

Testimony to the FDA Cardiovascular and Renal Drugs Advisory Committee

Serelaxin

(BLA 125468)

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(We have no financial conflicts of interest)

Reasons for opposing approval

- Serelaxin has exceedingly marginal, if any, benefits on subjective, transient, patient-reported dyspnea; no proven benefits on any objective cardiovascular outcomes
- Proposed indication bears little resemblance to primary endpoints studied
- Extremely poor generalizability of RELAX-AHF (~20% of all acute heart failure (AHF) inpatients would have met inclusion criteria)

Primary endpoints

- RELAX-AHF had two pre-specified co-primary endpoints, both subjective, patient-reported measures of dyspnea in the acute setting:
 - Responder analysis: Proportion of respondents with “moderately” to “markedly” improved dyspnea on a 7-point Likert scale within 24 hours after drug administration
 - VAS-AUC: Mean area under the curve (AUC) of subjective dyspnea on a 100-mm visual analog scale (VAS) over 5-day period after drug administration

FDA's standard for approval of serelaxin based on a single Phase III trial (expressed during a Feb. 3, 2009 pre-submission meeting)

“Sponsor said there would be two phase 3 studies. FDA told the sponsor that only 1 study would be required for the dyspnea indication if rejection of the global null hypothesis with the alpha level was controlled at the two-sided 0.00125 level by the Hochberg method. For this, at least one of the two dyspnea coprimary endpoints would have to have a $p < 0.00125$ and the other endpoint would have to demonstrate a trend consistent with the results on the first endpoint.” (FDA Briefing Document, p. 22)

Primary endpoint #1: Responder analysis

- Proportion of subjects with “moderate” or “marked” improvement in subjective dyspnea at 6, 12, and 24 hours after drug administration (ITT):
 - 26.9% and 25.9% in the serelaxin and placebo groups, respectively
 - OR 1.05 (95% CI: **0.81, 1.37**; p=0.7)

Primary endpoint #2: VAS-AUC

- VAS-AUC at Day 5:
 - 2756 vs. 2308 mm-hrs in serelaxin vs. placebo, respectively
 - Mean difference = 448 mm-hrs
 - $p=0.007$ (>0.00125 : FDA standard for approval without confirmatory trial)
- This mean difference was based not on *actual* VAS values for all subjects, but was instead driven *primarily* by the sponsor's chosen imputation method for subjects with worsening heart failure

Arbitrary imputation protocol for VAS scores in worsening heart failure

- All subjects with “worsening heart failure” (for which no criteria were provided *a priori* and, which was not subsequently adjudicated), regardless of severity, were automatically given worst possible VAS value (0) for all subsequent values through Day 5
- Twice as many placebo subjects had “worsening heart failure” as serelaxin subjects.
- Therefore, replacing raw VAS values with “0” for the remainder of their assessments disproportionately – and markedly – decreased VAS-AUC scores in placebo subjects relative to serelaxin subjects

