Impact of COVID-19 and risk mitigation in a global cardiovascular outcomes trial

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**PARADISE-MI**: Prospective ARNI versus ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction

**Primary objective**: To evaluate the efficacy and safety of LCZ696, compared to ramipril, in addition to conventional post-AMI treatment, in reducing the occurrence of composite endpoint of CV death, HF hospitalization and outpatient HF (time-to-first event analysis) in post-MI patients.

**Population**: Spontaneous AMI with the evidence of left ventricular dysfunction and/or pulmonary congestion associated with the index MI, without prior known history of chronic HF.
PARADISE-MI: Status

- Event-driven trial targeting a total of 708 primary endpoint events (first event of CV death, heart failure hospitalization, or outpatient heart failure)
- First patient enrolled in December 2016
- Recruitment completed in March 2020: 5,670 patients randomized in 41 countries
- One interim analysis (IA) was planned and performed with strict stopping boundaries
- Study is ongoing
COVID-19 Impact

Mitigation plan and strategies

Minimize treatment interruption (special courier delivery, increase drug stock at country depot/site)

CRF update to collect information related to COVID-19 impact

Develop options to manage impact of pandemic and maintain ability to answer the scientific question of interest

Consistent with findings in Hall, et al. 2020 which shows a >50% reduction in HF hospitalizations during the pandemic
Options Considered (May 2020)

For PARADISE-MI study, approximately 80% primary endpoint events had been accrued prior to the impact of the COVID-19 pandemic (March 1, 2020).

<table>
<thead>
<tr>
<th>Options</th>
<th>Impact / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do nothing</td>
<td><strong>Potential power loss</strong> for the primary analysis depending on possible dilution of treatment effect during the COVID-19 impacted phase</td>
</tr>
<tr>
<td>2. Close out the trial early</td>
<td><strong>Power loss</strong> for the primary analysis due to omitting 20% of information</td>
</tr>
<tr>
<td>Primary analysis using data censoring at March 1, 2020. All additional data used for supplementary analyses</td>
<td></td>
</tr>
<tr>
<td>3. Continue the trial but alter primary analysis</td>
<td><strong>Power loss</strong> for the primary analysis due to omitting 20% of information</td>
</tr>
<tr>
<td>Using data censoring at March 1, 2020; All additional data used for supplementary analyses</td>
<td></td>
</tr>
<tr>
<td>4. Add second interim analysis with data censoring at March 1, 2020. If study continues to the end, run primary analysis as planned based on all data.</td>
<td>Motivated by <strong>uncertain impact of COVID-19 pandemic</strong>. Allows investigation of the scientific question of interest based on data <strong>unaffected by the COVID-19 pandemic</strong> with <strong>limited power loss</strong></td>
</tr>
<tr>
<td>5. Re-evaluate in a few months</td>
<td></td>
</tr>
</tbody>
</table>
Proposed COVID-19 related supplementary analyses

- Analysis of primary endpoint data accrued prior to March 1\textsuperscript{st} 2020 (censoring at presumed global COVID-19 impact start date)
- Analysis of primary endpoint data accrued prior to a subject-specific COVID-19 impact start date, as derived from the new CRF
- Analysis of primary endpoint data accrued during the study, using a Cox model with a “during-COVID” indicator and it’s interaction with treatment as time-varying covariates
Relevant Guidance from The FDA

- Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, issued by FDA in June 2020:
  - “For a trial with a prospectively specified interim analysis plan, it may be possible to stop the trial earlier than planned or to add or modify an interim analysis and still maintain control over Type 1 error.”
  - “Any modification to the trial, including the original planned analyses, should not be based on data that reveal information on the treatment effect.”

- Consulted the FDA to seek advice on the proposed plan in response to the COVID-19 pandemic
Relevant Guidance from EU regulators and the ESC

- Expert Consensus Position Paper from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), Anker, et al. Jun 2020:
  - “In trials in which 80–90% of the recruitment has been completed, the DMC may be asked to **perform an interim analysis** to assess if the study question has already been answered.”
  - “It may also be useful to select a date to distinguish data collected before COVID-19 (‘BC’) and after COVID-19 (‘AC’) ... This will allow post-COVID-19 sensitivity analyses to be done and ensure for which part investigators may have the greatest confidence in the integrity of the data”

- Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, issued by CHMP, June 2020

- Meetings with European Health Authorities to seek their advice on COVID-19 related questions
  - Commented it may be useful to utilize the **estimand framework** to define which research question is being responded to for each analysis (including supplementary analyses)
Retrospectively constructed estimand in original PARADISE-MI study protocol

<table>
<thead>
<tr>
<th>Intercurrent event</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent treatment discontinuation</td>
<td>Treatment policy strategy</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>Hypothetical strategy</td>
</tr>
</tbody>
</table>

