Synopsis

Identifier: ZM2006/00167/00 **Study Number:** ITI101711

Title: A Dose Ranging Trial for the Evaluation of the Safety, Tolerability and Efficacy of Odiparcil in the Prevention of Venous Thromboembolism following Total Knee Replacement Surgery

Investigator(s): Multicenter study

Study center(s): 82 centers in 13 countries

Publication(s): None at the time of this report.

Study Period: 28 September, 2005 – 27 September, 2006

Phase of Development: IIB

Objectives:

The primary objective of the trial was to assess the safety and efficacy of odiparcil in the prevention of venous thromboembolism (VTE) following total knee replacement (TKR) and to provide evidence to enable the selection of a single dose of odiparcil for future investigation.

The secondary objective of this trial was to characterize the dose response, and PK/PD relationship of odiparcil.

Methodology:

This was a multi-center, double-blind, double dummy, randomized, dose ranging, comparator-controlled trial designed to assess the efficacy, safety, and tolerability of odiparcil in subjects who undergo TKR surgery. The trial consisted of a 28-day Screening Period, a 10±2-day Double-Blind Study Medication Period, and two Follow-up visits, one at 14±2 days and the second at 28±2 days after discontinuation of study medication. The total duration of a subject's participation in the study, including the screening period was up to 70 days. Following primary elective TKR, subjects received either 250 mg, 375 mg or 500 mg odiparcil every 12 hours (q12h) for 10±2 days or dose adjusted warfarin (International Normalized Ratio [INR] target range 2.0 to 3.0) for 10±2 days.

Number of subjects:

	Odiparcil 250mg	Odiparcil 375mg	Odiparcil 500mg	Warfarin
Planned, N	160	160	160	160
Randomized, N	237	245	239	237
Completed[1], n (%)	214 (90)	226 (92)	215 (90)	216 (91)
Total Number Subjects Withdrawn, n (%)	23 (10%)	19 (8%)	24 (10%)	21 (9%)
Withdrawn due to Adverse Events,[2] n (%)	11 (5%)	6 (2%)	12 (5%)	9 (4%)

1. Number of subjects who had a 28-day follow-up visit; subjects could have been withdrawn from study medication but remained in the study.
2. Number of subjects withdrawn from study medication due to an adverse event, may or may not be primary reason for withdrawal from the study

Diagnosis and main criteria for inclusion: Male or female subjects ≥35 years of age who were scheduled for primary elective unilateral total knee arthroplasty (i.e., first time the knee is being replaced on the operative side).

Treatment administration: Subjects were randomized to either odiparcil at doses of 250 mg, 375 mg, or 500 mg q12h or dose adjusted warfarin (INR of 2.0 to 3.0). The study medication consisted of 250mg, 375mg or 500mg odiparcil tablets and matching placebo as well as overencapsulated warfarin at strengths of 1mg, and 5mg, with matching placebo. Subjects were given three bottles containing odiparcil or matching placebo and two bottles of the comparator (warfarin or matching placebo). Subjects were instructed to take one tablet from each of the odiparcil bottles q12h and to take the comparator medication (warfarin or matching placebo) as directed by the investigator. Investigators were to dose adjust warfarin to a target INR of 2 to 3 according to their own practice and subject status. Placebo matched to warfarin was dose adjusted based on sham INR values to maintain the study blind.

Lot numbers: odiparcil 250 mg, 051070819; odiparcil 375 mg, 051096775; odiparcil 500 mg, 051070820; odiparcil placebo, 051070823, 051084355, and 051080852: warfarin 1 mg, 051073362, warfarin 5 mg, 05107537, warfarin placebo, 041059115.

Criteria for evaluation: The primary endpoint was the incidence of total VTE (proximal and distal deep vein thrombosis [DVT], non fatal pulmonary embolism [PE], and death due to VTE). This included any asymptomatic DVT assessed by mandatory bilateral venography at the end of the study or at early withdrawal, symptomatic DVT confirmed by objective testing, or symptomatic PE confirmed by objective testing at any time during the study. It also included any deaths related to VTE that occurred during the study and any subjects withdrawn from the Double-blind Treatment Period due to objectively confirmed symptomatic VTE.