Arbitrary imputation

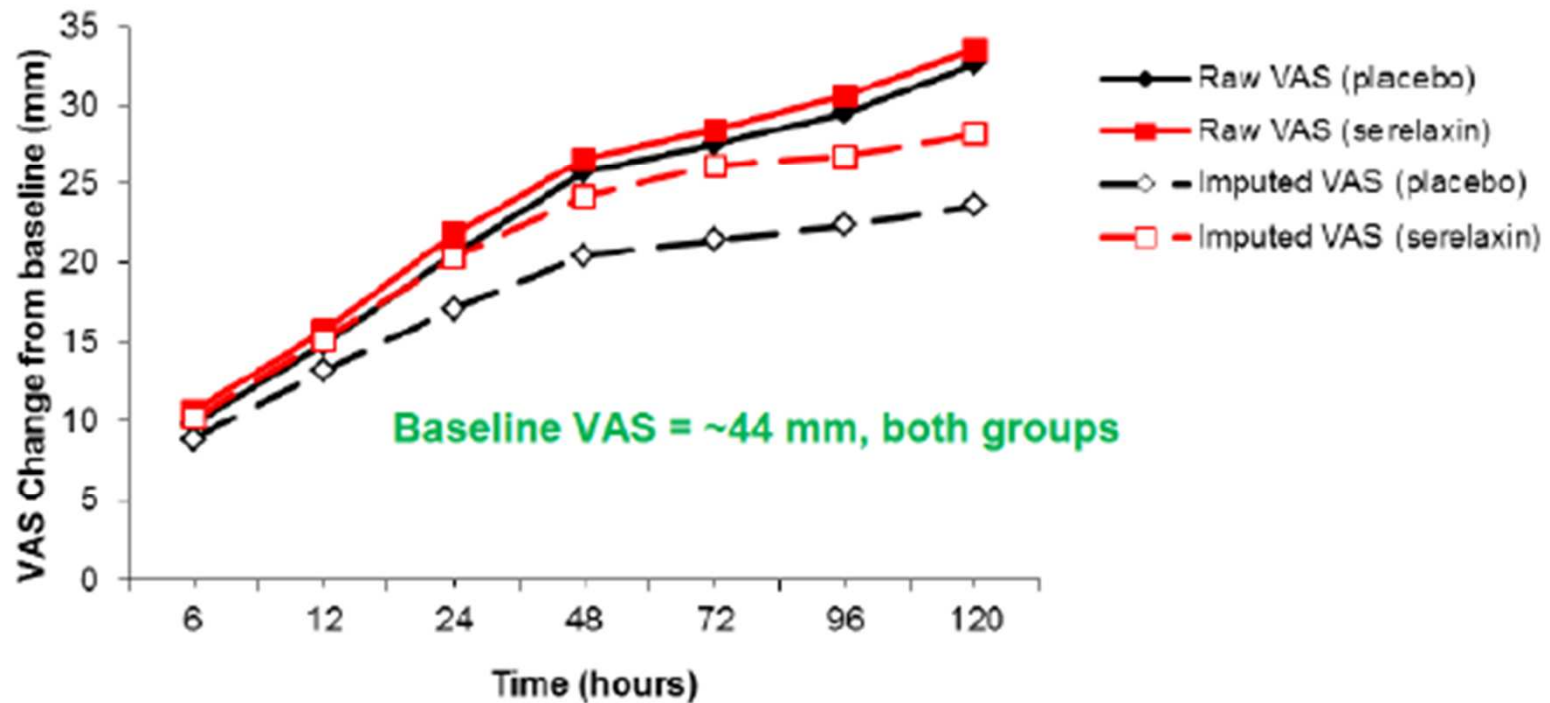
- Two-thirds (66%) of all serelaxin and placebo subjects with “worsening heart failure” through Day 14 had mild cases, which were adequately treated with additional infusions of IV diuretics or nitrates
- FDA, after conducting 6 different sensitivity analyses employing alternative, and less extreme, imputation protocols, concluded that:
 - *“It is notable that only the [sponsor’s chosen] prespecified imputation scheme which treats all degrees of severity of [worsening heart failure] equally keeps the p value below the prespecified 0.025 mark needed for success.” (p. 82)*

Arbitrary imputation

- *“As shown in the FDA statistical review, if raw VAS scores are used the difference in AUC-change from baseline in VAS scores over 5 days between groups was only 167.6.mm-hr (**$p = 0.21$**).” (p. 67)*
- Therefore, the actual difference between the serelaxin and placebo groups was just **1.4 mm** on a 100 mm scale at any one time for the first 5 days after drug administration, far below any conceivable threshold for clinical significance.

Actual (raw) VAS differences

Figure 8: Raw (using LOCF) VAS scores and imputed VAS scores at all assessments from 6 hours through Day 5



Dr. McDowell's analysis: Source: Sponsor's analysis dataset for VAS scores

Clinical significance of VAS score

- Even taking the sponsor's analysis at face value, what does the imputed mean difference in AUC-VAS really mean?
- “448 mm-hrs” over 5 days = **3.7 mm on a 100 mm scale** at any one time (448/120 hrs over 5 days).

Clinical (in)significance

Based on a 2004 study of VAS in AHF inpatients (Ander et al.) cited by FDA:

- “Patients who experience[d] **about the same** difficulty in breathing experience[d] a mean change of **2.7 mm** on the VAS (95% CI -4.2 mm to 9.5 mm).”
- “Patients who experience[d] **a little less** difficulty breathing or a little more difficulty breathing experienced a mean change of **21.1 mm** on the VAS (95% CI: 12.3 mm to 29.9 mm).” (p. 67-68)

Clinical (in)significance

Dr. Blank: *“Judging by [the Ander et al.] experience in what appeared to be a similar population, a 4 mm difference on a 100 mm dyspnea VAS does not appear to represent a clinically significant change.” (p. 16)*

We agree.

