Brain Aminopeptidase A Inhibition with Firibastat

to Prevent Left Ventricular Dysfunction after Acute Myocardial Infarction

RESULTS OF THE QUORUM TRIAL

Quantum Genomics Firibastat **o**r **R**amipril after Ac**u**te **M**yocardial Infarction for Prevention of Left Ventricular Dysfunction

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on behalf of the QUORUM investigators

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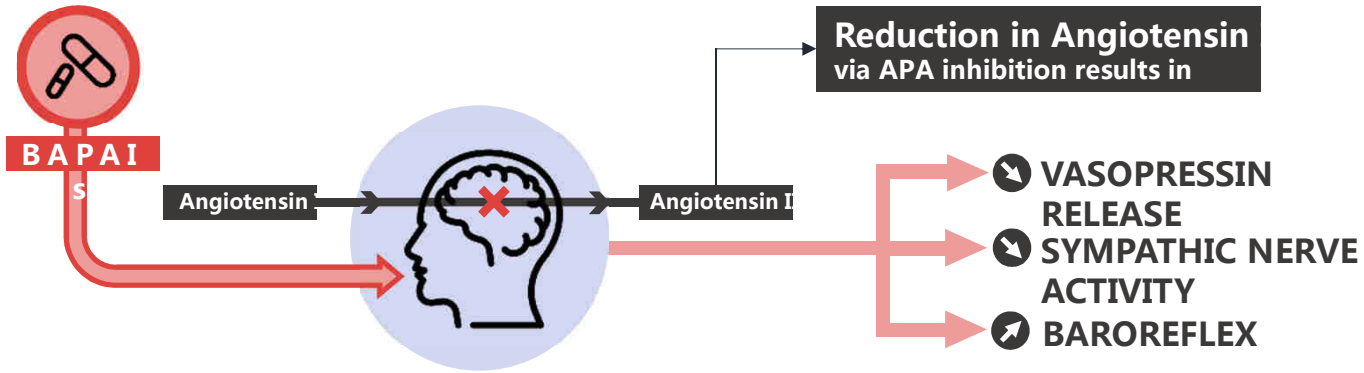
Disclosures

- **Gilles Montalescot is a consultant for** Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cell Prothera, CSL Behring, Europa, Idorsia, IRIS-Servier, Medtronic, MSD, Novartis, Pfizer, Quantum Genomics, Sanofi-Aventis

Brain Aminopeptidase A Inhibitors

Inhibition of Brain Aminopeptidase A prevents conversion of Angiotensin II into Angiotensin III



- **INCREASE** OF THE DIURESIS (urinary elimination)
- **LOWERING** VASCULAR RESISTANCE
- **CONTROLLING** HEART RATE

Marc *et al, Progress in Neurobiology* 2011
Gao *et al, Clinical Science* 2014
Marc *et al, Canadian Journal of Cardiology* 2020