Secondary efficacy variables included: incidences of proximal DVT, distal DVT, PE (fatal and non-fatal), death due to VTE (including PE), total symptomatic VTE, total asymptomatic VTE, and anti-IIa activity.

Safety variables included: incidence of major or clinically relevant bleeds, a composite endpoint of the incidence of VTE and/or major bleeding, incidence of increase in alanine

aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST), direct bilirubin or total bilirubin to >2xULN and >3xULN, adverse events (AEs), changes in laboratory parameters outside the range of clinical concern.

Any incidence of VTE, bleed, or death was assessed by an Independent Central Adjudication Committee (ICAC).

Pharmacokinetics/Pharmacodynamics (PK/PD) assessments were population PK parameters and anti-IIa activity via HCII.

Statistical methods: The primary efficacy analysis was based on the ICAC-adjudicated total VTE incidence recorded prior to early withdrawal from the study or up to 12 days after randomization/first dose of study treatment, for the ITT Population. The total VTE incidence in each treatment group was presented as the number and percentage of subjects experiencing any VTE and the associated 95% confidence interval (CI). If the total VTE incidence in the warfarin treatment group was 27.4% and an odiparcil dose was 20% worse than warfarin, the expected incidence in the odiparcil treatment group would be 32.9% and the upper bound of a 95% CI based on 160 subjects would be 40.2%. Therefore, if the warfarin total VTE incidence was 27.4%, the odiparcil dose was considered ineffective relative to warfarin if the upper bound of a 95% CI around the total VTE incidence was >40.2%. Relative comparisons of each odiparcil dose and warfarin were presented as the relative risk of total VTE and associated 95% CI. An odiparcil dose was considered to be worse than warfarin if the upper bound of a 95% CI around the relative risk of total VTE on that dose compared with warfarin was >1.47. Further investigative pairwise comparisons were performed using Fisher's exact test, with results presented as a 95% CI and associated significance level. A logistic model with a term for dosage of odiparcil (a continuous variable) was fitted to the total VTE incidence and the parameter estimate for the dosage term, together with the associated 95% CI, was used to characterize the VTE incidence/odiparcil dosage relationship. A negative value for the slope parameter implied that total VTE incidence decreased as odiparcil dosage increased.

Summary:

Efficacy Results: For all three odiparcil doses, the upper bound of the 95% CI for the primary endpoint was greater than the pre-specified value of 40.2%; thus, all doses of odiparcil were considered to be ineffective relative to warfarin.

Pairwise comparisons of the odiparcil treatment groups with warfarin showed a statistically significantly greater relative risk of ICAC-adjudicated total VTE in the odiparcil 250 mg and 375 mg treatment groups compared to warfarin, and approached significance in the odiparcil 500 mg group.

Primary Efficacy Results: ICAC-Adjudicated Incidence of Totoal VTE.				
	Odiparcil 250mg N=164	Odiparcil 375mg N=169	Odiparcil 500mg N=160	Warfarin N=157
Total VTE %, (95% CI)	45.1% (37.4, 53.1)	44.4% (36.8, 52.2)	41.3% (33.5, 49.3)	31.2% (24.1, 39.1)
Logistic regression	Estimate	Lower limit	Upper limit	p-value
Slope parameter	-0.001	-0.002	0.001	0.484
Total VTE, n (%)	74 (45.1)	75 (44.4)	66 (41.3)	49 (31.2)
RR (95% CI) odiparcil vs warfarin	1.45 (1.1, 1.9)	1.42 (1.1, 1.9)	1.32 (1.0, 1.8)	
p-value[1]	0.012	0.017	0.080	
p-value[2]	0.503	0.579		
p-value[3]	0.913			

1. Fisher's exact test (odiparcil vs warfarin)
2. Fisher's exact test (odiparcil 500mg vs odiparcil 250/375mg)
3. Fisher's exact test (odiparcil 375mg vs odiparcil 250mg)

The primary component of total VTE, was distal, asytomatic DVT in all treatment groups. Pulmonary embolism was rare, and no deaths occurred due to VTE.