Secondary, clinical endpoints not met

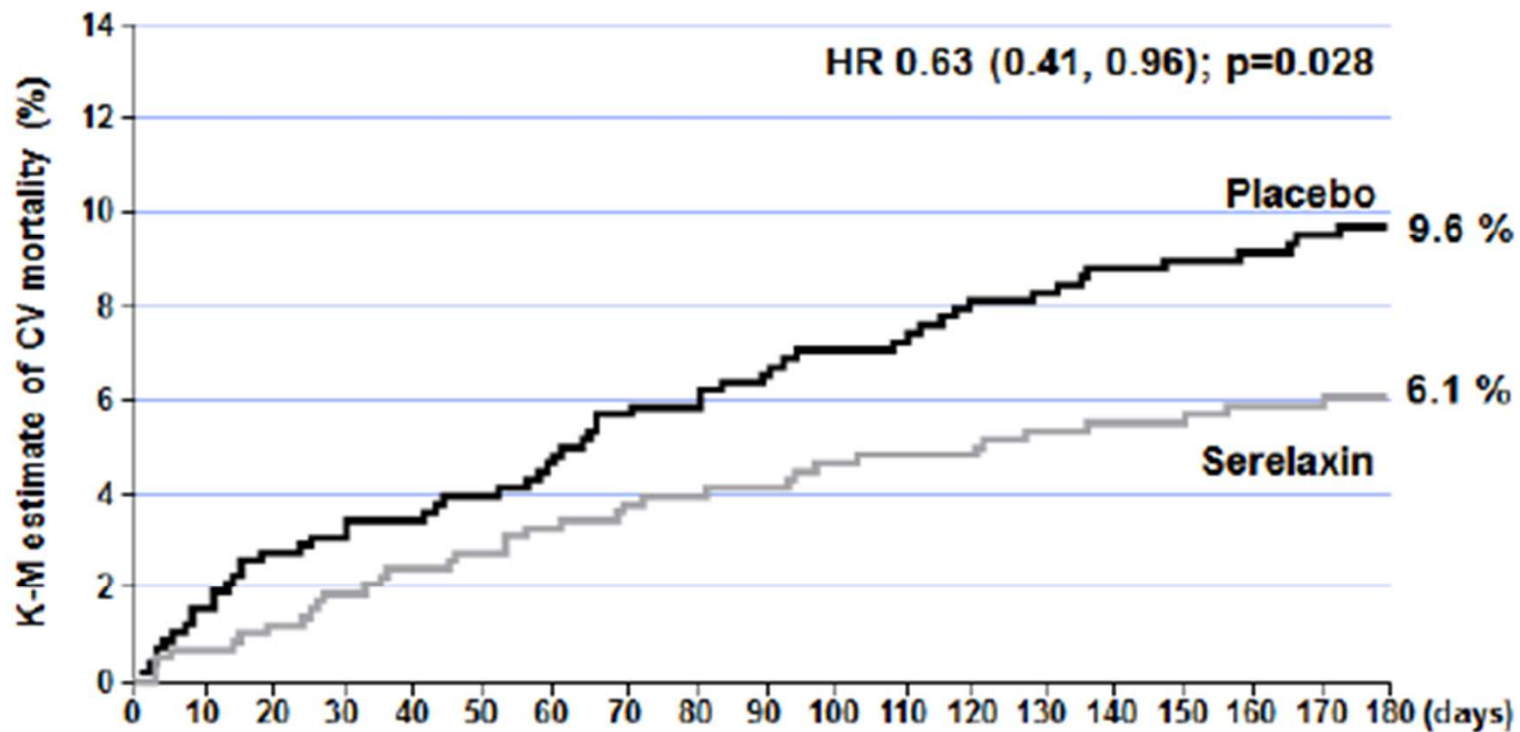
- Days alive and out of hospital through Day 60
 - 48.3 days vs. 47.7 days (serelaxin vs. placebo; $p=0.3682$)
- Cardiovascular death or re-hospitalization due to HF or RF through Day 60
 - 13.2% vs. 13.0% (serelaxin vs. placebo); $p=0.8945$
 - HR: 1.02 (95% CI: 0.74, 1.41)

CV mortality finding lacks biological plausibility

- CV mortality at day 180 was neither a primary nor secondary outcome, therefore mortality findings must be investigated in a larger, confirmatory trial before any conclusions can be drawn as to whether this represents a real or chance finding.
- Given that this was a post hoc analysis, the burden is therefore on the sponsor to demonstrate a convincing biological mechanism by which a drug given as a single infusion over 48 hours can result in a mortality benefit weeks and months into the future. For such one-time therapies, one would expect diverging survival curves in the days immediately following therapy, followed by a leveling off of residual effects and **increasingly parallel** curves.

