Brain Aminopeptidase A Inhibition with Firibastat for difficult to treat and resistant hypertension,

RESULTS OF THE FRESH TRIAL

Firibastat in treatment-**RES**istant **H**ypertension

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Disclosures

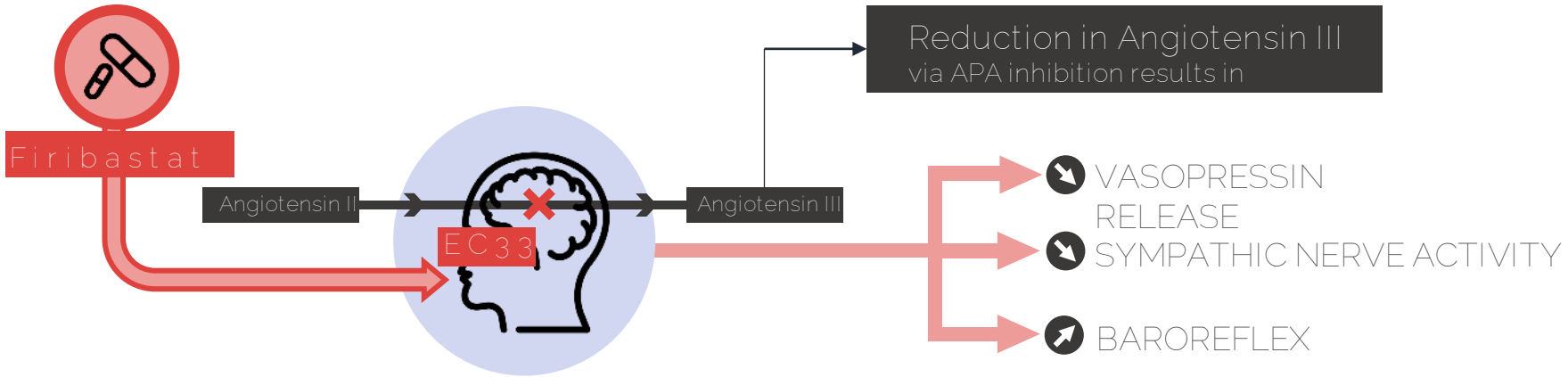
- **George Bakris** is a consultant for Bayer, KBP Biosciences, Ionis, Alnylam, Astra Zeneca, Quantum Genomics, Novo Nordisk, Janssen, Dia Medica Therapeutics, InREGEN

Background

- Incidence of resistant hypertension is estimated around 15%
- Patients with resistant hypertension are at higher risk of poor cardiovascular outcomes
- Salt-sensitivity, low renin levels and sympathetic nervous system overactivity are associated with resistant hypertension
- Resistant hypertension is more common in Black, elderly and obese subjects

Firibastat: Mechanism of Action

Inhibition of Brain Aminopeptidase A preventing conversion of Angiotensin II into Angiotensin III at brain level



- **Brain penetrating Prodrug of EC33**
- **Half life : 2 h (firibastat)**
  10-12 h (active metabolites)
- **No effect on blood pressure and HR in healthy volunteers**

