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ORIGINAL RESEARCH

Orally Inhaled Flecainide for Conversion of Atrial Fibrillation to Sinus Rhythm

INSTANT Phase 2 Trial

Jeremy N. Ruskin, MD,[a] A. John Camm, MD,[b] Christopher Dufton, PhD,[c] Anderson C. Woite-Silva, MD,[c] Ype Tuininga, MD, PhD,[d] Erik Badings, MD, PhD,[d] Jonas S.S.G. De Jong, MD, PhD,[e] Thomas Oosterhof, MD, PhD,[f] Ismail Aksoy, MD,[g] Aaf F.M. Kuijper, MD, PhD,[h] Isabelle C. Van Gelder, MD, PhD,[i] Vincent van Dijk, MD, PhD,[j] Dieter Nuyens, MD, PhD,[k] Dirk Schellings, MD, PhD,[l] Mark Young Lee, MD,[m] Peter R. Kowey, MD,[n] Harry J.G.M. Crijns, MD, PhD,[o] Jean Maupas, MD, MS,[c] Luiz Belardinelli, MD,[c] on behalf of the INSTANT Investigators

ABSTRACT

BACKGROUND INSTANT (INhalation of flecainide to convert recent-onset SympTomatic Atrial fibrillatioN to sinus rhyThm) was a multicenter, open-label, single-arm study of flecainide acetate oral inhalation solution (FlecIH) for acute conversion of recent-onset (≤48 hours) symptomatic atrial fibrillation (AF) to sinus rhythm.

OBJECTIVES This study investigated the efficacy and safety in 98 patients receiving a single dose of FlecIH delivered via oral inhalation.

METHODS Patients self-administered FlecIH over 8 minutes in a supervised medical setting using a breath-actuated nebulizer and were continuously monitored for 90 minutes using a 12-lead Holter.

RESULTS Mean age was 60.5 years, mean body mass index was 27.0 kg/m^2, and 34.7% of the patients were women. All patients had ≥1 AF-related symptoms at baseline, and 87.8% had AF symptoms for ≤24 hours. The conversion rate was 42.6% (95% CI: 33.0%-52.6%) with a median time to conversion of 14.6 minutes. The conversion rate was 46.9% (95% CI: 36.4%-57.7%) in a subpopulation that excluded predose flecainide exposure for the current AF episode. Median time to discharge among patients who converted was 2.5 hours, and only 2 patients had experienced AF recurrence by day 5. In the conversion-no group, 44 (81.5%) patients underwent electrical cardioversion by day 5. The most common adverse events were related to oral inhalation of flecainide (eg, cough, oropharyngeal irritation/pain), which were mostly of mild intensity and limited duration.

CONCLUSIONS The risk-benefit of orally inhaled FlecIH for acute cardioversion of recent-onset AF appears favorable. FlecIH could provide a safe, effective, and convenient first-line therapeutic option. (INhalation of Flecainide to Convert Recent Onset SympTomatic Atrial Fibrillation to siNus rhyThm [INSTANT]; NCT03539302) (J Am Coll Cardiol EP 2024;■:■-■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Massachusetts General Hospital, Boston, Massachusetts, USA; [b]St. George's University, London, United Kingdom; [c]InCarda Therapeutics, Newark, California, USA; [d]Deventer Hospital, Deventer, the Netherlands; [e]Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, the Netherlands; [f]Ziekenhuis Gelderse Vallei, Ede, the Netherlands; [g]Admiraal de Ruyter Ziekenhuis, Goes, the Netherlands; [h]Spaarne Gasthuis, Haarlem, the Netherlands; [i]University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [j]St Antonius Ziekenhuis, Nieuwegein, the Netherlands; [k]Hartcentrum Ziekenhuis Oost-Limburg, Genk, Belgium; [l]Slingeland Ziekenhuis, Doetinchem, the Netherlands; [m]Long Beach Medical Center, Long Beach, California, USA; [n]Lankenau Heart Institute, Wynnewood, Pennsylvania, USA; and the [o]Maastricht University Medical Center (MUMC), Maastricht, the Netherlands.

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ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug

AE = adverse event

AF = atrial fibrillation

C_{max} = maximum plasma concentration

ECV = electrical cardioversion

eTLD = estimated total lung dose

FlecIH = flecainide acetate inhalation solution

SR = sinus rhythm

Atrial fibrillation (AF) is a major global public health concern,[1] with an increasing prevalence caused by aging of the population. In the United States, the number of emergency department (ED) visits related to AF has been increasing steadily, with the majority (62%-69%) resulting in hospitalization.[2,3] There were an estimated 599,790 ED visits and 453,060 hospitalizations with AF as the primary diagnosis in the United States in 2014.[4] Thus, symptomatic AF represents a major burden in terms of resource utilization and costs, and has a significant negative impact on patient quality of life. There is, therefore, a major need for strategies that enable patients with recent-onset AF to be treated promptly and discharged home in sinus rhythm (SR), thereby avoiding hospital admission.

Pharmacological cardioversion with class IC antiarrhythmic drugs has been shown to be safe and effective in restoring SR in patients with recent-onset AF who have minimal or no structural heart disease.[5] The delivery of flecainide via oral inhalation has emerged as a novel approach to safe and rapid conversion of AF to SR.[6,7] Results of preclinical studies[8,9] have provided evidence that conversion can be achieved at lower doses, reduced systemic exposure, and less hemodynamic depression compared with the IV route when flecainide is administered via intratracheal instillation.

In keeping with the findings of these preclinical studies we reported results of an open-label, dose-escalation study[7] of flecainide acetate inhalation solution (FlecIH) delivered via oral inhalation for acute conversion of recent-onset AF to sinus rhythm. This initial study established safety and feasibility, while demonstrating a dose- and concentration-dependent increase in efficacy over an estimated total lung dose (eTLD) range of 30 to 120 mg. The 120 mg eTLD, which resulted in a conversion rate of 48% within 90 minutes of inhalation, was selected for further evaluation. In this study, we present the efficacy and safety results from the INSTANT (INhalation of flecainide to convert recent-onset SympTomatic Atrial fibrillatioN to sinus rhyThm) trial for patients with new or recurrent symptomatic paroxysmal AF of recent-onset who received 120 mg eTLD of FlecIH via oral inhalation.