Secondary Efficacy Results: Components of VTE Incidence								
	---------- Odiparcil ----------						Warfarin	
	250mg (N=164)		375mg (N=169)		500mg (N=160)		(N=157)	
Classification	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Total VTE	74	45.1 (37.4,53.1)	75	44.4 (36.8,52.2)	66	41.3 (33.5,49.3)	49	31.2 (24.1,39.1)
Proximal DVT	3	1.8 (0.4, 5.3)	3	1.8 (0.4, 5.1)	8	5.0 (2.2, 9.6)	1	0.6 (0.0, 3.5)
Asymptomatic	3	1.8 (0.4, 5.3)	3	1.8 (0.4, 5.1)	7	4.4 (1.8, 8.8)	1	0.6 (0.0, 3.5)
Symptomatic	0	0.0 (0.0, 2.2)	0	0.0 (0.0, 2.2)	1	0.6 (0.0, 3.4)	0	0.0 (0.0, 2.3)
Distal DVT	72	43.9 (36.2,51.9)	74	43.8 (36.2,51.6)	63	39.4 (31.8,47.4)	48	30.6 (23.5,38.4)
Asymptomatic	69	42.1 (34.4,50.0)	74	43.8 (36.2,51.6)	62	38.8 (31.2,46.8)	48	30.6 (23.5,38.4)
Symptomatic	3	1.8 (0.4, 5.3)	0	0.0 (0.0, 2.2)	1	0.6 (0.0, 3.4)	0	0.0 (0.0, 2.3)
PE	2	1.2 (0.1, 4.3)	1	0.6 (0.0, 3.3)	0	0.0 (0.0, 2.3)	1	0.6 (0.0, 3.5)
Fatal	0	0.0 (0.0, 2.2)	0	0.0 (0.0, 2.2)	0	0.0 (0.0, 2.3)	0	0.0 (0.0, 2.3)
Non-fatal	2	1.2 (0.1, 4.3)	1	0.6 (0.0, 3.3)	0	0.0 (0.0, 2.3)	1	0.6 (0.0, 3.5)
Death due to VTE	0	0.0 (0.0, 2.2)	0	0.0 (0.0, 2.2)	0	0.0 (0.0, 2.3)	0	0.0 (0.0, 2.3)
Asymptomatic DVT	69	42.1 (34.4,50.0)	74	43.8 (36.2,51.6)	64	40.0 (32.3,48.0)	48	30.6 (23.5,38.4)
Symptomatic DVT	3	1.8 (0.4, 5.3)	0	0.0 (0.0, 2.2)	2	1.3 (0.2, 4.4)	0	0.0 (0.0, 2.3)

N = total number of subjects with objectively confirmed symptomatic VTE, venographically detected VTE at early withdrawal or an evaluable venogram at study completion.

Safety Results:

- On-Therapy AEs were reported by 69% of the subjects overall, and the incidence of AEs was similar across treatment groups. Few AEs were reported by 10% or more subjects in any treatment groups, and included: nausea (14% overall), pyrexia (14% overall), constipation (11% overall), peripheral edema (11% overall), and postoperative anemia (9% overall).

- The most frequently reported AEs, assessed by the investigator as being related to study treatment, were nausea (6%), peripheral edema (5%), tachycardia (3%), and confusion (3%) and these were comparable across treatment groups.
- Serious adverse events were reported in 6% to 7% of subjects in the odiparcil treatment groups and in 4% of subjects in the warfarin group. Only two SAEs, wound dehiscence and atrial fibrillation (2 subjects each in the odiparcil 500 mg group), occurred in more than 1 subject in any treatment group.
- Only six AEs resulted in withdrawal from the study in two or more subjects and only one AE lead to withdrawal of more than one subject in any treatment group; pain in extremity lead to withdrawal from the study for 2 subjects in the 250 mg odiparcil group.
- A total of four major bleeding events were reported, two each in the 500 mg odiparcil group and in the warfarin group. Overall, there were too few major bleeding events to draw any meaningful conclusions.
- There were no deaths reported during the study.

