The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: ITI101724
Title: A randomised, double blind, double dummy, parallel group, placebo controlled study to evaluate the pharmacodynamic and pharmacokinetic response and safety and tolerability of SB424323 (250mg, 375mg and 500mg) administered twice daily for 16 weeks, on top of aspirin (325mg qd) in men and women with non valvular atrial fibrillation at a low or intermediate risk for stroke
Rationale: We conducted a randomized, dose ranging study to evaluate pharmacodynamic and pharmacokinetic response, safety and tolerability of odiparcil (250 mg, 375 mg and 500 mg) and placebo administered twice daily, in addition to aspirin 325 mg daily, with both investigational product and aspirin dosed for 16 weeks. The pharmacodynamic response was determined by measurement of the biomarker anti-IIa to detect changes in coaguability. This study was conducted according to the 2002 ACC/AHA/ESC treatment guidelines for patients with atrial fibrillation.
Phase: IIB
Study Period: 24Nov2005 - 28Dec2006
Study Design: This was a randomized, double-blind, double dummy, parallel group, placebo controlled, multi-center study to assess the pharmacokinetics, pharmacodynamics (as defined by anti-IIa activity), safety and tolerability of odiparcil in atrial fibrillation patients at a low/intermediate risk for stroke.
Centres: 173 centres in 25 countries
Indication: stroke prevention in patients with atrial fibrillation
Treatment: Subjects were randomized to receive either a dose of odiparcil (250mg, 375mg and 500mg) administered twice daily for 16 weeks, on top of aspirin (325mg qd) or placebo, administered twice daily for 16 weeks on top of aspirin (325 mg qd). Subjects were randomized into the study approximately 1 week following the screening visit, they remained on study drug for 16 weeks and were also evaluated during a 4 week follow-up period.
Objectives: The primary study objective was to characterize the relationship between anti IIa activity, a biomarker used to detect changes in coagulability, and odiparcil dosage.
Primary Outcome/Efficacy Variable: The primary endpoint was anti IIa activity over the course of the study.
Secondary Outcome/Efficacy Variable(s): The secondary pharmacodynamic and pharmacokinetic endpoints were: • Descriptive statistics of odiparcil concentrations at each time point • Population PK parameters, such as clearance (CL) and volume of distribution (V) of odiparcil. Dependant upon the final compartmental model describing odiparcil disposition, additional PK parameters may also be estimated. • Correlations between the PK of odiparcil and relevant safety and efficacy endpoints Secondary safety endpoints were: • Incidence of ischemic stroke, transient ischemic attack (TIA) and systemic embolism over the course of the study. • Incidence of major or clinically relevant bleeding events over the course of the study. • Incidence of elevated LFTs over the course of the study, • Incidence of elevated CPK levels over the course of the study,

- Incidence of adverse events over the course of the study.
- Change from baseline in standard clinical laboratory parameters at each visit.

Statistical Methods: Approximately 750 subjects were anticipated to be screened and 640 subjects randomized into the study, with a target of 480 evaluable subjects (assuming that 20% randomized subjects will not complete the study). Subjects were randomized in a 1:1:1:1 ratio to receive odiparcil 250 mg, 375 mg, 500 mg or placebo, all in addition to aspirin 325 mg.

The sample size of 120 evaluable subjects per arm was chosen to provide sufficient information on the safety of chronic dosing with odiparcil to allow progression into a phase III study in high risk AF patients.

Based on the anti-IIa levels recorded in a previous study (TEMPEST), the current study will have over 88% power to detect linear trends in biomarker levels across odiparcil dosages, using a two-sided 5% significance level. The power to detect a linear trend in the proportion of patients with anti-IIa levels over the cut-off of 2ug/mL is over 99%.

There are no *a priori* plans to conduct statistical testing on any given safety parameter. However, the power of the study with respect to two aspects of safety evaluation has been considered: comparing incidence of events on odiparcil group versus placebo; and comparing the incidence of events on odiparcil group to an assumed background incidence for a low/intermediate risk NVAF population receiving aspirin 325mg daily.

With respect to comparing incidence between odiparcil and placebo, for events occurring at a frequency of 1% to 3% in the placebo group, the study has at least 75% power to detect an absolute increase in incidence of 8 percentage points at the two-sided 5% level of significance (PASS 2002 software, chi-square test with continuity-correction applied, as an approximation to Fisher's Exact test, assuming all odiparcil groups are combined for this analysis). The power to detect an absolute increase of 10 percentage points would be over 90%.

