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COMPOUND NUMBER: PD 0348292

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NCT NO.: NCT00306254

PROTOCOL NO.: A5571010

PROTOCOL TITLE: A Phase 2B, Randomized, Multicenter, Dose-Ranging Study Assessing the Safety and Efficacy of PD 0348292 in the Prevention of Venous Thromboembolic Events (VTE) in Subjects Undergoing an Elective, Unilateral Total Knee Replacement

Study Center(s): Australia: 6; Canada: 10; Chile: 1; Colombia: 4; Czech Republic: 11; Denmark: 6; France: 3; Italy: 3: Poland: 7; Portugal: 3; Russian Federation: 4; Slovakia: 1; South Africa: 5; Spain: 6; United Kingdom: 3; United States: 35

Study Initiation and Completion Dates: 23 March 2006 to 27 July 2007

Phase of Development: Phase 2B

Study Objective(s):

- To estimate the dose of PD 0348292 that was equivalent to enoxaparin 30 mg twice daily (BID) for total venous thromboembolic events (VTE) in subjects undergoing an elective, unilateral total knee replacement (TKR);
- To characterize the dose-response of PD 0348292 in subjects undergoing an elective, unilateral TKR with respect to efficacy and safety endpoints; and
- To characterize the pharmacokinetics (PK) of PD 0348292 in subjects undergoing an elective, unilateral TKR.

METHODS

Study Design: This was a randomized, active-controlled, parallel-group, multicenter study with an adaptive dose range. PD 0348292 was administered orally in a double-blind fashion and enoxaparin (30 mg BID) was administered subcutaneously as an open-label comparator.

The study was originally planned for 1225 randomized subjects undergoing an elective, unilateral TKR; however, enrollment was allowed to continue to include up to approximately

300 additional subjects (Protocol Amendment 4). This was at the discretion of the Data Monitoring Committee (DMC) and was to allow for conduct of sufficient Dose-Decision Analyses (DDAs), thereby ensuring appropriate exploration of the dose range and adequate assessment of efficacy and safety.

Initially, subjects were randomized to 1 of 6 treatments: 0.1, 0.3, 0.5, 1, or 2.5 mg once daily (QD) of PD 0348292 or 30 mg BID of enoxaparin (1:1:1:1:1:2 ratio). Randomization was stratified by region (North America or ex-North America). Based on the results of a maximum of 4 DDAs, the dose range of PD 0348292 could be modified to include doses of 4 and 10 mg QD of PD 0348292. The dose range of PD 0348292 could be modified as follows:

- A dose arm of PD 0348292 could be pruned (ie, dropped) based on an unacceptable estimated incidence of total VTE. Specifically, the lowest dose arm of PD 0348292 could be pruned if the one-sided 90% lower confidence bound of the estimated odds ratio (OR) of VTE for that PD 0348292 dose arm relative to enoxaparin 30 mg BID was greater than 1.5;

- A dose arm of PD 0348292 could be pruned based on an unacceptable estimated incidence of major bleeding. Specifically, any dose arm of PD 0348292 in which the one-sided 90% lower confidence bound of the estimated major bleeding incidence was greater than 5% was to be pruned, or

- A higher dose arm of PD 0348292 (ie, 4 and 10 mg QD) could be added based on an acceptable estimated incidence of major bleeding.

The number of subjects randomized to enoxaparin 30 mg BID was planned to remain constant for each cohort of subjects, even if the number of PD 0348292 dose arms was decreased, while the remaining subjects in a cohort were to be equally reallocated to the remaining active PD 0348292 dose arms. Also, there were to be no more than 5 dose arms of PD 0348292 active at any time during the study, and the maximum dose of PD 0348292 that could be studied was 10 mg QD.

There were 3 periods in this study: screening (within 30 days before surgery, and included presurgery, surgery, and postsurgery days), treatment (6 to 14 days), and follow-up (32±4 days after final treatment dose).