However, a look at the Kaplan-Meier curve, restricted to CV mortality, shows **increasingly divergent** survival curves, something one would expect only with chronic or repeatedly administered acute therapy. (Figure taken from sponsor briefing document, p. 94)

Figure 7-28 Cardiovascular mortality through Day 180 - RELAX-AHF (ITT set)



Number at Risk

Placebo	580	559	547	535	523	514	444
Serelaxin	581	563	555	546	542	536	463

* Adjudicated up to Day 60

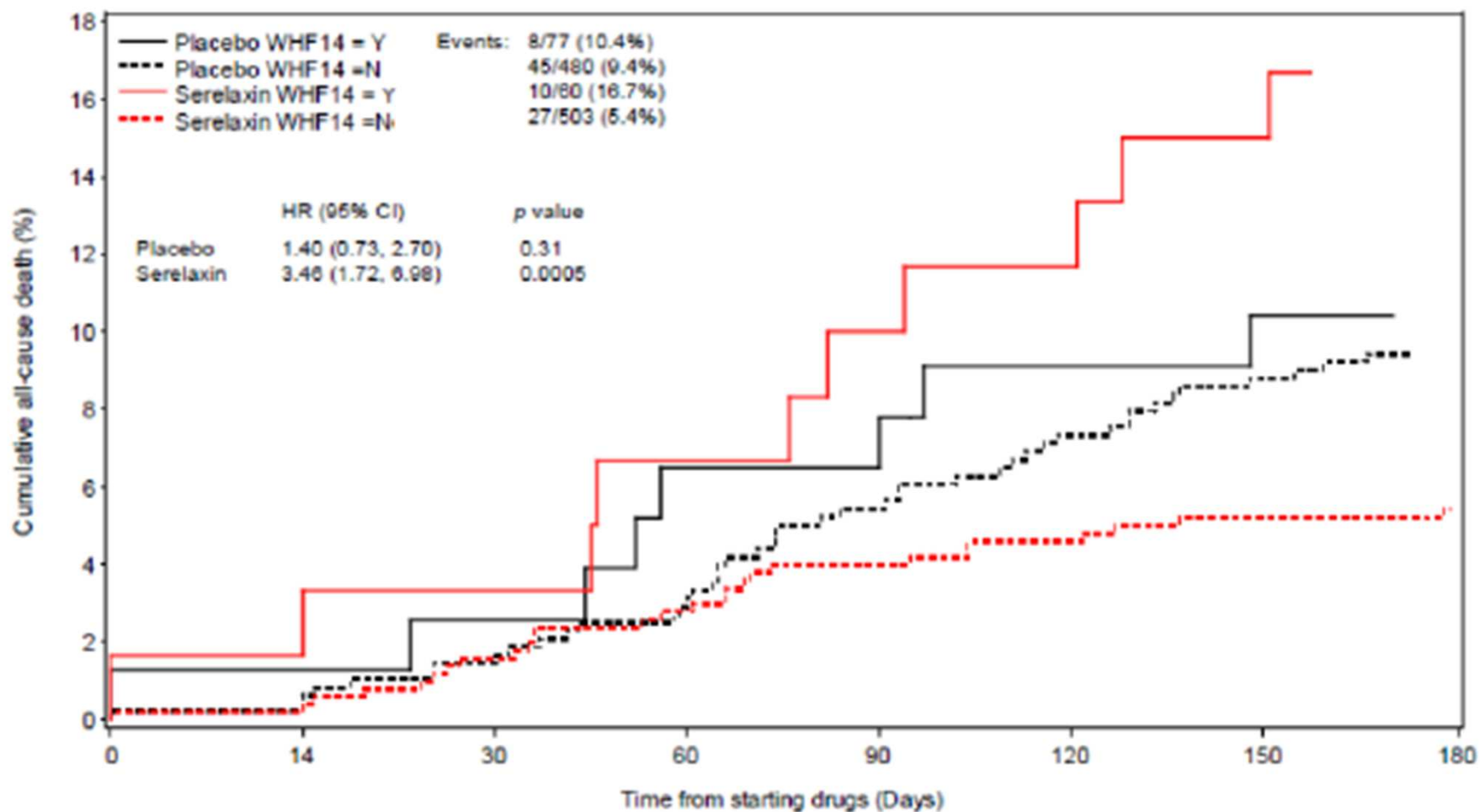
Of course, it could be argued that the initial differences in rates of worsening heart failure would not be reflected in CV mortality differences until a later time point, even as far out as 180 days for patients with severe decompensation and subsequently lengthy ICU stays

