The Safety of Pharmacological Cardioversion of Recent Onset Atrial Fibrillation with Orally Inhaled Flecainide

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Background

- Atrial fibrillation (AF) is the most common cardiac arrhythmia with an estimated (2010) global prevalence of 33.5 million.[1] Paroxysmal AF represents approximately 30% of all AF cases.
- Sinus rhythm (SR) can be re-established in patients with AF by electrical cardioversion (ECV) or pharmacological cardioversion (PCV). In Europe, there are several options for acute PCV (e.g., IV flecainide, IV propafenone, IV vernakalant, IV ibutilide); whereas in the US there are fewer options.
- In the US, IV ibutilide is the only antiarrhythmic agent currently approved for acute PCV of AF. Ibutilide has a conversion rate of AF to SR of ~40% in patients with recent-onset AF; however, its use is limited due to the risk of Torsades de Pointes that requires long periods (≥4 hours) of in-hospital monitoring.[2,3]
- 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.[4]
- Clinically important adverse events (AEs) known to be associated with acute PCV of recent-onset AF with antiarrhythmic agents (including IV flecainide) are bradycardia, hypotension, atrial flutter (AFL) with rapid ventricular rate (i.e., AFL with 1:1 AV nodal conduction), ventricular tachycardia (VT), and post-cardioversion sinus pause (and/or ventricular pause). These AEs are herein referred to as cardiovascular events (CVEs) of special interest.[5,6,7]
- Flecainide delivered via oral inhalation was shown to be efficacious in restoring SR in patients with recent-onset AF in a Phase 2, open-label trial INSTANT (INhalation of flecainide to convert recent-onset SympTomatic Atrial fibrillatioN to sinus rhyThm) trial.[8]
- We evaluated safety data from the INSTANT trial to assess the risk-benefit of flecainide acetate oral inhalation solution (FlecIH) for acute cardioversion of recent AF.

InRhythm (Orally Inhaled Flecainide)

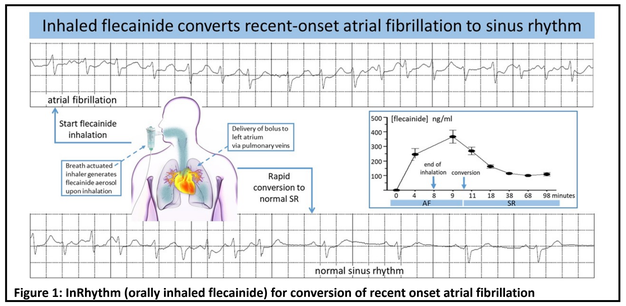

Figure 1: InRhythm (orally inhaled flecainide) for conversion of recent onset atrial fibrillation

- Oral inhalation of 120 mg eTLD (estimated total lung dose) 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).

Methods

- Safety was evaluated based on peak plasma concentrations of flecainide (Cmax), maximum QRS prolongation (ΔQRSmax), adverse events (AEs), and cardiovascular events (CVEs) of special interest for patients whose AF converted to SR with FlecIH (Conversion-Yes) and for those whose AF did not convert to SR (Conversion-No).
- Safety data are presented for patients receiving 120 mg eTLD FlecIH during an 8-minute inhalation period. Conversion rate excludes patients who had flecainide present in their pre-dosing blood samples.
- Patients who did not convert to SR were offered alternative treatment per investigator's discretion.

Patient Baseline Characteristics

Table 1: Baseline Characteristics by Conversion Status

Characteristic	Conversion-Yes (N = 40)	Conversion-No (N = 57)	All Patients (N=97)
Age (y)	61.2 ± 10.1	59.8 ± 13.3	60.4 ± 12.1
Male sex, n (%)	23 (57.5%)	41 (71.9%)	64 (66.0%)
White, n (%)	39 (97.5%)	52 (91.2%)	91 (93.8%)
Weight (kg)	84.4 ± 10.3	89.7 ± 17.0	87.5 ± 14.8
Height (cm)	179.4 ± 10.5	180.2 ± 9.2	179.9 ± 9.7
Body mass index (kg/m2)	26.4 ± 3.9	27.5 ± 3.8	27.0 ± 3.9
AF Duration ≥ 1 and ≤ 24 hours, n (%)	35 (87.5%)	51 (89.5%)	86 (88.7%)
AF Duration ≥ 24 and ≤ 48 hours, n (%)	5 (12.5%)	6 (10.5%)	11 (11.3%)
First AF Episode, n (%)	16 (40.0%)	21 (36.8%)	37 (38.1%)
Recurrent Paroxysmal Episode, n (%)	22 (55.0%)	33 (57.9%)	55 (56.7%)
AF Post-Cardiac Ablation, n (%)	2 (5.0%)	3 (5.3%)	5 (5.1%)
# Previous AF Episodes (excludes 1st episode pts)	2.2 ± 3.1	3.1 ± 2.7	2.7 ± 2.9
Patients with flecainide in predose PK sample, n (%)	2 (5.0%)	13 (22.8%)	15 (15.5%)

Data are mean ±SD unless otherwise noted.
*Safety population includes all patients receiving FlecIH

- Baseline characteristics were generally similar in the two conversion cohorts; however, the cohort of patients whose AF did not convert to SR had a higher proportion of males, a higher number of previous AF episodes and a higher proportion of patients with flecainide present in their systemic circulation prior to FlecIH dosing.

