Alleviation of AF related symptoms following acute conversion of recent-onset, symptomatic atrial fibrillation to sinus rhythm with flecainide acetate oral inhalation solution

A. John Camm[1], Harry Crijns[2], Arif Elvan[3], Ype Tuininga[4], Erik Badings[4], Aaf F.M. Kuijper[5], Jonas De Jong[6], Mark Lee[7], Dirk Schellings[8], Isabelle C. Van Gelder[9], Jeremy Ruskin[10], Peter Kowey[11], Christopher Dufton[12], Jean Maupas[12], and Luiz Belardinelli[12] on behalf of the INSTANT Investigators

[1]St. George's University, London, UK; [2]MUMC, Maastricht, NL; [3]Isala Clinics, Zwolle, NL; [4]Deventer Hospital, Deventer, NL, [5]Spaarne Gasthuis, Haarlem, NL; [6]OLVG, Amsterdam, NL; [7]Long Beach Memorial Medical Center, CA, USA; [8]Slingeland Ziekenhuis, Doetinchem, NL; [9]University Medical Center Groningen, Groningen, NL; [10]Mass General, MA, USA; [11]Lankenau Heart Institute, PA, USA; [12]InCarda Therapeutics, CA, USA.

Background

- InRhythm (Orally Inhaled Flecainide) is self-administered over an 8-minute period (two 3.5-minute inhalation periods separated by a 1-minute break) using a hand-held, breath-actuated nebulizer (AeroEclipse II BAN).
- The INSTANT (INhalation of flecainide to convert recent-onset SympTomatic Atrial fibrillatioN to sinus rhyThm) trial was an open-label, multicenter study of flecainide acetate oral inhalation solution (FlecIH) for acute conversion of symptomatic, recent-onset (< 48hrs), newly diagnosed AF or PAF to SR.[1]
- The initial dose-ranging study (Part A) established safety and feasibility, while showing a dose- and concentration-dependent increase in efficacy.[1] A 120 mg estimated total lung dose (eTLD) of flecainide was selected for further evaluation in INSTANT Part B, and the conversion rate for the combined cohort from Parts A/B was 49%.[2]
- Key objectives for acute pharmacological cardioversion in patients presenting with symptomatic, recent-onset episodes of newly diagnosed AF and PAF are:
  - Prompt restoration of SR
  - Symptom relief
  - Normalization of vital signs
  - Improvement of overall heart function (i.e., hemodynamics)
  - Avoidance of electrical cardioversion (ECV) and timely hospital discharge
- In the present study we examined symptoms, heart rate, time to discharge, need for ECV, and adverse events (AEs) by conversion status at 90 minutes post-dose reported among patients in the INSTANT trial who received a 120 mg eTLD of flecainide by oral inhalation.

Patient Baseline Characteristics

Table 1: Baseline Characteristics by Study Cohort

Characteristic	Conversion (N = 25)	No Conversion (N = 29)	P-value
Age (y)	63.3 ± 9.4	61.2 ± 13.5	0.515
Male sex, n (%)	15 (60.0%)	21 (72.4%)	0.335
White, n (%)	24 (96.0%)	26 (89.7%)	0.743
Body mass index (kg/m2)	26.2 ± 3.6	27.4 ± 3.9	0.235
Hypertension, n (%)	11 (44.0%)	5 (17.2%)	0.032
Hyperlipidemia, n (%)	6 (24.0%)	9 (31.0%)	0.565
Diabetes, n (%)	1 (4.0%)	0 (0.0%)	0.463
NYHA HF Class I, n (%)	2 (8.0%)	4 (13.8%)	0.675
NYHA HF Class II, n (%)	0 (0.0%)	1 (3.4%)	0.675
CHA_2DS_2-VASc Score	1.4 ± 1.2	1.3 ± 1.3	0.500
AF symptom duration, hours	11.9 ± 10.8	16.6 ± 10.4	0.023
First AF Episode, n (%)	9 (31.0%)	8 (32.0%)	1.000
Recurrent Paroxysmal AF Episode, n (%)	15 (60.0%)	18 (62.1%)	1.000
AF Post-Cardiac Ablation, n (%)	2 (8.0%)	2 (6.9%)	1.000
# Previous AF Episodes (excludes 1st episode pts)	2.3 ± 3.6	3.3 ± 3.2	0.028
Data are mean ±SD unless otherwise noted. Safety population (N=54)			