- **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

Study rationale and Objectives

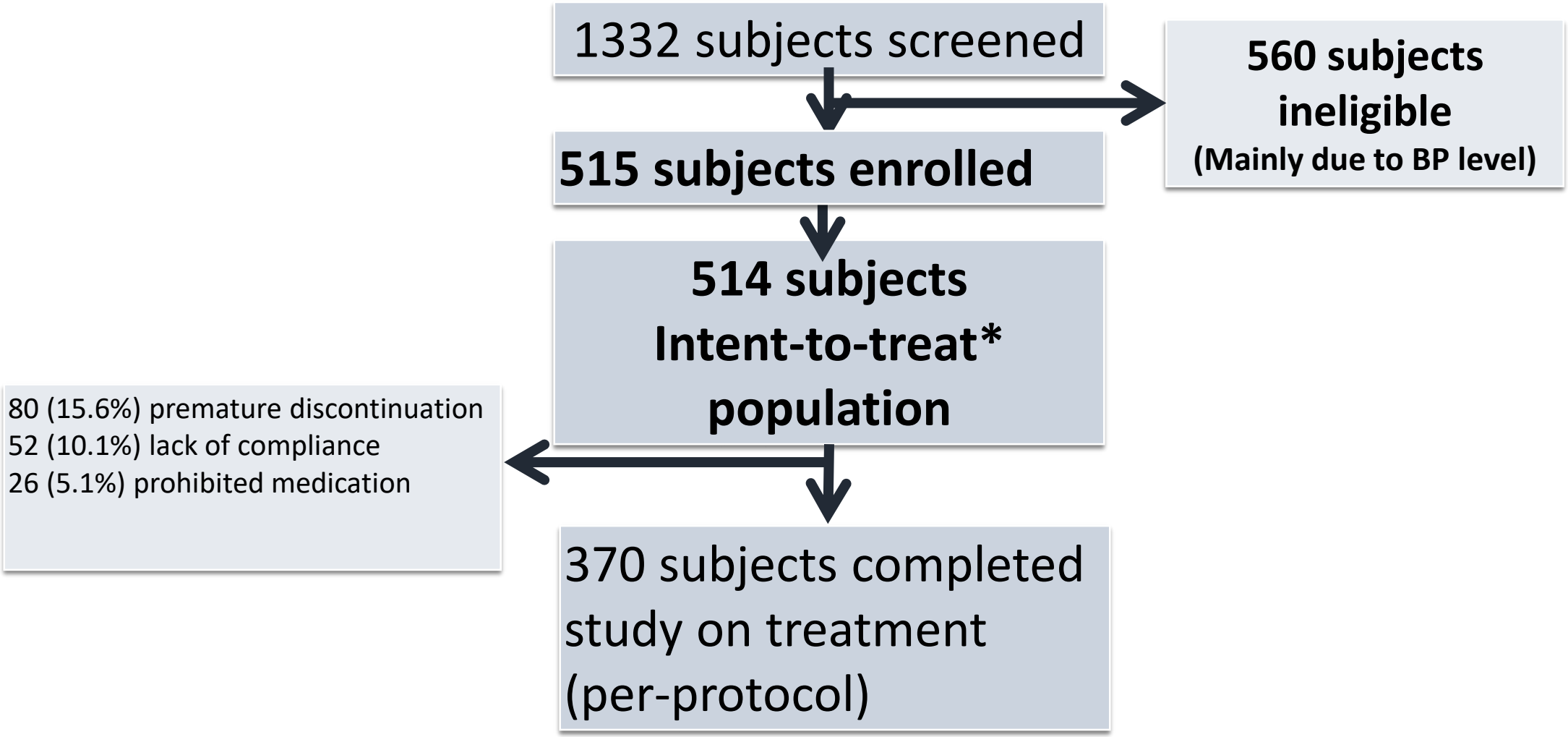
FRESH primary objective is to assess efficacy and safety of firibastat (vs placebo) on top of baseline therapy to decrease blood pressure in difficult-to-treat or resistant hypertensive patients.

FRESH main selection criteria

- **Inclusion criteria**
  - Uncontrolled Primary HTN (SBP 140-180 mmHg at screening)
  - Despite being treated with 2 classes of antihypertensive drugs (difficult-to-treat) or at least 3 classes including a diuretic (resistant)
  - With medication adherence >80% during the Run-in Period
  - Mean systolic daytime ABP >135 mmHg after the Run-in Period while on their current chronic antihypertensive treatments.

- **Exclusion criteria**
  - eGFR rate<30ml/min/1.73m2
  - Type-I DM or Type-2 DM with A1C>8% or treated with short-acting insulin