METHODS

DESIGN. This was an open-label, multicenter, phase 2 study to evaluate the efficacy and safety of an orally inhaled flecainide acetate solution (FlecIH) for acute conversion of recent-onset symptomatic AF to SR (NCT03539302). Details of the study design have been previously reported.[7]

The study was conducted at 20 centers in the Netherlands, Belgium, and the United States. The protocol was approved by the independent ethics committee at each participating site. Patient safety was monitored by an independent data and safety monitoring board. Written informed consent was obtained from all participants before any protocol-specific screening procedures or administration of study drug.

PARTICIPANTS. This analysis includes all patients who received 120 mg eTLD of FlecIH (FlecIH-103 formulation) in the dose-ranging[7] and cohort expansion stages of the trial. Eligible patients included adults age 18 to 85 years who presented with newly diagnosed or recurrent symptomatic paroxysmal AF of ≤48 hours duration based on patients' reported time of onset of symptoms. Exclusion criteria included hemodynamic instability, persistent AF, recent use of antiarrhythmic drugs (12 weeks for amiodarone, 7 days for other AADs), or any contraindication to flecainide (eg, NYHA functional class III-IV HF, LVEF <45%, ongoing myocardial ischemia). Patient subgroups are referred to as "population" (eg, safety population). Although restricted to randomized studies, "intention-to-treat" (ITT) population in this study includes all patients enrolled in the study to conform with study protocol terminology.

PROCEDURES. Patients were monitored using cardiac telemetry and 12-lead electrocardiograms (ECGs) for at least 45 minutes before inhalation of study drug. Vital signs and blood samples for pharmacokinetic (PK) analysis were collected at serial time points before, during, and after the inhalation period, and at the time of conversion to SR, if applicable. Ambulatory ECG data were collected from the time of

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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informed consent to the end of the 90-minute observation period.

Patients were given a 120 mg eTLD flecainide solution via nebulization at a flow rate of 5 L/min, as previously described.[7] Study drug was administered over 2 inhalation periods of 3.5 minutes each, separated by a 1-minute break.

If conversion to SR did not occur during the 90-minute observation period, the investigator could offer standard-of-care therapy (eg, rate control, electrical cardioversion [ECV], or pharmacological cardioversion), except for ibutilide, procainamide, and sotalol, which were not permitted because of increased risk of QT prolongation. Discharge was allowed at any time after the observation period at the discretion of the investigator. All patients receiving study drug, regardless of treatment outcome, were reassessed via telephone call on day 2 and day 5 ± 1, which coincided with the end of study (EOS).

OUTCOMES. The primary efficacy outcome was the rate of conversion of AF to SR within a 90-minute observation period following completion of inhalation. AF symptom improvement at the end of the 90-minute observation period and time to discharge were specified as secondary outcomes to support the evaluation of efficacy. Other secondary outcomes included tolerability, pharmacokinetics (maximum flecainide plasma concentration), and pharmacodynamics (ECG intervals, vital signs). Safety was assessed through the incidence and severity of adverse events (AEs). Cardiovascular AEs of special interest (CV-AESIs) previously associated with flecainide (ie, hypotension, bradycardia, sinus pause postcardioversion, and atrial flutter [AFL] with 1:1 atrioventricular [AV] conduction) were assessed separately.

STATISTICAL ANALYSIS. All participants who received the study drug were included in the safety population. Participants who received the full assigned dose of the drug were included in the PK population. Patients in AF at the start of inhalation who received the full assigned dose or converted to SR before completion of the full assigned dose were included in the modified intention-to-treat population (mITT).

A descriptive analysis was conducted to summarize the baseline population. Continuous data were reported as mean and SD, whereas categorical variables were expressed in frequencies and percentages. The Student's *t*-test was used to compare continuous variables and the Fisher exact test was used to compare categorical variables. Statistical significance was assumed at $P < 0.05$. Statistical analyses were performed using SAS® software, version 9.4, and R, version 4.1.

All reported AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 23.1).

RESULTS

DISPOSITION. A total of 111 patients were screened for the study from October 2019 through December 2021. The flow diagram in Figure 1 summarizes the disposition of patients who were screened and enrolled. Nine patients were excluded due to screen failure. Four patients were enrolled but converted to sinus rhythm spontaneously before inhalation and did not receive study drug. The remaining 98 patients constitute the safety population. Four subjects were excluded from the mITT population (n = 94) for not receiving the full assigned dose of study drug. In addition, 5 patients did not receive the full assigned dose of study drug because of conversion before end of inhalation and were excluded from the PK population (n = 89).

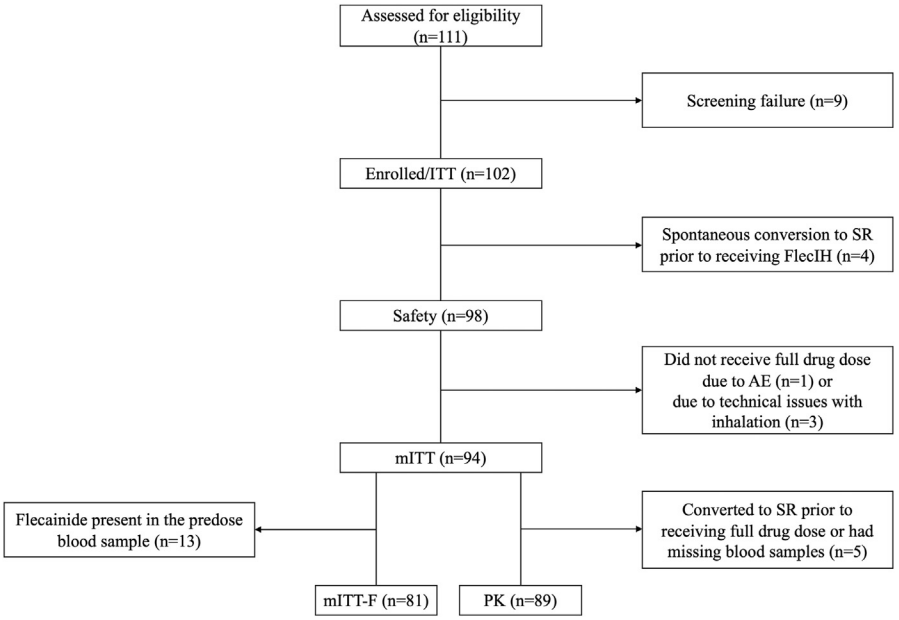
Thirteen patients in the mITT population had flecainide present in the predose blood sample (mean: 158 ± 139 ng/mL; range 28-525 ng/mL). A post hoc analysis of the primary efficacy endpoint was conducted on a subset of the mITT population that excluded these patients (mITT-F population; n = 81).