However, a 60- or 180-day CV mortality difference *attributable to serelaxin* of the scale seen in RELAX-AHF would require a substantial difference in the number of severely decompensated subjects across the two groups shortly following drug administration

This was not seen. **Two thirds (66%)** of all subjects with worsening heart failure through Day 14 were successfully treated with IV diuretics or nitrates. Only **16** subjects in the placebo group and **11** in the serelaxin group with worsening heart failure required IV pressors, positive inotropes, mechanical ventilation, or ultrafiltration through Day 14.

(p. 77)

Figure 12: All Cause death through Day 180 by Treatment and WHF



Reviewer's analysis: WHF_mortality_plot.sas, safety population, all-cause death occurred prior to Day 14 were excluded from the analysis, Applicant's dataset: AEVENT

While it is possible that serelaxin was indeed responsible for the CV mortality differences at 60 and 180 days (e.g., through prevention of irreversible cardiac remodeling in the acute phase), until the confirmatory trial currently underway is concluded, the RELAX-AHF mortality findings can only be considered hypothesis-generating and should certainly not factor into today's decision on approval.

Blinding compromised?

- Dr. Blank: *“The serelaxin solution is frothy when shaken and the placebo solution is not. This may have caused unblinding.”* (p. 40)
- The fact that both primary endpoints were subjective and that the one purportedly statistically significant outcome was exceedingly marginal (~4 mm on a 100 mm subjective scale) means that even a few unblinded investigators (and patients) may have unintentionally skewed the results in favor of serelaxin

Overly broad indication

- “improve the symptoms of acute heart failure through reduction of the rate of worsening of heart failure”
- The sole symptom measured in either primary outcome was *dyspnea at rest*.
- AHF symptoms are not restricted to dyspnea at rest (particularly for NYHA Class I-III patients):
 - Dyspnea on exertion
 - Peripheral edema
 - Other pulmonary edema/low EF sx (cough, wheezing, fatigue, chest pain, etc...)
- “reduction of the rate of worsening of heart failure” implies an improvement in some objective measure of heart failure severity. No such rigorous objective indicators of heart failure progression (e.g. EF) were systematically measured as part of a prespecified outcome.

Overly broad indication: all AHF patients?

- Wang et al. (2014) compared RELAX-AHF inclusion criteria and study population with 196,770 AHF patients in the Acute Decompensated Heart Failure National Registry-United States (ADHERE-US) and ADHERE-International (ADHERE-I) registries.
- Registries consist of adult inpatients with a primary or secondary discharge diagnosis of acute decompensated heart failure from 2001 to 2009, with consecutive enrollment encouraged.

Overly broad indication: all AHF patients?

- Only **16.2%** of ADHERE-International and **20.7%** of ADHERE-US patients eligible for RELAX-AHF
- RELAX-AHF eligible patients significantly more likely to be older, female, have **higher SBP** on presentation, more well **preserved ejection fraction, better renal function**, in addition to a host of other indicators of a markedly healthier AHF population (all $p < 0.05$)
- Not surprisingly, therefore: “In-hospital mortality was lower in RELAX-AHF-type than in non-RELAX-AHF-type patients, even after multivariable adjustment (**HR 0.59**; 95% CI: 0.53–0.66; $P < 0.0001$).”

Overly broad indication: all AHF patients?