PD 0348292 was administered orally in double-blind fashion and enoxaparin 30 mg BID was administered subcutaneously (SC; abdomen) as an open-label comparator. Subjects began treatment 6 to 8 hours postoperatively with PD 0348292 or 12 to 24 hours postoperatively with enoxaparin 30 mg BID, or longer if the investigator responsible for the subject determined that satisfactory postoperative hemostasis had not yet occurred. All subjects were treated for a minimum of 6 days and a maximum of 14 days, allowing the investigational site the flexibility to schedule the bilateral venogram while the subject was still on study medication.

Assessments included vital signs, urinalysis, ophthalmic questions, physical examinations, medical history including usage of tobacco and alcohol, prior and concomitant medications, 12-lead electrocardiograms (ECGs), clinical signs/symptoms of myocardial infarction, blood sampling for cardiac enzymes and D-dimer, chemistry, hematology, TKR completion time, study medication administration, total volume bleeding, total transfusion volume (if applicable), adverse events, clinical signs/symptoms of deep vein thrombosis (DVT)/ pulmonary embolism (PE), venography, compression ultrasound, diagnosis of PE, ventilation-perfusion scans, pulmonary angiography, spiral computerized tomography (CT), magnetic resonance imaging (MRI), pharmacokinetic sampling, pharmacogenomic sampling (optional), and bilateral venography.

Number of Subjects (Planned and Analyzed): Although the study was originally planned for 1225 randomized subjects, the DMC recommended after the second DDA that approximately 300 additional subjects be included to ensure appropriate exploration of the dose range and adequate assessment of efficacy and safety (Protocol Amendment 4). A total of 1411 subjects were randomized to treatment at 99 sites in 16 countries: 1389 (98%) were treated with at least 1 dose of study drug and 103 (7.3%) discontinued from the study. The overall subject disposition by treatment group is summarized in Table S1.

Table S1. Subject Disposition

Parameter	Number of Subjects (%)							
	PD 0348292							Enoxaparin 30 mg BID
	0.1 mg QD	0.3 mg QD	0.5 mg QD	1.0 mg QD	2.5 mg QD	4.0 mg QD	10.0 mg QD	
Assigned to Treatment	62	141	186	207	203	141	69	402
Treated	61	141	183	202	200	140	65	397
Completed	58 (93.5)	134 (95.0)	169 (90.9)	184 (88.9)	184 (90.6)	131 (92.9)	57 (82.6)	369 (91.8)
Discontinued	3 (4.8)	7 (5.0)	14 (7.5)	18 (8.7)	16 (7.9)	9 (6.4)	8 (11.6)	28 (7.0)
During Treatment	3 (4.9)	3 (2.1)	7 (3.8)	11 (5.4)	10 (5.0)	6 (4.3)	7 (10.8)	17 (4.3)[a]
During Follow-up	0	4 (2.8)	7 (3.8)	7 (3.5)	6 (3.0)	3 (2.1)	1 (1.5)	10 (2.5)

Abbreviations: QD = once daily; BID = twice daily

[a] Note that 1 subject in the enoxaparin group was not accounted for in the source for this table, who was the only subject discontinued as being "lost to follow-up" and was determined to have discontinued during the treatment phase.

Diagnosis and Main Criteria for Inclusion: Subjects were male or female, age 18 or more years, scheduled for elective, unilateral TKR, willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures, and having evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) had been informed of all pertinent aspects of the study.

Critical criteria for exclusion included recent history or significant risk of abnormal bleeding, ischemic stroke or myocardial infarction, use of anticoagulation/direct thrombin inhibitors/thombolytic therapy within 7 days of TKR surgery or a condition requiring long-term anticoagulation therapy, or significant adverse reaction to an anticoagulant.

Study Treatment: Up to 7 doses of PD 0348292 could be studied. The initial cohorts of subjects were to be randomized to the 5 lowest doses of PD 0348292 (0.1, 0.3, 0.5, 1, or 2.5 mg QD) or enoxaparin 30 mg BID (1:1:1:1:1:2 ratio), stratified by region (North America or ex-North America); 2 higher PD 0348292 doses of 4 and 10 mg QD could be added based on results of DDAs.

