DOI: 10.47799/pimr.1001.02

Novel Class of Central Renin Angiotensin Aldosterone System Inhibitor: Firibastat

Nidhi Maheshwari[1], Vandana Tayal[2]*

[1]Assistant Professor, Department of Pharmacology, School of Medical Sciences and Research (SMS&R), Sharda University, Greater Noida, Uttar Pradesh
[2]Professor, Department of Pharmacology, Maulana Azad Medical College & Associated Hospitals, New Delhi, Tel.: 9968604217

Corresponding Author:
Vandana Tayal, Professor, Department of Pharmacology, Maulana Azad Medical College & Associated Hospitals, New Delhi, Tel.: 9968604217
E-MAIL: vandana_tayal@yahoo.com

Date of Submission: 11/12/2021 **Date of Review: 05/01/2022** **Date of Acceptance: 21/01/2022**

ABSTRACT

Hypertension is one of the most important risk factors for the development of ischemic heart diseases, stroke, disability, vascular dementia, heart failure, renal dysfunction, retinopathy, and premature death. Despite the use of two or more blood pressure lowering medications, a considerable proportion of patients show poor control. Current antihypertensive medications show the limitation of use and effect in obese population, certain races like black population and also in renal impairment. Thus, there is an impending need to develop novel classes of antihypertensive agents acting on new targets with diversified mechanisms of action to more effectively manage raised blood pressure. With the introduction of the recent concept of overactive brain renin angiotensin system in cardiovascular disorders, attempts have been made to identify a molecule with the potential of inhibiting aminopeptidases involved in the formation of Angiotensin III. A novel aminopeptidase A inhibitor, also a prodrug Firibastat is currently undergoing development in Phase III clinical trials for hypertension as well as chronic heart failure. We hereby, provide an updated summary of evidence generated so far with Firibastat and also a glimpse into the therapeutic potential of this novel candidate extending beyond the spectrum of essential hypertension

KEYWORDS: obese, Fibribastat, Hypertension, Heart failure, Obese, Central Aminopeptidase A Inhibitor, Resistant Hypertension

INTRODUCTION

Hypertension (HTN) is the leading cause of cardiovascular disease and premature death worldwide. With rapid urbanization, increasing elderly population, increase in body mass index, the prevalence of hypertension is increasing. It is one of the most important risk factors of ischemic heart diseases, stroke, disability, vascular dementia, heart failure, renal dysfunction, retinopathy, and premature death. [1, 2]

Effective blood pressure (BP) management has been shown to decrease cardiovascular risk and the incidence of stroke, heart attack and heart failure. [3] Several pharmacological treatments including systemic renin-angiotensin system (RAS) blockers, calcium-channel blockers, and diuretics are available for treating hypertension both as monotherapy as well as in combination. [4]Despite use of these drugs, a substantial proportion of the hypertensive population(>50%) as well as certain ethnic origins like black population has uncontrolled or suboptimally controlled hypertension [3] . Also, there are reports indicating a considerable increase in resistant hypertension [1] .

Thus, there is an impending need to develop novel classes of antihypertensive agents acting on new targets with diversified mechanisms of action to more effectively manage raised BP. [4] Some of the important targets that are being explored are various enzyme-catalyzed degradation of vasoactive peptides, hormones and related receptors that play a key role in BP regulation and cardiovascular function. [2]

Recently, various studies have introduced the concept of overactive brain RAS in hypertension and other cardiovascular diseases. [1, 3] In the brain RAS, two membrane-bound zinc metalloproteases, aminopeptidase A(APA) and aminopeptidase N (APN), are involved in the metabolism of angiotensin II(AngII) and angiotensin III (AngIII) respectively. AngIII is the major peptide in brain responsible for stimulatory BP control. Brain APA converts Ang II to Ang III, the latter acts on Angiotensin type 1 receptor (AT_1R) to increase BP and arginine-vasopressin (AVP) release. [4]

Hence, curbing the effect of brain Ang III via central APA inhibitor, constitutes a novel approach to develop an anti-hypertensive strategy. Firibastat, a first-in-class, brain APA inhibitor has been developed as a centrally acting antihypertensive agent.

