AZALEA-TIMI 71

A Multicenter, RandomiZed, Active-ControLled Study to Evaluate the Safety and Tolerability of Two Blinded Doses of Abelacimab Compared with Open- Label Rivaroxaban in Patients with Atrial Fibrillation

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on behalf of the AZALEA-TIMI 71 Steering Committee & Investigators

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Scientific Session Late-Breaking Clinical Trial

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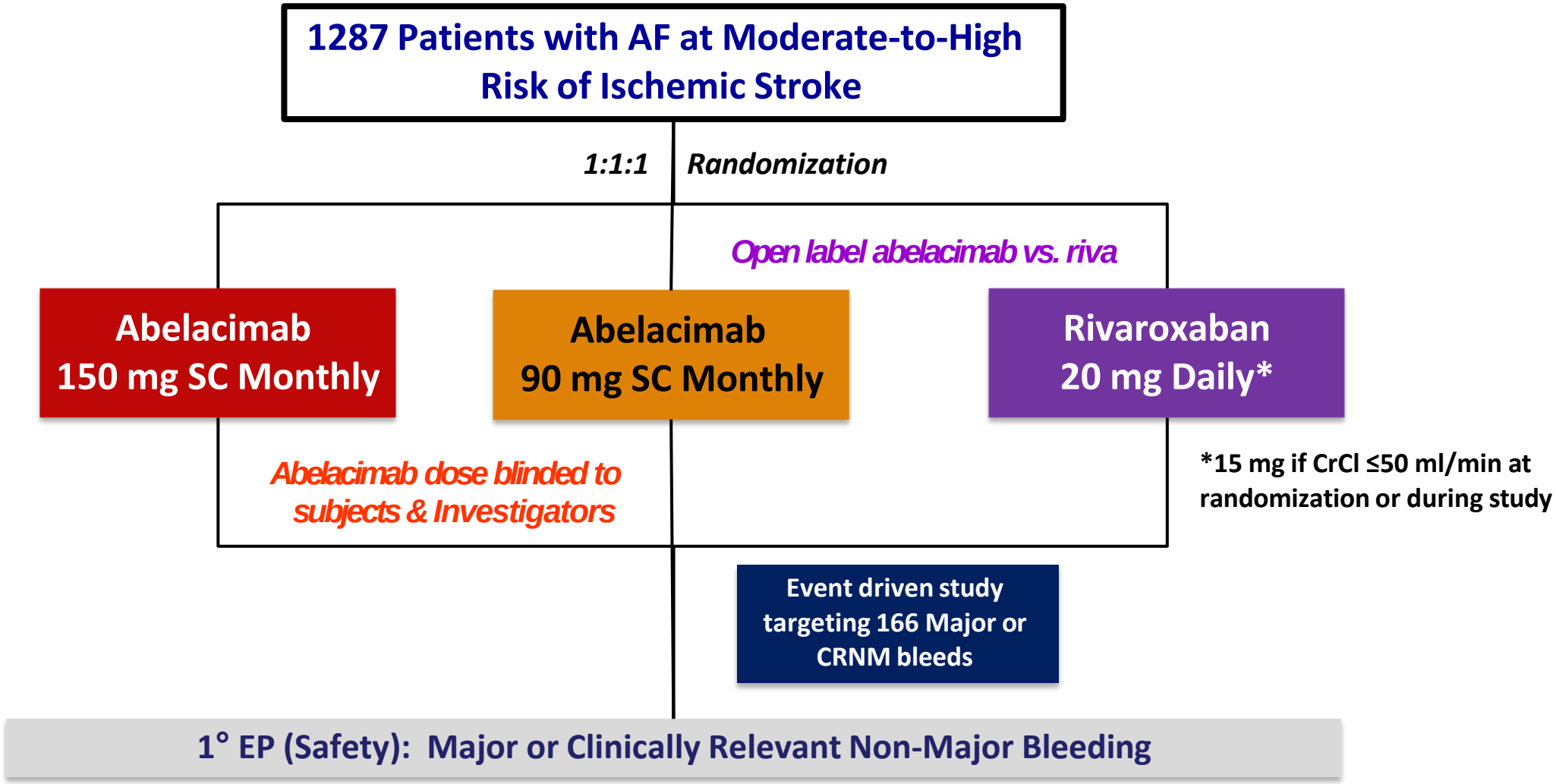
AIM of the study

