Protocol No.	CS747S-B-A4003
Title:	Phase IV, non-comparative, open label, multicenter, 28-week switching study of prasugrel maintenance dose from clopidogrel in patients with acute coronary syndrome (ACS) who underwent a percutaneous coronary intervention (PCI) in Taiwan
Study Sponsor:	DAIICHI SANKYO TAIWAN LTD. 7F.-1, No. 308, Sec. 2, Bade Road Taipei, TAIWAN, R.O.C. PPD https://www.daiichisankyo.com.tw/

Amendment History

Date	Amendment Number	Amendment Type
14 May 2018	Initial version	Not applicable
10 Jan 2019	01	Substantial

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Clinical Trial Protocol Approval

CS747S-B-A4003
Phase IV, non-comparative, open label, multicenter, 28-week switching study of prasugrel maintenance dose from clopidogrel in patients with acute coronary syndrome (ACS) who underwent a percutaneous coronary intervention (PCI) in Taiwan.

PPD
DIRECTOR OF DEVELOPMENT &
MEDICAL AFFAIRS DEPARTMENT
DAIICHI SANKYO, TAIWAN

_____ DATE

_____ SIGNATURE

PPD
DIRECTOR, MEDICAL AFFAIRS
DAIICHI SANKYO, JAPAN

_____ DATE

_____ SIGNATURE

PPD
BIOSTATISTICIAN
LINICAL

_____ DATE

_____ SIGNATURE

PPD
MEDICAL WRITER
LINICAL

_____ DATE

_____ SIGNATURE

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the package insert, and other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice E6.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.

Signature of Investigator	Date

Investigator Name (print or type)

Investigator's Title

Name of Facility

Location of Facility (City)

REASON FOR SUBSTANTIAL AMENDMENT 01

This amended study protocol is prepared with the following changes:

- To include the optional follow-up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment based on the approved reimbursement of prasugrel for 12 months by the National Health Insurance Administration (NHIA). The study was initially planned for a final Visit 5 at Week 28, and there is now an optional Visit 6 at the maximum of 12 months $P2Y_{12}$ inhibitor treatment after ACS underwent PCI(at investigators' discretion).
- To add, based on communicated usual clinical practice, the possibility of a previous new loading dose of clopidogrel before the maintenance dose clopidogrel which will be flexibly considered between 2 and 8 weeks based on investigator's previous usual practice, which in any case will be always before any study procedure and therefore before the switch to prasugrel.
- To precise the lower limits for exclusion based on hemoglobin < 10.5 g/dL or hematocrit < 30% is referred at screening, and any severe left ventricular systolic dysfunction, EF < 35% will exclude patients if within 3 months before screening or baseline.
- To reduce, based again on communicated usual clinical practice on marketed products, the need of contraception for women to one single method instead of current two to collect data as similar to real world clinical setting.
- To precise the definition of non-compliance with study drug separately by study period
- To precise ticagrelor maintenance will be dosed as bid, clopidogrel maintenance as once daily, aspirin maintenance as per day, and prasugrel as once daily.
- To precise the compliance formula to discount lost tablets but not returned.

Detailed changes are summarized in the following table:

Section	Page	Old text	New text
Heading	All	Final Version 1.0	Amendment 01, Final Version 1.0
	All	14/May/2018	10/Jan/2019
Cover	1	<<blank>>	<<New row with amendment history>>
Reason for substantial amendment 01	4	<<blank>>	<<New section with details of the substantial amendment 01>>
Summary Study design	15	28-week switching study	28 weeks (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) switching study
	15	28-WEEK SWITCHING STUDY:	28-WEEK (OPTIONALLY UP TO A MAXIMUM 12 MONTHS OF $P2Y_{12}$ INHIBITOR TREATMENT AFTER ACS UNDERWENT PCI) SWITCHING STUDY:
	15	P2Y12 reactive unit (PRU)	$P2Y_{12}$ reaction unit (PRU)
	15	PERIOD 2 (+24 weeks)	PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])