BASELINE CHARACTERISTICS. Among patients who received the study drug (n = 98), there were no significant differences in demographics and baseline characteristics between patients in the conversion-yes group and those in the conversion-no group. These data are summarized in Table 1.

Among patients enrolled, 57.1% had a recurrent paroxysmal AF episode; 37.8%, their first diagnosed episode; and 5.1%, a recurrent episode after previously undergoing AF ablation. Patients with recurrent AF had a mean of 2.7 episodes before enrollment. The mean duration of symptoms for the presenting or index AF episode was 12.7 hours before enrollment.

CONVERSION OF AF TO SR. In total, 40 patients (42.6%; 95% CI: 33.0%-52.6%) in the mITT population (n = 94) had their AF converted to SR during the observation period (Figure 2). The median time to conversion was 14.6 minutes (IQR: 20.7 minutes) from start of inhalation, and 75.0% of all conversions of AF to SR occurred within the first 30 minutes. Of interest, only 2 of the 13 patients (15%) with flecainide present in the predose blood sample had their AF converted to SR during the observation period. The conversion

FIGURE 1 Patient Flow Diagram



Flow chart of patients assessed for participation in the trial, subgroup disposition, and criteria for exclusion from study subgroups. AE = adverse event; ITT = intention-to-treat population; FlecIH = flecainide acetate inhalation solution; mITT = modified intention-to-treat population; PK = pharmacokinetic; SR = sinus rhythm.

TABLE 1 Baseline Characteristics

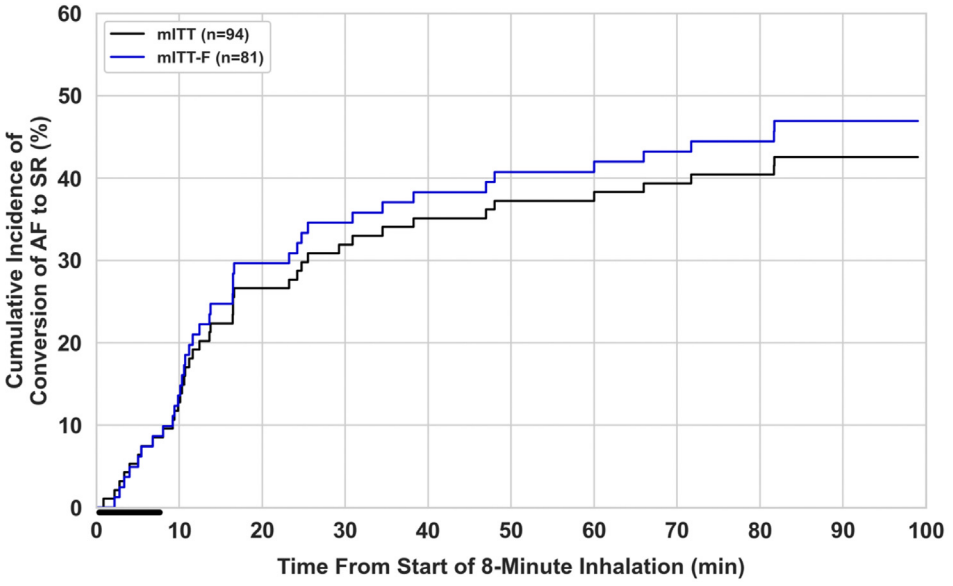
	Safety (n = 98)	mITT (n = 94)	
	Total (n = 98)	Conversion-Yes (n = 40)	Conversion-No (n = 54)
Age, y	60.5 ± 12.1	61.2 ± 10.1	60.1 ± 13.5
Male sex	64 (65.3)	23 (57.5)	40 (74.1)
White	92 (93.9)	39 (97.5)	49 (90.1)
Body mass index, kg/m^2	27.0 ± 3.9	26.4 ± 3.9	27.6 ± 3.9
Medical comorbidities			
Hypertension	29 (29.6)	15 (37.5)	14 (25.9)
Hyperlipidemia	25 (25.5)	10 (25.0)	13 (24.1)
Diabetes	2 (2.0)	1 (2.5)	1 (1.9)
Coronary artery disease	4 (4.1)	1 (1.0)	3 (5.6)
NYHA HF functional class I	10 (10.2)	3 (7.5)	6 (11.1)
NYHA HF functional class II	1 (1.0)	0 (0.0)	1 (1.9)
CHA_2DS_2-VASc Score	1.3 ± 1.3	1.3 ± 1.2	1.3 ± 1.4
AF at presentation and previous history			
AF symptom duration, h	12.7 ± 9.7	11.5 ± 10.0	13.5 ± 9.7
First AF episode	37 (37.8)	16 (40.0)	19 (35.2)
Recurrent	56 (57.1)	22 (55.0)	32 (59.2)
Postablation	5 (5.1)	2 (5.0)	3 (5.6)
Previous AF episodes	2.7 ± 2.9	2.7 ± 2.9	3.0 ± 2.7

Data are mean ± SD or n (%).
AF = atrial fibrillation; mITT = modified intention-to-treat population.

rate excluding these 13 patients (mITT-F, n = 81) was 46.9% (95%CI: 36.4%, 57.7%). The plasma levels in these 13 patients ranged from 27.6 to 525.3 ng/mL with a mean of 158 ± 139 ng/mL. However, the time to conversion in the mITT-F population was comparable to the mITT population (Figure 2). Patients receiving rate control medications before inhalation (n = 48) and those not receiving these medications (n = 46) had similar rates of conversion (43.8% vs 41.3%, respectively; $P = 0.837$).

