2. SYNOPSIS

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Name of Sponsor Company: Janssen-Cilag SAS
Name of Finished Product: Pariet®
Name of Active Ingredient: Rabeprazole

Individual Study Table

Referring to Part of the Dossier

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Studied Period: **From:** 17 November 2009 (First site opened) **Clinical Phase**: 1
To: 26 March 2010 (Last patient last visit)

Study Title: Influence of rabeprazole on the magnitude of the antiplatelet action of clopidogrel. A prospective, placebo and active treatment-controlled, open-label, randomized 3-way cross over study in healthy subjects.

Objectives:

Primary Objective

- To compare the effect of rabeprazole and placebo on inhibition of platelet function, as measured by the vasodilator-stimulated phosphoprotein (VASP) phosphorylation level, after 7 daily standard 75 mg doses of clopidogrel in healthy male subjects**.** VASP assay was chosen, as it is the primary pharmacodynamic (PD) measure of platelet aggregation and was used in the interaction study between omeprazole and clopidogrel. The primary analysis was performed on all subjects included and in whom VASP phosphorylation level was determined during the 3 Study Periods (Completers population).

Secondary Objectives

- To perform secondary analysis in subjects who are Good Antiplatelet Responders to clopidogrel during the Placebo Period. Good Antiplatelet Responders were defined as subjects in whom the VASP index on Day 7 relative to Day 1 was decreased by at least 30%. This was expected to occur in 65 to 75% of recruited subjects.
- To perform secondary evaluations in the population of Good Antiplatelet Responders to clopidogrel in order to determine: the difference in the magnitude of inhibition of platelet aggregation (IPA) under clopidogrel treatment after the co-administration of rabeprazole compared to placebo; the difference in the magnitude of IPA under clopidogrel treatment after the co-administration of omeprazole compared to placebo as a positive control to demonstrate assay sensitivity of the study; the difference in the magnitude of IPA under clopidogrel treatment after the co-administration of rabeprazole compared to omeprazole.
- To perform secondary analyses in the Completers population (all included subjects in whom VASP phosphorylation level was determined during the 3 Study Periods) to assess: the difference in the magnitude of IPA under clopidogrel treatment after the co-administration of omeprazole compared to placebo as a positive control to demonstrate assay sensitivity of the study; the difference in the magnitude of IPA under clopidogrel treatment after the co-administration of rabeprazole compared to omeprazole.
- To compare the influence of rabeprazole and omeprazole on the rate and extent of plasma concentration exposure of clopidogrel and its major metabolite (carboxylic acid metabolite) as measured by clopidogrel and its major metabolite (carboxylic acid metabolite), area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0-24)}$, maximum plasma concentration (C_{max}) and elimination half-life ($t_{½}$) during

the active Treatment Periods compared to the Placebo Period at Day 7.

- To assess the influence of cytochrome P450 isoenzyme 2C19 (CYP2C19) polymorphism on clopidogrel PD and pharmacokinetic (PK) responses by comparing wild-type CYP2C19 homozygotes *1 / *1 to heterozygotes *1 / any mutated non-functional allele (*2 and *3).

Exploratory Objectives

- To compare the influence of rabeprazole and omeprazole on the rate and extent of plasma concentration exposure of clopidogrel active metabolite as measured by the clopidogrel active metabolite AUC_{0-24} and C_{max} during the active Treatment Periods compared to the Placebo Period at Day 7. This assessment was to be performed only if the assay for the active metabolite could be successfully set up and validated. Because the inactive carboxylic acid metabolite of clopidogrel is the major circulating metabolite in human plasma, and the active metabolite is unstable, the exposure and PK parameters for clopidogrel were indirectly determined by quantifying the inactive carboxylic acid metabolite (major metabolite).

Methodology: This was a prospective, placebo- and active-controlled, open label, randomized 3-way crossover Phase 1 study. The study consisted of a Screening Visit (Screening Period lasted from Days-21 to -7), and 3 Study Periods (7 days each) separated by 2 to 3 weeks of washout. The subjects received clopidogrel 75 mg with rabeprazole 20 mg, omeprazole 20 mg, or placebo in a crossover manner. Blood samples for PK, PD, pharmacogenomic and safety analyses were collected at protocol-specified time points in the study. Safety was monitored throughout the study.