To evaluate the bleeding profile of abelacimab relative to rivaroxaban in patients with AF at moderate-to-high risk of stroke.

Methods

- Event-driven, randomized, active-controlled, blinded endpoint, parallel-group study.
- 1287 participants across the globe in 95 study sites.
- The primary endpoint is a composite of the rate of major or clinically relevant non-major bleeding events.
- Patients were randomized 1:1:1 and administered subcutaneous (SC) abelacimab 150 mg once-monthly, abelacimab 90 mg once-monthly, or rivaroxaban 20 mg daily.

Trial Design



Key Inclusion Criteria

- Age ≥55 years
- Any history of AF or atrial flutter with planned anticoagulation
- CHA_2DS_2-VASc ≥4 *or*

  CHA_2DS_2-VASc = 3 with at least one of the following factors:
  - Planned concomitant use of antiplatelet medications
  - CrCl ≤50 ml/min

DMC Recommendation

September 14, 2023

"The IDMC members unanimously agreed to recommend termination of the AZALEA trial because of the substantially greater than anticipated reduction in major and clinically relevant non-major bleeds in the abelacimab arms compared to rivaroxaban and a benefit:risk ratio favoring abelacimab."

Results (I)

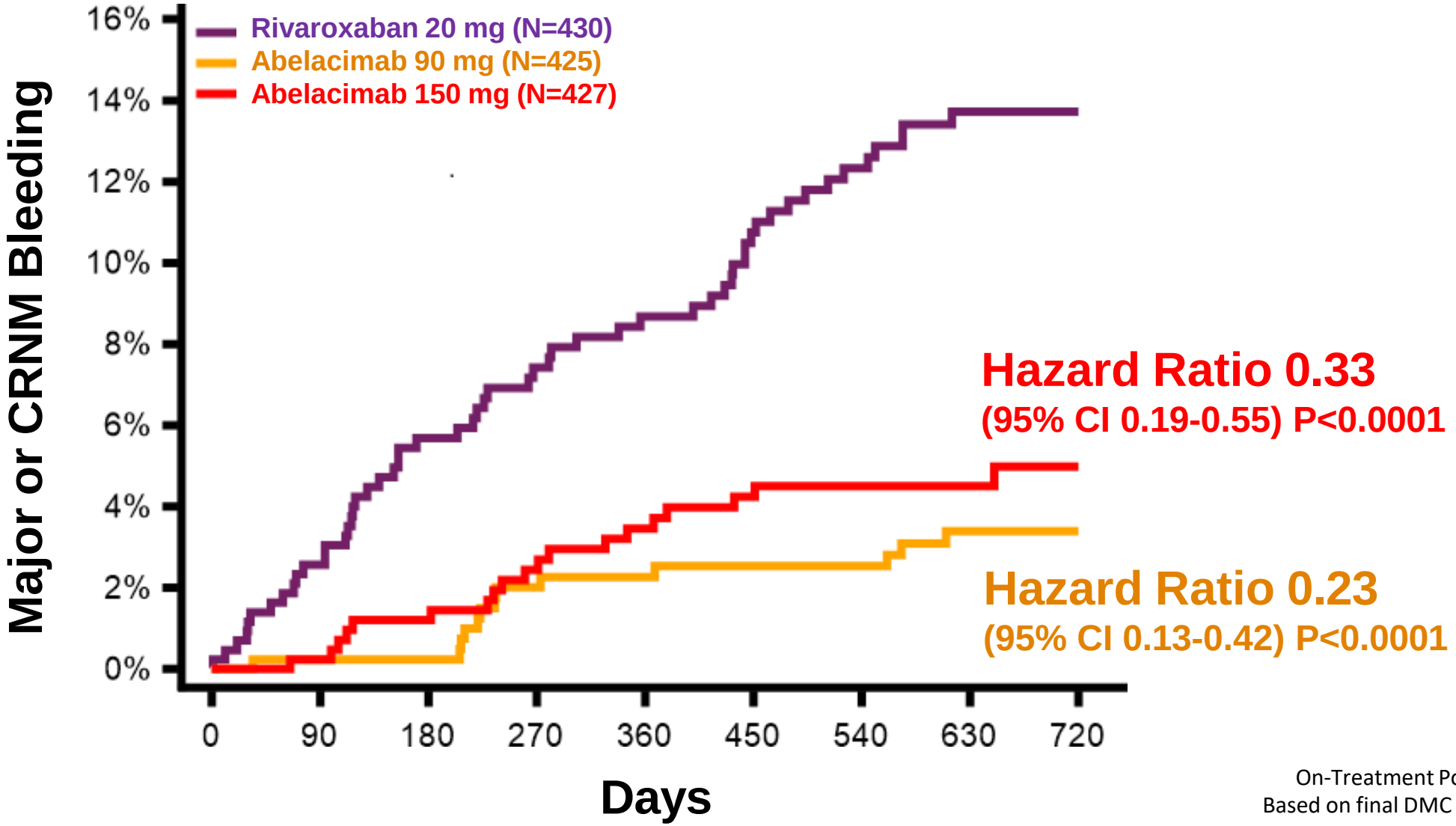
- Follow –up median: 1.8 years (IQR 1.7-1.9).