Chemistry of Firibastat

Firibastat(RB150), is the first known representative of a new class of completely non-peptide, orally active, brain APA inhibitor. The chemical name of the compound is [(3S,3'S)-4,4'-Disulfanediylbis (3-aminobutane-1-sulfonic acid]. The molecular formula of Firibastat is $C_8H_{20}N_2O_6S_4$ and molecular weight is 368.5g/mol. [5, 6] It is a pro drug which is composed of two molecules of EC33 [(S)- 3amino-4mercapto-butyl sulfonic acid] linked by a disulfide bond .Figure 1 Firibastat is currently undergoing Phase 3 studies and is being developed by Quantum Genomics, for the treatment of hypertension and chronic heart failure.

Mechanism of Action

Firibastat is a novel inhibitor of APA (a 160-kDa homodimeric type II membrane-bound monozinc aminopeptidase), which is an important component of the brain RAS contributing to the formation of Ang III. The APA enzyme hydrolyzes the N-terminal glutamate or aspartate residue from peptidic substrates such as Ang II or cholecystokinin-8 to form Ang III.

Firibastat, when given orally crosses the intestinal, hepatic, or the blood– brain barrier through the large neutral amino acid transporter 1 [5]. The disulphide bond present in the structure of firibastat prevents the interaction of its thiol group with the zinc atom which is essential for the catalytic activity of APA. The brain reductases however rapidly cleave the disulphide bond in firibastat molecule, releasing two molecules of its active moiety, EC33, which inhibits APA, thereby inhibiting the formation of AngIII. Firibastat thus reduces BP and improves cardiovascular dysfunction through inhibition of Ang III mediated Figure 2

1. Sympathetic stimulation,

2. Increased AVP release into the circulation from the posterior pituitary potentiating sodium and water retention,

3. Left ventricular dilatation

4. Inhibition of baroreceptor reflex at the nucleus tractus solitarius. [2]

Pharmacokinetic Parameters

Firibastat, after oral administration is rapidly absorbed from the gastrointestinal tract in humans, with a median t_{max} of 1.5 h (range 0.75–3 h). It is partially converted to its active metabolite EC33 by reductases present in the gastrointestinal tract. AUC_{last} and C_{max} have been shown to follow a dose proportional increasing trend. The median AUC_{last} and C_{max} of firibastat achieved after a single dose of 1000 mg has been reported to be 206.2 ng/mL and 55 ng/ml, respectively, suggesting a low oral bioavailability. However, the active site of firibastat is brain, and hence its plasma concentration is a mere reflection of fraction of administered drug. The median $t_{1/2}$of firibastat ranges from 1-2 hr. The drug doesn't have a primary renal excretion nor is metabolized by liver enzymes. The renal clearance is <2% (65.6 L/hr) after single administration of 1000mg dose. [5]

Adverse Effects

Firibastat has shown good tolerability profile in several clinical studies. The most frequent adverseevents reportedwere headaches (4%) and skin reactions (3%). No angioedema was reported. No change in potassium, sodium, and creatinine blood level were observed. [3]

Drug Interactions

In-vitro assays of firibastat at 10 micromol/L with fluorometric substrates have shown that it does not significantly inhibit the human recombinant cytochrome P450s (CYPs) (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). [5]