- Baseline characteristics were similar in the two cohorts; however, the Conversion cohort had a greater proportion of patients (p<0.05) with a history of hypertension, a shorter duration of AF symptoms at presentation, and fewer previous AF episodes compared to the No Conversion cohort.

Methods

- Data are presented for patients in the INSTANT trial Part A/B receiving a 120 mg eTLD of flecainide whose AF was successfully converted to SR ("Conversion" group; N=25) versus those whose AF did not convert to SR ("No Conversion" group; N=29).
- Conversion of AF to SR was determined using 12-lead Holter monitoring during a 90-minute observation period. Patients in the No Conversion cohort were offered alternative treatment per the investigator discretion. Symptoms, vital signs, time to discharge, and the need for ECV were evaluated through Day 5.

Ventricular Rate

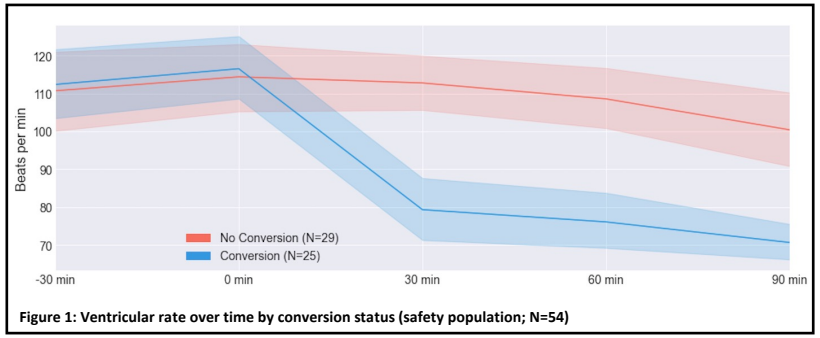

Figure 1: Ventricular rate over time by conversion status (safety population; N=54)

- Mean ±SD ventricular rate at 90 minutes was 70.6 ±12.5 bpm in the Conversion cohort compared to 100.4 ± 29.4 bpm in the No Conversion cohort (p<0.001).

AF-Related Symptoms

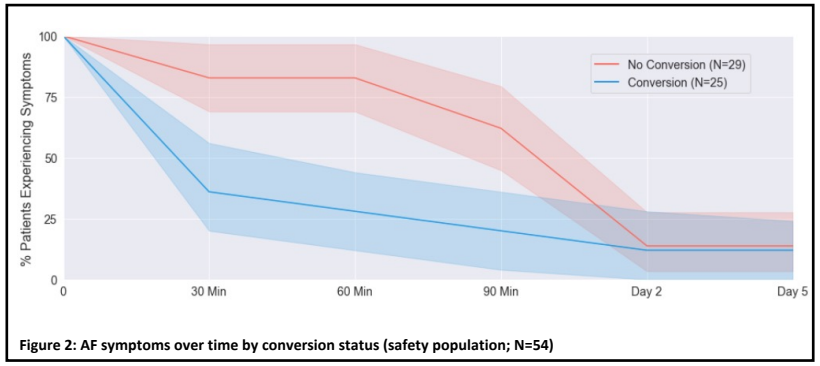

Figure 2: AF symptoms over time by conversion status (safety population; N=54)

- At baseline, all patients (100%) had at least one AF-related symptom: palpitations (85%), chest discomfort (39%), shortness of breath (37%) and dizziness (35%).
- At 90 minutes, 80.0% of the Conversion cohort were asymptomatic compared to 37.9% of the No Conversion cohort (p<0.001).