Number of Subjects: Planned: 36
Analyzed: 36 (Of the 39 subjects who were enrolled, 36 completed the study)

Demographics:

Male	39 (100%)
Mean Age (yrs)	33 years (range: 19 to 49 years)
Race	Caucasian (100%)

Diagnosis and Criteria for Inclusion: Healthy male subjects, aged between 18 and 50 years, with a body mass index between 18 and 30 kg/m^2, inclusive, and body weight not less than 50 kg.

Test Drugs (Batch/Lot No): Rabeprazole sodium (batch number: 9FSTR00) in combination with clopidogrel (batch number: 3345).

Dosage: 20 mg rabeprazole once daily for 7 days, in combination with 75 mg clopidogrel once daily for 7 days.

Route: Oral

Duration of Treatment: 7 days per treatment period (total of 21 days), rapeprazole taken in one Treatment Period.

Reference Therapy (Batch/Lot No): Omeprazole (batch number: KK6911) and Placebo (batch number: R14983).

Dosage: 20 mg omeprazole once daily for 7 days; placebo once daily for 7 days. Both taken in combination with 75 mg clopidogrel once daily for 7 days.

Route: Oral

Criteria for Evaluation:

Pharmacodynamics: Phosphorylated VASP, expressed as platelet reactivity index (PRI, %) calculated from the mean fluorescence intensity (MFI) of samples incubated with prostaglandin E (PGE)1 alone or with both PGE1 and adenosine diphosphate (ADP) simultaneously.
A change from baseline in PRI (delta PRI) on clopidogrel was calculated for each of the 3 treatments. The responsiveness to clopidogrel was measured with ADP-induced platelet aggregometry at 5, 10, and 20 µM concentrations for each of the 3 treatments. ADP-induced platelet aggregation variables included maximum platelet aggregation (MAP), residual platelet aggregation (RPA).

Additional (Post hoc) PD Endpoint
IPA was calculated predose and at 4 hours postdose on Day 6 and Day 7for each of the 3 treatments as follows: IPA% = [MPA (Day 1) – MPA (Day 7)]/MPA (Day 1) x 100.

Pharmacokinetics: Serial blood samples for the determination of plasma concentrations of clopidogrel, its major metabolite (carboxylic acid metabolite), and its active metabolite were collected in each treatment group. Derived PK parameters (time of maximum concentration [t_{max}], AUC_{0-24}, apparent terminal rate constant [λ_z], $t_{1/2}$ and C_{max}) for clopidorgrel and its metabolites were estimated by non-compartmental analysis at steady-state (Day 7). Blood samples for the determination of plasma concentrations of omeprazole, 5-hydroxy-omeprazole, rabeprazole and rabeprazole thioether were collected on Day 7 (at 3 hours and 4 hours) during the respective PPIs treatments.

Pharmacogenomics: Pharmacogenomic analysis for variations (**2* and **3*) in the *CYP2C19* gene on Day 1 to identify poor, intermediate and extensive metabolizers (PM, IM, EM) of CYP2C19.

Safety: Adverse events (AEs), clinical laboratory evaluations (hematology, serum chemistry, urinalysis), vital signs, 12-lead electrocardiogram (ECG), and physical examination.

Statistical Methods:

Analysis Populations

PD Population: Subjects who received study drug (including placebo) and had at least one measured concentration at a scheduled PD time point after start of dosing for at least 1 PD analyte. Subjects who were replaced were not included in this population.
Two PD populations were defined:

- Completers Population: Subjects in whom a VASP phosphorylation level was determined during the 3 treatments on Day 7, predose [primary and some secondary PD analyses].
- Good Antiplatelet Responders Population: Subjects in the Completers population who responded to clopidogrel during the clopidogrel + placebo treatment (i.e., decrease in VASP index by at least 30%) [some secondary PD analyses].