REDUCTION OF AF SYMPTOMS. All 94 patients from the mITT population had AF symptoms during the screening phase. The most common symptom reported was palpitations (87.2%), followed by chest discomfort (37.2%), dyspnea (33.0%), and lightheadedness (29.8%). By the end of the observation period, 92.5% of patients from the conversion-yes group reported improvement in symptoms compared with 51.9% of patients from the conversion-no group ($P < 0.001$). The majority of patients whose AF converted to SR were asymptomatic (70.0%) by the end of the observation period, which was >2-fold higher ($P < 0.001$) than that observed in the conversion-no group (Figure 3).

FIGURE 2 Time to Conversion of AF to SR



		Time From Start of 8-Minute Inhalation (min)						
		0	15	30	45	60	75	90
mITT Population	# At risk	94	73	64	61	58	56	54
	# Events	0	21	9	3	3	2	2
	Cumulative Incidence (%)	0	22.3	31.9	35.1	38.3	40.4	42.6
mITT-F Population	# At risk	81	61	53	50	47	45	43
	# Events	0	20	8	3	3	2	2
	Cumulative Incidence (%)	0	24.7	34.6	38.3	42.0	44.4	46.9

Cumulative percentage of patients whose atrial fibrillation (AF) converted to SR from the start of inhalation to the end of the observation period in the mITT population (black curve) and in a subgroup of the mITT population, excluding patients with flecainide present before dosing (mITT-F population, blue curve). Abbreviations as in Figure 1.

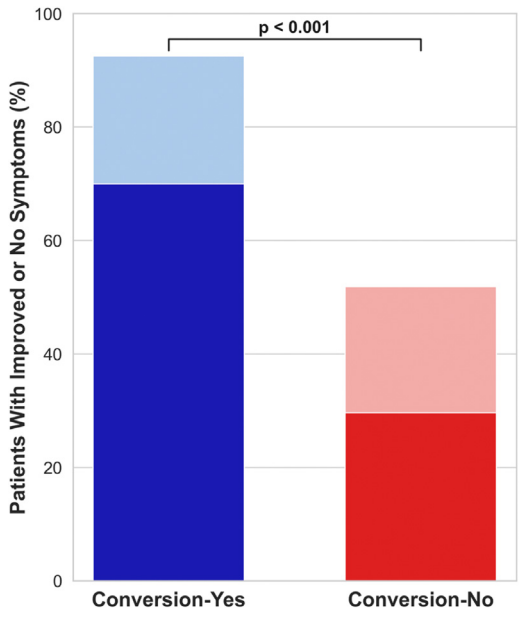
In total, 21 (52.5%) patients in the conversion-yes group were previously receiving concomitant rate control medications during the observation period compared with 27 (50.0%) patients in the conversion-no group. There were 8 (14.8%) patients whose AF did not convert to SR with inhaled flecainide who underwent ECV before the end of the observation period.

POST-OBSERVATION PERIOD UNTIL EOS. None of the patients who successfully converted to SR after inhalation of the study drug had a recurrence of AF before discharge on day 1, while 2 patients presented with AF recurrence by day 5 (EOS). From the onset of inhalation, the median time to discharge in the conversion-yes group was 2.5 hours (IQR: 0.9 hours), including the protocol-mandated 90-minute observation period, whereas for the conversion-no group, it was 3.5 hours (IQR: 1.4 hours).

Patients who received study drug and did not convert to SR during the observation period were eligible to immediately transition to standard-of-care treatment. Of these patients, 44 received ECV (95.4% converted successfully) and 1 patient received oral flecainide the day after inhalation and converted to SR. One patient received IV flecainide before the 90-minute timepoint and subsequently underwent ECV after the observation period. In total, 11 patients converted spontaneously to SR after the 90-minute observation period, with no further interventions (8 patients before discharge and 3 after discharge). In addition, 3 patients were still in AF at the time of discharge and remained in AF until the EOS.

PHARMACOKINETICS AND PHARMACODYNAMICS OF FLECAINIDE. Peak plasma concentration (C_{max}) was observed approximately 1 minute after completion of dosing (Figure 4), with a mean value of 367 ±

FIGURE 3 AF Symptoms at 90 Minutes by Conversion Status



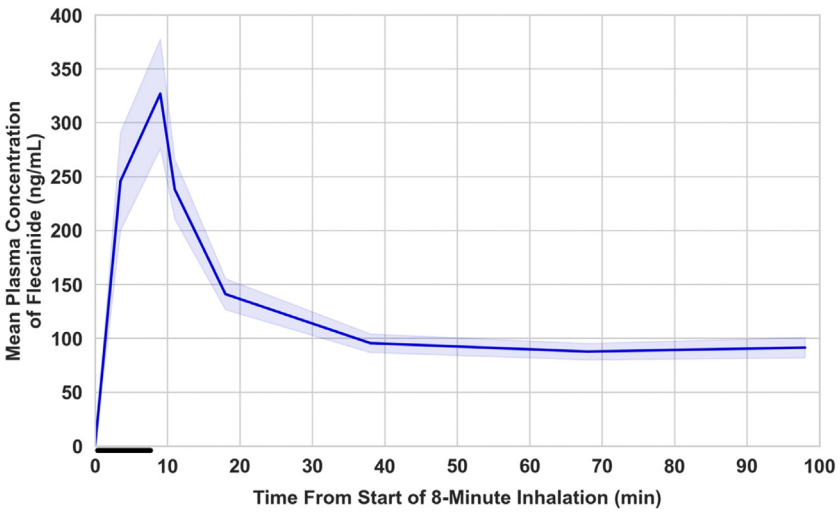
Percentage of patients with no symptoms (dark colors) or improved symptoms (light colors) of AF at 90 minutes after the end of inhalation of flecainide relative to conversion status. All patients had at least 1 or more atrial fibrillation-related symptom at baseline.

217 ng/mL, with similar levels between groups (conversion-yes: 332 ± 209 ng/mL and conversion-no: 390 ± 221 ng/mL). The C_{max} values observed ranged from 28 to 913 ng/mL, with a coefficient of variation of 59.1%. The majority of patients (75%) had C_{max} values above 200 ng/mL, the lower end of the therapeutic range of oral and intravenous flecainide for the suppression of premature ventricular contractions,[10] and no patient had a C_{max} value above 1,000 ng/mL, a level that has been associated with an increased risk of cardiovascular adverse events.[10,11] Mean plasma concentrations were below 200 ng/mL within 15 to 20 minutes after the start of inhalation and remained below this level for the remainder of the observation period.