Time to Discharge

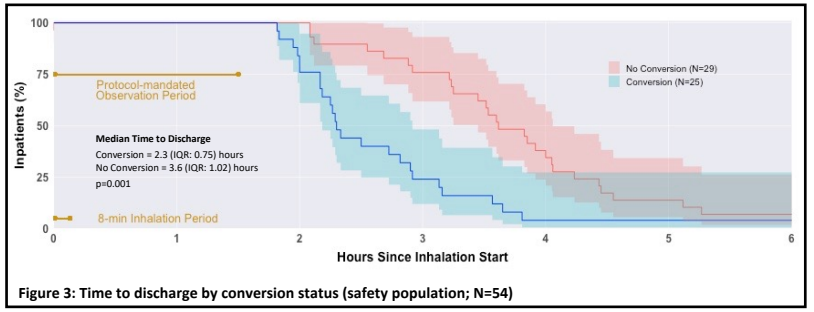

Figure 3: Time to discharge by conversion status (safety population; N=54)

- In the No Conversion cohort, 23 (79.3%) patients had undergone ECV by Day 5. In the Conversion cohort, 1 (4.0%) patient experienced AF recurrence and no patients had undergone ECV by Day 5 (0.0%; p<0.001).

Adverse Events

- The most frequently reported AEs were cough (43.0%), dyspnea (13.0%), and oropharyngeal pain (13.0%); these AEs were transient, and none led to discontinuation of inhalation. AEs of cough (48.3% and 36.0%, respectively) and dyspnea (17.2% and 8.0%, respectively) were slightly more common in the No Conversion cohort compared to the Conversion cohort.
- Serious adverse events (SAEs) were reported in 1 patient in the No Conversion cohort (bradycardia) and in 2 patients in the Conversion cohort (cough, exacerbation of asthma).
- Two (2) patients in the No Conversion cohort experienced CV events (1 patient each with atrial flutter with 1:1 AV conduction, bradycardia/hypotension) compared to 2 patients in the Conversion cohort (bradycardia, bradycardia/hypotension). The bradycardia and atrial flutter events in the No Conversion cohort were considered serious but neither patient required treatment and both events resolved without sequelae.

Conclusions

- As expected, patients whose AF converted to SR with inhaled flecainide had a reduction in ventricular rate accompanied by symptom relief within 30 minutes of initiation of dosing.
- Median time to discharge was 2.3 hours and nearly all patients whose AF converted to SR with inhaled flecainide were discharged from the hospital in less than 4 hours.
- SR was maintained and ECV was not required for patients whose AF converted to SR with inhaled flecainide during the 5-day observation period.
- The safety profile of inhaled flecainide was generally similar for patients whose AF converts to SR and in patients whose AF does not convert to SR.
- A placebo-controlled Phase 3 trial (RESTORE-1) designed to confirm these Phase 2 results has initiated enrollment in July of 2022 at sites in the United States, Canada, and Europe.

References

1. Crijns HJ, Elvan A, Al-Windy N, et al. (2022). Circ Arrhythm Electrophys, 15(3): 157-164.
2. Crijns HJ, Elvan A, Tuininga Y, et al. 2022 Heart Rhythm Society Meeting.

Predictors of Successful Cardioversion of Recent-Onset Atrial Fibrillation to Sinus Rhythm with Orally Inhaled Flecainide

Jeremy Ruskin[1], Christopher Dufton[2], Jean Maupas[2], Harry Crijns[3], Arif Elvan[4], Jonas De Jong[5], Thomas Oosterhof[6], Ype Tuininga[7], Erik Badings[7], Ismail Aksoy[8], Dieter Nuyens[9], Vincent van Dijk[10], A. John Camm[11], Peter Kowey[12], and Luiz Belardinelli[2] on behalf of the INSTANT Investigators