PD 0348292 was administered orally in double-blind fashion and enoxaparin 30 mg BID was administered subcutaneously (SC; abdomen) as an open-label comparator. Subjects began treatment 6 to 8 hours postoperatively with PD 0348292 or 12 to 24 hours postoperatively with enoxaparin 30 mg BID, or longer if the investigator responsible for the subject determined that satisfactory postoperative hemostasis had not yet occurred. All subjects were treated for a minimum of 6 days and a maximum of 14 days, allowing the investigational site the flexibility to schedule the bilateral venogram while the subject was still on study medication. All doses of PD 0348292 and enoxaparin administered in this study are shown in Table S2.

Table S2. Treatment Groups and Administration Routes

Treatment Group	Dose Strength	Administration
PD 0348292	0.1 mg QD	Oral
	0.3 mg QD	
	0.5 mg QD	
	1 mg QD	
	2.5 mg QD	
	4 mg QD[a]	
	10 mg QD[a]	
Enoxaparin	30 mg BID	Subcutaneous injection

Abbreviations: BID = twice daily, DDA = dose-decision analysis, QD = once daily
[a] The 4 and 10 mg QD PD 0348292 doses added as a result of DDAs

The first dose of PD 0348292 or enoxaparin was administered in an inpatient setting following an elective, unilateral TKR. Subjects were not required to come in for an additional visit between hospital discharge and final treatment visit unless required following physician and/or coordinator guidance on presence of signs and symptoms of a VTE or other safety events. Subjects randomized to PD 0348292 continued study drug treatment after discharge and were sent home with 3 bottles of medication and instructed regarding dosing.

Subjects took 4 capsules per day. The 4 capsules were taken at the same time and at the same time of the day (within ±2 hours allowed day-to-day) during the treatment period. Subjects randomized to enoxaparin 30 mg BID continuing study drug treatment after discharge; prefilled syringes were sent with the subject upon discharge from the hospital. Instructions for administration were provided to the subject and/or caretaker.

Efficacy Evaluations: The primary efficacy endpoint was the incidence of total VTE (proximal or distal DVT, or PE) as determined by a central imaging core laboratory (Perceptive Informatics). Total VTE was defined as any postoperative lower extremity DVT, or PE, occurring anytime during the treatment period. The treatment period was initially defined as the time from the first dose until:

- 12 hours after the last dose of enoxaparin, or
- 24 hours after the last dose of PD 0348292.

Subsequently (at the time of the second DDA), a newly characterized modified treatment period (MTP) extended the original post-last dose treatment period through the date of last dose plus 1 calendar day for PD 0348292 and enoxaparin. The original treatment period was then renamed the protocol-defined treatment period (PDTP). The protocol defined treatment period remained as the primary timeframe for analysis.

Secondary efficacy endpoints were likewise assessed during the treatment period as defined above. These endpoints included:

- Incidence of proximal DVT or PE;
- Incidence of proximal DVT;
- Incidence of distal DVT; and
- Incidence of PE.

Subjects were examined for signs and symptoms of DVT (eg, swelling, localized pain, redness, heat, localized warmth) and PE (eg, unexplained shortness of breath, chest pain that got worse with a deep breath, coughing on chest movement, coughing up blood) throughout the study (inclusive of treatment and follow-up periods). If subjects presented with signs and symptoms of VTE before the last dose of study treatment, the investigational site performed a thorough assessment per protocol for presence or absence of a VTE; this assessment included a diagnostic procedure (eg, imaging).

All images (eg, compression ultrasound [CUS], venography, ventilation-perfusion [VQ] scans) for VTE were read and diagnosed by a central imaging core laboratory (Perceptive Informatics). The image interpretations by the central imaging core laboratory were used as the final and official readings regarding capture of VTE diagnosis for study report purposes.

VTEs (DVT or PE) that occurred during the treatment period were captured on the Local Evaluation of DVT/PE CRF and were considered efficacy endpoints. If an event met the

serous adverse event (SAE) reporting criteria, regardless of fatal or nonfatal outcome, it was reported in a timely fashion as an SAE and was entered into the safety database. However, it was not reported on the SAE summary table; rather, it was included in the summary efficacy tables as an efficacy endpoint.