Rationale and Study Objective

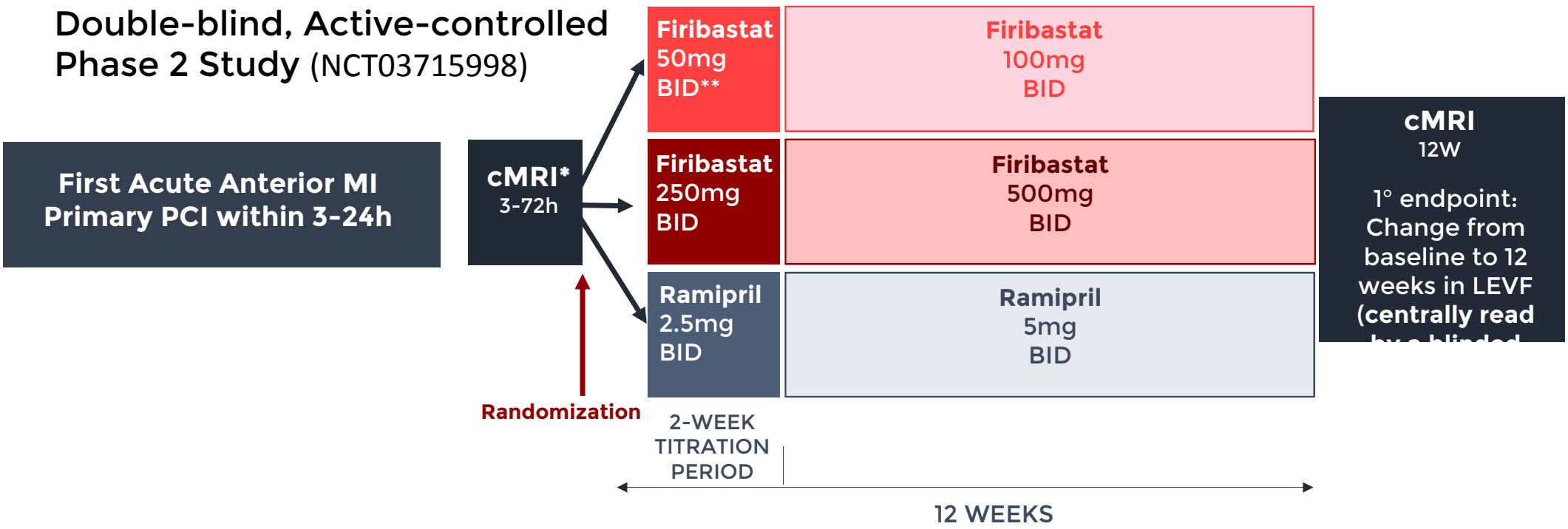
- **Firibastat** is the first-in-class of the Brain AminoPeptidase A Inhibitors (BAPAIs)
- **Firibastat** inhibits aminopeptidase A and reduces brain Angiotensin III production resulting in a decrease of vasopressin release and sympathetic nerve activity
- **Firibastat** improves left ventricular ejection fraction (LVEF) in rats[1] and mice[2] and, reduces filling pressures without any decrease in systemic blood pressure and, reduces myocardial fibrosis after acute MI
- **QUORUM primary objective** is to compare the effects of two oral doses of firibastat to those of ramipril on change from baseline in left ventricular ejection fraction assessed by cardiac MRI after 12-week treatment

[1]Huang et al, Cardiovasc Res 2013

[2]Boitard et al, Journal of Molecular and Cellular Cardiology 2019

QUORUM Study Design

Multicenter, Randomized, Double-blind, Active-controlled Phase 2 Study (NCT03715998)