[1]Mass General, MA, USA; [2]InCarda Therapeutics, CA, USA; [3]MUMC, Maastricht, NL; [4]Isala Clinics, Zwolle, NL; [5]OLVG, Amsterdam, NL; [6]Gelderse Vallei Ziekenhuis, Ede, NL; [7]Deventer Hospital, Deventer, NL; [8]Admiraal De Ruyter Ziekenhuis, Goes, NL; [9]Hartcentrum Ziekenhuis Oost-Limburg, Genk, NL; [10]St Antonius Ziekenhuis, Nieuwegein, NL; [11]St. George's University, London, UK; [12]Lankenau Heart Institute, PA, USA.

Background

- In Europe, IV flecainide is a first-line therapy for pharmacological cardioversion of AF in patients who are hemodynamically stable and have minimal or no structural heart disease.[1]
- Despite the use of weight adjusted dosing (e.g., 2 mg/kg administered over 10 minutes) IV flecainide has been found to be less effective for acute conversion of recent onset AF to sinus rhythm (SR) in patients who are taller and heavier than average.[2]
- Obese patients are hypervolemic and their cardiac output increases in proportion to their weight.[3] Consequently, in obese patients the same dose of an antiarrhythmic drug delivered into the systemic circulation may result in lower plasma concentration of the drug, akin to dilution of the drug.
- "Drug-dilution" due to the increased blood volume and the structural and electrical remodeling in the atria of obese patients have been shown to exacerbate the underlying substrate for AF and to decrease the efficacy of NaCh blockers.
- Changes that render AF less responsive to NaCh blockers include: 1) Increased atrial diameter; 2) Atrial inflammation and fibrosis; 3) Slowing and increased heterogeneity of intra-atrial conduction, and; 4) shortening of atrial action potentials and refractory periods.[4,5]
- The INSTANT trial was an open-label, multicenter study of flecainide acetate oral inhalation solution (FlecIH) for acute conversion of recent-onset, symptomatic AF to SR.[6]
- Oral inhalation of a 120 mg estimated total lung dose (eTLD) of flecainide was self-administered over an 8-minute period (two 3.5-minute inhalation periods separated by a 1-minute break) using a hand-held, breath-actuated nebulizer (AeroEclipse II BAN).
- Data for the 120 mg eTLD group in the INSTANT trial were examined to determine if anthropometric measures or other baseline patient characteristics were significant predictors of cardioversion success with inhaled flecainide.

Patient Baseline Characteristics

Table 1: Baseline Characteristics by Study Cohort

Characteristic	Normal (N=33)	Overweight (N=33)	Obese/Severe Obese (N=17)
Age (y)	59.8 ± 10.3	60.7 ± 12.7	56.9 ± 15.6
Male sex, n (%)	24 (72.7%)	22 (66.7%)	10 (58.8%)
White, n (%)	32 (97.0%)	30 (90.9%)	16 (94.1%)
Body mass index (kg/m2)	23.4 ± 1.6	27.3 ± 1.4	32.6 ± 2.3
Hypertension, n (%)	7 (21.2%)	9 (27.3%)	8 (47.1%)
Hyperlipidemia, n (%)	7 (21.2%)	11 (33.3%)	4 (23.5%)
Diabetes, n (%)	0 (0.0%)	0 (0.0%)	1 (5.9%)
NYHA HF Class I, n (%)	4 (12.1%)	2 (6.1%)	2 (11.8%)
NYHA HF Class II, n (%)	0 (0%)	1 (3.0%)	0 (0%)
CHA_2DS_2-VASc Score	0.9 ± 1.0	1.4 ± 1.6	1.5 ± 1.2
AF symptom duration, hours	15.2 ± 12.4	11.0 ± 6.7	11.9 ± 11.1
First AF Episode, n (%)	15 (45.5%)	11 (33.3%)	10 (58.8%)
Recurrent Paroxysmal AF Episode, n (%)	17 (51.5%)	20 (60.6%)	6 (35.3%)
AF Post-Cardiac Ablation, n (%)	1 (3.0%)	2 (6.1%)	1 (5.9%)
# Previous AF Episodes (excludes 1st episode pts)	1.3 ± 0.6	2.9 ± 3.9	2.4 ± 1.6
Data are mean ±SD unless otherwise noted. Safety population (N=83)			