VTEs that occurred during the follow-up period were reported as AEs and SAEs, if they met the SAE reporting criteria. SAEs occurring during the follow-up period were entered into the safety database and were included in the SAE summary table. A Local Evaluation of PE/DVT CRF was also completed.

Pharmacokinetic and Outcomes Research Evaluations:

Evaluations for PK parameters and Outcomes Research are described in supplemental reports.

Safety Evaluations: The primary safety endpoint was the incidence of total bleeding (defined as major and/or minor bleeding) during the treatment period. Using guidance from the European Agency for the Evaluation of Medicinal Products and the International Society on Thrombosis and Haemostasis, bleeding was categorized as major or minor.

For bleeding data, assessments were produced for the protocol-defined and modified treatment periods.

Secondary safety endpoints were:

- Incidence of major bleeding;
- Incidence of minor bleeding;
- Incidence of all-cause mortality;
- Incidence of liver enzyme values>3 times the upper limit of normal (ULN) for aspartate aminotransferase (AST) and alanine aminotransferase (ALT); and
- Incidence of adverse events (AEs) and serious adverse events (SAEs) and changes in clinical laboratory parameters.

Statistical Methods: Sample size was determined based on the study objective of estimating the dose of PD 0348292 equivalent to enoxaparin 30 mg BID for total VTE in subjects undergoing an elective, unilateral TKR. Clinical study simulations were performed using 2 integrated biomarker models (Factor Xa and All Drugs) to assess various study designs (including sample size).

Under the Factor Xa model, there was a 100% probability that the PD 0348292 dose equivalent to enoxaparin 30 mg BID for total VTE was ≤2.5 mg QD; under the All Drugs model, the probability was 93% that the equivalent dose was ≤10 mg QD. The estimated median VTE and major bleeding frequencies assumed for enoxaparin 30 mg BID were approximately 29% and 1.5%, respectively, under both models.

Results from clinical study simulations indicated that, with this study design, a fixed total sample size of 735 subjects with bilateral venograms adequate for evaluation or symptomatic, objectively confirmed DVT and/or PE, as determined by the central imaging core laboratory and 1225 randomized subjects available for major bleeding assessment would provide at least 82% probability (power) that the selected dose of PD 0348292 had true total VTE and major bleeding incidences within a factor of 1.3 of enoxaparin 30 mg BID (under either the Factor Xa [95% power] or all drugs models [82% power]). The estimated study sample size included an estimated 40% nonevaluable/missing venogram rate. NOTE: Given the high correlation between VTE and major bleeding for a given dose, the study sample size (1225 randomized subjects) was based upon the number of subjects available for assessment for major bleeding rather than the number of subjects available for assessment of VTE.

The primary efficacy analysis was based on the full analysis set (FAS) for the protocol defined treatment period and the primary efficacy endpoint of incidence of total VTE. The dose of PD 0348292 equivalent to enoxaparin 30 mg BID for total VTE (Deq_{292}) and its 95% confidence interval (CI) were estimated using a logistic regression model. The primary efficacy analysis was repeated using the per protocol analysis set (PPAS) to check for robustness of results.

To aid in the characterization of the dose-response of PD 0348292 for the primary and secondary efficacy endpoints, the following descriptive statistics (non-model-based estimates and CIs) were provided based on the FAS:

- The estimated incidence and associated 95% CI for each PD 0348292 dose arm and enoxaparin 30 mg BID; and
- The estimated risk ratio and associated 95% CI for each PD 0348292 dose arm relative to enoxaparin 30 mg BID.

In addition, the dose-response relationship between PD 0348292 and the primary efficacy endpoint of total VTE incidence was displayed graphically showing the observed frequencies, dose-response curve estimated by the logistic regression model described above and its lower and upper 95% confidence bounds. Results for enoxaparin 30 mg BID were displayed on the same graph.

To aid in the characterization of the dose-response of PD 0348292 for the safety endpoints of total, major and minor bleeding, all-cause mortality, and liver enzyme abnormalities, the following descriptive statistics (nonmodel based estimates and CIs) were provided; these were based on the safety analysis set (SAS).

