



# **Late-Breaking Clinical Trials Randomized Trials**

## D-LBCT01

### Late-Breaking Clinical Trials

### Randomized Trials

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#### D-LBCT01-01

##### ETRIPAMIL NASAL SPRAY FOR ACUTE TERMINATION OF SPONTANEOUS EPISODES OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA (NODE-301)

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**Introduction:** Etipamil is a rapid onset of action, short-acting L-type calcium channel blocker formulated for intranasal administration. Etipamil nasal spray (NS) is being developed to terminate paroxysmal supraventricular tachycardia (PSVT). The NODE-1 dose-ranging study demonstrated efficacy and safety of etipamil NS 70 mg for termination of SVT induced in patients in EP laboratories. The NODE-301 study tested the hypothesis that etipamil NS 70 mg is superior to and safe compared with placebo in terminating spontaneous, sustained episodes of PSVT when self-administered outside a healthcare environment.

**Methods:** NODE-301 is a pivotal Phase 3, multicenter, event-driven study evaluating the efficacy and safety of etipamil NS 70 mg when taken for termination of a spontaneous episode of PSVT. The primary efficacy endpoint is time to conversion of a positively-adjudicated PSVT episode after study drug administration. NODE-301 enrolled 431 subjects ( $\geq 18$  years of age) with an ECG-documented history of sustained PSVT at 77 US and Canadian sites. Following screening, subjects self-administered an etipamil NS 70 mg test dose at the investigational sites in sinus rhythm while their rhythm and blood pressure were monitored for 30 minutes. Subjects who successfully passed the test dose ( $n=419$ ) were randomized to self-administer etipamil NS 70 mg or placebo NS for treatment of PSVT that occurred outside the hospital or emergency room. Study drug treatment group assignment was double-blinded and randomized in a 2:1 ratio (etipamil:placebo). At enrollment, 40% of subjects also were taking chronic prophylactic oral drug

therapy (e.g., beta-blocker, verapamil or diltiazem) for PSVT. **Applications:** During follow-up (median 39 days), 198 subjects experienced symptoms of PSVT and proceeded to apply a cardiac monitoring system to their chest to record their ECG rhythm. Subjects then performed a vagal maneuver to try to terminate the episode. If PSVT symptoms persisted, subjects then self-administered etipamil 70mg or placebo intranasally while seated with their head upright. A positively-adjudicated, vagal-maneuver refractory episode of PSVT occurred in 156 subjects (median age 60 years, 64% female) who administered NS during spontaneous, sustained PSVT.

**Next Steps/Future:** NODE-301 is the first trial testing whether a novel NS, containing the calcium-channel blocker etipamil, is effective and safe for acute termination of PSVT when self-administered by individuals experiencing their tachyarrhythmias in a medically-supervised setting. Primary and key secondary clinical endpoints will be presented. NODE-301 may have important implications regarding the treatment paradigm for acute management of PSVT.

#### D-LBCT01-02

##### A RANDOMIZED TRIAL OF SUBCUTANEOUS VERSUS TRANSVENOUS DEFIBRILLATOR THERAPY: THE PRAETORIAN TRIAL

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**Introduction:** Complications related to the transvenous lead remain a concern among patients treated with a transvenous implantable cardioverter-defibrillator (TV-ICD). The subcutaneous ICD (S-ICD) was designed to reduce lead-related complications by utilizing an entirely extrathoracic placement of the system, circumventing the heart and vasculature. No randomized, controlled trials that compare the two therapies have been published to date.

**Methods:** We conducted an investigator-initiated, interna-

tional, multicenter, randomized, noninferiority trial (PRAETORIAN; ClinicalTrials.gov number, NCT01296022) in which patients with a class I or IIa indication for ICD therapy and without the need for bradycardia, cardiac resynchronization or antitachycardia pacing were assigned to receive either an S-ICD or a TV-ICD. The primary end point of the trial was a composite of device-related complications and inappropriate shocks during a median follow-up of 4 years, and an upper 95% confidence limit of 1.45 for the hazard ratio of the primary end point was used to test for noninferiority. Secondary end points included death from any cause (including sudden cardiac death) and appropriate ICD therapy.

**Applications:** A total of 849 patients (426 S-ICD and 423 TV-ICD) were randomized in the trial, with similar baseline characteristics in the two groups. The trial population was 20% female, with a median age of 63 years (55–70 years), and 69% had ischemic cardiomyopathy with a median left ventricular ejection fraction of 30% (25–35%). Outcome data of the primary and secondary end points will be presented in the Late Breaking Clinical Trial session.

**Next Steps/Future:** Recommendations on S-ICD implantation in United States and European guidelines are based on nonrandomized trials. PRAETORIAN is the first randomized, clinical trial to evaluate the safety and efficacy of the S-ICD as compared with the TV-ICD and provides further evidence to define the role of subcutaneous defibrillation in the prevention of sudden cardiac death in patients with conventional primary and secondary prevention ICD indications.