Section	Page	Old text	New text
	15	[…] to the end of the 28-week MD treatment period […]	[…] to the end of the 28-week prasugrel MD treatment, or the maximum 12-month of P2Y12 inhibitor treatment after ACS underwent PCI. […]
Summary Number of Subjects	15	200 enrolled	200 under prasugrel treatment
Summary Dose Levels	15	Prasugrel 3.75 mg	Prasugrel 3.75 mg once daily.
Summary Duration of Treatment	16	Maximum 12 months per subject	Maximum 12 months of $P2Y_{12}$ inhibitor treatment per subject
Summary Period of Evaluation	16	<<blank>>	Optional MD treatment of up to a maximum overall 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI (Period 1 of 4 weeks + Period 2 of up to a maximum overall 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
Summary Inclusion criteria	16	• clopidogrel maintenance dose (MD) of 75 mg and aspirin 81-100 mg for 4-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI • or ticagrelor MD of 90 mg bid and aspirin 81-100 mg for 2-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg and aspirin 81-100 mg for 2-4 weeks following ticagrelor LD of 180 mg at the time of PCI • or clopidogrel maintenance dose (MD) 75 mg and aspirin 81-100 mg for 4-8 weeks following ticagrelor LD of 180 mg at the time of PCI	• clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI • or ticagrelor MD of 90 mg bid and aspirin 81-100 mg per day for 1-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-4 weeks (either directly or via clopidogrel loading dose [LD] of 300 mg or 600 mg) following ticagrelor LD of 180 mg at the time of PCI • or clopidogrel maintenance dose (MD) 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following ticagrelor LD of 180 mg at the time of PCI • or based on investigator's judgement with at least 2 weeks continues use of clopidogrel MD and aspirin 81-100 mg per day before switching to prasugrel and maximum 8 weeks $P2Y_{12}$ inhibitors MD treatment (prasugrel is not allowed)

Section	Page	Old text	New text
Summary Exclusion criteria	16	(5) Subject with hemoglobin <10.5 g/dL, or hematocrit < 30%	(5) Subject with hemoglobin <10.5 g/dL, or hematocrit < 30% at screening
	16	(6) Subject with severe left ventricular systolic dysfunction, EF < 35%	(6) Subject with severe left ventricular systolic dysfunction, EF < 35% within 3 months before baseline (visit 2)
	16	(10) Female pregnant or of child bearing potential, unless she has a negative serum pregnancy test at screening and agrees to use two methods of contraception during the study	(10) Female pregnant or of child bearing potential, unless she has a negative serum pregnancy test at screening and agrees to use at least one method of contraception during the study
Summary Endpoints	17	P2Y12 reactive unit (PRU)	P2Y12 reaction unit (PRU)
	17	PERIOD 2 (+24 weeks)	PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])
Primary endpoint	17	[…] after 28-week MD treatment weeks.	[…] after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI […]
Secondary variables	18	• Minor and clinically relevant bleeding events after 28 MD treatment weeks • Major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, stent thrombosis and revascularization after 28 MD treatment weeks • All cause deaths after 28 MD treatment weeks • Adverse events after 28 MD treatment weeks	• Minor and clinically relevant bleeding events after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) • Major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, stent thrombosis and revascularization after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) • All cause deaths after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) • Adverse events after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor

Section	Page	Old text	New text
			treatment after ACS underwent PCI)
Summary Main criteria for evaluation and analysis	18	P2Y12 reactive unit (PRU)	P2Y12 reaction unit (PRU)
	18	PERIOD 2 (+24 weeks)	PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])
	19	Primary variable: Incidence of major bleeding events (non-coronary artery bypass grafting [CABG] thrombolysis in myocardial infarction (TIMI) major) after 28 MD treatment will be summarized with their corresponding 95% confidence interval, including median times to events as per Kaplan-Meier estimates.	Primary variable: Incidence of major bleeding events (non-coronary artery bypass grafting [CABG] thrombolysis in myocardial infarction (TIMI) major) after 28 MD treatment period (optionally maximum 12-month $P2Y_{12}$ inhibitor treatment period after ACS underwent PCI) will be summarized with their corresponding 95% confidence interval, including median times to events as per Kaplan-Meier estimates.
	19	Secondary variables: Incidence of events after 28 MD treatment (minor or clinically relevant bleeding events, major adverse cardiovascular events) will be summarized with their corresponding 95% confidence interval, including median times to events as per Kaplan-Meier estimates. Percentage of all cause deaths and adverse events after 28 MD treatment will be summarized with their corresponding 95% confidence interval.	Incidence of events (minor or clinically relevant bleeding events, major adverse cardiovascular events) after 28 MD treatment weeks up to maximum 12-month P2Y12 inhibitor treatment after ACS underwent PCI, based on investigator's discretion, will be summarized with their corresponding 95% confidence interval, including median times to events as per Kaplan-Meier estimates. Percentage of all cause deaths and adverse events after 28 MD treatment weeks (optionally up to a maximum 12 months of P2Y12 inhibitor treatment after ACS underwent PCI, based on investigator's discretion) will be summarized with their