- The estimated incidence and associated 95% CI for each PD 0348292 dose arm and enoxaparin 30 mg BID;
- The estimated risk ratio and associated 95% CI for each PD 0348292 dose arm relative to enoxaparin 30 mg BID.

In addition, the dose-response relationship between PD 0348292 and the primary safety endpoint of total bleeding incidence was displayed graphically showing the observed frequencies, dose-response curve estimated by a logistic regression model and its lower and upper 95% confidence bounds.

The dose-response relationship between PD 0348292 and the secondary safety endpoint of major bleeding incidence was also displayed graphically. Results for enoxaparin 30 mg BID were displayed on the same graph.

Descriptive statistics were provided for AE data and laboratory data. In addition, any changes assessed by physical examinations, vital signs, and ECGs were described.

To protect subjects from excessive VTE and major bleeding, and to allow for investigation of higher doses of PD 0348292 (ie, 4 and 10 mg QD), a maximum of 4 DDAs were planned. These analyses were based primarily on VTE and major bleeding data and at each DDA the dose range of PD 0348292 could be modified. In addition to the dose pruning and adding rules of the DDAs, the Data Monitoring Committee (DMC) could recommend modifying the study design if there was strong evidence that the therapeutic window was narrower or the dose range higher (ie, >10 mg QD) than anticipated.

An unblinded statistician not directly involved with the study performed the DDAs and provided the results only to the DMC. No randomization information for individual subjects was reported to the DMC as part of the DDAs; however, unblinded aggregate results were reported. Summary data, by treatment group, were unblinded and actual treatment group designations were used (ie, there was no masking of treatment groups). Interim results from the DDAs were blinded to persons directly working on the study. A small subset of the study team not involved in the day-to-day operation of the study was informed of the DDA results; however, they did not have access to the unblinded aggregate data.

A dose that had been pruned could not be re-entered into the study during a subsequent DDA. The same dose pruning and adding rules described above were to be utilized if an "early" DDA was triggered. The outcomes of the 3 DDAs that occurred during the study are noted in Table S3.

Table S3. Outcomes of DDAs

DDA	Outcome
1	Prune 0.1 mg QD; add 4 mg QD
2	Prune 0.3 mg QD; add 10 mg QD
3	Prune 0.5 mg QD

Abbreviations: DDA = Dose Decision Analysis,
QD = once daily

An interim analysis of safety parameters (in addition to total VTE and major bleeding) was conducted to allow the DMC to assess if there were any safety concerns that might necessitate altering, suspending, or terminating the study. The timing of this analysis coincided with the third DDA.

RESULTS

Subject Disposition and Demography: A total of 1411 subjects were randomized to treatment at 99 sites in 16 countries: 1389 (98%) were treated with at least 1 dose of study drug and 103 (7.3%) discontinued from the study (Table S1).

The data sets analyzed, including those pertaining to the protocol-defined and modified treatment periods, are displayed by treatment group in Table S4.

Table S4. Data Sets Analyzed

Parameter	Number of Subjects (%)							
	PD 0348292							Enoxaparin 30 mg BID
	0.1 mg QD	0.3 mg QD	0.5 mg QD	1.0 mg QD	2.5 mg QD	4.0 mg QD	10.0 mg QD	
Assigned to Treatment	62	141	186	207	203	141	69	402
Treated (SAS)	61	141	183	202	200	140	65	397
Analyzed for Efficacy:								
PPAS (PDTP)	35 (56.5)	86 (61.0)	104 (55.9)	118 (57.0)	110 (54.2)	73 (51.8)	27 (39.1)	186 (46.3)
PPAS (MTP)	36 (58.1)	87 (61.7)	104 (55.9)	119 (57.5)	112 (55.2)	73 (51.8)	27 (39.1)	221 (55.0)
FAS (MTP)	36 (58.1)	91 (64.5)	104 (55.9)	121 (58.5)	114 (56.2)	74 (52.5)	27 (39.1)	223 (55.5)
FAS (PDTP)	35 (56.5)	89 (63.1)	104 (55.9)	120 (58.0)	112 (55.2)	74 (52.5)	27 (39.1)	188 (46.8)
Analyzed for Safety								
Adverse events	60 (96.8)	139 (98.6)	178 (95.7)	201 (97.1)	199 (98.0)	140 (99.3)	64 (92.8)	388 (96.5)
Laboratory data	59 (95.2)	140 (99.3)	181 (97.3)	199 (96.1)	195 (96.1)	137 (97.2)	63 (91.3)	389 (96.8)