Additional (Post hoc) PD Populations
In addition to the PD populations defined in the statistical analysis plan, the following PD populations were defined post hoc and used for some additional PD analyses:

- VASP Low Responder Population: Subjects in the Completers population who had a low response to clopidogrel during the clopidogrel + placebo treatment based on delta PRI. VASP Low Responders were defined as subjects in whom the VASP index on Day 7 (predose) relative to Day 1 was decreased by less than 30%.
- IPA Responder Population: Subjects in the Completers population who responded to clopidogrel during the clopidogrel + placebo treatment based on IPA. IPA Responders were defined as subjects in whom the IPA on Day 7 (predose) relative to Day 1 was increased by at least 30%.
- IPA Low Responder Population: Subjects in the Completers population who had a low response to clopidogrel during the clopidogrel + placebo treatment based on IPA. IPA Low Responders were defined as subjects in whom the IPA on Day 7 (predose) relative to Day 1 was increased by less than

30%.

PK Population: Subjects who completed the study and received study drug (including placebo), and had at least 1 measured concentration at a scheduled PK time point after start of dosing for at least 1 PK analyte [all PK summaries].

Safety Population: Subjects who received at least 1 dose of study drug [demographic and safety summaries].

Pharmacodynamic Analysis: Individual PRI, delta PRI, and ADP-induced aggregation data were summarized using descriptive statistics. For all primary and secondary comparisons, linear mixed effect models was fitted by hour to the delta PRI data as the dependent variable, and sequence, treatment, and period as fixed effects and subject as a random effect. Using the least-squares (LS) means and estimated intra-subject variance, 90% confidence intervals (CIs) were calculated for the difference in means between rabeprazole versus placebo. For the primary comparison only, non-inferiority was concluded if the upper limit of the 90% CIs fell below 10%. This non-inferiority limit was chosen because it represented the difference between omeprazole and placebo (10.7% in absolute value, 13.4% in relative value) which prompted the Food and Drug Administration's and the Agence Francaise de Securite Sanitaire des Produits de Sante's warnings on PPIs interaction with clopidogrel.

Additional (Post hoc) PD Analyses

Additionally, the following additional analyses were performed:
A linear mixed effects model with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect was performed by genotype. Statistical comparisons of the relative change in VASP PRI (delta PRI) were performed in the Completers and VASP Responder populations. In addition these comparisons were performed in the VASP Low Responders population which was defined post hoc.

A linear mixed effects model with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect was performed by genotype. Statistical comparisons of the IPA induced by 10 and 20 μM ADP, were performed in the Completers and VASP Responder populations. In addition, these comparisons were performed in the VASP Low Responders, IPA Responders, and IPA Low Responders populations which were defined post hoc.

A linear mixed effects model with sequence, period, genotype, treatment, and treatment by genotype interaction as fixed effects and subject nested within sequence as a random effect was performed by treatment. Statistical comparisons of the IM and EM groups were performed for the relative change in VASP PRI (delta PRI) in the Completers population. These comparisons were performed using the IPA variable induced by 20 μM ADP in the Completers population which was defined post hoc.

Pharmacokinetic Analysis: Plasma concentration of clopidogrel and its metabolites and its derived PK parameters were listed, graphically displayed and summarized by descriptive statistics for each treatment. PPI parent and metabolite concentrations were listed and summarized by descriptive statistics, for the respective PPI treatment. A linear mixed effects model was performed to evaluate the effect of co-administration of rabeprazole and omeprazole on the primary PK parameters AUC_{0-24} and C_{max} of clopidogrel and its metabolites. These analyses were performed for clopidogrel, the active metabolite, and clopidogrel major metabolite. At the time of this report, the assay for the active metabolite of clopidogrel had been validated.

Clopidogrel Additional (Post hoc) PK Analyses

In addition to what was specified in the protocol, similar analyses were performed in the CYP2C19 EM and IM groups separately. The IM and EM groups were also compared by treatment with results based on linear mixed effects model with fixed effects for sequence, period, predictive CYP2C19 phenotype, treatment by treatment interaction and subject nested within sequence as a random effect.