Preclinical Studies in hypertension and heart failure

The effect of firibastat has been studied in two experimental models of hypertension: the Spontaneously Hypertensive Rat (SHR), and the Deoxycortisterone acetate (DOCA)–salt hypertensive rat. [1] In contrast to intravenous injections only, intracerebroventricular injections of EC33 was seen to reduce the BP in these two hypertensive models indicating its central antihypertensive action. Mean arterial BP has been shown to be reduced after 2 hours of administration of firibastat with maximal reduction seen between 5 and 9 hours (up to 49 ± 10 mm Hg). The effect gradually declined until 15 hours and disappeared after 24 hours. This has been explained to be due to an approximately 34% reduction in the APA activity along with a suppression in AVP release by 32% which resulted in about 146% increase in diuresis and 61% increase in natriuresis. These effects were observed 5 hours after administration of 15 mg/kg of Firibastat. On the contrary, studies conducted in normotensive Wistar Kyoto (WKY) rats and normotensive Beagle dogs showed no effect on BP, indicating that firibastat might not be a hypotensive agent. [7]

Further, oral treatment with firibastat for four weeks post Myocardial Infarction (MI) in mice has been observed to improve cardiac function and also attenuate both cardiac hypertrophy and fibrosis. A decrease in expression of cardiac biomarkers for heart failure was found to be more effective than enalapril treatment. [8]

Four-week preclinical toxicity studies including safety pharmacology and pharmacokinetic studies conducted in rats and dogs reported that firibastat up to 1g/kg is well tolerated. The bioavailability of firibastat is lower in rats (<1 %) compared to that in dogs (30 %). [5]

No effect on systemic RAS has been seen in these studies. However, concomitant administration of oral firibastat (100mg/kg) with enalapril (1 mg/kg) in SHR reported a significant BP decrease (-16.4 ± 3.1 mmHg) suggesting a synergistic effect of inhibition of both brain as well as systemic RAAS. [7]

Clinical Efficacy & Safety Studies

In Phase 2a randomized, double-blind, placebo controlled, multicentric, two period crossover study to explore efficacy and safety of firibastat, 34 adult patients were enrolled with raised systolic BP (140-180 mmHg) and diastolic BP (90-