Abbreviations: QD = once daily; BID=twice daily; PDTP = protocol-defined treatment period; MTP = modified treatment period; FAS = full analysis set; PPAS = per protocol analysis set; SAS = safety analysis set

The FAS was defined as all randomized subjects who received at least 1 dose of study medication (ie, at least 1 capsule of PD 0348292 or at least 1 injection of enoxaparin) and:

- had bilateral venograms adequate for evaluation as determined by the central imaging core laboratory; or
- had symptomatic, objectively confirmed DVT or PE; or
- were asymptomatic and for whom bilateral venography could not be performed, but unilateral venography demonstrated thrombus (asymptomatic subjects with unilateral venography not demonstrating thrombus were excluded from the FAS).

The PPAS was defined as the FAS, excluding subjects who were major protocol violators. The SAS was defined as all randomized subjects who received at least 1 dose of study medication (ie, treated subjects).

The demographic and baseline characteristics of the subjects in this study were comparable across the treatment groups. The majority of subjects in each treatment group were female, white, and age 65 years and over.

Primary Efficacy Results: The dose of PD 0348292 equivalent to enoxaparin 30 mg BID for total VTE and its 95% CI were estimated to be 1.16 (0.56, 2.41) mg QD using the protocol-defined treatment period. The modified treatment period yielded similar results.

The observed incidence of total VTE during the protocol-defined treatment period was 37.1%, 37.1%, 28.8%, 19.2%, 14.3%, 1.4%, and 11.1% for PD 0348292 doses of 0.1, 0.3, 0.5, 1, 2.5, 4, and 10 mg QD, respectively. The observed incidence for enoxaparin was 18.1%. The modified treatment period yielded similar results.

The primary efficacy analysis was repeated using the PPAS to check for robustness of results. Using the PPAS and protocol-defined treatment period, the dose of PD 0348292 equivalent to enoxaparin 30 mg BID for total VTE and its 95% CI were estimated to be 1.17 (0.56, 2.43) mg QD. Similar results were obtained using the PPAS and modified treatment period.

There was a statistically significant log (dose) response for PD 0348292 ($p<0.0001$ for the estimated slope parameter), resulting in dose-related decreases in the model-predicted incidence of total VTE. Similar results were obtained using the modified treatment period.

Secondary Efficacy Results: The observed incidence of proximal DVT or PE (combined) was 5.7%, 3.4%, 3.8%, 4.2%, 2.7%, 0%, and 3.7% for PD 0348292 doses of 0.1, 0.3, 0.5, 1, 2.5, 4, and 10 mg QD, respectively. The observed incidence for enoxaparin was 3.7%.

The observed incidence of proximal DVT was 5.7%, 3.4%, 3.8%, 3.3%, 1.8%, 0%, and 3.7% for PD 0348292 doses of 0.1, 0.3, 0.5, 1, 2.5, 4, and 10 mg QD, respectively. The observed incidence for enoxaparin was 2.1%.

The observed incidence of PE was 0%, 0%, 0%, 0.8%, 0.9%, 0%, and 0% for PD 0348292 doses of 0.1, 0.3, 0.5, 1, 2.5, 4, and 10 mg QD, respectively. The observed incidence for enoxaparin was 1.6%.

The observed incidence of distal DVT was 34.3%, 34.8%, 27.9%, 17.5%, 11.6%, 1.4%, and 11.1% for PD 0348292 doses of 0.1, 0.3, 0.5, 1, 2.5, 4, and 10 mg QD, respectively. The observed incidence for enoxaparin was 16.0%.