## D-LBCT01-03

### CONVERGENCE OF EPICARDIAL AND ENDOCARDIAL RF ABLATION FOR THE TREATMENT OF SYMPTOMATIC PERSISTENT AF

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**Introduction:** The effectiveness of catheter ablation for persistent and longstanding persistent AF (PsAF) is limited and has led to the development of hybrid epicardial/endo-cardial ablation techniques to achieve a more comprehensive lesion set with durable transmural lesions. A prospective randomized comparison of these approaches has not been performed. CONVERGE (NCT01984346) is the first prospective, multi-center, randomized controlled trial to evaluate safety and effectiveness of minimally invasive combined epicardial/endo-cardial ablation (Convergent) compared to standalone endocardial catheter ablation (Control) for the

treatment of PsAF.

**Methods:** PsAF patients, >18 to <80 years, refractory to class I/III AADs were randomized 2:1 to Convergent Vs Control at 27 sites (US and UK). Unlike other PsAF ablation trials, CONVERGE imposed no limits on the duration of AF and allowed left atrial sizes up to 6cm, making it the only ablation trial thus far to include a substantial portion of patients with longstanding persistent AF. Primary effectiveness was freedom from AF/AFL/AT absent new or increased dosage of previously failed class I/III AADs through 12-mo. In addition to ECGs at each visit, a 24-hr holter at 6-mo and 12-mo was performed. Primary safety was incidence of major adverse events (MAE) within 30 days of the Convergent procedure.

**Applications:** One hundred fifty-three patients (102 Convergent, 51 Control) were treated. The baseline characteristics were similar (Convergent Vs Control, Age: 63.7 Vs 65.1 yrs, Male: 78% Vs 53%, BMI: 33 Vs 35.1). The mean (min, max) years since PsAF diagnosis were 4.4 (0.5, 26.0) Vs 4.5 (0.6, 26.0) yrs. The primary effectiveness hypothesis of superiority of Convergent over Control was achieved (Table 1). The primary safety endpoint was achieved. The MAE rate of 7.8% (8/102) was lower than the prespecified point estimate (12%). No deaths or AE fistula occurred. All but one MAE resolved without sequela.

**Next Steps/Future:** The Convergent procedure combining epicardial and endocardial ablation has acceptable safety and provides superior effectiveness as compared to the standalone endocardial catheter ablation for the treatment of PsAF.

Parameter	Convergent ablation arm	Standalone endocardial catheter ablation arm	Difference (Convergent - Control)	p-value
Freedom from AF/AFL/AT from 3-month blanking period through the 12-months* without imputation of missing data as failure n%, (95% Confidence Interval)	67.7% (67/99) (58.5%–76.9%)	50.0% (25/50) (36.1%–63.9%)	17.7% in favor of Convergent	0.036
Freedom from AF/AFL/AT from 3-month blanking period through the 12-months* with imputation of missing data as failure n%, (95% Confidence Interval)	65.7% (67/102) (56.5%–74.9%)	49.0% (25/51) (35.3%–62.7%)	16.7% in favor of Convergent	0.047
≥90% burden reduction at 12 months* n%, (95% Confidence Interval)	80% (60/75) (70.9%–89.1%)	56.8% (25/44) (42.2%–71.5%)	23.2% in favor of Convergent	0.007
Freedom from AF through 12 months* n%, (95% Confidence Interval)	71% (72/102) (61.7%–79.4%)	51% (26/51) (37.3%–64.7%)	20.0% in favor of Convergent	0.017

\*Without new/ increased dosage of previously failed class III AADs  
AADs: anti-arrhythmic drugs; AF: atrial fibrillation; AFL: atrial flutter; AT: atrial tachycardia.

## D-LBCT01-04

### PERSISTENT ATRIAL FIBRILLATION ABLATION WITH A CONTACT FORCE SENSING CATHETER: THE PROSPECTIVE MULTICENTER PRECEPT TRIAL