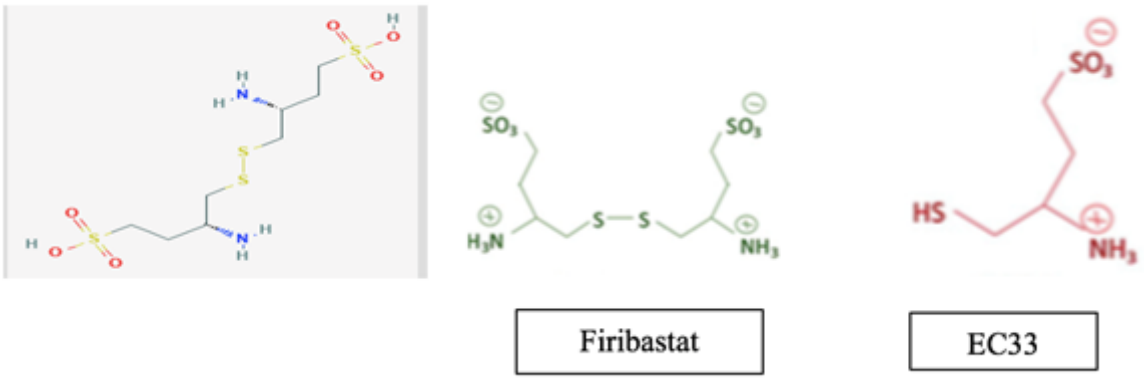

Figure 1: Chemical structure of Firibastat and its prodrug EC-33

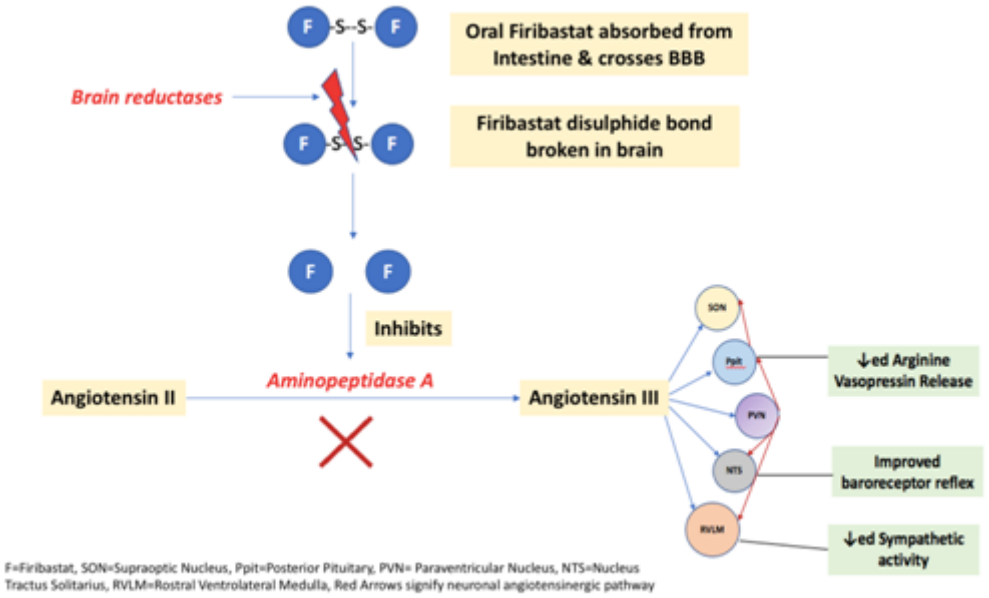

Figure 2: Mechanism of blood pressure lowering by Firibastat in brain

110 mm Hg) on 0-2 antihypertensive agents with mean BMI of 26.8±3.3 kg/m^2. Firibastat was given at a twice daily dose of 250 mg for 1 week, titrated to 500 mg twice daily for next 3 weeks. The results revealed a decrease in the SystolicBP, by around 3-5 mm Hg. This decrease was further pronounced in the participants who had a higher baseline BP, indicating that firibastat acts as an anti-hypertensive agent and not a hypotensive agent. Overall firibastat was well tolerated with mild adverse events. However, few treatment emergent serious side effects that led to the withdrawal of firibastat were rash and facial swelling, vestibular disorder, and arthralgia. This short duration of exposure with firibastat was not associated with any significant changes in the plasma and urine hormonal levels of renin, aldosterone, cortisol etc. [9]

The Phase 2b trial of firibastat, (The NEW-HOPE trial) was conducted in high risk (n=256), diverse population of overweight and obese [mean BMI of 33.0±5.2kg/m^2] hypertensive individuals of mixed racial background, for a treatment period of 8 weeks. Approximately half of the population was black and close to 30% had type 2 diabetes mellitus. The black population was included as the prevalence of obesity, cardiac and renal complications, early onset of HTN, and resistant HTN is more in this population. This was an open-label, randomized, multicentric study in confirmed stage II primary HTN with a mean automated office BP (AOBP) of systolic 153.9±7.3 mm Hg and diastolic 91.5±8.5mmHg. Results of the trial revealed a significant fall ($p<0.0001$) in mean AOBP for both systolic (decrease by 9.5 mmHg) and diastolic (decrease by 4.2 mm Hg) at the end of 8 weeks. This decrease in blood pressure was consistent

and significant across all age-groups, gender, races, obese-overweight. Around 70% patients were controlled on 500 mg twice daily dosing of firibastat. Firibastat was generally well tolerated in this diverse population with headache and skin rash being the most reported adverse events. The skin reactions discontinued with stopping the drug and were suspected to be due to the sulfhydryl group of the active metabolite of firibastat. Serious adverse events were also reported in this study with causality established with one episode of erythema multiforme. There were no changes in serum electrolytes or renal profile of the patients as reported with many first line antihypertensive agents.

[Table 1 about here.]

[Table 2 about here.]

