b>
<b>ST + LT</b>	<b>23 (0.7%)</b>	<b>17 (1.3%)</b>	<b>0.52 (0.3, 1.0)</b>
<b>SMQ MACE ST</b>	<b>58 (1.8%)</b>	<b>25 (2.0%)</b>	<b>0.90 (0.6, 1.5)</b>
<b>ST + LT</b>	<b>100 (3.1%)</b>	<b>41 (3.2%)</b>	<b>0.96 (0.7, 1.4)</b>

# Summary

- Patient populations comparable across studies
  - Low events rates (<2% annual rate for Custom MACE)
- Consistent results for Custom MACE and SMQ MACE when excluding PT “increased CPK”
- ST+LT results (including follow-up of rescued subjects) were consistent with the ST results
- MACE results were not dependent on statistical method used
- Analyses of all endpoints yielded estimates of common odds ratio <1 and upper bounds for 95% CI<1.8

# Acknowledgements

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