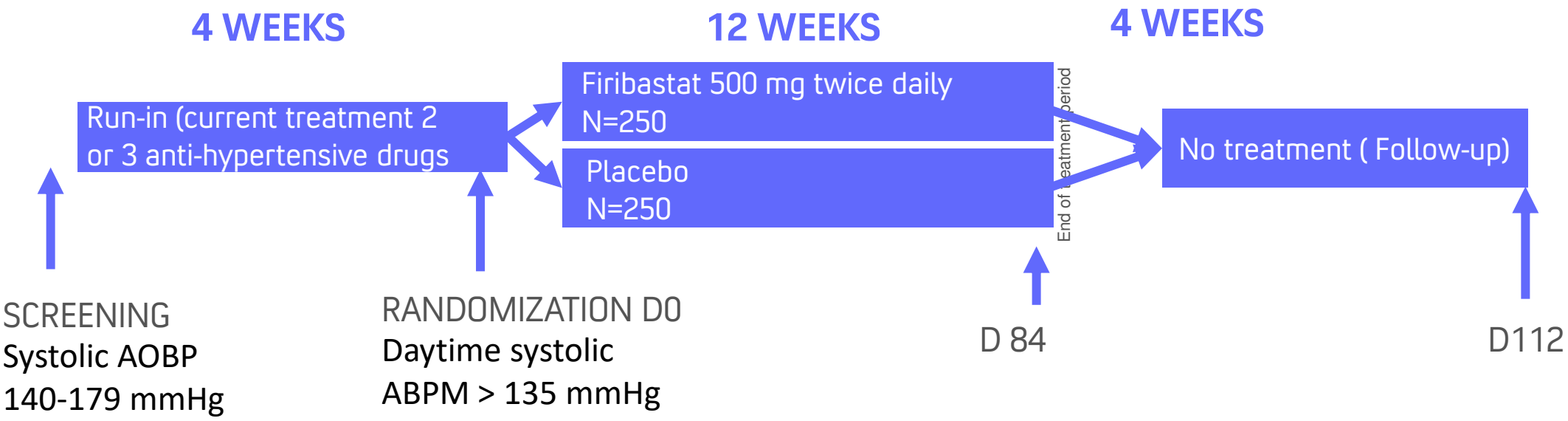
Study population



* All patients who took at least one capsule and with at least one post-baseline blood pressure assessment

FRESH Study Design

Multicenter (75 sites,11 countries) Randomized, Double-blind, Placebo-controlled Phase 3 Study



