Novel Trial Designs in T2D to Satisfy Regulatory Requirements for CV Safety

Anders Svensson  MD, PhD
Head of Global Clinical Development – Metabolism,
F Hoffmann – LaRoche Ltd.
Basel, Switzerland

• Overview of Planned Phase 3 Program
  - 3 studies:
    • Core Phase 3 study
    • Monotherapy study
    • Study vs. active comparators (DPPIV and Pioglitazone)

  - Studies under consideration (timing TBD):
    • One year monotherapy study for EU filing (comparison to SU)

  • Mechanistic studies:
    - CV imaging to support CV potential advantage
    - Insulin clamp to evaluate beta-cell function
    - Studies to support FDCs (metformin, pioglitazone)
• Core Phase 3 Study – Objectives
  
  - General Objectives
    • To support the registration for the treatment of type 2 diabetes as an adjunct therapy to diet and exercise
    • To eliminate with high confidence any unreasonable increased cardiovascular risk when used in patient with type 2 diabetes as add-on to standard of care as compared to placebo
  
  - Specific objectives:
    • Primary:
      - To assess the effects vs. placebo, added on to standard of care, on glycemic control (as assessed by HbA1c) after 24 weeks in type 2 diabetes mellitus patients sub-optimally controlled on their current anti-diabetic therapy
      - To assess the effects of vs. placebo, added on to standard of care, on major adverse cardiovascular events (MACE) in type 2 diabetes patients
    • Secondary:
      - To assess the overall safety and tolerability, with a particular focus on cardiovascular effects, when added to standard of care management of diabetes and cardiovascular disease risk factors

• Core Phase 3 Study – General Design

<table>
<thead>
<tr>
<th>N=6030</th>
<th>Filing analysis</th>
<th>End of study</th>
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<tbody>
<tr>
<td>20% standard T2D</td>
<td>Treatment</td>
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<tr>
<td>80% high CV risk</td>
<td>Standard of Care (SoC) + Dose A</td>
<td>(2 Weeks)</td>
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<td>(6 months + ~64 months)</td>
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<tr>
<td></td>
<td>Standard of Care (SoC) + Dose B</td>
<td>(2 Weeks)</td>
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<td></td>
<td>Standard of Care (SoC) + Placebo</td>
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- **Primary Endpoints**: HbA1c, MACE

- **Allowed treatment combinations**
  - add-on to metformin
  - add-on to SU
  - add on to Met + SU (EU)
  - add- on TZDs
  - add-on to insulin
  - add-on to DPP1IV
  - add-on to GLP1

* No treatment modification allowed in SoC treatment until 6 months. Then optimization of SoC treatment if needed. Specific conditions in III
• Study Schedule

- Initial screening period: \( \leq 2 \text{ weeks} \)
- 2-week single blind placebo run-in period:
  - to determine compliance with study medication.
  - Subjects with \( < 80\% \) compliance, determined from pill count, will be withdrawn from participating in the study
- Double-blind treatment period:
  - the duration is event-driven and
  - will be determined by the accrual of the requisite number of adjudicated and positively confirmed primary occurrences of the composite MACE endpoint.
  - Subjects will be allocated to receive one of three treatments in a 1:1:1 ratio
- Dose A, dose B or matching placebo tablet will be given once daily (QD) in the morning

• Study Schedule

- Primary glycemic efficacy endpoint:
  - HbA1c change from baseline to 24 weeks
- Primary cardiovascular composite endpoint:
  - CV death, MI and stroke (MACE) will be event-driven
  - will be assessed at two timepoints:
    - First, when 137 adjudicated and confirmed first occurrences of the primary CV endpoint are accrued and,
    - Second, when 687 confirmed events are accrued.
- Follow-up:
  - All patients that have received at least one dose of study medication will have a telephone follow-up visit 2 weeks after their last visit
  - All patients will receive contemporary management of type 2 diabetes and cardiovascular risk factors according to local, country-specific standards of care.
  - After week 24 the dose of RO4998452 will be force-titrated to the high dose except in the event of hypoglycemia or if the high dose is not tolerated by individual patients.
• Study Population ("All comers" approach):

  • Metformin:
    – monotherapy
    – in combination with OADs
  • Insulin:
    – monotherapy
    – in combination with ≤ 2 OADs
  • SU:
    – monotherapy
    – in combination with OADs
  • TZD:
    – monotherapy (not indicated in EU)
    – in combination with OADs
  • DPPIV inhibitors (potential small sample size)
    – monotherapy
    – in combination with OADs
  • GLP1 agonists (potential small sample size)
    – monotherapy
    – in combination with OADs

  Note: Only Regimen Excluded:
  - Diet and exercise alone
  - ≥ 2 OADs in addition to insulin

Stratification

- Within each background anti-diabetic regimen the randomization to the three treatment arms (Dose A or Dose B of active treatment or placebo) will be stratified:
  - Six collectively exhaustive and mutually exclusive background therapies (See next slide for proposed scheme)
  - A minimum of 405 patients are needed to test the glycemic efficacy within each of the six background antidiabetic regimens (135 per treatment arm to provide >90% power to detect a difference of at least 0.5% between treatment arms assuming a standard deviation of 1.2% with an estimated withdrawal rate of 10%).

- By CV risk:
  - Patients at higher cardiovascular risk with evidence of established cardiovascular disease (documented coronary, cerebrovascular or peripheral artery disease) with onset between ≥ 30 days and ≤ 5 years prior to screening and who are stable in the Investigators’ opinion (at least 80% of patients)
  - Patients with moderate risk based on cardiometabolic risk factors, including type 2 diabetes (no more than 20% of patients)

- By HbA1c at screening
  - ≤ 8.0%
  - > 8.0%
Background Anti-Diabetic Therapy

All patients will fall within one of the following six exhaustive and mutually exclusive regimens of background anti-diabetic treatment at Screening:

1. Metformin monotherapy
2. Metformin + sulfonylurea
3. Sulfonylurea alone or combined with any non-metformin, non-incretin or non-TZD oral therapy
4. TZD alone or combined with sulfonylurea, metformin, metformin plus sulfonylurea, or any other oral therapy with or without metformin and/or sulfonylurea, but not any incretin-based oral or injected therapy
5. Any approved incretin-based therapy (DPP-4 inhibitor or GLP-1 analogue) alone or combined with sulfonylurea or metformin or TZD and any triple or quadruple therapy regimen which includes an incretin-based therapy.
6. All insulins, alone or combined with any 1 or 2 antidiabetic agents

Thank you for your attention