Advantages of Firibastat

a. Firibastat is effective as a monotherapy and also has synergistic effect in decreasing BP in combination with other antihypertensives like thiazides, Angiotensin Converting Enzyme (ACE) inhibitors in high risk hypertensive racial minorities. [3, 9]

b. In early phase clinical trials, firibastat has been shown to be an effective anti-hypertensive in black population where monotherapy with ACE inhibitors or AT_1R blockers may be less effective. [3]

c. Firibastat has also shown effective BP control in obese population which is more at risk for resistant hypertension. [3]

d. Firibastat does not influence renal parameters unlike other antihypertensive agents like thiazide diuretics, spironolactone, systemic RAS inhibitors with which caution is advised with eGFR<30 ml/min. With further trials, it might emerge as an antihypertensive safe in renal failure. [10]

e. Preclinical studies suggest that firibastat treatment is as effective as enalapril treatment in preventing fibrosis and improving cardiac dysfunction in patients of chronic heart failure and after acute MI.

What's Upcoming with Firibastat?

1. The Phase III program of firibastat (FRESH Study) is under design comprising of two studies- one to confirm its efficacy and the other to prove its safety. The efficacy study is planned to be conducted in 502 resistant HTN adult patients. Oral firibastat at a dose of 500 mg twice daily will be compared with matching placebo in addition to their current chronic antihypertensive treatments for a period of 12 weeks. The primary end point of the study is systolic AOBP in mm Hg from Day 1 to Day 84. [11]The safety study is planned to enroll 750 patients, with 100 out of these continuing firibastat for 1 year while the rest for a period of 6 months. [12]

2. An ongoing Phase 2b clinical trial in 295 subjects assesses the role of firibastat after acute MI for prevention of left ventricular dysfunction (QUORUM Study). In this dose-titrating study, oral firibastat is being compared with ramipril for over 12 weeks. Two doses of firibastat are being tested, a low dose of 50 mg twice daily titrated to 100mg twice daily and a regular dose of 250 mg twice daily titrated to 500 mg twice daily. The primary end point in this study is the change from baseline in the Left ventricular ejection fraction (LVEF) after 12 weeks of treatment [13]. Recently the interim results of this study were presented at the European Society of Cardiology Meeting in August 2021 demonstrating better efficacy of Firibastat compared to Ramipril in severe patients with low ejection fraction. [14] This study has been planned based on the findings from an experimental study conducted in MI models of Male Wistar Rats. Firibastat at a dose of 50 mg/kg/day subcutaneous or 150 mg/kg/day oral was shown to be as effective as Losartan 50 mg/kg oral twice daily to inhibit cardiac dysfunction further to MI. Firibastat treatment (150 mg/kg/day) was as effective as enalapril treatment (1 mg/kg/day) for improving cardiac function without affecting systolic blood pressure.

3. Based on the findings of Phase 2b trial of Firibastat, that it did not impact renal function, an ongoing study investigates a single dose of 500 mg in 14 healthy volunteers and 14 severe renal failure patients.

The summary of all clinical trials has been mentioned in Tables 1 and 2

CONCLUSION

Aminopeptidase A play a major role in the brain RAS. Its overactivity results in an increase in sympathetic tone, left ventricular dilation and cardiac dysfunction. Firibastat, a pro drug, emerges as a novel class of centrally acting RAAS inhibitor that exerts its mechanism by inhibiting the enzyme APA, thereby curbing the effect of Angiotensin III. It seems to be a promising drug for control of difficult-to-treat or potentially resistant hypertension and, should be initiated as soon as possible after ischemic injury, to ensure the rapid normalization of the brain RAS.

Conflict of Interest: Nil

ACKNOWLEDGEMENTS: NIL

Financial Support: Nil

Author Contribution

Dr Nidhi Maheshwari was involved with designing of the study, acquisition of data, literature search and interpretation. She took the responsibility of being accountable to all matters related to it. The manuscript drafts were written and repeatedly revised by her to produce the final version.