- The median change in FXI from baseline to 3 months was -97% (IQR: -50 to -99) in the 90 mg group and -99% (IQR: -98 to -99) in the 150 mg group.
- The **primary endpoint** was reduced in the abelacimab 150 mg group (2.7 per 100 Pt-years) compared with the rivaroxaban group (8.1 per 100 Pt-year) (HR 0.33, 95%CI: 0.19-0.56, P<0.0001) and in the abelacimab 90 mg group (1.9 per 100 Pt-years) compared with the rivaroxaban group (HR 0.23, 95%CI:0.13-0.42, P<0.0001).

Baseline Characteristics

Characteristic	Value
Age, years, median (IQR)	74 (69-78)
Female Sex (%)	44
CHA_2DS_2-VASc Score, median (IQR)	5 (4-5)
3-4 (%)	46
5 (%)	31
≥6 (%)	22
Prior Ischemic Stroke (%)	15
Prior Bleed (%)	7
Creatinine Clearance ≤ 50 mL/min (%)	21

Pooled data; no differences between treatment arms

Primary Endpoint



On-Treatment Population
Based on final DMC Datacut

Results (II)

- Other endpoints of major bleeding, GI bleeding and clinically relevant non-major bleeding (but not intracranial hemorrhage) were also significantly reduced in the abelacimab groups compared with the rivaroxaban group.
- The incidence rate of gastrointestinal bleeding was 0.1 in the abelacimab 150 mg group, 0.1 in the 90 mg abelacimab 90 mg group and 2.1 in the rivaroxaban group (HR 0.07, 95%CI: 0.01-0.50 and HR 0.07, 95%CI: 0.01-0.51, respectively).