Peak QRS intervals were generally observed a few minutes after C_{max} levels were achieved (**Figures 4 and 5A**). The mean maximum increase in QRS interval was 8.1 ± 6.0 ms and was similar in the conversion-yes and the conversion-no groups (8.2 and 8.1 ms, respectively). The mean changes over time in QRS interval duration were also similar between groups (**Figure 5A**).

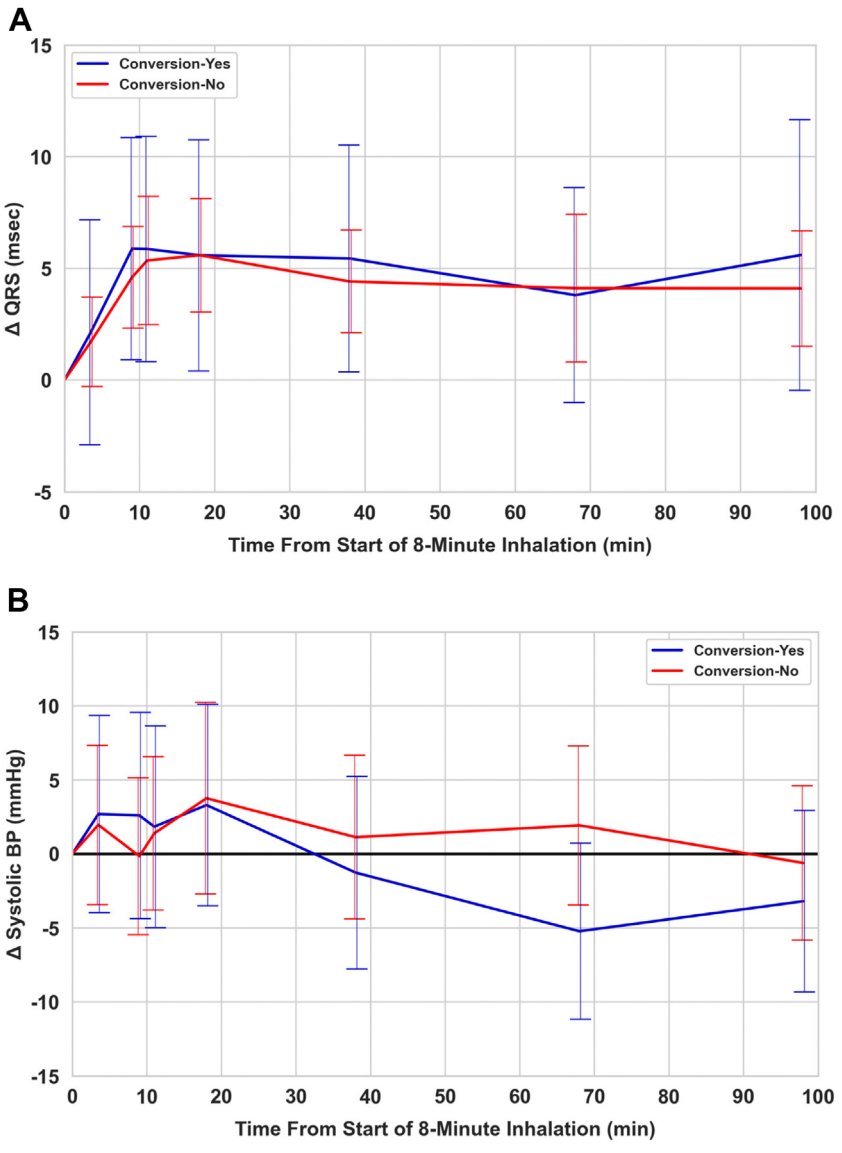
As expected, patients whose AF converted to SR presented with an immediate decrease in mean ventricular rate, from 118.6 ± 22.0 beats/min at baseline to 75.9 ± 21.0 beats/min at the time of conversion, followed by a progressive decrease over time, whereas patients who remained in AF exhibited little

FIGURE 4 Plasma Concentration of Flecainide Over Time



Mean plasma concentrations for the pharmacokinetic population, excluding patients with flecainide present before dosing (n = 77). The shaded area represents the 95% CIs interpolated between each timepoint.

FIGURE 5 Change in QRS Interval and Systolic Blood Pressure Over Time



(A) Mean change from baseline in QRS interval duration by conversion status. (B) Mean change from baseline in systolic blood pressure (BP) by conversion status. Error bars represent the 95% CI.

change in ventricular rate (Table 2). Systolic blood pressure did not differ between groups (conversion-yes: 125.6 ± 21.3 mm Hg vs conversion-no: 123.9 ± 15.7 mmHg, at baseline), with both groups having comparable blood pressure levels at the end of the 90-minute observation period (Figure 5B). Similarly, there were no significant differences in diastolic blood pressure between groups.

ADVERSE EVENTS. Treatment-emergent AEs were reported by 67% of patients in the safety population, and nearly all (97.3%) were mild or moderate in severity. The majority of adverse events (84%) were reported within 40 minutes of the start of inhalation and were of limited duration. The time of onset of adverse events was independent of conversion status (Figure 6).

The most frequently reported AE (>5%) was cough (38.8%), followed by oropharyngeal discomfort (9.2%), AFL (8.2%), oropharyngeal pain (7.1%), dyspnea (7.1%), and salivary hypersecretion (7.1%). Episodes of cough were generally short epochs lasting a

