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Clinical Study Synopsis for Public Disclosure

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BI Proprietary Name: Pradaxa			
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Report Date: 23 Jan 2015	**Trial No. / Doc. No.:** 1160.128 / c02727395-01	**Dates of Trial:** 21 Dec 2011 - 23 Jul 2014	**Date of Revision:** Not applicable

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Title of Trial:	A prospective, open label study evaluating the efficacy of two management strategies (pantoprazole 40 mg q.a.m. and taking Pradaxa® with food [within 30 minutes after a meal]) on gastrointestinal symptoms (GIS) in patients newly on treatment with Pradaxa® 150 mg b.i.d., 110 mg, or 75 mg b.i.d. for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)
Coordinating Investigator:	[redacted]
Trial Sites:	Multicenter trial in 103 sites in the United States and Canada
Publications:	Data from this trial have not been published.
Clinical Phase:	IV
Objectives:	The primary objective of this trial was to determine the relative efficacy of two interventions (pantoprazole 40 mg once daily taken in the morning; or administration of Pradaxa with food, within 30 minutes after a meal) on GIS in patients with NVAF taking open-label Pradaxa in accordance with the current local label (US: 150 mg or 75 mg twice daily; Canada: 150 mg or 110 mg twice daily) to reduce the risk of stroke and systemic embolism.
Methodology:	Prospective, randomized, open label trial
No. of Subjects:	
Planned:	Enroll: approximately 1600 patients Enter: approximately 1200 patients treated with Pradaxa to result in approximately 144 patients with GIS Treat: approximately 72 patients per GIS management strategy
Actual:	Enrolled: 1221 patients Entered: 1067 patients treated with Pradaxa Randomized to a management strategy: 117 Pradaxa after a meal: Entered: 59 Treated: 59 Analyzed (for primary endpoint): 59 Pradaxa + pantoprazole 40 mg: Entered: 58 Treated: 58 Analyzed (for primary endpoint): 58

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Diagnosis:	non-valvular atrial fibrillation (NVAF)
Main Criteria for Inclusion:	Male and female patients ≥18 years of age with documented NVAF for whom Pradaxa was indicated per the current local label, but who were Pradaxa naïve. (Patients who had begun Pradaxa therapy within 7 days prior to potential enrollment in the trial were considered to be Pradaxa naïve.)
BI Investigational Product:	Pradaxa
Dose:	In the United States: 75 mg or 150 mg twice daily in accordance with current local label. In Canada: 110 mg or 150 mg twice daily in accordance with current local label.
Mode of Admin.:	Oral
Batch No.:	75 mg: 102179A (080343), 108799A (PA3167) 110 mg: 206795, 303400, 304645, 301971, 305802 150 mg: 102144 (080568), 108412 (PA1742), 205513, 205868
Add-on Product:	Pantoprazole
Dose:	40 mg once daily
Mode of Admin.:	Oral
Batch No.:	JKK0515A, C201833, C302229, PA40118, CV3331A, CN9030A
Duration of Treatment:	Pradaxa: 3 months (plus up to an additional 8 weeks depending on when GIS developed during the course of treatment with Pradaxa) Initial Gastrointestinal Symptom Management: • Pradaxa twice daily plus pantoprazole 40 mg once daily in the morning (4 weeks) OR • Pradaxa taken with food, within 30 minutes after a meal (4 weeks) If GIS did not resolve during the first 4 weeks of GIS management, then the alternate GIS management strategy was to be added and the initial strategy continued: • Pradaxa taken with food, within 30 minutes after a meal, plus pantoprazole 40 mg once daily in the morning (4 weeks)

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Criteria for Evaluation:

Efficacy:

Primary endpoint: The rate of complete effectiveness of pantoprazole 40 mg once daily in the morning and administration of Pradaxa within 30 minutes after a meal at 4 weeks.

Secondary endpoints: Efficacy data collected at 8 weeks post onset of symptoms were considered secondary. Comparisons across all time points (including Week 4 and Week 8) were based only on the two randomized management strategies as randomized at symptom onset.

- Rate of complete, rate of partial, and rate of complete or partial relief of GIS at each week.
- Time between symptom onset and first observed complete or partial effectiveness.
- Time between symptom onset and last observed symptom.

Safety:

Bleeding and other adverse events reported.

Statistical Methods:

Number and percent of patients experiencing complete effectiveness up to Week 4 was to be presented for each management strategy, and for the difference between the two strategies. Ninety five percent two-sided confidence intervals were to be constructed for each management strategy, and for the difference between the two strategies using the Clopper Pearson approach.

The primary endpoint (rate of complete relief of GIS) was analyzed based on last observation carried forward (LOCF) data up to the last observed time or up to adding another management strategy.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

A total of 1221 patients were screened at 103 study sites in the US (81 sites) and Canada (22 sites).