- Baseline characteristics were similar in the two cohorts; however, patients with a BMI ≥25 kg/m² had a higher frequency of hypertension, a higher CHA_2DS_2-VASc score, and a greater number of previous AF episodes compared to patients with BMI <25 kg/m².

Methods

- Logistic regression was performed on an array of patient and disease characteristics to identify predictors of cardioversion success at 90 minutes post-dose. Potential interactions (p< 0.01) were examined by boundary restriction and scatter plot analyses.
- A total of 98 patients received a 120 mg eTLD of flecainide by oral inhalation. This analysis was performed on a subgroup of patients in the 120 mg eTLD cohort who did not have systemic flecainide present prior to initiation of study drug (efficacy = 81 patients, safety = 83 patients).
- Body Mass Index (BMI) subgroups were defined as: Normal: < 25 kg/m²; Overweight: ≥25 and < 30 kg/m²; Obese: ≥30 and < 35 kg/m²; Severe Obese: ≥35 kg/m².

Logistic Regression Model

Table 2: Logistic Regression Model for Predictors of Cardioversion Rate at 90 Minutes Post-dose

Predictor Variable	Coefficient	Std. Error	z value	Pr(>|z|)
Height	1.027	0.346	2.972	0.003*
Weight	-1.026	0.365	-2.808	0.005*
BMI	3.223	1.170	2.756	0.006*
Gender (male)	-2.047	0.967	-2.117	0.034
CHA_2DS_2-VASc Score	-0.416	0.440	-0.946	0.344
Age	0.027	0.040	0.672	0.501
NYHA	-0.719	1.143	-0.630	0.529
AF Symptom Duration	-0.030	0.050	-0.600	0.549
AF Episode (1st diagnosis)	-0.298	0.586	-0.509	0.611
AF Episode (post-ablation)	-0.270	1.178	-0.229	0.819

*Potential interaction (p<0.01). Outcome variable = AF conversion to SR by 90 minutes post-dose

- Height, weight, and BMI were significant predictors of cardioversion success (p<0.01). BMI was the predictor variable with the greatest coefficient (β) in the model.

Conversion of AF to SR

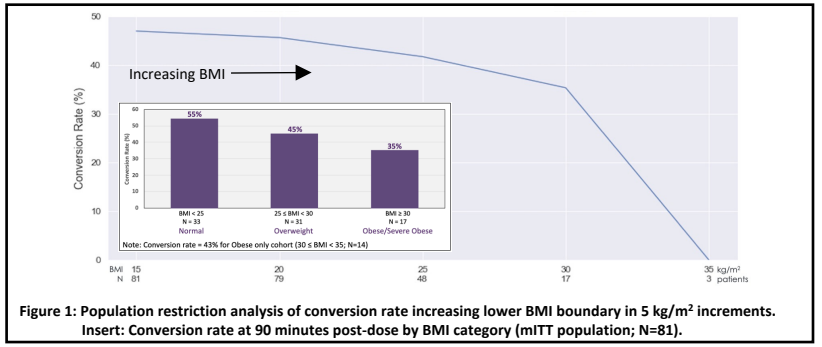

Figure 1: Population restriction analysis of conversion rate increasing lower BMI boundary in 5 kg/m² increments. Insert: Conversion rate at 90 minutes post-dose by BMI category (mITT population; N=81).

