Global Drug Development
CD&A

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

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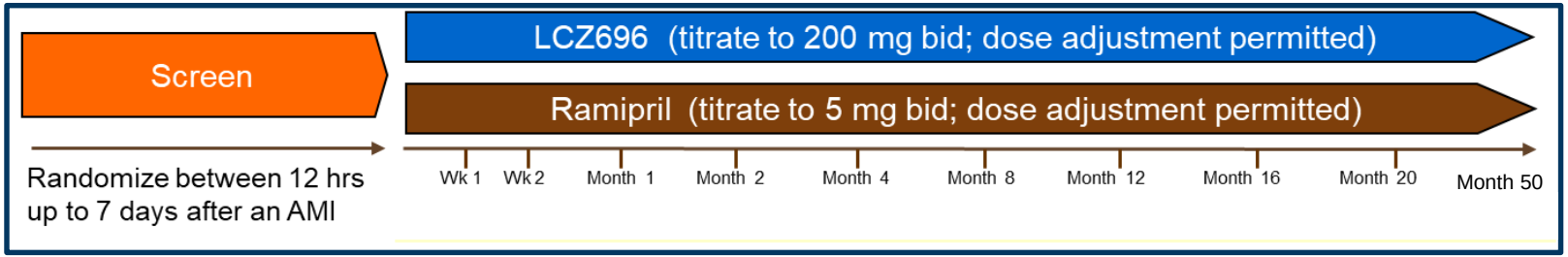
PARADISE-MI: Prospective ARNI versus ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction

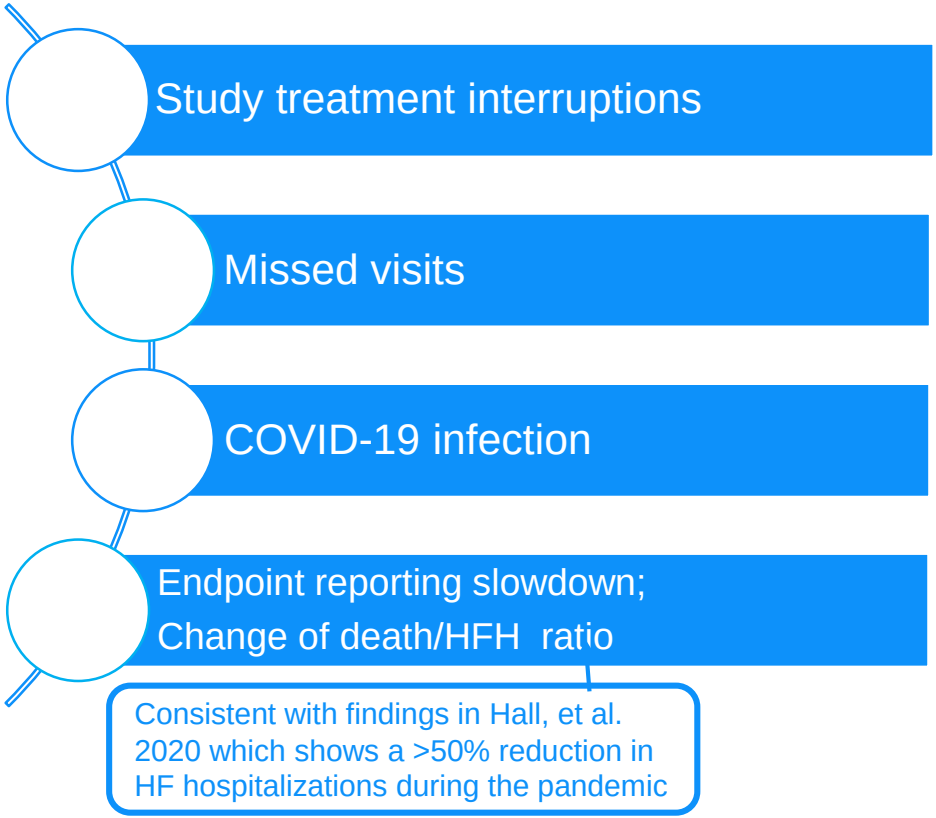


Primary objective	To evaluate the efficacy and safety of LCZ696, compared to ramipril, in addition to conventional post-AMI treatment, in reducing the occurrence of composite endpoint of CV death, HF hospitalization and outpatient HF (time-to-first event analysis) in post-MI patients.
Population	Spontaneous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

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).

	Options	Impact / Comments
1	**Do nothing**	**Potential power loss** for the primary analysis depending on possible dilution of treatment effect during the COVID-19 impacted phase
2	**Close out the trial early** Primary analysis using data censoring at March 1, 2020. All additional data used for supplementary analyses	**Power loss** for the primary analysis due to omitting 20% of information
3	**Continue the trial but alter primary analysis** Using data censoring at March 1, 2020; All additional data used for supplementary analyses	**Power loss** for the primary analysis due to omitting 20% of information
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.	Motivated by **uncertain impact of COVID-19 pandemic**. Allows investigation of the scientific question of interest based on data **unaffected by the COVID-19 pandemic** with **limited power loss**
5	**Re-evaluate in a few months**	

Would require amendment & consultation with major Health Authorities

Proposed COVID-19 related supplementary analyses

- Analysis of primary endpoint data accrued prior to March 1st 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

Intercurrent event	Strategy
Permanent treatment discontinuation	Treatment policy strategy
Non-CV death	Hypothetical strategy

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 **death from non-CV related causes**?

Hypothetical estimand in a world without COVID-19 pandemic

Potential new intercurrent events	Strategy
Treatment discontinuation due to COVID-19	Hypothetical strategy
Death related to Covid-19	Hypothetical strategy
COVID-19 infection	Treatment policy strategy
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)	Hypothetical strategy

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

Not directly measurable at the patient-level

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)

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

Hypothetical estimand in a world without COVID-19 pandemic

New intercurrent events	Strategy
Presumed onset of COVID-19 pandemic impact on study (addresses all direct and indirect factors like treatment and accurate collection of endpoints)	Hypothetical strategy

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

New intercurrent events	Strategy
Presumed onset of COVID-19 pandemic impact on study (addresses all direct and indirect factors like treatment and accurate collection of endpoints)	Treatment policy strategy

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

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**?

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

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 interprete 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

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- **Estimands team**

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  Melanie Wright

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Thank you

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