Primary endpoint : change from baseline in unattended SBP at 12 weeks

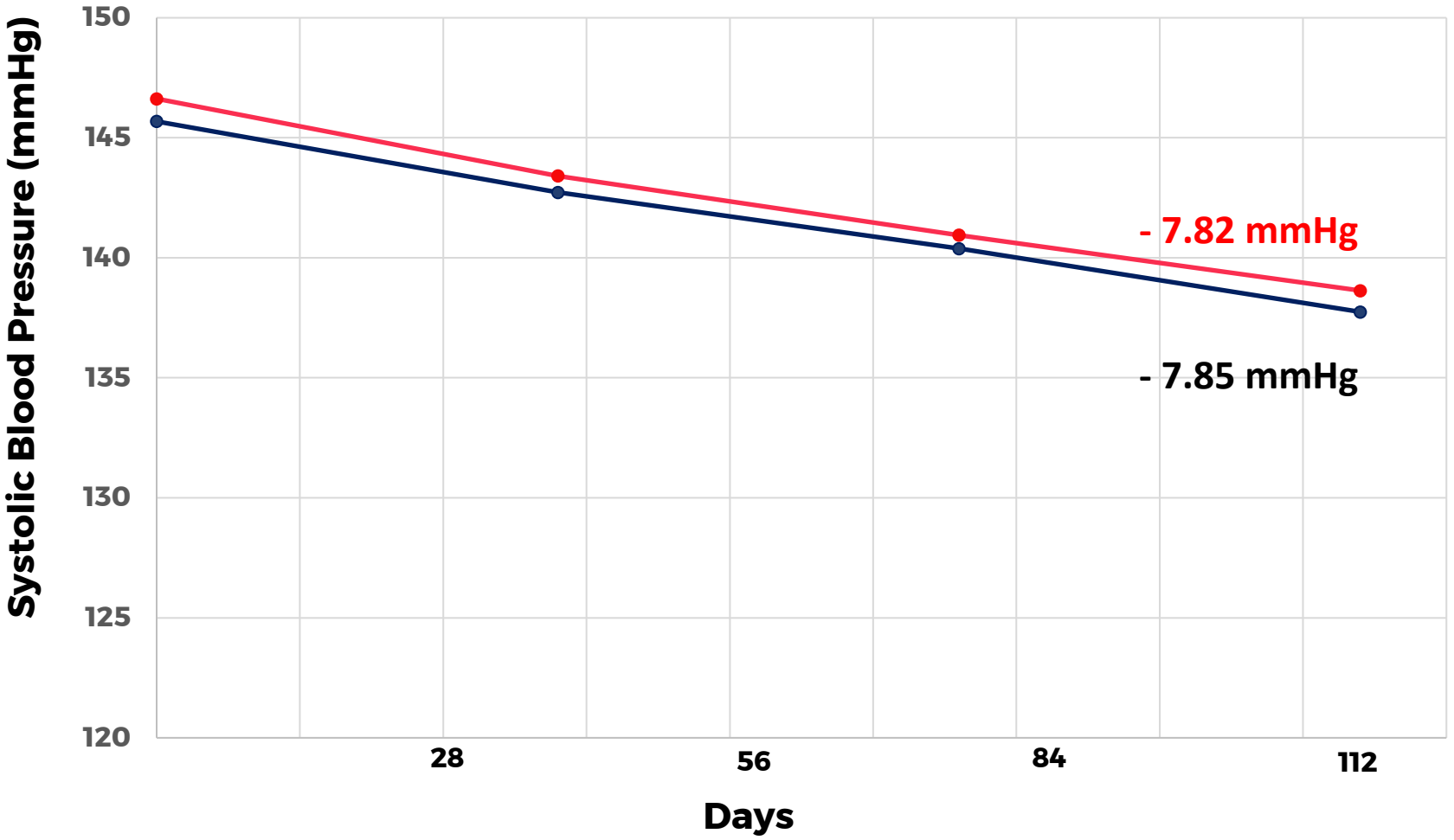
NCT04277884

Baseline characteristics

	Firibastat N=255	Placebo N=259	All N=514
Age (Year)	64.40 (9.94)	62.42 (11.69)	63.40 (10.89)
Male (%)	143 (56.1%)	157 (60.6%)	300 (58.4%)
Caucasian n (%) Black n(%)	205 (80.4%) 37 (14.5%)	213 (82.2%) 33 (12.7%)	418 (81.3%) 70 (13.6%)
BMI kg/m^2 Obese n (%)	31.98 (5.89) 151 (59.2%)	32.77 (6.05) 165 (63.7%)	32.38 (5.98) 316 (61.5%)
Treatment-resistant	185 (72.5%)	190 (73.4%)	375 (73.0%)
Systolic AOBP	146.62 (12.37)	145.68 (11.87)	146.15 (12.12)
Diastolic AOBP	84.30 (11.31)	83.99 (12.18)	84.14 (11.75)
Systolic 24h ABPM	146.52 (10.56)	149.19 (12.99)	147.87 (11.91)
Systolic Daytime ABPM	149.68 (10.80)	152.75 (13.35)	151.23 (12.24)
Systolic Nighttime ABPM	137.85 (14.47)	138.73 (17.05)	138.30 (15.81)