PPI PK Analysis

Plasma concentrations of omeprazole, 5-hydroxy-omeprazole, rabeprazole, and rabeprazole thioether on Day 7

were measured to verify proton pump inhibitor (PPI) exposure during the 2 PPI Study Periods. For each PPI, sampling was done 3 and 4 hours postdose. These data were summarized using descriptive statistics.

PK-PD Relationship:

Additional (Post hoc) PK/PD Analyses

Additional analyses were performed to assess the relationship between delta PRI and key PK parameters for clopidogrel and its metabolites (AUC_{0-24} and C_{max}) in the Completers population. Estimates were based on a random intercepts model predicting delta PRI from each PK parameter with the predose delta PRI value as a covariate.

Pharmacogenomic Analysis: The influence of CYP2C19 polymorphism on clopidogrel PD and PK responses was explored by comparing EM (CYP2C19 homozygotes *1/*1) to IM (CYP2C19 heterozygotes *1/*2 or *1/*3).

Safety Analysis: Safety parameters were summarized with descriptive statistics where appropriate.

SUMMARY – CONCLUSIONS:

RESULTS:

PHARMACODYNAMIC RESULTS

Primary Pharmacodynamic Analysis

Platelet Reactivity in Completers

The administration of rabeprazole + clopidogrel in the population of Completers resulted in a mean increase in delta PRI of 0.4% with a 90% CI for mean difference in LS means ranging from -3.1% to 3.8% compared to clopidogrel + placebo. The administration of omeprazole + clopidogrel in this same population resulted in a mean increase in delta PRI of 2.0% with a 90% CI for mean difference in LS means ranging from -1.5% to 5.5% compared to clopidogrel + placebo. Neither of these treatment differences exceeded the 10% non-inferiority criterion based on the upper bounds of the 90% CI. In all the following tables, Treatment A = 20 mg rabeprazole + 75 mg clopidogrel, Treatment B = 20 mg omeprazole + 75 mg clopidogrel, and Treatment C = placebo + 75 mg clopidogrel.

Statistical Comparison of the Relative Change in VASP Platelet Reactivity Index (delta PRI [%]) on Day 7 by Treatment – Completers

			Pairwise Comparisons		
Treatment*	**N**	**LS Mean (95% CI)**	**Pair**	**Difference**	**90% CI**
A	36	-32.1 (-38.8, -25.5)	A-B	-1.6	(-5.1, 1.8)
B	36	-30.5 (-37.5, -23.9)	A-C	0.4	(-3.1, 3.8)
C	36	-32.5 (-39.2, -25.9)	B-C	2.0	(-1.5, 5.5)

Note: delta PRI = [Day 7 - Day 1/Day 1]*100. LS = Least-squares; CI = Confidence interval. Results based on linear mixed effects model with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect.
*Treatment A = 20 mg rabeprazole + 75 mg clopidogrel; Treatment B = 20 mg omeprazole + 75 mg clopidogrel
Treatment C = Placebo + 75 mg clopidogrel.

Subjects classified as EM had greater reductions in PRI in response to clopidogrel than IM subjects. The decreased response following concomitant PPI administration was more evident in EM subjects than IM subjects. In both CYP2C19 phenotype populations, the effect of omeprazole tended to be greater than rabeprazole, however, there were no statistical differences across treatments within CYP2C19 phenotypes. The following table summarizes these data.

Statistical Comparison of the Relative Change in VASP Platelet Reactivity Index (delta PRI [%]) on Day 7 by CYP2C19 Phenotype and Treatment – Completers

Phenotype	Treatment*	N	LS Mean (95% CI)	Pairwise Comparison		
				Pair	Difference	90% CI
EM	A	23	-38.5 (-47.4, -29.7)	A-B	-2.4	(-6.9, 2.1)
	B	23	-36.1 (-45.0, -27.3)	A-C	1.5	(-3.0, 6.1)
	C	23	-40.0 (-48.9, -31.2)	B-C	3.9	(-0.6, 8.4)
IM	A	12	-21.8 (-32.8, -10.7)	A-B	-1.4	(-6.5, 3.8)
	B	12	-20.4 (-31.5, -9.3)	A-C	0.3	(-5.0, 5.5)
	C	12	-22.0 (-33.1, -10.9)	B-C	1.6	(-3.6, 6.9)