There were 1067 patients who met eligibility criteria, were entered into the study, and began treatment with Pradaxa. Of these, 950 patients were not randomized to a GIS management strategy:

- 854 (80%) did not report GIS:
  - 754 patients completed 3 months of Pradaxa treatment and
  - 100 patients discontinued the study early;
- 48 (4.5%) reported GIS prior to the EOT visit, but before they were randomized:
  - 32 patients' GIS had resolved without treatment and

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- 16 patients had discontinued the study early (4 of these patients reported that GIS had resolved);

- 48 (4.5%) patients reported at the EOT visit experiencing GIS at some point during the study (despite instructions to report this to the study site at the time GIS occurred, they did not):
  - 26 patients' GIS had resolved without treatment,
  - 4 patients had ongoing GIS, and
  - 18 patients discontinued the study early.

Ultimately, among the 950 patients who were never randomized, GIS resolved without treatment in 62 patients:

- 32 who reported GIS before EOT and completed the study,
- 4 who reported GIS before EOT and discontinued early, and
- 26 who reported GIS at EOT.

A total of 117 (11.0%) patients reported GIS and were randomized to a GIS treatment strategy.

All patients who were randomized used the assigned GIS management strategy. Approximately 75% of patients taking Pradaxa after a meal and 81% of patients adding pantoprazole completed the 4 week treatment period; 4.3% of patients discontinued the study during the initial strategy period due to worsening of GIS (Pradaxa after a meal: 3 patients [5.1%]; pantoprazole: 2 patients [3.4%]). During the combined management strategy period, 1 (1.7%) patient in each group discontinued the study due to worsening of GIS.

The demographic characteristics of the randomized and never randomized patients were generally well balanced. The patients were about two thirds male, >90% non-Hispanic and white, approximately 69 years of age, weighing approximately 96 kg, and about half ex-smokers. There was a numerically higher percentage of patients with a history of alcohol consumption among the randomized patients (61.5%) than the never randomized patients (56.8%), a numerically higher percentage of never smokers among the randomized patients (47.0%) than the never randomized patients (41.2%), and a numerically higher percentage of women among randomized patients (35.9%) than the never randomized patients (32.0%). The clinical significance of these findings was unknown.

At baseline, there was a higher incidence of use of medications that may also cause GIS like symptoms in the randomized patients (e.g. nonsteroidal anti-

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inflammatory drugs and glucocorticoids).

Gastrointestinal disorders, general disorders, food allergy, and drug hypersensitivity were somewhat more common in the randomized patients.

The demographic characteristics of patients who developed GIS were similar to those of patients who never developed GIS. The most notable difference was the higher percentage of patients with a history of alcohol consumption among the patients who developed GIS (63.4%) compared to the patients who never developed GIS (55.9%). The clinical significance of this finding is unknown.

In the treated set, the demographic characteristics of the Pradaxa after a meal group and the pantoprazole group were similar. The most notable differences were in race (Pradaxa after a meal: 98.3% white; pantoprazole 91.4% white), smoking status (Pradaxa after a meal: 42.4% never smoked; pantoprazole 51.7% never smoked; Pradaxa after a meal: 50.8% ex-smoker; pantoprazole 41.4% ex-smoker), and alcohol status (Pradaxa after a meal: 67.8% history of alcohol consumption; pantoprazole 55.2% history of alcohol consumption).

The most common primary GIS experienced by the patients in the treated set was heartburn, reported by almost half the patients in both management strategy groups (Pradaxa after a meal: 45.8%; pantoprazole: 48.3%). Epigastric burning and nausea were reported more frequently in the pantoprazole group. Epigastric discomfort, epigastric pain, excessive burping/belching, and upper abdominal discomfort were reported more frequently in the Pradaxa after a meal group.

Of the patients with compliance data in the entered set, over 90% were within the compliance boundaries of 80% to 120% of the expected number of capsules taken. The majority of patients in the Pradaxa after a meal group were compliant, i.e., at all face-to-face visits reported taking Pradaxa within 30 minutes after a meal always or most of the time. Over 90% of patients taking pantoprazole who had compliance recorded were within the compliance boundaries of 80% to 120% of the expected number of tablets taken.

Efficacy Results: Primary Endpoint

Both initial management strategies (taking Pradaxa after a meal and adding pantoprazole 40 mg daily) provided complete relief of the primary GIS in over 55% of patients who reported GIS (Pradaxa after a meal: 55.9%; pantoprazole: 67.2%).

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Efficacy Results (continued):

Secondary Endpoints

Patients with unresolved GIS after 4 weeks of the initial management strategy rated GIS intensity as mild or moderate.

Partial effectiveness after 4 weeks of the initial management strategy was reported by 7 (11.9%) patients taking Pradaxa after a meal and 11 (19.0%) pantoprazole patients.