TABLE 2 Electrocardiographic Parameters by Conversion Status

	Ventricular Rate (beats/min)		QRS Interval (ms)		QTcF (ms)		JTcF (ms)	
Conversion	No	Yes	No	Yes	No	Yes	No	Yes
Baseline	119 ± 28.9	119 ± 22.0	90.9 ± 6.9	91.7 ± 12.7	392 ± 17.2	395 ± 18.0	301 ± 15.8	303 ± 12.0
Mid-dosing	120 ± 24.8	121 ± 20.5	92.8 ± 7.3	93.8 ± 15.0	393 ± 16.0	394 ± 18.2	300 ± 14.5	300 ± 14.8
1 min postdose	117 ± 23.6	104 ± 25.7[a]	95.7 ± 8.4	97.5 ± 15.2	399 ± 14.8	400 ± 19.9	303 ± 13.5	302 ± 15.2
3 min postdose	116 ± 23.2	96 ± 27.6[a]	96.4 ± 10.8	97.5 ± 15.4	400 ± 16.8	401 ± 20.5	304 ± 14.8	303 ± 16.8
10 min postdose	115 ± 24.3	90 ± 24.0[a]	96.6 ± 9.6	97.2 ± 15.8	399 ± 16.1	403 ± 18.7	302 ± 14.6	306 ± 14.7
30 min postdose	116 ± 24.9	81 ± 19.7[a]	95.4 ± 8.5	97.1 ± 15.6	398 ± 16.5	403 ± 18.4	303 ± 15.8	306 ± 14.8
60 min postdose	117 ± 25.0	76 ± 15.6[a]	94.4 ± 7.8	97.2 ± 15.7	398 ± 16.5	408 ± 19.4[a]	303 ± 16.1	311 ± 15.8[a]
90 min postdose	113 ± 32.4	74 ± 13.5[a]	95.1 ± 8.7	97.3 ± 16.9	398 ± 17.0	408 ± 21.6[a]	303 ± 15.3	311 ± 17.4

Modified intention-to-treat population (mITT) (n = 94). Data are mean ± SD. [a]Statistical difference between conversion groups ($P < 0.05$).
QTcF = QT interval corrected using the Fridericia's formula; JTcF = JT interval corrected using the Fridericia's formula.

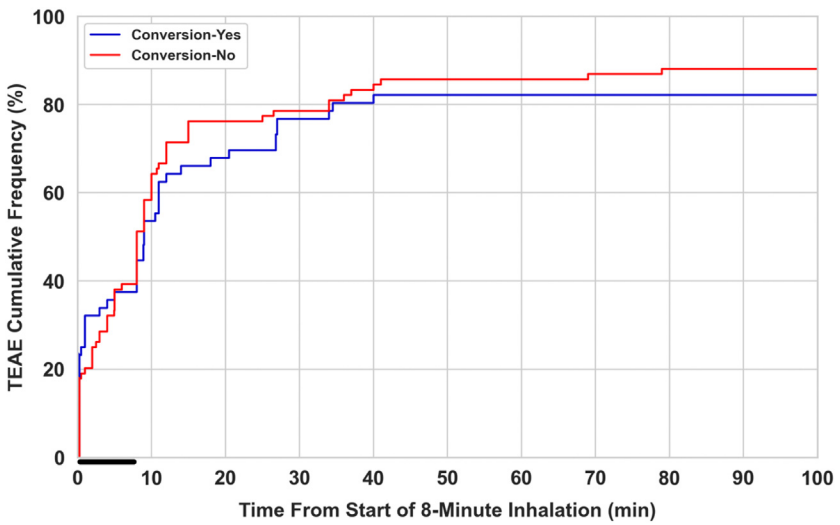
few seconds and none of these events led to discontinuation of study drug administration. Mean C_{max} was similar in patients who coughed (373 ± 227 ng/mL) and in those who did not cough (354 ± 224 ng/mL; $P = 0.689$). Conversion rates were also similar between both groups (41.7% and 43.1%, respectively). Among the 7 patients who developed slow AFL (≥2:1 AV conduction rate), 2 converted from AF to AFL before conversion to SR within 90 minutes of treatment and the other 5 underwent ECV to restore SR.

Five (5.1%) patients experienced a total of 6 CV-AESIs, 3 of which were asymptomatic (see Supplemental Table 1 for narratives of these events). One patient had bradycardia with secondary hypotension, 2 patients had hypotension only, and 1 patient had bradycardia only. One patient had transient AFL with 1:1 AV conduction that converted to SR within 90 minutes of inhalation of study drug. Among the 6 CV-AESIs, 2 were considered severe (bradycardia and AFL), and 4 were mild or moderate. No patient required medication such as positive inotropic or chronotropic drugs or vasopressors.

DISCUSSION

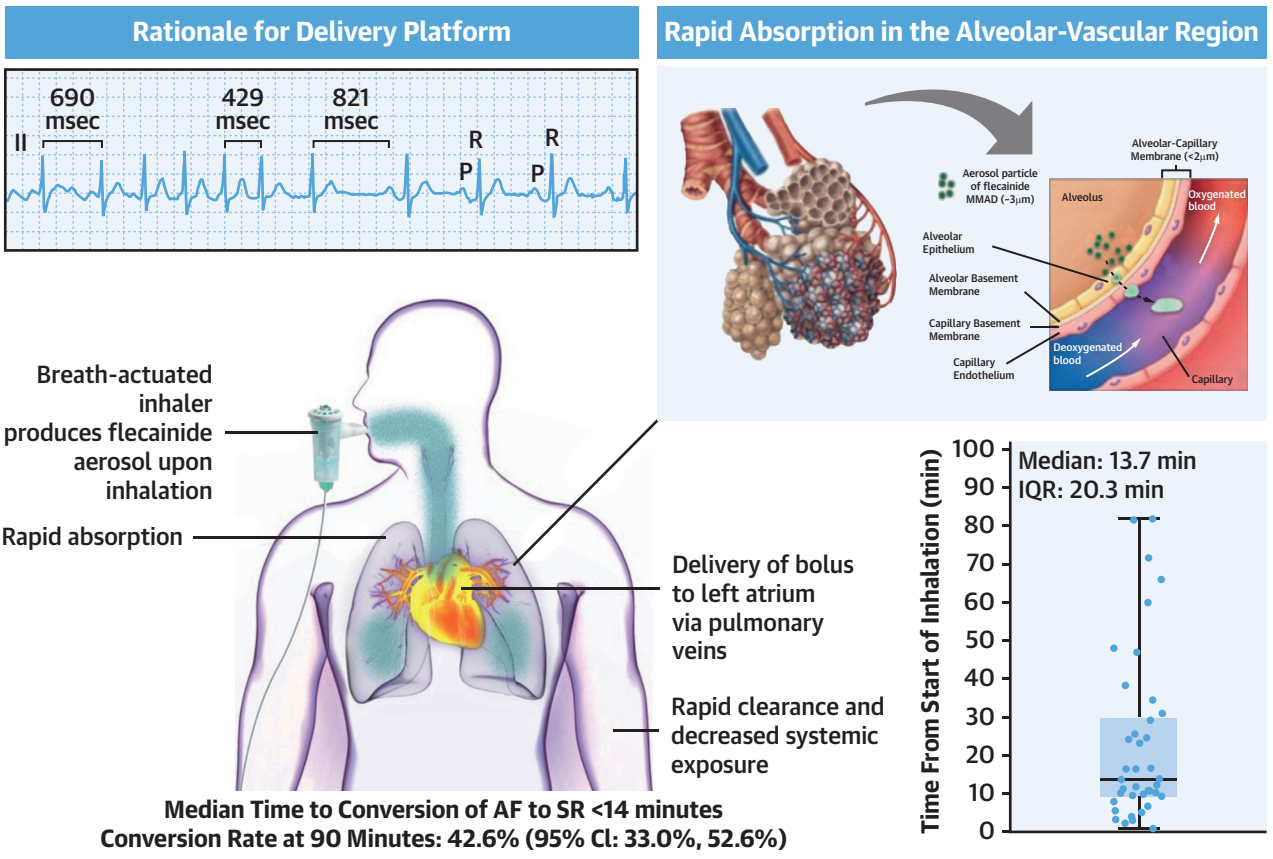
This phase 2, open-label, multicenter study evaluated the safety and efficacy of 120 mg eTLD flecainide acetate administered via oral inhalation for the