Note: delta PRI = [Day 7 - Day 1/Day 1]*100. LS = Least-squares; CI = Confidence interval; EM = Extensive metabolizer (*1/*1). IM = Intermediate metabolizer (*1/*2). Results based on linear mixed effects model with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect.
*Treatment A = 20 mg rabeprazole + 75 mg clopidogrel; Treatment B = 20 mg omeprazole + 75 mg clopidogrel.
Treatment C = Placebo + 75 mg clopidogrel.

Secondary Pharmacodynamic Analyses

Platelet Reactivity in VASP Good Antiplatelet Responders

The administration of omeprazole + clopidogrel in the VASP Good Antiplatelet Responder population (subjects having greater than a 30% decrease from baseline in PRI in the clopidogrel + placebo Treatment Period) resulted in a mean increase in delta PRI of 7.5% with a 90% CI for mean difference in LS means ranging from 2.5% to 12.6% compared to clopidogrel + placebo. This exceeded the 10% non-inferiority criteria based on the upper bounds of the 90% CI and demonstrated an adequate level of sensitivity to detect drug induced changes in platelet aggregation in the VASP Good Antiplatelet Responder population. The administration of rabeprazole + clopidogrel in the VASP Good Antiplatelet Responder population resulted in a mean increase in delta PRI of 3.4% with a 90% CI for mean difference in LS means ranging from -1.7% to 8.5% compared to clopidogrel + placebo. This value does not exceed the 10% non-inferiority criterion based on the upper bounds of the 90% CI. Therefore, in this subset of subjects, rabeprazole but not omeprazole was shown to be not inferior to placebo. The following table summarizes these data.

Statistical Comparison of the Relative Change in VASP Platelet Reactivity Index (delta PRI [%]) on Day 7 by Treatment –VASP Good Antiplatelet Responders

Treatment*	N	LS Mean (95% CI)	Pairwise Comparisons		
			Pair	Difference	90% CI
A	18	-47.3 (-52.5, -42.1)	A-B	-4.1	(-9.2, 1.0)
B	18	-43.2 (-48.4, -38.0)	A-C	3.4	(-1.7, 8.5)
C	18	-50.7 (-55.9, -45.6)	B-C	7.5	(2.5, 12.6)

Note: delta PRI = [Day 7 - Day 1/Day 1]*100. LS = least-squares; CI = confidence interval.
Results based on linear mixed effects model with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect.
*Treatment A = 20 mg rabeprazole + 75 mg clopidogrel; Treatment B = 20 mg omeprazole + 75 mg clopidogrel.
Treatment C = Placebo + 75 mg clopidogrel.

All but 3 of the VASP Good Antiplatelet Responders were classified as EM. As a result, the responses observed in the subset of VASP Good Antiplatelet Responders classified as EM were similar to the overall VASP Good Antiplatelet Responder population. Two VASP Good Antiplatelet Responders became Low Responders when omeprazole was combined with clopidogrel and one VASP Good Antiplatelet Responder became a Low Responder when rabeprazole was combined with clopidogrel.

Inhibition of Platelet Aggregation (IPA) induced by 20 µM ADP – Completers

Based on the secondary endpoint of IPA induced by 20 µM ADP, the addition of rabeprazole to clopidogrel had a minimal effect on platelet aggregation when compared to clopidogrel + placebo. The lower bounds of the 95% CI for the LS mean IPA value observed in the rabeprazole group did not fall below the responder threshold defined as at least 30% IPA. In the omeprazole group, the lower bounds of the 95% CI for the LS mean IPA value observed in the omeprazole group did fall below the responder threshold defined as at least a 30% IPA.