Dr Vandana Tayal initiated the study. She served as the scientific advisor and critical reviewer, gave valuable inputs

and helped shape the final version of the manuscript. The original idea was conceived by her and final version of manuscript has been approved under her supervision

REFERENCES

1. Keck M, Hmazzou R, Llorens-Cortes C. Orally Active Aminopeptidase A Inhibitor Prodrugs: Current State and Future Directions. CurrHypertens Rep. 2019;21(7):50–50.
2. Arendse LB, Danser A, Poglitsch M, Touyz RM, Burnett JC, Llorens-Cortes C et al. Novel Therapeutic Approaches Targeting the Renin-Angiotensin System and Associated Peptides in Hypertension and Heart Failure. Pharmacol Rev. 2019;71(4):539–70.
3. Ferdinand KC, Balavoine F, Besse B, Black HR, Desbrandes S, Dittrich HC. Efficacy and Safety of Firibastat, A First-in-Class Brain Aminopeptidase A Inhibitor, in Hypertensive Overweight Patients of Multiple Ethnic Origins. Circulation. 2019;140(2):138–184.
4. Llorens-Cortes C, Touyz RM. Evolution of a New Class of Antihypertensive Drugs: Targeting the Brain Renin-Angiotensin System. Hypertension. 2020;75(1):6–15.
5. Balavoine F, Azizi M, Bergerot D, Mota D, Patouret N, Roques R et al. Llorens-Cortes C. Randomised, double-blind, placebo-controlled, dose-escalating phase I study of QGC001, a centrally acting aminopeptidase a inhibitor prodrug. Clin Pharmacokinet. 2014;53(4):385–95.
6. National Center for Biotechnology Information ; 2021,. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Firibastat.
7. Marc Y, Gao J, Balavoine F, Michaud A, Roques BP, Llorens-Cortes C. Central antihypertensive effects of orally active aminopeptidase A inhibitors in spontaneously hypertensive rats. Hypertension. 2012;60(2):411–419.
8. Boitard SE, Marc Y, Keck M, Mougenot N, Agbulut O, Balavoine F et al. Brain renin-angiotensin system blockade with orally active aminopeptidase A inhibitor prevents cardiac dysfunction after myocardial infarction in mice. J Mol Cell Cardiol. 2019;127:215–237.
9. Azizi M, Courand PY, Denolle T, Delsart P, Zhygalina V, Amar L et al. A pilot double-blind randomized placebo-controlled crossover pharmacodynamic study of the centrally active aminopeptidase A inhibitor, firibastat, in hypertension. J Hypertens. 2019;37(8):1722–1730.
10. Sinha AD, Agarwal R. Clinical Pharmacology of Antihypertensive Therapy for the Treatment of Hypertension in CKD. Clin J Am Soc Nephrol. 2019;14(5):757–64.
11. Bakris G, Quantum Genomics SA. Firibastat in Treatment-resistant Hypertension (FRESH) ; 2021,. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04277884.
12. Firibastat Phase III to start by end of the year ; 2019,. Available from: https://www.edisongroup.com/publication/firibastat-phase-iii-to-start-by-end-of-the-year/25253/.
13. Quantum Genomics SA. Firibastat or Ramipril After Acute Myocardial Infarction for Prevention of Left Ventricular Dysfunction (QUORUM) ; 2018,. Available from: https://clinicaltrials.gov/ct2/show/NCT03715998?term=Firibastat&cond=Cardiovascular+Diseases&draw=2&rank=2.
14. Leenen F, Ahmad M, Marc Y, Llorens-Cortes C. Specific Inhibition of Brain Angiotensin III Formation as a New Strategy for Prevention of Heart Failure After Myocardial Infarction. J Cardiovasc Pharmacol. 2019;73(2):82–91.
15. ; 2022,. Available from: //www.globenewswire.com/news-release/2021/08/27/2287568/0/en/Quantum-Genomics.