After 2 weeks, subjects were up-titrated if systolic blood pressure ≥110 mmHg

35 European centres in France, Germany, Hungary, Poland, Spain, Slovakia, UK

cMRI: *Cardiac Magnetic Resonance Imaging (MRI)*

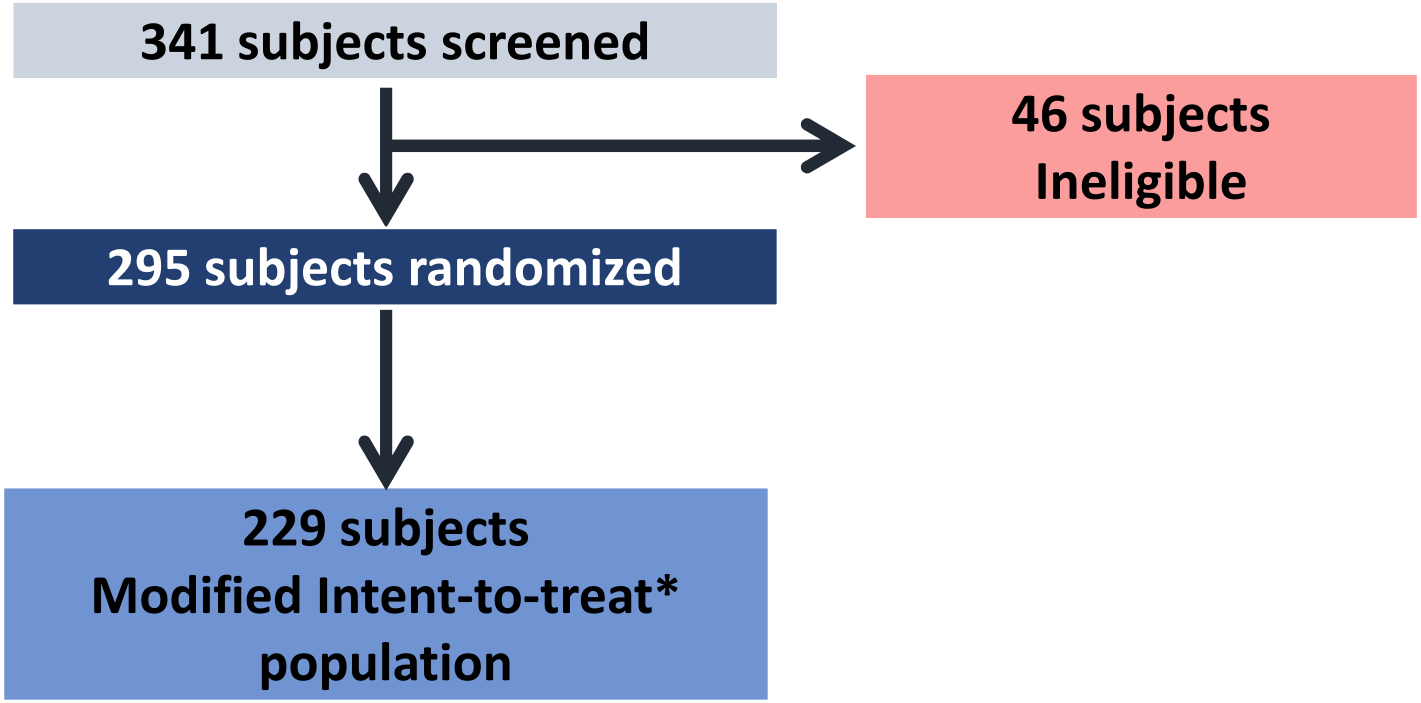
BID: *Bis in Die (twice a day)*

Statistical Assumptions and Sample size

- **Superiority trial versus ramipril** (hierarchical step-down testing procedure)
- **Primary efficacy endpoint** change from Baseline in **LVEF** assessed by **cMRI*** (blinded core-lab) on Day 84
- **Randomization** 1:1:1
- **2-sided 5% nominal level of significance, power 90%**
- **Standard deviation** of the primary efficacy : 10%.
- **Minimum absolute difference** of 5% for LVEF between groups
- **10% drop-out**
- **98 subjects** per group: overall **294** subjects.

***cMRI:** Cardiac Magnetic Resonance Imaging (MRI)*

Study Population



* All patients who took at least one dose and with at least one post-baseline EF assessed par cardiac MRI.

Baseline characteristics

	Firibastat 100 mg BID N= 72	Firibastat 500 mg BID N=77	Ramipril 5mg BID N=80
Gender, male *(n, %)*	55 (76.4%)	59 (76.6%)	60 (76%)
Age, *(years, mean±SD)*	56.9±10.2	58.9±11.2	58.2±10.8
Body Mass Index *(kg/m² mean±SD)*	28.2±4.6	27.8±4.3	27.7±4.4
Hypertension *(n, %)*	40 (55.6%)	45 (58.4%)	39 (48.8%)
Dyslipidemia *(n, %)*	33 (45.8%)	30 (39.0%)	30 (37.5%)
Diabetes *(n,%)*	11 (15.3%)	11 (14.3%)	12 (15.0%)
Time to PCI *(hour, mean±SD)*	6.2±3.7	6.0±6.2	6.5±4.4
LAD culprit artery *(n, %)*	71 (98.6 %)	74 (96.1%)	77 (96.3%)
TIMI flow 3 after PCI *(n,%)*	49 (94.2%)	51 (86.4%)	56 (93.3%)
RAS blockers before admission* *(n*	31 (43.1%)	33 (42.9%)	25 (31.3%)
Baseline LVEF *(%, mean±SD)*	52.70±10.36	51.42±10.26	49.88±10.95