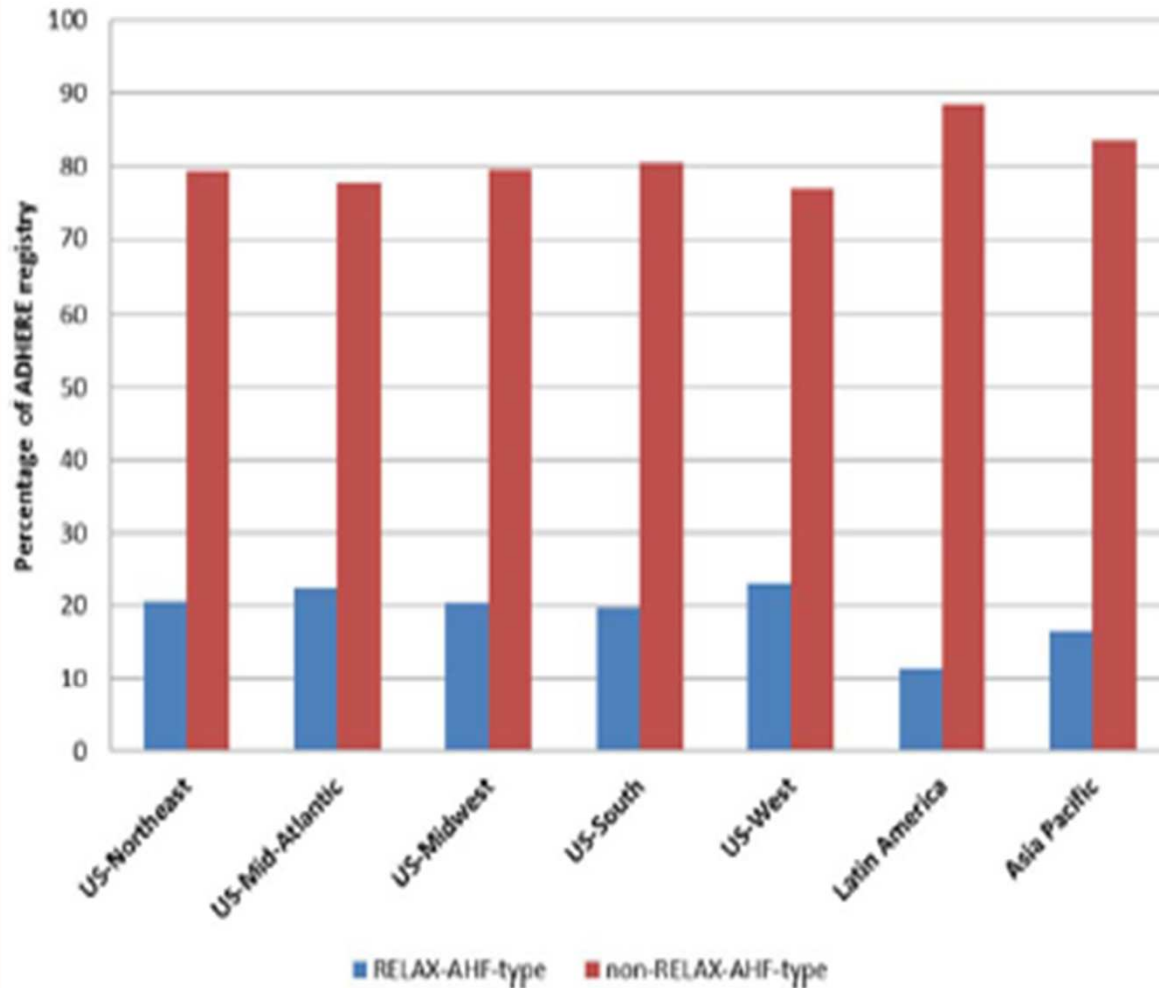


Figure 1. Percentage of Acute Decompensated Heart Failure National Registry (ADHERE) registries that meet or do not meet Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) entry criteria by region. US indicates United States.

Jan 24: EMA rejects serelaxin on identical grounds laid out by FDA's Dr. Blank

“The [EMA] Committee noted that the study results did not demonstrate a benefit for short-term relief of dyspnoea over up to 24 hours, and although some benefit was shown over 5 days **it was not clear how this was of clinical relevance.**

Furthermore, **the Committee had concerns about the way the effectiveness of the medicine in the study had been analysed.** The results included calculated values for a number of patients who had died or had required additional treatment for worsening symptoms and whose actual data were not used.

...Since only one main study was included in the application, further studies would be needed to confirm the effectiveness of [serelaxin] in the treatment of acute heart failure.

EMA rejection

“Although the safety of [serelaxin] seemed acceptable, in view of the uncertainties about the benefits of treatment the CHMP was of the opinion, at that point in time, that **the benefits of Reasanz did not outweigh its risks and recommended that it be refused marketing authorisation.**”

Conclusion

- Serelaxin has exceedingly marginal, if any, benefits on subjective, patient-reported dyspnea
- Serelaxin has no proven benefits on any objective cardiovascular outcomes
- Proposed indication bears little resemblance to primary endpoints studied
- Extremely poor generalizability of RELAX-AHF (~20% of all AHF inpatients would have met inclusion criteria)