FIGURE 6 Treatment-Emergent Adverse Events Over Time



Cumulative frequency of treatment-emergent adverse events (TEAE) from the start of inhalation by conversion status in the modified intention-to-treat population (n = 94).

CENTRAL ILLUSTRATION **Oral Inhalation of Flecainide for Rapid Conversion of AF to SR**



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AF = atrial fibrillation; MMAD = median mass aerodynamic diameter; SR = sinus rhythm.

conversion of symptomatic paroxysmal AF of recent-onset (≤48 hours) to SR. The results of the current study confirm the findings reported in the previous dose-ranging study demonstrating that flecainide delivered via oral inhalation can be safe and efficacious for acute conversion of symptomatic recent-onset AF (Central Illustration).[7]

The principal goal for acute management of recent-onset symptomatic AF is to relieve symptoms by slowing the ventricular rate, which can be accomplished either by restoring SR (rhythm control) using pharmacological (eg, flecainide, vernakalant) or ECV, or with rate control therapies such as beta-blockers or calcium-channel blockers.[5] Although rhythm and rate control therapies are not mutually exclusive, the restoration of SR has the added benefit of regularizing the rhythm and restoring A-V synchrony and left atrial transport function, leading to greater improvement in cardiac function and hemodynamics.[12,13]

Recent clinical trials have demonstrated significant improvements in cardiovascular outcomes with early rhythm control strategies for nonpermanent AF compared with rate control alone.[14,15] Among the choices for rhythm control, flecainide (oral or IV) can be used in patients with recent-onset AF with no known contraindications. The 300 mg oral tablet formulation is associated with a conversion rate of 33% to 68% at 2 to 4 hours after dosing, respectively, and a mean time to conversion of 86 to 162 minutes.[16-20] In comparison, a 10-minute to 30-minute IV infusion of 2 mg/kg of flecainide results in a conversion rate of 69% (vs 16% for placebo) assessed at ≤2 hours after administration.[21]

CONVERSION OF AF TO SR. The overall conversion rate was 42.6% within 90 minutes of completion of inhalation, with the majority (75.0%) of the conversions occurring within the first 30 minutes (median

14.6 minutes). This rapid onset of action and restoration of SR following inhaled flecainide compares favorably with the time to conversion for the oral formulation.

Of note, we found that the conversion rate was much lower in patients who had flecainide present in the systemic circulation before dosing compared with those who did not have predose exposure to flecainide (15.3% and 46.9%, respectively). This finding indicates that these patients either had a breakthrough AF event during long-term treatment with oral flecainide or were treated with a loading dose (ie, pill-in-the-pocket) in a failed attempt at acute cardioversion. This observation may represent a subpopulation that is resistant to flecainide. This finding is consistent with previous studies[22] suggesting that patients with AF who do not respond to a pharmacological rhythm control therapy are less likely to undergo a successful pharmacological cardioversion during subsequent AF episodes.

REDUCTION OF AF SYMPTOMS. Although a significant improvement in symptoms was noted in the conversion-yes group (92.5%) at the 90-minute endpoint, approximately one-half (51.9%) of patients in the conversion-no group also reported an improvement in symptoms (**Figure 3**). The improvement in symptoms in the latter group may be explained in part by the fact that 19% of patients underwent ECV and/or were given concomitant rate control medications before the 90-minute timepoint.

PHARMACOKINETICS AND PHARMACODYNAMICS OF FLECAINIDE. Mean C_{max} was within the therapeutic range (ie, 200-1,000 ng/mL) previously established for oral and intravenous flecainide for the suppression of premature ventricular contractions;[10] however, C_{max} was not predictive of cardioversion success in the current study (conversion-yes: 332 ± 209 ng/mL vs conversion-no: 390 ± 221 ng/mL). This finding is similar to that reported by Suttorp et al[23] for patients given 2 mg/kg IV flecainide, in which plasma levels measured at 15 minutes from the start of the infusion (ie, near C_{max} for a 10-minute IV infusion) were not statistically different among those patients whose AF converted to SR (530 ± 230 ng/mL) vs those who remained in AF (410 ± 260 ng/mL). The lack of a positive relationship between C_{max} and conversion rate in our study could be caused by at least 2 potential factors: 1) the high coefficient of variation in C_{max} (>60%) and the limited sample size of our study; and 2) the wide range of therapeutic plasma flecainide levels reported in the literature. Of note, in our previous study,[7] a positive correlation was observed between C_{max} values and conversion rates at the doses of 30, 60, and 120 mg: 127 ng/mL (10%), 213 ng/mL (35%), and 386 ng/mL (48%), respectively.