With respect to the second aspect, comparing the incidence of events in the combined odiparcil groups to an assumed background incidence for the population, the power depends on what the background incidence is considered to be. For example if for a given event it is thought to be 1%, and this is not increased by exposure to odiparcil, it can be estimated how likely it is that we can rule out (by means of a confidence interval) an increase in incidence beyond a certain level in subjects treated with odiparcil. The following table describes, for three examples of background incidence, the power that is achieved for ruling out various degrees of elevated incidence (based on a Binomial distribution assumption, use of exact confidence intervals and a null hypothesis of no elevation due to odiparcil).

Power achieved for ruling out elevated incidences with 120 patients per group

Background incidence (expected number of observed events in the combined odiparcil groups)	**Probability of observing at least one event**	**Elevated incidence to be ruled out (Upper limit of confidence interval, 1-sided 97.5%)**	**Power**
3% (11)	> 0.9999	8.0%	99%
		7.0%	92%
		6.0%	71%
1% (4)	0.9732	5.0%	>99%
		4.0%	97%
		3.0%	71%
0.3% (1)	0.6610	2.4%	90%
		2.1%	90%
		1.8%	71%

From this table we can conclude that the study is well-powered to rule out an increase of 4 percentage points or more, if treatment with odiparcil does not increase the incidence of events that would otherwise occur at a frequency of 3%. For events occurring at a

frequency of 1%, the study is well powered to rule out an increase in incidence to beyond 4% , but power is reduced with respect to ruling out increases of three-fold or less. If the background incidence of events is 0.3%, the study is only well-powered to rule out an increased incidence of seven-fold or higher.
The primary population for analysis and reporting both safety and biomarker data will be the Intent-to-Treat population. This will include subjects who were randomized and received at least one dose of study medication.

Study Population: Subjects with newly diagnosed atrial fibrillation or subjects previously diagnosed with atrial fibrillation with a low or intermediate risk for stroke were eligible for participation in the study

- Subjects diagnosed with paroxysmal AF, persistent AF or permanent AF were all eligible for participation in the study. Subjects with atrial flutter did not qualify for the study.
- Subjects previously diagnosed with hyperthyroidism, with normal thyroid function and continued AF were eligible for participation in the study.
- Subjects must have had a documented episode of atrial fibrillation within 6 months prior to the screening visit
- Documentation must have been from a 12 lead ECG, monitor strip(s) from telemetry, holter monitor event recording, or any other diagnostic modalities routinely used to document AF
- If no documentation existed, sites were permitted to perform a 12 lead ECG, telemetry, holter monitor, event recording, telephonic monitoring or any other diagnostic modalities routinely used to document AF, to obtain documentation of an atrial fibrillation rhythm; the diagnostic modalities were allowed to be performed at the screening visit (after the informed consent was signed) or after the screening visit but prior to randomization.

A subject was considered at a low or intermediate risk for stroke if one of the following applied:

- Subjects ≤60 years of age with no heart disease
- Subjects <60 years of age with heart disease but no risk factors (defined as: heart failure, left ventricular ejection fraction less than 35%, diabetes, history of hypertension and prior embolic event)
- Subjects ≥60 yrs and <75 years of age with no risk factors and no heart disease

Subjects were excluded from the study if they met any of the following critieria:

- Previous myocardial infarction, stroke (ischemic or hemorrhagic), TIA or other cardiovascular event
- Subjects with mechanical prosthetic valve or rheumatic valvular disease
- History of hypertension, diabetes (defined as medical treatment for the disease within the past year) or prior embolic event
- Subjects that are controlling diabetes by diet and exercise only, may be eligible for the study if the results of HbA1c ≤7.
- Subjects with a LVEF less than 35%
- Subjects that are greater than 75 years of age at the screening visit or subjects that will become greater than 75 years of age during their participation in the study.

- Subjects with hepatic disease as defined by any ALT, AST or bilirubin abnormality at the screening visit.
- Subjects with chronic liver disease (e.g. Hepatitis C)
- Renal insufficiency as defined by creatinine clearance less than 30 ml/min
- Subjects requiring treatment with Class III anti-arrhythmic drugs
- Subjects with an ongoing requirement for any anti-thrombotic drug therapy such as a vitamin K antagonist, heparin (standard unfractionated or low molecular weight), heparinoid, direct thrombin inhibitor, GPIIb/IIIA receptor antagonist, thrombolytic agent or intravenous dextran.
- Subject requires ongoing treatment with clopidogrel.
- Subject requires ongoing treatment with amiodarone or dofetilide.
- Subject requires ongoing treatment with a calcium channel blocker.
- History of aspirin sensitivity or any contraindication to aspirin
- History of gastrointestinal bleed or gastrointestinal intolerance when taking aspirin
- Subjects with a history of hypercoagulable syndrome or vasculitis
- Subjects with conditions that subject them to an increased risk of bleeding such as:
  - Previous gastrointestinal bleeding
  - Hemorrhagic disorders
  - History of intraocular, spinal, intracranial, retroperitoneal bleeding
- Major surgical procedure or major hemorrhagic event within 30 days prior to screening visit
- Subjects with anemia as defined by hemoglobin <12 g/dL.
- NVAF secondary to other reversible disorders such as thyrotoxicosis.