- Population restriction analysis revealed a negative correlation between BMI and conversion rate. This trend was also observed on subgroup analysis by BMI category (p = 0.166; Wilcoxon Rank Sum Test).
- Clinically significant conversion rates were observed for patients with BMI values that were considered Normal (BMI <25 kg/m² = 55%), Overweight (BMI ≥25 and <30 kg/m² = 45%), and Obese (BMI ≥30 and <35 kg/m² = 43%).
- None of the patients in the Severe Obese cohort (BMI ≥ 35 mg/m²; N=3) had their AF successfully converted to SR.

Flecainide Peak Plasma Concentration

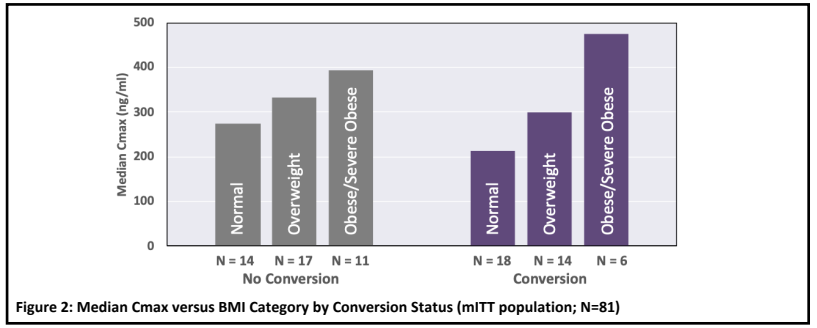

Figure 2: Median Cmax versus BMI Category by Conversion Status (mITT population; N=81)

- A positive correlation between flecainide peak plasma concentrations (Cmax) and BMI category was observed in both the Conversion and No Conversion cohorts.

Adverse Events

- The most frequently reported adverse events (AEs) were cough (41.0%), dyspnea (8.4%), and oropharyngeal pain (8.4%). These AEs were transient, and none led to discontinuation of inhalation.
- The most frequently reported AEs were generally similar by BMI category; however, the frequency of cough was greater in patients with BMI ≥ 25 kg/m² (50.0%) compared to patients with BMI < 25 kg/m² (27.3%).
- Serious adverse events (SAEs) were reported in 0 (0.0%) patients with BMI < 25 kg/m² compared to 3 (6.0%) patients with BMI ≥ 25 kg/m².
- Two obese patients had CV events that were considered serious (bradycardia and atrial flutter with 1:1 AV conduction) but neither patient required treatment and both events resolved without sequelae.

Conclusions

- BMI was identified as the strongest predictor of successful cardioversion in a logistic regression model and conversion rate appears to be attenuated in cohorts with higher BMI, which is consistent with results from previous studies.[2,7]
- Clinically significant conversion rates were observed across all BMI categories except BMI ≥ 35 kg/m² (severe obese); however, due to the small sample size of this group (N = 3) these data should be interpreted with caution.
- The mechanism(s) underlying the reduced efficacy of inhaled flecainide to terminate AF in patients with higher BMI is yet to be determined. However, it is unlikely to be due to "drug-dilution" effects and more likely to be due to structural and electrical atrial remodeling seen in obese patients leading to changes in the underlying "AF substrate".
- These findings are hypothesis-generating and will require further study to determine the optimal dosing of inhaled flecainide in patients with BMI ≥ 35 kg/m².

References

1. Hindricks G, Potpara T, Dagres N, et al. (2021). Eur Heart J, 42:373-498.
2. Zeemering S, Lankveld TAR, Bonizzi P, et al. (2018). Europace. 20(7):e96-e104.
3. Kaltman AJ, Goldring RM. (1976). Am J Med. 60(5):645-53.
4. McCauley MD, Hong L, Sridhar A, et al. (2020). Circ Arrhythm Electrophysiol. 13(8):e008296.
5. Abed, HS et al. (2013) Heart Rhythm. 10,(1): 90-100.
6. Crijns HJ, Elvan A, Al-Windy N, et al. (2022). Circ Arrhythm Electrophysiol, 15(3): 157-164.
7. Ornelas-Loredo et al. (2020) JAMA Cardiol. 5(1): 57-64.