Primary endpoint

Change from baseline in unattended Automatic Office Systolic Blood Pressure



Adjusted change from baseline in systolic AOBP

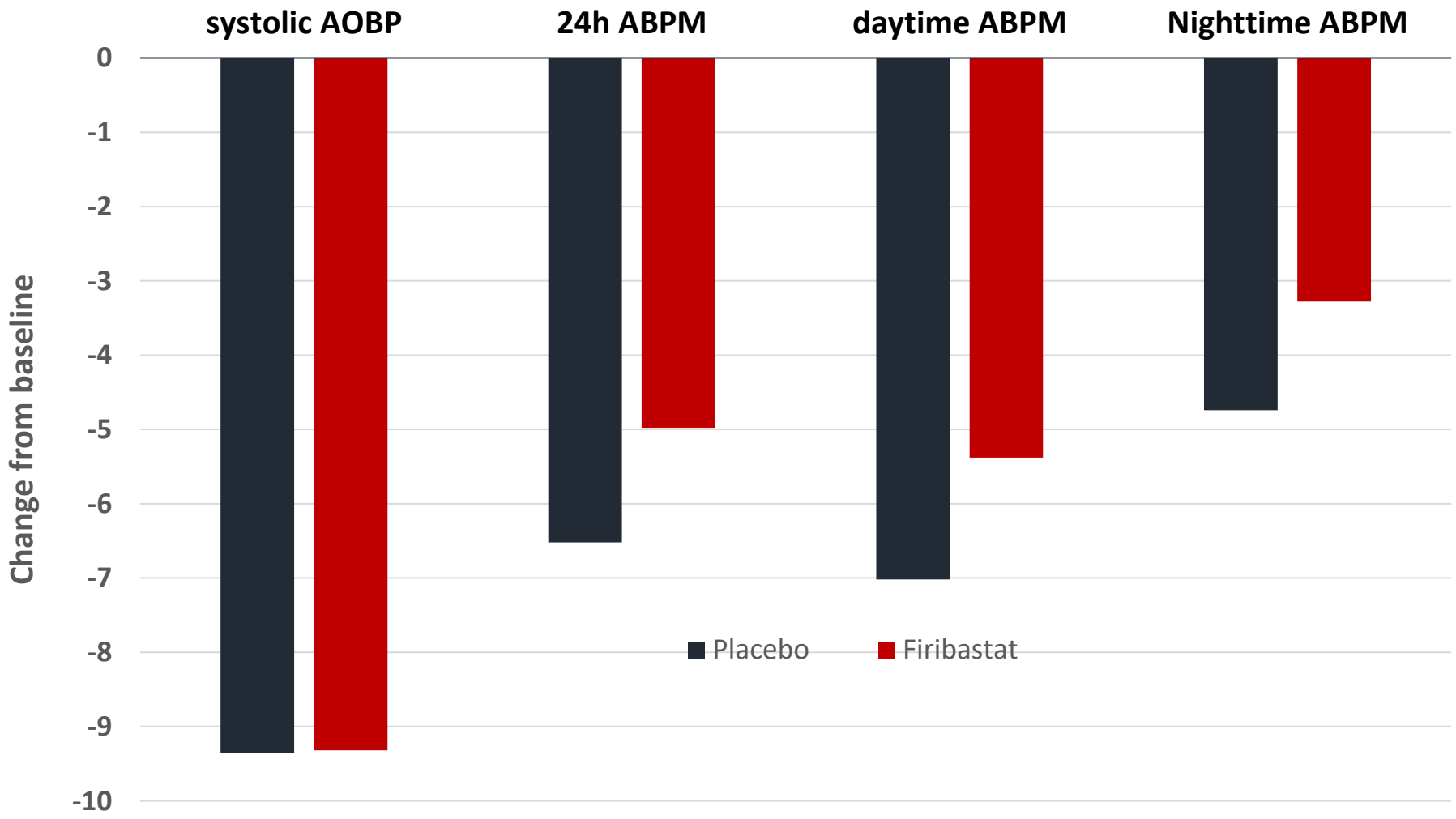
Firibastat 500 mg BID : -7.82 mmHg

Placebo: -7.85 mmHg

Adjusted difference : +0.03 mmHg

p=0.98

Secondary endpoints



AOBP = Automatic Office Blood Pressure ; ABPM = Ambulatory Blood Pressure Monitoring

Safety

- No serious related adverse events
- No change in liver enzymes

	Firibastat 500mg BID N=255	**Placebo** N=259
Potassium blood level (mEq/L)	**+0.07 ±0,38**	**-0,02 ±0,39**
eGFR (mL/min/m²)	**-2.0 ±9.0**	**-1.6 ±9.4**
Hypotension (n, %)	**3 (1.2%)**	**6 (2.3%)**

Allergic Skin reactions (related or potentially related)

(centrally adjudicated)

	Firibastat 500mg BID N=255		Placebo N=259	
	Events	Patients (n, %)	Events	Patients (n, %)
Allergic Skin reaction (adjudicated)	14	13 (5.1%)	1	1 (0.4%)
Exanthema	7		1	
Skin rashes	6		0	
Prurit	1		0	

No skin reaction was reported as serious adverse event

Conclusion

- Firibastat failed to demonstrate efficacy to decrease unattended office systolic blood pressure in patients with difficult-to-treat and resistant hypertension
- Results are consistent across all the sub-groups and secondary endpoints
- Firibastat is well tolerated – Most common adverse events are skin reactions (5.1%)