Statistical Comparison of IPA Induced by 20 µM ADP on Day 7 by Treatment – Completers

			Pairwise Comparisons		
Treatment*	**N**	**LS Mean (95% CI)**	**Pair**	**Difference**	**90% CI**
A	36	39.4 (32.4, 46.4)	A-B	4.3	(-0.1, 8.8)
B	36	35.1 (28.1, 42.1)	A-C	-0.8	(-5.3, 3.7)
C	35	40.2 (33.1, 47.2)	B-C	-5.1	(-9.6, -0.6)

LS = Least-squares; CI = Confidence interval.
Results based on linear mixed effects model with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect.
*Treatment A = 20 mg rabeprazole + 75 mg clopidogrel; Treatment B = 20 mg omeprazole + 75 mg clopidogrel.
Treatment C = Placebo + 75 mg clopidogrel.

When IPA induced by 20 µM ADP in Completers was examined by CYP2C19 phenotype, subjects classified as EM had greater levels of platelet inhibition in response to clopidogrel compared to subjects classified as IM. The lower bounds of the 95% CI for the LS mean IPA value observed in EMs did not fall below the responder threshold defined as at least a 30% IPA in any treatment group. In IMs, the lower bounds of the 95% CI for the LS mean IPA value fell below the responder threshold defined as at least a 30% IPA for each treatment group.

Statistical Comparison of IPA induced by 20 µM ADP on Day 7 by CYP2C19 Phenotype and Treatment – Completers

				Pairwise Comparisons		
Phenotype	**Treatment***	**N**	**LS Mean (95% CI)**	**Pair**	**Difference**	**90% CI**
EM	A	23	45.7 (37.3, 54.1)	A-B	4.3	(-1.3, 9.9)
	B	23	41.4 (33.0, 49.8)	A-C	-0.9	(-6.7, 4.9)
	C	23	46.7 (38.1, 55.2)	B-C	-5.3	(-11.0, 0.5)
IM	A	12	30.3 (15.0, 45.6)	A-B	3.9	(-4.4, 12.3)
	B	12	26.4 (11.0, 41.7)	A-C	-2.3	(-10.9, 6.2)
	C	12	32.6 (17.3, 48.0)	B-C	-6.3	(-14.8, 2.2)

LS = Least-squares; CI = Confidence interval; EM = Extensive metabolizer (*1/*1); IM = Intermediate metabolizer (*1/*2).
Results based on linear mixed effects model with sequence, period, and treatment as fixed effects and subject nested within sequence as a random effect.
*Treatment A = 20 mg rabeprazole + 75 mg clopidogrel; Treatment B = 20 mg omeprazole + 75 mg clopidogrel.
Treatment C = Placebo + 75 mg clopidogrel.

PHARMACOKINETIC RESULTS

Clopidogrel

Co-administration of omeprazole or rabeprazole did not impact the overall exposure (AUC_{0-24}) to clopidogrel. The 90% CIs for the ratios of mean AUC_{0-24} for both treatments fell within the 80% to 125% bioequivalence limits. The clopidogrel peak plasma concentrations (C_{max}) decreased with co-administration of omeprazole and rabeprazole by approximately 7% and 14%, respectively. The 90% CI for the ratio of mean C_{max} fell within the bioequivalence range of 80% to 125% for omeprazole (90% CI : 81.56% to 106.48%) while the 90% CI for the

ratio of mean C_{max} fell outside the 80% to 125% bioequivalence range for rabeprazole (90% CI: 75.10% to 98.04%).

Plasma exposure to clopidogrel in subjects classified as CYP2C19 EM was somewhat higher compared to IM, in all treatment groups. Compared with the clopidogrel + placebo treatment, the addition of omeprazole and rabeprazole reduced overall clopidogrel exposure (AUC_{0-24}) and maximum clopidogrel exposure (C_{max}) in subjects classified as CYP2C19 IM. In CYP2C19 EM, co-administration of omeprazole or rabeprazole did not impact the AUC_{0-24} or C_{max} of clopidogrel. The 90% CIs for the ratios of mean AUC_{0-24} and C_{max} for both treatments fell within the 80% to 125% bioequivalence limits.