* RAS blockers were interupted prior to randomization

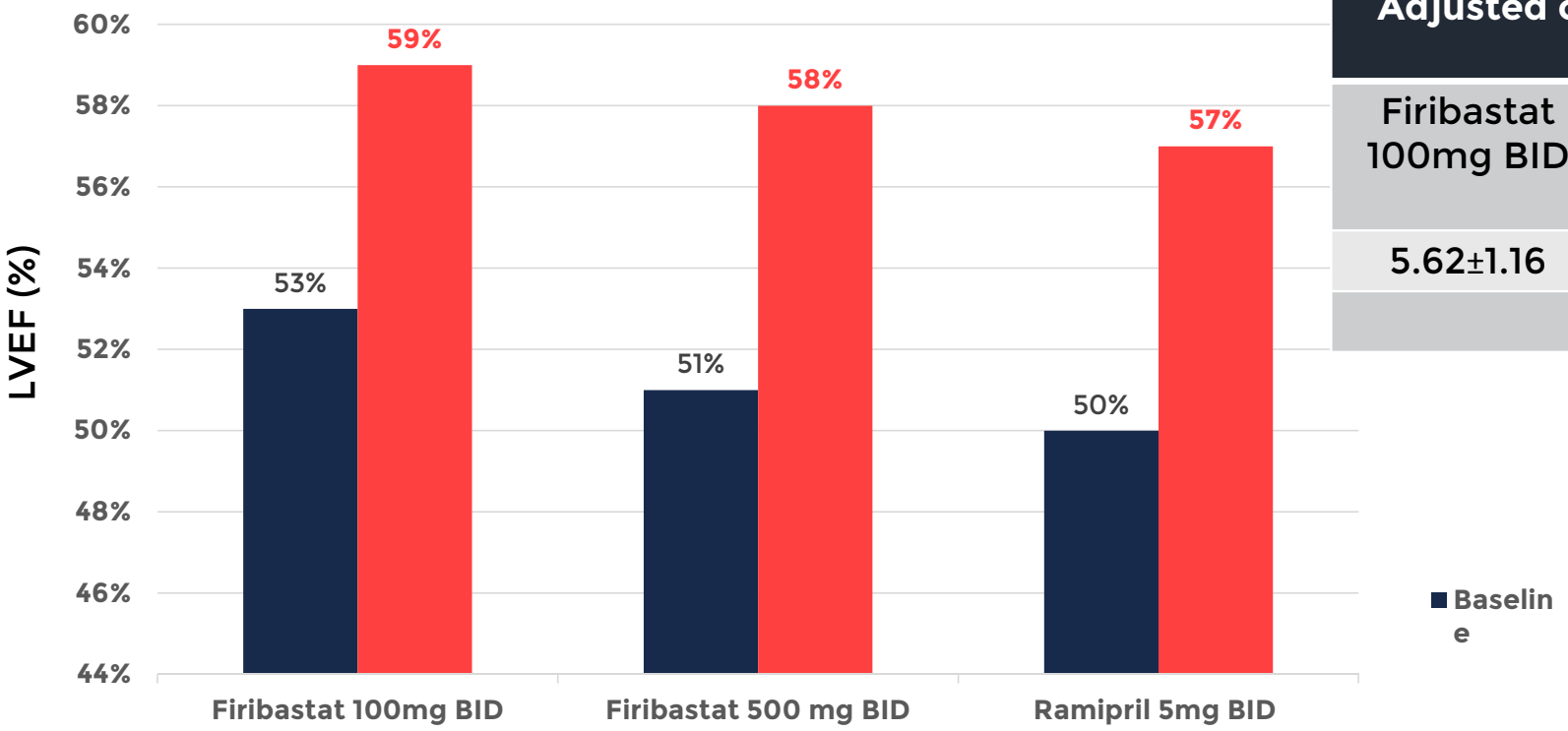
Final Dose achieved at day 84

After 2 weeks, subjects were up-titrated if systolic blood pressure ≥110 mmHg

Firibastat GROUPE A N= 72	50 mg BID →	N=15 (21%)
	100 mg BID →	**N=57 (79%)**
Firibastat GROUPE N= 77	250 mg BID →	N=15 (19%)
	500 mg BID →	**N=62 (81%)**
Ramipril GROUPE C N= 80	2.5 mg BID →	N=26 (32%)
	5 mg BID →	**N=54 (67%)**

Primary Endpoint

Change from baseline to 12 weeks in Left Ventricular Ejection Fraction (LVEF) assessed by cardiac MRI



Adjusted change from baseline in LVEF (%)		
Firibastat 100mg BID	Firibastat 500mg BID	Ramipril 5mg BID
5.62±1.16	5.31±1.11	5.66±1.12