Primary scientific question of interest / Estimand:
What would be the relative risk reduction (HR) for **Entresto vs Ramipril** (regardless of treatment discontinuation) for **Entresto vs Ramipril** (regardless of treatment discontinuation)

in patients with LV systolic dysfunction and/or pulmonary congestion following an AMI, in the primary endpoint, as measured by the **time to first composite endpoint of CV death, HFH and outpatient HF**, in the absence of **death from non-CV related causes**?
Hypothetical estimand in a world without COVID-19 pandemic

<table>
<thead>
<tr>
<th>Potential new intercurrent events</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment discontinuation due to COVID-19</td>
<td>Hypothetical strategy</td>
</tr>
<tr>
<td>Death related to Covid-19</td>
<td>Hypothetical strategy</td>
</tr>
<tr>
<td>COVID-19 infection</td>
<td>Treatment policy strategy</td>
</tr>
<tr>
<td>Indirect or direct COVID-19 related events potentially leading to unrealized endpoints (e.g., patient does not want to or cannot go to hospital/site to report HF event)</td>
<td>Hypothetical strategy</td>
</tr>
</tbody>
</table>

- Use of a global or local impact date(s) allow to simplify intercurrent events

Redundant if global or local impact date(s) used for censoring

1. Fixed global COVID-19 impact date (1Mar20)
2. Country- or site-specific date (external data?)
3. Patient-specific dates derived based on new COVID CRF information (could also be used to derive site-specific censoring to avoid informative censoring)
### Hypothetical estimand in a world without COVID-19 pandemic

<table>
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<tr>
<th>New intercurrent events</th>
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<tr>
<td>Presumed onset of COVID-19 pandemic impact on study (addresses all direct and indirect factors like treatment and accurate collection of endpoints)</td>
<td>Hypothetical strategy</td>
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**New primary scientific question of interest / Estimand:**

What would be the relative risk reduction (HR) for **Entresto vs Ramipril** (regardless of **treatment discontinuation**) in patients with LV systolic dysfunction and/or pulmonary congestion following an AMI, in the primary endpoint, as measured by the time to first composite endpoint of CV death, HFH and outpatient HF, in the absence of **COVID-19 pandemic** and **death from non-CV related causes**?
## Estimand irrespective of COVID-19 pandemic

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<tr>
<td>Presumed onset of COVID-19 pandemic impact on study (addresses all direct and indirect factors like treatment and accurate collection of endpoints)</td>
<td>Treatment policy strategy</td>
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Another scientific question of interest:

What would be the relative risk reduction (HR) for **Entresto vs Ramipril** (regardless of treatment discontinuation) in patients with LV systolic dysfunction and/or pulmonary congestion following an AMI, in the primary endpoint, as measured by the **time to first composite endpoint of CV death, HFH and outpatient HF**, regardless of **COVID-19 pandemic** and in the absence of **death from non-CV related causes**?

Is this a meaningful estimand? Impact of COVID-19 in the future world (to which we want to generalize) is unlikely to be represented by specific study experience.
Discussion and conclusions

- **PARADISE-MI** is a 5-year study in 5,670 post-MI patients with **80%** of the primary endpoint information accrued prior to the COVID-19 pandemic.

- **Uncertainty** about the impact of COVID-19 on the remaining **20%** of the study:
  - Hospitalisations for HF that would have occurred in the absence of the pandemic may not happen during lock-down periods due to impaired health care systems and patients’ fear of infection.
  - Potential change in the composition of the primary endpoint.
  - Treatment discontinuations/interruptions.
  - Pandemic ongoing but hospitals and patients learning to better manage over time.
  - Quantitative assessment of impact on treatment effect currently not possible due to blinding and confounding by event reporting delays.

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Discussion and conclusions

- The **scientific question** is whether Entresto is superior to ramipril in reducing the risk of primary composite endpoint events (first event of CV death, hospitalization for HF, or outpatient HF)
  - Study planned long before the pandemic – may interpret the original question as being in a world without COVID-19

- To which setting do we want to **generalize the results?**
  - Early close out with censoring at the start of COVID-19 impact would address the estimand in a world without COVID-19 at the cost of power loss
  - A 2nd IA would address the estimand in a world without COVID-19 (if positive) at the cost of minimal power loss overall under original assumptions.
  - A final analysis at the end of the study based on all data would address the estimand irrespective of COVID-19
    - Estimand may be questionable since unlikely to be representative for future world

- Final analysis at the end of the study based on all data can also be used to address the **original scientific question**
  - No change in estimand but accept potentially increased noise in 20% of data
  - Characterization of event rates and treatment effect sizes prior and during pandemic useful to facilitate interpretation of the results
    - If the impact of COVID-19 turns out to be minor, the analysis based on all data seems most reliable
    - If there is a major impact, the pre-COVID data are more relevant
Acknowledgement

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- **Estimands team**
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  Melanie Wright
Reference

Thank you