Clopidogrel Carboxylic Acid Metabolite

Co-administration of omeprazole or rabeprazole did not impact the overall exposure (AUC_{0-24}) to clopidogrel carboxylic acid metabolite. The 90% CIs for the ratios of mean AUC_{0-24} for both treatments fell within the 80% to 125% bioequivalence limits.

Co-administration of omeprazole or rabeprazole reduced maximum exposure (C_{max}) to clopidogrel carboxylic acid metabolite by approximately 17% and 18%, respectively. The 90% CIs for the ratios of mean C_{max} for both treatments fell outside the 80% to 125% bioequivalence limits.

Exposure to clopidogrel carboxylic acid metabolite in subjects classified as CYP2C19 EM was similar to the overall population. In subjects classified as CYP2C19 IM, the addition of omeprazole and rabeprazole had little effect on overall clopidogrel carboxylic acid metabolite exposure (AUC_{0-24}) relative to clopidogrel + placebo. However, the addition of omeprazole and rabeprazole reduced maximum clopidogrel carboxylic acid metabolite exposure (C_{max}) in subjects classified as CYP2C19 IM relative to clopidogrel + placebo.

Clopidogrel Active Metabolite

Co-administration of omeprazole reduced clopidogrel active metabolite overall exposure (AUC_{0-24}) and maximum exposure (C_{max}) by approximately 18% and 32%, respectively. The 90% CIs for the ratios of mean AUC_{0-24} and C_{max} fell outside the 80% to 125% bioequivalence limits.

Co-administration of rabeprazole reduced clopidogrel active metabolite overall exposure (AUC_{0-24}) and maximum exposure (C_{max}) by approximately 12% and 28%, respectively. The 90% CI for the ratio of mean AUC_{0-24} fell within the bioequivalence range of 80% to 125%. The 90% CI for ratio of mean C_{max} fell outside the 80% to 125% bioequivalence limits.

This effect was to a greater extent in EM subjects than in IM subjects. Regardless of treatment, plasma exposure to the active metabolite was always lower in subjects classified as IM compared to EM.

SAFETY RESULTS

A total of 18 (46.2%) subjects experienced at least one TEAE during the study. Overall, infections and infestations (6 [15.4%] subjects), gastrointestinal disorders (5 [12.8%] subjects), and skin and subcutaneous tissue disorders (5 [12.8%] subjects) were the most frequently reported SOC. The most frequently occurring AEs were nasopharyngitis and epistaxis reported in 3 (7.7%) subjects each. The incidence of TEAEs was similar across the 3 treatments. All TEAEs were mild or moderate. One SAE (moderate arthralgia) occurred, but the subject completed the study. Three subjects withdrew from the study after Period 1 due to AEs. There were no trends or clinically relevant changes noted in mean clinical laboratory findings, vital signs, or ECG data following dosing.

CONCLUSIONS:

Pharmcodynamic

Based on VASP platelet reactivity (delta PRI) in Completers, the addition of rabeprazole or omeprazole to clopidogrel did not result in treatment differences exceeding the 10% non-inferiority criterion based on the upper bounds of the 90% CI. The study was unable to demonstrate a significant difference in clopidogrel effect on platelet reactivity in the study population mediated by exposure to rabeprazole versus omeprazole.

However, these results must be interpreted with caution in light of the fact that a lower than expected omeprazole effect on clopidogrel antiplatelet activity was also observed in this population.

Based on VASP platelet reactivity (delta PRI) in the VASP Good Antiplatelet Responders, rabeprazole but not omeprazole was shown to be non-inferior to placebo when added to clopidogrel.

The effect of rabeprazole on VASP platelet reactivity (delta PRI) was shown to be non-inferior to placebo when added to clopidogrel in either Completers or VASP Good Antiplatelet Responders, regardless of different genotype status (EM or IM) although the EM showed greater reductions in VASP platelet reactivity (delta PRI) than IM.

The effect of omeprazole on VASP platelet reactivity (delta PRI) did not meet the non-inferiority criterion versus placebo when added to clopidogrel in VASP Good Antiplatelet Responders, but was shown to be non-inferior in Completers. The effect of omeprazole tended to be greater than rabeprazole in either EM or IM populations; however, there were no statistical differences across treatments within CYP2C19 genotypes.