Symptomatic DVT was observed in 1 subject treated with PD 0348292 0.5 mg QD, and in 1 subject in the enoxaparin treatment group.

Secondary efficacy endpoint results obtained during the modified treatment period were similar to those obtained during the protocol-defined treatment period.

The results from the primary endpoint subgroup summaries for the treatment and follow-up periods were similar to those for the primary endpoint.

Biomarkers: D-dimer Results: Mean and median D-dimer concentrations were comparable across all PD 0348292 doses and enoxaparin 30 mg BID at each time point. Mean concentrations at end of treatment were approximately 3-fold higher than presurgery mean values, and median values were approximately 6-fold higher. At the follow-up visit, mean D-dimer concentrations had decreased to less than 2-fold higher than presurgery values, and median concentrations were approximately 4-fold higher than presurgery values.

Pharmacokinetic and Outcomes Research Results: The results of outcomes research are presented in a supplemental report. The pharmacokinetic results are presented in a supplemental pharmacokinetics report.

Safety Results: A total of 992 subjects in all PD 0349292 dose groups and 397 subjects in the enoxaparin group were evaluable for safety analysis. Overall, PD 0348292 and enoxaparin were well tolerated by most subjects enrolled in this study; with 0.7% of the 0.3 mg, 1.1% of the 0.5 mg, 1.0% of the 1.0 mg, 1.0% of the 2.5 mg, 0.7% of the 4.0 mg, and 3.1% of the 10 mg PD 0348292 dose groups and 0.8% of the enoxaparin 30 mg BID group discontinuing the study due to treatment-related adverse events during the treatment period. No deaths and no unexpected adverse events were reported. A total of 236 treatment-related AEs were reported during the treatment period by 135 subjects (13.6% of 992 subjects evaluable for AEs) who received PD 0348292, and a total of 96 treatment-related AEs were reported by 63 subjects (15.9% of 397 subjects evaluable for AEs) who received enoxaparin. The percentage of subjects experiencing treatment-related AEs in each of the PD 0348292 groups during the treatment period was as follows: 11.5% in the 0.1 mg group, 12.1% in the 0.3 mg group, 11.5% in the 0.5 mg group, 12.9% in the 1 mg group, 16.5% in the 2.5 mg group, 12.9% in the 4 mg group, and 20.0% in the 10 mg group, respectively, compared with 15.9% in the enoxaparin group. Treatment-related SAEs occurred in 1.4% of subjects in the 0.3 mg dose group, 1.1% in the 0.5 mg dose group, and 3.1% of the 10 mg PD 0348292 dose groups during the treatment period. No treatment-related SAEs were reported in subjects in the other PD 0348292 dose groups. In the enoxaparin group, 0.8% of subjects reported treatment-related SAEs during the treatment period.

During the follow-up period, the percentage of subjects in the PD 0348292 dose groups with treatment-related AEs was generally low and comparable to the enoxaparin group: 1.6% in the 0.1 mg group, 1.4% in the 0.3 mg group, 2.7% in the 0.5 mg group, 1.5% in the 1 mg group, 1.0% in the 2.5 mg group, 1.4% in the 4 mg group, and 1.5% in the 10 mg group, compared with 2.0% in the enoxaparin group. The incidence of treatment-related SAEs was low in the follow-up period: 0.5% in the 1 mg PD 0348292 dose groups had SAEs during this period, compared with 0.8% in the enoxaparin group. Most subjects recovered or were recovering from these events at the last visit of the study.

Conclusion(s): In this randomized, double-blind, multicenter, Phase 2B study in subjects undergoing total knee replacement surgery, PD 0348292 was well tolerated. A PD 0348292 dose of 1.16 mg was estimated to be equivalent to enoxaparin 30 mg BID for total VTE in subjects undergoing elective, unilateral TKR. The incidence of total bleeding in subjects treated with PD 0348292 showed generally higher numerical values compared with enoxaparin. The higher incidence of total bleeding was mainly driven by higher minor bleeding, as the incidence of major bleeding was similar between subjects treated with PD 0348292 and enoxaparin.