	p=0.789	

Other MRI Parameters
(change from baseline)

	Firibastat 100mg BID N=72	Firibastat 500mg BID N=77	Ramipril 5mg BID N=80
Left ventricular ejection fraction (%)	+5.62±1.2	+5.31±1.10	+5.66±1.12
End-diastolic Volume (mL)	+14.17±4.50	+12.66±4.28	+9.36±4.34
End-systolic Volume (mL)	-0.45±3.34	-0.40±3.19	-3.13±3.24
Infarct Mass (g)	+22.75±2.72	+27.19±2.79	+27.15±2.59

Major Adverse Cardiac Events (MACE - Centrally

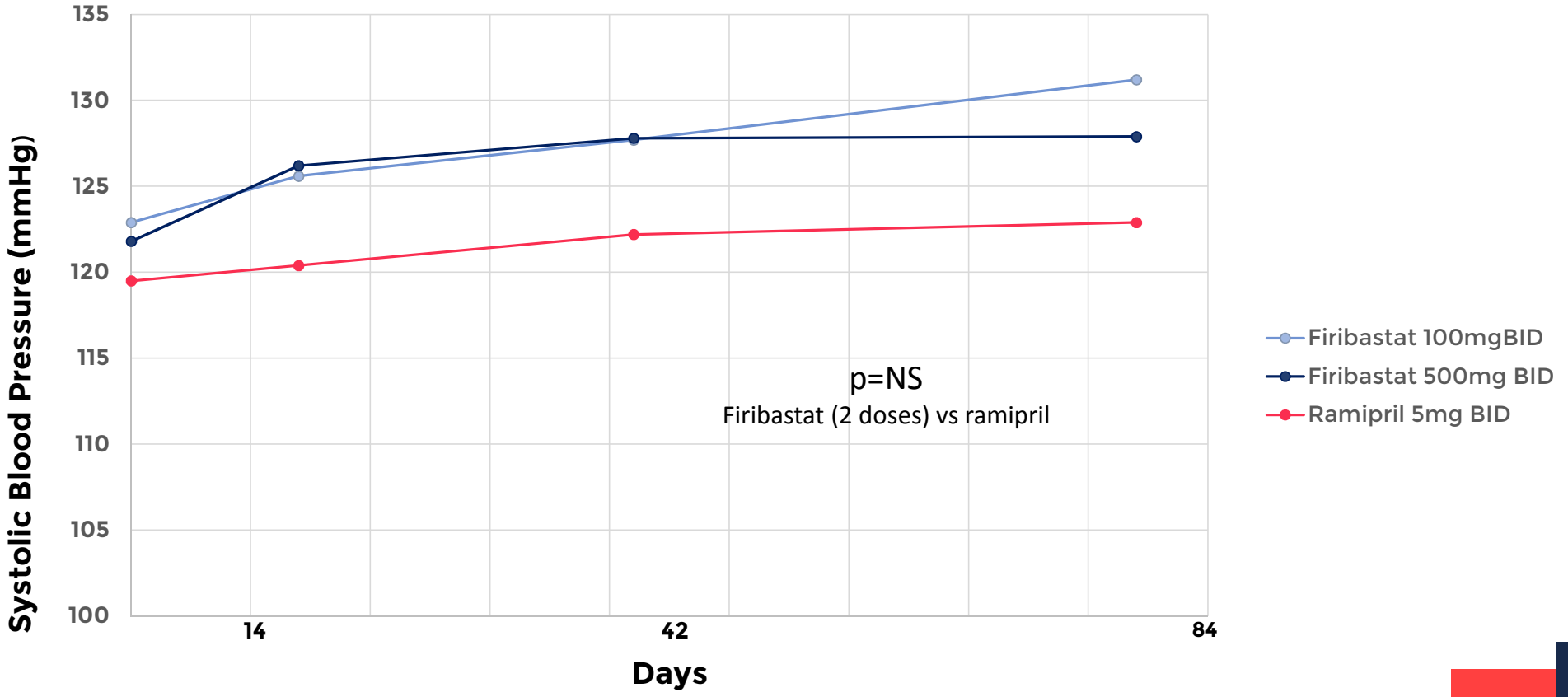
	Firibastat 100mg BID N=98	Firibastat 500mg BID N=98	Ramipril 5mg BID N=98
Major Cardiac Events subjects (*n*,%)	10 8 (8.2%)	8 6 (6.1%)	6 5 (5.1%)
Cardiovascular Deaths (*n*)	2	1	1
New MI (*n*)	3	0	3
Cardiac Hospitalizations (*n*)	7	8	2