The rapid decrease in plasma concentrations to subtherapeutic levels (ie, <200 ng/mL) within 15 to 20 minutes (**Figure 4**) and minimal prolongation of the QRS interval (**Figure 5A**) observed in this study likely contributed to a lower incidence of adverse effects compared with IV administration. This is consistent with data from a porcine model demonstrating that, despite comparable peak plasma levels with IV and intratracheal administration of flecainide, IV administration had a significantly larger systemic exposure (ie, AUC), which resulted in worsening left ventricular contractility and hypotension.[24]

Ventricular tachycardia and hypotension are 2 adverse events associated with flecainide administration that are of particular concern in higher-risk patients, ie, those with heart failure, ischemic, and other forms of structural heart disease. Inhibition of peak I_{Na} by flecainide leads to slowing of conduction velocity in the ventricular myocardium resulting in widening of the QRS interval, which when excessively prolonged becomes a harbinger for ventricular tachycardia and bundle branch block.[25,26] In addition, the decrease in peak I_{Na} leads to a reduction in calcium entry resulting in a negative inotropic effect, and hence, an increased risk of LV dysfunction and hypotension.[27,28] The magnitude of QRS interval prolongation induced by flecainide has been shown to correlate with the drug's negative inotropic and hypotensive effects.[24] Therefore, the magnitude of QRS interval prolongation by flecainide can be viewed as a harbinger not only for arrhythmia, but also for hypotension.

In the present study, the maximum prolongation in QRS interval duration was only 8.2 ms, which is ~3-fold lower than that reported for IV flecainide.[29] Thus, orally inhaled flecainide at a dose of 120 mg eTLD is likely to be associated with a lower risk for drug-induced arrhythmia and clinically significant hypotension. No patient developed ventricular tachycardia or bundle branch block, and only 3 patients developed transient hypotension (3.1%). None of these events required treatment other than IV saline (Supplemental Table 1). In comparison, hypotension has been reported in 5.8 to 9.7% of patients who received IV flecainide,[21] whereas the incidence of hypotension for oral flecainide is 1%.[20]

Statistical differences in corrected QT and JT intervals observed at later timepoints in the study

(Table 2) were not considered clinically significant and were unlikely to be related to flecainide given the rapid decline in plasma levels to below the therapeutic range. These changes were likely due to the marked difference (>30 beats/min) in heart rate between conversion groups. Alternatively, the differences observed may be caused by overestimation of QTc duration when applying Fridericia's formula to patients with a normal heart rate.[30]

ADVERSE EVENTS. The most prevalent AEs were those related to oral inhalation of flecainide (eg, cough, oropharyngeal irritation, oropharyngeal pain, dyspnea, and increased salivation), with nearly all these being considered of mild intensity and short duration. The lack of differences in C_{max} and conversion rate among patients who did/did not experience cough during inhalation also indicates that these inhalation-related adverse events appear to have minimal or no effect on the delivery and subsequent response to inhaled flecainide. Consistent with the PK profile (Figure 4) and time to conversion (Figure 2), nearly all AEs occurred within 40 minutes of the start of inhalation (Figure 6). This allows for the rapid assessment of clinical response and safety, as well as the ability to quickly transition patients to other treatments if AF fails to convert to SR following oral inhalation of flecainide.

Administration of class IC antiarrhythmic drugs is associated with proarrhythmic events, such as bradycardia, sinus pauses at conversion, slow or rapid AFL (≥2:1 or 1:1 AV conduction, respectively), junctional escape rhythm, AV block, intraventricular delay, and ventricular tachycardia in approximately 4% to 7% of cases.[20,21] In the present study, there were 6 CV-AESIs reported (6 of 98, 6.0%), with 2 considered severe (2%) and 4 considered mild or moderate, but none required medication (Supplemental Table 1). Bradycardia was observed in 2 patients (2 of 98; 2.0%), and 1 patient developed AFL with 1:1 AV conduction and rapid ventricular rate that converted to SR within the 90-minute observation period. In total, 7 additional patients (7.1%) developed slow AFL, 2 of whom converted to SR without further intervention, whereas 5 underwent successful ECV. During acute cardioversion with oral flecainide, the reported incidence of bradycardia is 7.6%, slow AFL is 6.5%, and rapid AFL with 1:1 AV conduction is 1.9%,[20] whereas with IV flecainide the incidences of bradycardia and AFL are in the range of 1.5 to 3%.[21]

The results of the present study support the potential use of inhaled flecainide for acute cardioversion of recent-onset AF in less resource-intensive settings, decreasing the need for acute treatment in the ED or hospital admission. As such, inhaled flecainide has the potential to reduce the burden on patients with paroxysmal AF by providing rapid relief of symptoms and prompt restoration of SR and decrease health care resource utilization and costs by avoiding hospitalization and ECV.

STUDY LIMITATIONS. The main limitations of this study are the small number of patients enrolled, the open-label design, and lack of randomization with a control group. Additional randomized, placebo-controlled studies are needed to confirm the safety and efficacy of inhaled flecainide. The limited sample size, combined with high variability in flecainide plasma levels achieved with oral inhalation, made it difficult to identify a clear exposure-response relationship. Further development of the inhalation platform should focus on greater ease, tolerability, and consistency of delivery of flecainide at the requisite doses to achieve higher conversion rates and more predictable outcomes.

CONCLUSIONS

The risk-benefit of orally inhaled flecainide acetate for acute cardioversion of recent-onset AF appears favorable and could provide a safe, effective, and convenient first-line therapeutic option for conversion of recent-onset AF. The delivery of flecainide by oral inhalation in the hospital/ED setting has the potential to provide a rapid and practical treatment, reducing rates of hospitalization and health care costs. Further studies are needed to confirm the findings of the current study on the clinical effectiveness and safety of inhaled flecainide.

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ADDRESS FOR CORRESPONDENCE: Dr Jeremy N. Ruskin, Cardiac Arrhythmia Service GRB 8, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114, USA. E-mail: jruskin@mgh.harvard.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE: Inhaled flecainide for conversion of paroxysmal AF to SR may reduce rates of hospitalizations, ECV, and health care costs.

TRANSLATIONAL OUTLOOK: Assessment of safety and effectiveness in a larger randomized controlled trial will lead to a better understanding of the utility of inhaled flecainide for the acute conversion of symptomatic AF to SR.

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APPENDIX For a supplemental table, please see the online version of this paper.