	Placebo	**Odiparcil 250 mg**	**Odiparcil 357 mg**	**Odiparcil 500 mg**
Number of Subjects: (Intent to Treat)	111	108	115	119
Planned, N	120	120	120	120
Randomised, N	112	109	117	119
Completed, n (%)	98 (88)	98 (90)	97 (83)	106 (89)
Total Number Subjects Withdrawn, N (%)	14 (13)	11 (11)	20 (17)	13 (12)
Withdrawn due to Adverse Events n (%)	0	0	0	0
Withdrawn for other reasons n (%)	14 (13)	11 (11)	20 (17)	13 (12)
Demographics	**Placebo**	**Odiparcil 250 mg**	**Odiparcil 375 mg**	**Odiparcil 500 mg**
N (ITT)	111	108	115	119
Females: Males	31:80	33:75	334:81	32:87
Mean Age, years (SD)	58.7	57.6	56.7	56.8

	(11.41)	(10.32)	(10.12)	(10.53)
Hispanic or Latino, n (%)	30 (27)	31 (29)	27 (23)	33 (28)
Non Hispanic/Latino, n (%)	81 (73)	77 (71)	88 (77)	86 (72)

Primary Efficacy Results:

A full evaluation of the relationship between dosage of odiparcil and anti-IIa activity was not conducted based on a decision to discontinue development of odiparcil based upon the efficacy results from the DVT prophylaxis study.

However, measurement of the anti-IIa values demonstrate that there was an increase in the mean trough anti-IIa levels with increasing dose of odiparcil as shown in the table below.

	Placebo (N=111)	**Odiparcil 250 mg (N=108)**	**Odiparcil 375 mg (N=115)**	**Odiparcil 500 mg (N=119)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Week 1	0.28 (0.252) (n=92)	1.62 (1.447) (n=91)	2.27 (1.711) (n=100)	2.58 (1.701) (n=103)
Week 4	0.27 (0.199) (n=93)	1.64 (1.556) (n=88)	2.04 (1.595) (n=91)	3.07 (2.78) (n=99)
Week 8	0.26 (0.095) (n=84)	1.42 (1.326) (n=83)	2.37 (1.584) (n=84)	2.89 (1.956) (n=98)
Week 16	0.25 (0.00) (n=78)	1.71 (1.683) (n=77)	1.67 (1.585) (n=80)	2.76 (2.143) (n=89)

Any on therapy adverse event was defined as an AE with onset from the time the subject is randomized into the study until the subject has completed the follow up period. An on therapy SAE was defined as an SAE with onset from the time the subjects signs the informed consent until the subject has completed the follow up period.

	Placebo N=111	**Odiparcil 250 mg N=108**	**Odiparcil 375 mg N=115**	**Odiparcil 500 mg N=119**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	42 (38)	45 (42)	50 (43)	52 (44)
Nasopharyngitis	4 (4%)	2 (2%)	6 (5%)	3 (3%)
Dizziness	2 (2%)	5 (5%)	2 (2%)	3 (3%)
Headache	3 (3%)	1 (<1%)	2 (2%)	5 (4%)
Palpitations	2 (2%)	1 (<1%)	3 (3%)	2 (2%)
Diarhoea	1 (<1%)	1 (1%)	1 (<1%)	4 (3%)

Serious Adverse Events - On-Therapy

2 events were considered by investigators to be related to study medication

The number of SAEs reported was similar across treatment groups. On therapy SAEs were reported for a total of 20 subjects (4%); 5 subjects in the placebo treatment groups, 6 subjects in the odiparcil 250 mg treatment group, 6 subjects in the odiparcil 375 mg treatment group and 3 subjects in the odiparcil 500 mg treatment groups experienced SAEs. No individual on therapy SAE occurred in 1% or more of the subjects.

No subject experienced a fatal SAE.