Bleeding Endpoints

Endpoint (ISTH Definition)	Riva 20 mg (N=430) Incidence Rate	Abelacimab 150 mg (N=427) Incidence Rate	HR (95% CI)	P Value	Abelacimab 90 mg (N=425) Incidence Rate	HR (95% CI)	P-Value
Major + CRNM Bleeding	8.1	2.7	0.33 (0.19-0.55)	<0.001	1.9	0.23 (0.13-0.42)	<0.001
Major Bleeding	3.7	1.0	0.26 (0.11-0.61)	0.002	0.7	0.19 (0.07-0.50)	<0.001
GI Bleeding	2.1	0.1	0.07 (0.01-0.50)	0.008	0.1	0.07 (0.01-0.51)	0.009
ICH	0.6	0.3	0.50 (0.09-2.72)	0.42	0.6	1.03 (0.26-4.10)	0.97
CRNM Bleeding	4.6	1.8	0.39 (0.21-0.75)	0.004	1.1	0.25 (0.11-0.54)	<0.001

Incidence rates per 100 Pt-years

On-Treatment Population
Based on final DMC Datacut

Results (III)

Secondary outcomes for abelacimab 150 mg vs. abelacimab 90 mg vs. rivaroxaban:

- Stroke or systemic embolism: 1.1% vs. 1.4% vs. 1.0% (p = 0.81; p = 0.45)
- Ischemic stroke: 1.1% vs. 1.3% vs. 0.7%
- All-cause mortality: 2.4% vs. 2.8% vs. 3.1%
- Net clinical outcome, a composite of ischemic stroke, systemic embolism, major or clinically relevant nonmajor bleed, and all-cause death: 5.5%, 5.6%, 11.3% ($P < 0.001$ for both comparisons).

Abelacimab was well- tolerated overall, and injection-site reactions were uncommon.

Secondary Endpoints

Endpoint	Riva 20 mg (N=430) Incidence Rate	Abelacimab 150 mg (N=427) Incidence Rate	HR (95% CI)	P Value	Abelacimab 90 mg (N=425) Incidence Rate	HR (95% CI)	P-Value
Stroke or SEE	1.0	1.1	1.13 (0.41-3.12)	0.81	1.4	1.45 (0.55-3.80)	0.45
Stroke	1.0	1.1	1.13 (0.41-3.12)	0.81	1.4	1.45 (0.55-3.80)	0.45
Ischemic	0.7	1.1	1.59 (0.52-4.85)	0.42	1.3	1.82 (0.61-5.45)	0.28
Hemorrhagic	0.3	0	N/A	N/A	0.1	0.51 (0.05-5.62)	0.58
All-Cause Death	3.1	2.4	0.77 (0.41-1.46)	0.43	2.8	0.93 (0.51-1.71)	0.83
Net Clinical Outcome	11.3	5.5	0.49 (0.33-0.71)	<0.001	5.6	0.49 (0.34-0.73)	<0.001

Net Clinical Outcome: Ischemic Stroke, Systemic Embolism, Major or CRNM Bleed, All-Cause Death Incidence rates per 100 Pt-years

On-Treatment Population
Based on final DMC Datacut

Safety

	Rivaroxaban 20 mg (N=430)	Abelacimab 150 mg (N=427)	P Value	Abelacimab 90 mg (N=425)	P-Value
Adverse Event (%)					
Any	79	82	0.29	81	0.50
Serious	35	31	0.22	33	0.60
Led to D/C of Study Drug	6	6	0.65	6	0.85
Injection Site Reaction	N/A	3	N/A	2	NA

On-Treatment Population
Based on final DMC Datacut

Conclusions

- The results of this phase II trial indicate that both the tested doses of abelacimab (90 mg and 150 mg monthly) are superior to rivaroxaban 20 mg daily in reducing bleeding events among patients with AF and a high CHA_2DS_2-VASc score.
- A phase III trial (LILAC-TIMI 76) is assessing the safety and efficacy of abelacimab 150 mg compared with placebo among patients with AF deemed unsuitable for anticoagulation.
- If an anti-factor XIa therapeutic strategy will indeed provide effective anticoagulation with a lesser effect on hemostasis, we may well be able to expand our capacity to prevent unwanted thrombotic events in large sectors of populations, including patients with high bleeding and thrombotic risks.