How to cite this article: Maheshwari N, Tayal V. **Novel Class of Central Renin Angiotensin Aldosterone System Inhibitor: Firibastat**. Perspectives in Medical Research. 2022;10(1):3-7
DOI: 10.47799/pimr.1001.02

Sources of Support: Nil: ,

LIST OF TABLES

Phase/Concept	Study Design	Baseline Characteristics	Comorbid Conditions	Dosing of Firibastat	Primary end point	Adverse Events	Reference
Phase 1 (First in Human-Pharmacokinetics Study)	Randomized (3:1), Double blinded,Placebo controlled,single-ascending oral dose (eight sequential doses) N=56 Duration=Single dose	Mean Age= 32.7±4.2 years Mean BMI= 23.3 ± 2.7 kg/m2	Healthy males	10, 50, 125, 250, 500, 750, 1,000 and 1,250 mg	Safety & Tolerability For 1000 mg dose: Cmax= 55ng/ml, Tmax=3 hrs, t1/2= 1.6 hrs	Orthostatic hypotension	Balavoine Fet al2014 [5]
Phase 2 a (Pilot Study)	Randomized (1:1), Double blinded, Placebo controlled, Multicentric, 2 Period crossover N=34 Duration =Four weeks	Mean Age= 56.6±9.1 years Mean BMI= 26.8 ± 3.3 kg/m2 Mean BP= 148.6 ± 10.2/ 95 ± 6.6 mmHg	Nil	Frequency=Twice daily Dose= 250 mg BD for 1 week f/b 500 mg BD for 3 weeks	Mean change in day time ambulatory SBP=↓2.7 (95% CI -6.5 to +1.1)mmHg (p=0.157)	Rash, skin allergy, facial oedema, arthralgia, vestibulitis	Azizi M et al 2019 [9]
Phase 2b (New Hope Trialin Stage 2 Hypertension)	Randomized, Open label, Multicentric, Single Arm N=256 Duration=8 weeks	Mean Age= 58.3±9.9 years Mean BMI= 33 ± 5.2 kg/m2 Mean BP= 153.9 ± 7.3/ 91.5± 8.5 mmHg Black & Hispanic population (54%)	Obesity (64.8%) Type 2 Diabetes Mellitus (28.5%)	Frequency=Twice daily Dose= 250 mg BD for 2 week f/b 500 mg BD	Mean change in systolic AOBP= ↓9.5 (95% CI -10.7 to -7.3)mmHg (p<0.0001)	Skin Rash, Headache, Erythema multiforme	Ferdinand KC 2019 [3]

BMI= Body Mass Index, BP= Blood Pressure, BD= Twice daily, f/b= followed by, SBP=Systolic Blood Pressure AOBP=Automated BloodPressure, MI=Myocardial Infarction, Duration=Duration of therapy,N= Number of participants

Table 1: Summary of Fibribastat clinical studies

Phase 2b (Firibastat vs Ramipril after acute MI QUORUM Study)	Randomized, Double-blind, Active-controlled, Parallel Group N=295 Duration =12 weeks	Post MI patients	Frequency=Twice daily Group A Firibastat50 mg BD for 2 week f/b 100 mg BD vs Group B Firibastat250 mg BD for 2 week f/b 500mg BD vs Group C Ramipril 2.5 mg BD	Increase in LVEF Group A 53 to 59% vs Group B 51 to 58% vs Group C 50 to 57% Subgroup of severe disease (LVEF<50%) ↑ in LVEF 5.32 ± 1.67% Vs 3.51 ± 1.64%	Skin Reac-tions	Quantum Genomics announce-ment [15]
Phase 3 (Firibastat in Treatment Resistant Hyperension-FRESH study)	Randomized (1:1), Double-blind,Placebo controlled, Multicentric N=502 Duration=12 weeks		Frequency=Twice daily Dose= 250 mg BD for 2 week f/b 500 mg BD	Mean change in systolic AOBP (Results not published)	Results not pub-lished	FRESH Study [11]

BMI= Body Mass Index, BP= Blood Pressure, BD= Twice daily, f/b= followed by, SBP=Systolic Blood Pressure AOBP=Automated BloodPressure, MI=Myocardial Infarction,Duration=Duration of therapy,N=Number of participants

Table 2: Summary of Fibribastat clinical studies