Combined complete or partial effectiveness after 4 weeks of the initial management strategy was reported by 40 (67.8%) patients taking Pradaxa after a meal and 50 (86.2%) pantoprazole patients.

Complete effectiveness after 4 weeks of using the combined GIS management strategies (8 weeks, total treatment) was reported by 6 of 14 (42.9%) patients in the Pradaxa after a meal group and 5 of 15 (33.3%) pantoprazole patients.

Partial effectiveness after 4 weeks of the combined management strategies (8 weeks, total treatment) was reported by 6 of 14 (42.9%) patients taking Pradaxa after a meal and 7 of 15 (46.7%) pantoprazole patients.

Complete or partial effectiveness after 4 weeks of the combined management strategies (8 weeks, total treatment) was reported by 12 of 14 (85.7%) patients taking Pradaxa after a meal and 12 of 15 (80.0%) pantoprazole patients.

Patients in the pantoprazole group achieved complete effectiveness in a shorter period of time (at the first visit after randomization [GIS 3]: Pradaxa after a meal 39.0%, pantoprazole 51.7%).

As a single GIS management strategy, adding pantoprazole 40 mg daily provided complete effectiveness in more patients (after 4 weeks of treatment: Pradaxa after a meal 55.9%; pantoprazole 67.2%) and in a shorter period of time than Pradaxa after a meal (after 1 week of treatment: Pradaxa after a meal 39.0%; pantoprazole 51.7%).

Combining GIS management strategies provided incremental benefit for patients who continued to experience GIS after 4 weeks of a single strategy.

The mean time to first complete effectiveness was 12.1 days for patients who received Pradaxa after a meal and 10.7 days for patients who received pantoprazole. The time to first partial effectiveness calculations were based on too few data points to draw meaningful conclusions.

The mean time between GIS onset and last observed GIS was 23.5 days for patients who received Pradaxa after a meal and 23.9 days for patients who received pantoprazole.

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Safety Results:

Adverse events in the entered set

In the entered set (N= 1067), half the patients (543, 50.9%) treated with Pradaxa reported at least one AE; 246 (23.1%) patients had a Pradaxa-related AE; no patients had a pantoprazole-related AE; 110 (10.3%) patients had one or more AEs that led to discontinuation of study drug; 118 (11.1%) patients had SAEs; 7 (0.7%) of the patients with SAEs died as a result; in two cases, the fatal SAE was considered to be drug-related; 91 patients (8.5%) had other significant AEs. No events indicating drug-induced liver injury were noted.

No SAEs were GIS as defined in this study.

Adverse events of special interest were identified using Standard MedDRA Queries. Bleeding events occurred in 13 (1.22%) patients, myocardial infarction occurred in 3 (0.28%) patients, stroke occurred in 13 (1.22%) patients, and systemic embolism other than stroke occurred in 2 (0.20%) patients.

Adverse events in patients who developed GIS

A total of 213 patients (20.0%) developed GIS: 117 patients who were randomized and 96 patients, who were not randomized; 854 patients never developed GIS during the study. Severe AEs (GIS: 45, 21.1%; never GIS: 52, 6.1%) and AEs that led to discontinuation (GIS: 48, 22.5%; never GIS: 62, 7.3%) were more common in patients who developed GIS. Serious AEs (GIS: 20, 9.4%; never GIS: 98, 11.5%) and deaths (GIS: 1, 0.5%; never GIS: 6, 0.7%) were more common among patients who never developed GIS. Pradaxa-related AEs were more frequent in patients who developed GIS (GIS: 171, 80.3%; never GIS: 75, 8.8%), presumably due to the incidence of GIS.

Adverse events in the treated set

In the treated set (N = 117), the AE profiles of patients taking Pradaxa after a meal and patients adding pantoprazole to their Pradaxa regimen were similar. Overall, 88 (75.2%) patients in the treated set reported at least one AE. Twelve (10.3%) patients in the treated set reported at least one severe AE. Serious AEs were reported by five (4.3%) patients; none of these were considered to be drug related. Adverse events leading to discontinuation were reported by 18 (15.4%) patients, and Pradaxa-related AEs were reported for 62 (53.0%) patients in the treated set. No deaths occurred in the treated set.

In the treated set, gastrointestinal disorders were the most common category of AEs; most of the GI events were considered drug-related; and GI disorders made up the majority of AEs leading to discontinuation.

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No clinically meaningful changes in laboratory values, vital signs, or physical findings were noted in this study.

Conclusions:

The primary objective of this study was to test two GIS management strategies (taking Pradaxa 30 minutes after a meal or adding pantoprazole 40 mg daily) in patients who developed GIS while taking Pradaxa. Both strategies were found to be helpful, providing complete or partial relief to the majority (78.6%) of patients who utilized them. For patients who continued to report incomplete relief after 4 weeks of one GIS management strategy, combining the two strategies provided an incremental benefit. No safety concerns were identified with the two management strategies.