No MACE was considered as treatment-related

All MACEs have been reviewed and validated by an independant review committee

Safety

Systolic Blood Pressure



Safety

Change from baseline in laboratory tests

	Firibastat 100mg BID N=98	**Firibastat** 500mg BID N=98	**Ramipril** 5mg BID N=98
Sodium (mEq/L)	**2.28**±2.83	**1.93**±3.28	**2.07**±2.94
Potassium (mEq/L) Hyperkaliemia, n (%)	**0.21**±0.46 1 (1%)	**0.28**±0.44 2 (2%)	**0.31**±0.56 3 (3%)
eGFR (mL/min/m²) Renal adverse events, n (%)	**-4.76**±12.65 **0 (0%)**	**-5.22**±14.51 4 (4%)	**-6.08**±13.55 5 (5%)
Blood Glucose (mmol/L)	**-1.29**±1.72	**-1.59**±2.90	**-1.79**±3.01

Safety

Adverse Events (AE)

	Firibastat 100mg BID N=98		Firibastat 500mg BID N=98		Ramipril 5mg BID N=98	
	Events	Patients (n, %)	Events	Patients (n, %)	Events	Patients (n, %)
All Adverse Events	99	49 (50%)	129	63 (64%)	133	54 (55%)
Related Adverse Events	24	15 (16%)	28	21 (21%)	26	15 (15%)
Serious Related Adverse Events	0	0 (0%)	1	1 (1%)	1	1 (1%)

Allergic Skin reactions (related or potentially related)

	Firibastat 100mg BID N=98	Firibastat 500mg BID N=98	Ramipril 5mg BID N=98
Allergic Skin reactions	4 (4%)	10 (10%)	5 (5%)
Maculo-papular rash and generalized rash	4	7 (including one serious AE)	3 (including one serious AE)
Pruritus	0	1	1
Angioedema	0	0	1
DRESS Syndrome	0	1	0

All skin reactions have been reviewed and validated by an independant skin reactions review committee

Conclusion

- **Firibastat (100 mg BID or 500 mg BID) was not superior to active comparator ramipril (5 mg BID) to prevent left ventricular dysfunction after first acute anterior MI**
- **Firibastat has a global safety profile similar to that of ramipril**
- **Firibastat (whatever the dose, 100 mg BID or 500 mg BID) showed a trend to a better hemodynamic safety profile than ramipril**

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