Appendix 1

Study Report AXAFA - AFNET 5

Tables

Table 1: Primary outcomes in the AXAFA-AFNET 5 trial (ablation set), including details of the type of bleeding

	All patients	**Apixaban**	**VKA**
Patients with primary endpoint: composite of all-cause death, stroke or major bleeding	45/633 (7.1%)	22/318 (6.9%), non-inferiority p=0.0002	23/315 (7.3%)
Death	2 (0.3%)	1 (0.3%)	1 (0.3%)
Stroke or TIA	2 (0.3%)	2 (0.6%)	0
Major bleeding (BARC 2-5)	45 (7.1%)	20 (6.2%)	25 (7.9%)
Bleeding requiring medical attention (BARC 2)	24 (3.8%)	12 (3.7%)	12 (3.8%)
Bleeding with hemoglobin drop of 30 to <50 g/l or requiring transfusion (BARC 3a)	9 (1.4%)	5 (1.6%)	4 (1.3%)
Bleeding with hemoglobin drop ≥50 g/l, or requiring surgery or iv vasoactive agents, or cardiac tamponade (BARC 3b)	11 (1.7%)	3 (0.9%)	8 (2.5%)
Intracranial hemorrhage (BARC 3c)	1 (0.2%)	0	1 (0.3%, fatal)
TIMI major bleeding (Intracranial bleed, or bleeding resulting in a hemoglobin drop of ≥ 50 g/l, or bleeding resulting in death within 7 days)	4 (0.6%)	1 (0.3%)	3 (1%)
ISTH major bleeding	24 (3.8%)	10 (3.1%)	14 (4.4%)
Bleeding event by clinical type			
Tamponade	7 (1.1%)	2 (0.6%)	5 (1.6%)
Access site bleed	27 (4.3%)	12 (3.8%)	15 (4.8%)
Bleeding requiring transfusion of red blood cells	3 (0.5%)	2 (0.6%)	1 (0.3%)
Other major bleed	7 (1.1%)	5 (1.6%)	2 (0.6%)

Table 2: Results of Non-Inferiority test of Difference in Proportion of Apixaban to VKA

	Apixaban (N=318)	VKA (N=315)	Non-Inferiority Margin (Δ)	Non-inferiority p-value	Difference (90 % Non-Inferiority CI) Apixaban-VKA	Superiority p-value
Primary Endpoint	22 (6.9%)	23 (7.3%)	7.5%	0.000185	-0.38% (-4.03%, 3.26%)	0.878155

Table 3: Secondary outcomes in the AXAFA-AFNET 5 trial

	All patients	**Apixaban**	**VKA**
	n=633	n=318 (n=317 5 mg BD, n=1 2.5 mg BD)	n=315 (n=127 warfarin, n=102 phenprocoumon, n=86 acenocoumarol)
time from randomization to ablation, days, median (q1, q3)	35.0 (20.0, 50.0)	34.0 (18.0, 48.0)	36.0 (21.0, 52.0)
Nights spent in hospital after index ablation, median (q1, q3)	3 (2, 5)	2 (1, 5)	3 (2, 7)
ACT during ablation, seconds, median (q1, q3)	325.0 (285.0, 370.0)	310.0 (273.0, 350.0)	348.5 (304.0, 396.0)
Number of subjects with all ACT values in range (n, %)	234 / 631 (37.1%)	73 / 316 (23.1%)	161 / 315 (51.1%)
Number of subjects with at least one ACT value < 250 (n, %)	214 / 631 (33.9%)	130 / 316 (41.1%)	84 / 315 (26.7%)
Number of subjects with at least one ACT value < 300 (n, %)	397 / 631 (62.9%)	243 / 316 (76.9%)	154 / 315 (48.9%)
Number of bleeding events (n)	118	54	64
Patients without recurrence of atrial fibrillation (n, %)	434 / 619 (70.1%)	217 / 311 (69.8%)	217 / 308 (70.5%)
Quality of life			
SF-12 physical component score at end of study, median (q1, q3), n	48.6 (42.0, 54.2), n=564	48.4 (41.9, 54.2), n=289	48.8 (42.2, 54.4), n=275
Change in SF-12 physical component score at end of study compared to baseline (Δ PCS), median (q1, q3), n	2.5 (-2.1, 8.1), n=547, p<0.001*	2.4 (-2.2, 7.9), n=280	2.8 (-2.0, 8.3), n=267
SF-12 mental component score at end of study, median (q1, q3), n	54.4 (46.0, 58.6), n=565	54.2 (45.8, 58.3), n=290	54.5 (46.6, 59.7), n=267
Change in SF-12 mental component score at end of study compared to baseline (Δ MCS) n (%), median (q1, q3), n	1.2 (-3.2, 8.0), n=548, p<0.001*	0.4 (-3.6, 8.0), n=281	1.6 (-2.8, 8.3), n=267
Karnofsky score at end of study, median (q1, q3), n	100 (90, 100), n=619	100 (90, 100), n=311	100 (90, 100), n=308
Change in Karnofsky score at end of study compared to	10 (0, 10), n=619	10 (0, 10), n=311	10 (0, 10), n=308