The responses in PM in both populations and IM in VASP Good Antiplatelet Responders were not statistically evaluated due to very small sample size.

The CYP2C19 *2 loss-of-function allele is associated with diminished effectiveness of clopidogrel. EM subjects may therefore be a suitable subset population to consider in exploring the clopidogrel/PPI drug interaction.

In the VASP Good Antiplatelet Responders, all but 3 subjects were classified as EM. In this subset of subjects, rabeprazole but not omeprazole was shown to be not inferior to placebo. Omeprazole did not meet the non-inferiority criterion in comparison with rabeprazole.

Based on the secondary endpoint of IPA induced by 20 μM ADP, the addition of rabeprazole to clopidogrel had a minimal effect on platelet aggregation when compared to clopidogrel + placebo. The lower bounds of the 90% CI for the LS mean IPA value observed in the rabeprazole group did not fall below the IPA responder threshold defined as at least a 30% increase in IPA. In the omeprazole group, the lower bounds of the 90% CI for the LS mean IPA value observed in the omeprazole group did fall below the IPA responder threshold.

Pharmacokinetic

Co-administration of omeprazole or rabeprazole with clopidogrel did not affect the overall exposure (AUC_{0-24}) of clopidogrel or its major circulating metabolite. The clopidogrel C_{max} decreased by approximately 7% and 14%, respectively, when clopidogrel was co-administered with omeprazole or rabeprazole compared to clopidogrel + placebo. The clopidogrel carboxylic acid metabolite C_{max} decreased by approximately 17% and 18%, respectively, when clopidogrel was co-administered with omeprazole or rabeprazole compared to clopidogrel + placebo.

Omeprazole administration reduced exposure to the active metabolite of clopidogrel relative to placebo and this reduction did not seem to impact the overall PD effect. Overall exposure (AUC_{0-24}) and maximum exposure (C_{max}) to the active metabolite were decreased by approximately 18% and 32%, respectively. The 90% CIs for the ratios of mean AUC_{0-24} and C_{max} fell outside the 80% to 125% bioequivalence limits.

Exposure to active metabolite of clopidogrel was reduced to a lesser extent by rabeprazole relative to placebo and this reduction did not seem to impact the overall PD effect. Overall exposure (AUC_{0-24}) and maximum exposure (C_{max}) to the active metabolite was reduced by approximately 12% and 28%, respectively. The 90% CI for the ratio of mean AUC_{0-24} fell within the bioequivalence range of 80% to 125%. The 90% CI for ratio of mean C_{max} fell outside the 80% to 125% bioequivalence limits.

These changes in plasma exposure of the active metabolite with co-administration with omeprazole or rabeprazole with clopidogrel were not associated with changes in median t_{max} and only minor change in mean $t_{1/2}$ ($t_{1/2}$ was about 1 and 2 hours longer with co-administration with omeprazole and rabeprazole, respectively).

Regardless of treatment, exposure to the active metabolite was always lower in subjects classified as the IM phenotype compared to subjects classified as the EM phenotype.

The main results of this study indicate that, under our experimental conditions:

In the study population, neither omeprazole nor rabeprazole showed significant inhibition of clopidogrel's effects on platelet aggregation as measured by the VASP assay.

In the Good Antiplatelet Responders, rabeprazole was non-inferior to placebo as related to clopidogrel antiplatelet activity, and this regardless of CYP2C19 genotypes (EM or IM).

In the Good Antiplatelet Responders, omeprazole did not meet non-inferiority criterion to placebo as related to clopidogrel antiplatelet activity. In this population, omeprazole did not meet non-inferiority to placebo in EM subjects.

The extent of the effect of PPI therapy on the antiplatelet effect of clopidogrel is greater in subjects with the EM CYP2C19 phenotype than in those with the IM CYP2C19 phenotype.

Rabeprazole decreased the clopidogrel active metabolite exposure, but this reduction did not seem to impact the overall PD effect

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