	Placebo N=111	**Odiparcil 250 mg N=108**	**Odiparcil 375 mg N=115**	**Odiparcil 500 mg N=119**
Subjects with non-fatal SAEs, n (%)	5 (5)	6 (6)	6 (5)	3(3)
Cardiac disorders				
Any event	1 (<1%)	2 (2%)	0	1 (<1%)
Atrial fibrillation	0	1 (<1%)	0	0
Cardiac failure	0	1 (<1%)	0	0
Coronary artery	1(<1%)	0	0	0
Disease Myocardial infarction	1 (<1%)	0	0	0
Tachycardia	0	0	0	1 (<1%)
Infections and infestations				
Any event	1(<1%)	1(<1%)	1(<1%)	1(<1%)
Appendicitis	0	2 (2%)	0	0
Pneumonia	0	1(<1%)	1(<1%)	0
Nervous system disorders				
Any event	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Cerebral infarction	0	0	1 (<1%)	0
Dizziness	0	1 (<1%)	0	0
Syncope	1 (<1%)	0	0	0
Syncope vasovagal	0	0	0	1 (<1%)
General disorders and administration site conditions				
Any event	1(<1%)	1(<1%)	1(<1%)	0
Fatigue	0	1(<1%)	0	0
Pain	1(<1%)	0	0	0
Pyrexia	0	0	1(<1%)	0
Gastrointestinal disorders				
Any Event	1 (<1%)	0	0	1 (<1%)
Abdominal pain	0	0	0	1 (<1%)
Intra-abdominal haemorrhage	1(<1%)	0	0	0
Injury, poisoning and procedural complications				
Any event	0	0	2 (2%)	0

Humerus fracture	0	0	1 (<1%)	0
Lower limb fracture	0	0	1 (<1%)	0
Upper limb fracture	0	0	1 (<1%)	0
Hepatobiliary disorders				
Any event	0	0	1 (<1%)	0
Bile duct stone	0	0	1 (<1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Any event	0	0	1 (<1%)	0
Prostate cancer	0	0	1 (<1%)	0
Psychiatric disorders				
Any event	0	0	0	1 (<1%)
Depression	0	0	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders				
Any event	1(<1%)	0	0	0
Pulmonary embolism	1(<1%)	0	0	0
Subjects with fatal SAEs, n (%)				
	n (%) [related]	**n (%) [related]**		

Conclusion:
Establishing a dose relationship between anti-IIa activity and odiparcil dose was the primary objective of this study. As indicated in the table listed under "Primary Efficacy Results," evaluation of the trough PD samples indicates that the trough anti-IIa levels increase by dose at each visit.

The secondary objective of involving a full evaluation of the pharmacodynamic and pharmacokinetic endpoints including the relationship between dosage of odiparcil and anti-IIa activity was not conducted based on a decision to discontinue development of odiparcil based upon the efficacy results from the DVT prophylaxis study.

The results around the secondary safety endpoints are described below:
The study was not powered to detect a difference in stroke/TIA/systemic embolic events due to the low event rate (<2%) in patients with NVAF at a low to moderate risk for stroke. However, these events were recorded as part of the safety evaluation. Only two of the events reported during the study met criteria and were adjudicated to stroke and TIA; one in the placebo group and one in the odiparcil 375 mg groups.
Both major and minor bleeding were adjudicated for the study. The incidence of major bleeding was extremely low in this study with only 1 adjudicated event meeting the definition of major bleed. The incidence of minor bleeding was also low with similar event rates across treatment groups.

There were no notable changes in standard laboratory tests over time with few reports of laboratory values of potential clinical concern. Changes in CPK, LFTs and bone markers were of special interest in this study. The results demonstrate that there was a very low incidence of elevated CPKs during the study; the incidence of elevated CPKs was similar across treatment groups. There was also a low incidence of elevated LFT parameters (AST, ALT, bilirubin) during the study. As with the CPK values, the incidence of elevated LFT values was similar across treatment groups. Due to the low number of samples collected for bone markers, no conclusion can be made with regards to the effect of odiparcil, in any group, on bone markers.

Adverse events were reported by 42 subjects in the placebo treatment groups, 45 subjects in the odiparcil 250 mg treatment group, 50 subjects in the odiparcil 375 mg treatment group and 52 subjects in the odiparcil 500 mg treatment group. Serious adverse events were reported by 5 subjects in the placebo treatment groups, 6 subjects in the odiparcil 250 mg treatment group, 6 subjects in the odiparcil 375 mg treatment group and 3 subjects in the odiparcil 500 mg treatment group. No fatalities were reported.

In a non valvular atrial fibrillation population at a low to moderate risk for stroke, odiparcil demonstrated an increase in trough values of anti-IIa with an increasing dose of odiparcil. The safety profile of all doses of odiparcil studied (250 mg, 375 mg and 500 mg) was similar to that of placebo.

Publications: No publication

Date updated: 19-Aug-2008