On Therapy AEs Reported in Greater than 1% of Subjects in Any Treatment Group (ITT Population)

	Odiparcil			Warfarin	Total
	250mg (N=235)	375mg (N=243)	500mg (N=239)	(N=237)	(N=954)
Any event	176 (75%)	167 (69%)	164 (69%)	154 (65%)	661 (69%)
Nausea	27 (11%)	35 (14%)	40 (17%)	33 (14%)	135 (14%)
Pyrexia	40 (17%)	28 (12%)	29 (12%)	34 (14%)	131 (14%)
Constipation	29 (12%)	25 (10%)	26 (11%)	29 (12%)	109 (11%)
Edema peripheral	27 (11%)	23 (9%)	28 (12%)	25 (11%)	103 (11%)
Anemia postoperative	20 (9%)	21 (9%)	24 (10%)	19 (8%)	84 (9%)
Vomiting	19 (8%)	15 (6%)	21 (9%)	13 (5%)	68 (7%)
Body temperature increased	18 (8%)	21 (9%)	13 (5%)	14 (6%)	66 (7%)
Insomnia	17 (7%)	11 (5%)	16 (7%)	13 (5%)	57 (6%)
Tachycardia	11 (5%)	12 (5%)	19 (8%)	12 (5%)	54 (6%)
Pruritus	11 (5%)	14 (6%)	10 (4%)	9 (4%)	44 (5%)
Dizziness	8 (3%)	9 (4%)	14 (6%)	11 (5%)	42 (4%)
Hemoglobin decreased	10 (4%)	12 (5%)	10 (4%)	9 (4%)	41 (4%)
Pain in extremity	8 (3%)	10 (4%)	13 (5%)	9 (4%)	40 (4%)
Contusion	7 (3%)	13 (5%)	8 (3%)	9 (4%)	37 (4%)
Anemia	9 (4%)	9 (4%)	10 (4%)	6 (3%)	34 (4%)
Urinary retention	10 (4%)	5 (2%)	9 (4%)	7 (3%)	31 (3%)
Erythema	7 (3%)	9 (4%)	7 (3%)	6 (3%)	29 (3%)
Headache	10 (4%)	9 (4%)	6 (3%)	3 (1%)	28 (3%)
Hypokalemia	8 (3%)	9 (4%)	5 (2%)	6 (3%)	28 (3%)
Hypotension	9 (4%)	4 (2%)	6 (3%)	9 (4%)	28 (3%)
Dyspepsia	6 (3%)	7 (3%)	6 (3%)	5 (2%)	24 (3%)
Arthralgia	6 (3%)	6 (2%)	7 (3%)	4 (2%)	23 (2%)
AST increased	4 (2%)	4 (2%)	10 (4%)	5 (2%)	23 (2%)
Diarrhea	2 (<1%)	9 (4%)	6 (3%)	5 (2%)	22 (2%)
Rash	3 (1%)	5 (2%)	11 (5%)	3 (1%)	22 (2%)
Confusional state	10 (4%)	5 (2%)	5 (2%)	1 (<1%)	21 (2%)
Gamma-glutamyltransferase increased	4 (2%)	4 (2%)	8 (3%)	5 (2%)	21 (2%)
ALT increased	4 (2%)	5 (2%)	6 (3%)	4 (2%)	19 (2%)
Urinary tract infection	3 (1%)	4 (2%)	6 (3%)	5 (2%)	18 (2%)
Anxiety	4 (2%)	6 (2%)	3 (1%)	4 (2%)	17 (2%)
Blister	2 (<1%)	4 (2%)	7 (3%)	2 (<1%)	15 (2%)
Blood potassium decreased	6 (3%)	3 (1%)	4 (2%)	2 (<1%)	15 (2%)
Somnolence	2 (<1%)	6 (2%)	2 (<1%)	5 (2%)	15 (2%)

Pharmacokinetics/Pharmacodynamics Results: Since the development of odiparcil has been discontinued, no formal PK/PD analyses were performed.

Conclusions:

Odiparcil was safe and well tolerated, but the results of this clinical trial do not warrant continued investigation of odiparcil as a potential replacement for warfarin for the prevention of VTE in a major orthopedic surgery population.

Date of Report: June 2007