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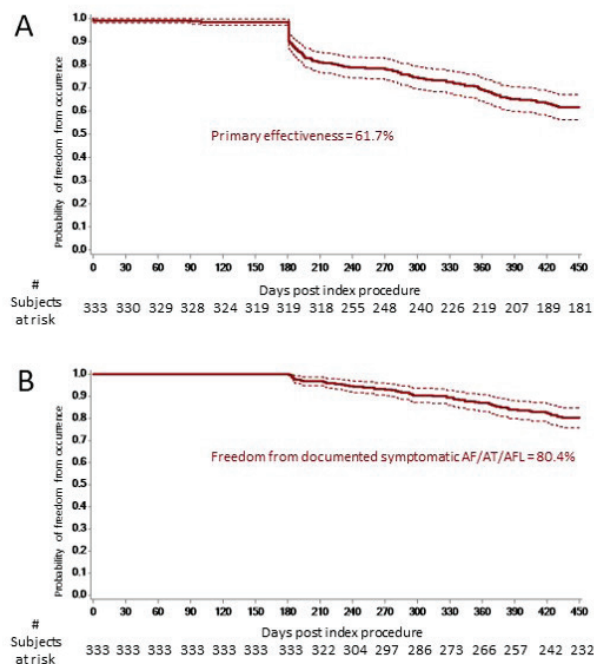
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**Introduction:** The safety and effectiveness of catheter ablation for paroxysmal AF has been well studied. In contrast, robust evidence is lacking on persistent AF (PsAF) ablation. No ablation catheter is currently approved by the FDA for PsAF. PRECEPT is the first FDA-regulated study to evaluate the safety and effectiveness of radiofrequency catheter ablation (RFA) for PsAF using a porous tip contact force (CF)-sensing catheter.

**Methods:** The prospective, multicenter, nonrandomized study was conducted at 27 US and Canadian sites and enrolled 381 patients with documented symptomatic drug-refractory PsAF. Ablation included pulmonary vein isolation with additional left-atrial targets permitted at investigators' discretion. Arrhythmia recurrences were assessed by electrocardiogram, Holter, and monthly transtelephonic monitoring for up to 15 months post-ablation, with a 3-month medication adjustment period followed by a 3-month therapy consolidation period. Primary effectiveness success was defined as freedom from documented AF/atrial tachycardia (AT)/atrial flutter (AFL) recurrence and additional 5 failure modes at 15 months. Clinical success was defined as freedom from documented symptomatic AF/AT/AFL recurrence. Patients' quality-of-life (QOL) improvement was evaluated using the Atrial Fibrillation Effect on Quality-of-Life (AFEQT) score.

**Applications:** Of the enrolled participants, 348 (70.7% male,  $65.4 \pm 8.7$  yrs, CHA2DS2-VASc score  $2.3 \pm 1.5$ ) underwent RFA as the safety population, while 333 met eligibility as the effectiveness population. Primary adverse event (PAE) rate was 3.8%. At 15 months, Kaplan Meier analyses estimated the primary effectiveness of 61.7% and clinical success rate of 80.4% (Figure). Compared to pre-ablation, AFEQT composite score increased from  $60.0 \pm 21.6$  to  $88.2 \pm 15.0$  as early as 6-month post-ablation and sustained through 15-month follow-up ( $89.1 \pm 15.7$ ), exceeding Clinically Important Difference ( $\pm 5$  points) in majority of subjects.

**Next Steps/Future:** These results demonstrate the clinical safety, effectiveness, and QOL of PsAF RFA. PAE rate was low and similar to historical data of paroxysmal AF ablation.



## D-LBCT01-05

### SMART WATCHES SIGNIFICANTLY IMPROVE ADHERENCE TO ORAL ANTICOAGULATION THERAPY AMONG PATIENTS WITH ATRIAL FIBRILLATION

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**Introduction:** Long-term oral anticoagulation (OAC) therapy can significantly reduce thromboembolic complications in patients with atrial fibrillation (AF). However, adherence to therapy is a challenge for patients who receive this treatment.

**Methods:** In this multicenter, prospective randomized controlled trial, 160 patients with AF who were prescribed long-term OAC therapy were randomly divided into 2 groups: the smart watch reminder group and the standard care group. Both groups received regular follow-up calls and were scheduled for outpatient visits. In the smart watch reminder group, OAC adherence was also ensured by a smart watch with daily intake reminders, an intake error (including delayed or missed doses) alarm, as well as an immediate telephone feedback function. The Morisky Medication Adherence Scale (MMAS-8), a self-reported adherence measure, and the proportion of days covered (PDC), an objective measure, were used to evaluate adherence to OAC therapy. Adherence to treatment was defined as a score of 8 on MMAS-8 or as a PDC cutoff of  $\geq 80\%$ .

**Applications:** To evaluate the effects of a smart watch that can send medication reminders on long-term OAC adherence in patients with AF.

**Next Steps/Future:** The demographics, CHA2DS2-VASc scores, HAS-BLED scores, comorbidities, and combined

medications were comparable between the 2 groups. In the standard care group, the proportion of patients with an MMAS-8 score of 8 decreased from 66.3% in the first month to 40% in the ninth month. Similarly, the proportion of patients with  $PDC \geq 80\%$  dropped from 75% in the first month to 30% in the ninth month in this group. In the smart watch reminder group, the proportion of patients with an MMAS-8 score of 8 increased from 62.5% in the first month to 77.8% in the ninth month, while the proportion of patients with  $PDC \geq 80\%$  remained  $>90\%$  over the 9 months ( $p < 0.005$ ).