Time to Conversion of AF to SR

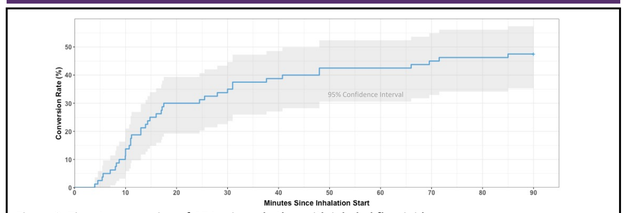

Figure 2: Time to conversion of AF to sinus rhythm with inhaled flecainide
Note: Figure excludes patients with systemic flecainide present prior to dosing with study drug.

- The conversion rate at 90 minutes post-dose was 47.5% (95% CI: 36.6, 58.4).
- Median time to conversion was 14.6 (IQR: 20.7) minutes from start of inhalation.

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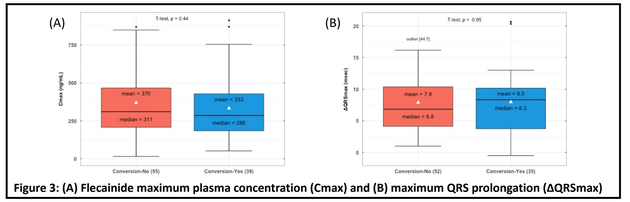

Figure 3: (A) Flecainide maximum plasma concentration (Cmax) and (B) maximum QRS prolongation (ΔQRSmax)

- Cmax (mean±SD) was similar in patients whose AF converted (333±222 ng/mL) and in patients whose AF failed to convert to SR (370±229 ng/mL); no patient had a Cmax ≥ 1000 ng/mL.
- ΔQRSmax (mean±SD) was similar in patients whose AF converted (8.0±4.7 msec) and in patients whose AF failed to convert to SR (7.9±6.6 msec).
- One patient had a ΔQRSmax >30msec. This patient had a baseline QRS of 103 msec and had rate dependent right bundle branch block (RBBB). At 2 minutes after completion of inhalation a transient RBBB was observed. Vital signs were stable throughout the 90-minutes observation period.

Adverse Events

Table 2: Frequency of Treatment Emergent Adverse Event by Preferred Term

Preferred Term	Conversion-Yes (N = 40)	Conversion-No (N = 57)	All Patients (N=97)
Cough*	15 (37.5%)	19 (33.3%)	34 (35.0%)
Oropharyngeal discomfort	5 (12.5%)	3 (5.3%)	8 (8.2%)
Oropharyngeal pain	3 (7.5%)	5 (8.8%)	8 (8.2%)
Dyspnea	2 (5.0%)	5 (8.8%)	7 (7.2%)
Salivary hypersecretion	1 (2.5%)	5 (8.8%)	6 (6.2%)

Number (%) of subjects with at least 1 AE in each system organ class (SOC) for all preferred terms with a frequency >5% in all patients.
*Epoch of reflex cough lasting several seconds only.

- The most frequent AEs (>5%) were cough, oropharyngeal discomfort, oropharyngeal pain, dyspnea and salivary hypersecretion; none led to discontinuation of inhalation.
- The most frequent AEs were similar in patients whose AF converted and in patients whose AF failed to convert to SR.

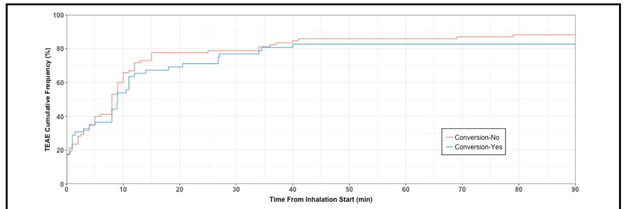

Figure 4: Time of onset for treatment emergent adverse events within 90 minutes of dosing

- Nearly all (>80%) treatment emergent adverse events (TEAEs) occurred within 40 minutes of the start of dosing and were of limited duration.

CV Events of Special Interest

Table 3: CV Events (CVEs) of Special Interest for 120 mg FlecIH by AF Conversion Status

	Non-Serious CVEs		Serious CVEs	
	Conversion-Yes (N=40)	Conversion-No (N=57)	Conversion-Yes (N=40)	Conversion-No (N=57)
Atrial Flutter 1:1 AV Conduction	0	0	0	1
Bradycardia	2	1	0	1
Hypotension	1	2	0	0
Sinus Pause Post-cardioversion	0	0	0	0
Ventricular Tachycardia	0	0	0	0

Note: Number of subjects with at least 1 CVE in each category.

- Nearly all CVEs were transient and asymptomatic.
- None required treatment and all resolved without sequelae, including those considered serious.

Conclusions

- All CV events of special interest observed were previously reported to be associated with oral or IV flecainide.
- Nearly all adverse events and all CV events of special interest had an onset of less than 40 minutes from the start of inhalation.
- No patients had a flecainide plasma level >1000 ng/ml that is associated with significant increase in the risk of serious CVEs of special interest.
- The mean maximum QRS prolongation was ∽3-fold lower than that reported for IV flecainide.
- 120 mg flecainide administered via oral inhalation achieves conversion rate similar to those reported for oral and IV flecainide for conversion of recent onset of AF to SR.
- Patients whose AF failed to convert to SR with FlecIH did not experience any adverse consequences that required treatment or limited subsequent treatment of their AF.
- The risk-benefit of orally inhaled flecainide acetate inhalation solution for the acute cardioversion of recent AF is highly favorable and may provide a safe, effective and more convenient approach compared to ECV and PCV with IV antiarrhythmic drugs.
- A 400-patient, placebo-controlled Phase 3 trial (RESTORE-1) will begin enrollment in the United States, Canada and Europe in the first half of 2022.

References

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