baseline (Δ Karnofsky), median (q1, q3),			
Cognitive Function (Montreal Cognitive Assessment, MoCA)			
Cognitive function at end of study (MoCA), median (q1, q3), n	28.0 (26.0, 29.0), n=607	28.0 (26.0, 29.0), n=305	28.0 (26.0, 29.0), n=302
Abnormal MoCA at baseline (<26), n (%)	141 (23.2%)	75 (24.6%)	66 (21.9%)
Change in MoCA at end of study compared to baseline, Median (q1, q3), n	1.0 (-1.0, 2.0), n=597, p<0.001*	0.0 (-1.0, 2.0), n=301	1.0 (-1.0, 2.0), n=296
Change in patients with abnormal MoCA at end of study compared to baseline, n (%)	141/607 (23.2%), -7.2%, p=0.005*	75/305 (24.6%) -5.1%	66/302 (21.9%) -9.2%

Table 4: Acute brain lesions detected by high resolution diffusion-weighted magnetic resonance imaging

	All patients (n=323)	**Apixaban** (n=162)	**VKA** (n=161)	**P value**
No lesion	239 (74.0%)	118 (72.8%)	121 (75.2%)	0.635
Exactly one lesion	46 (14.2%)	27 (16.7%)	19 (11.8%)	0.211
Exactly two lesions	21 (6.5%)	7 (4.3%)	14 (8.7%)	0.111
More than two lesions	17 (5.3%)	10 (6.2%)	7 (4.3%)	0.463

Table 5: Summary of Serious Adverse Events

	Apixaban (N=328)		VKA (N=327)		All Subjects (N=655)	
System organ class	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any serious adverse event	88 (26.8%)	167	93 (28.4%)	174	181 (27.6%)	341
Cardiac disorders	45 (13.7%)	62	48 (14.7%)	58	93 (14.2%)	120
General disorders and administration site conditions	19 (5.8%)	21	23 (7.0%)	26	42 (6.4%)	47
Surgical and medical procedures	21 (6.4%)	26	21 (6.4%)	28	42 (6.4%)	54
Infections and infestations	9 (2.7%)	9	13 (4.0%)	15	22 (3.4%)	24
Injury, poisoning and procedural complications	9 (2.7%)	9	11 (3.4%)	13	20 (3.1%)	22

Nervous system disorders	9 (2.7%)	10	7 (2.1%)	9	16 (2.4%)	19
Vascular disorders	8 (2.4%)	10	8 (2.4%)	8	16(2.4%)	18
Renal and urinary disorders	4 (1.2%)	4	5 (1.5%)	6	9 (1.4%)	10
Gastrointestinal disorders	4 (1.2%)	4	2 (0.6%)	3	6 (0.9%)	7
Musculoskeletal and connective tissue disorders	3 (0.9%)	3	2 (0.6%)	2	5 (0.8%)	5
Respiratory, thoraic and mediastinal disorders	2 (0.6%)	2	2 (0.6%)	2	4 (0.6%)	4
Investigations	1 (0.3%)	1	2 (0.6%)	2	3 (0.5%)	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3%)	1	2 (0.6%)	2	3 (0.5%)	3
Ear and labyrinth disorders	1 (0.3%)	1	0	0	1 (0.2%)	1
Psychiatrc disorders	1 (0.3%)	2	0	0	1 (0.2%)	2
Skin and subcutaneous tissue disorders	1 (0.3%)	2	0	0	1 (0.2%)	2