Section	Page	Old text	New text
			corresponding 95% confidence interval.
Summary Study schedule and anticipated date of completion	19	May-Jul 2018: EC/IRBD/Health Authorities submission Nov 2018 – May 2020: Recruitment and treatment period Jun-Jul 2020: Database lock Oct-Nov 2020: Clinical Study Report	May-Jul 2018: EC/IRB/Health Authorities submission Nov 2018 - Aug 2020: Recruitment and treatment period Sep-Oct 2020: Database lock Jan-Feb 2021: Clinical Study Report
Table of contents	20		<<updated>>
5.2 Study rationale	27	<<blank>>	Based on investigator's discretion, the study will offer this second period until maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI to assess bleeding events, major adverse cardiovascular events (MACE), and all cause deaths.
6.1.1.1 Primary Ogjective	29	P2Y12 reactive unit (PRU)	P2Y12 reaction unit (PRU)
6.1.2 Period 2	29	6.1.2 PERIOD 2 (+24 weeks)	6.1.2 PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])
6.1.2.1 Primary objective	30	[…] to the end of the 28-week MD treatment period	[…] to the end of the 28-week MD treatment period (optional maximum 12-month $P2Y_{12}$ inhibitor treatment period after ACS underwent PCI)
6.1.2.2 Secondary objectives	30	[…] to the end of the 28-week MD treatment period	[…] to the end of the 28-week MD treatment period (optional maximum 12-month $P2Y_{12}$ inhibitor treatment period after ACS underwent PCI)
6.2.1.1 Primary Endpoint	31	P2Y12 reactive unit (PRU)	P2Y12 reaction unit (PRU)
6.2.2 Period 2	31	6.2.2 PERIOD 2 (+24 weeks)	6.2.2 PERIOD 2 (+ 24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])
6.2.2.1 Primary endpoint	31	[…] after 28-week MD treatment period	[…] after 28 MD treatment weeks or up to maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
6.2.2.2 Secondary endpoints	31	[…] after 28-week MD treatment period	[…] after 28 MD treatment weeks or up to maximum 12-month $P2Y_{12}$

Section	Page	Old text	New text
			inhibitor treatment after ACS underwent PCI)
7.1 Overall study design and plan	33	[…] 28-week	[…] 28-week (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion)
	33	(a) clopidogrel maintenance dose (MD) of 75 mg and aspirin 81-100 mg for 4-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI; or (b) ticagrelor MD of 90 mg bid and aspirin 81-100 mg for 2-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg and aspirin 81-100 mg for 2-4 weeks following ticagrelor LD of 180 mg at the time of PCI; or (c) clopidogrel maintenance dose (MD) 75 mg and aspirin 81-100 mg for 4-8 weeks following ticagrelor LD of 180 mg at the time of PCI	(a) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI; or (b) ticagrelor MD of 90 mg bid and aspirin 81-100 mg per day for 1-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-4 weeks (either directly or via clopidogrel loading dose [LD] of 300 mg or 600 mg) following ticagrelor LD of 180 mg at the time of PCI; or (c) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following ticagrelor LD of 180 mg at the time of PCI; or (d) based on investigator's judgement with at least 2 weeks continues use of clopidogrel MD and aspirin 81-100 mg per day before switching to prasugrel and maximum 8 weeks $P2Y_{12}$ inhibitors MD treatment (prasugrel is not allowed)
	33	Eligible subjects will receive open-label prasugrel MD 3.75 mg and aspirin 81-100 mg. The investigator's judgement will be followed […]	Eligible subjects will receive open-label prasugrel MD 3.75 mg once daily and aspirin 81-100 mg per day. The investigator's discretion will be followed […]
	33	After signing the study informed consent, subjects will enter a flexible screening period based on the investigator's judgement	After signing the study informed consent, subjects will enter a flexible screening period based on the investigator's discretion
	33	[…] Period 2 of +24-week prasugrel MD treatment	[…] Period 2 of +24-week prasugrel MD treatment (optionally up to a maximum 12 months of

Section	Page	Old text	New text
			$P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
	33	[…] treatment week 28 visit	[…] treatment week 28 visit (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion)
Figure 1	34		<<updated>>
7.2 Discussion of study design, including the choice of control groups	34	This trial is designed as a phase 4, multicenter, non-comparative, open label, 28-week switching study […]	This trial is designed as a phase 4, multicenter, non-comparative, open label, 28 weeks (optionally up to a maximum 12 months of P2Y12 inhibitor treatment after ACS underwent PCI) switching study […]
	34	(a) clopidogrel maintenance dose (MD) of 75 mg and aspirin 81-100 mg for 4-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI; or (b) ticagrelor MD of 90 mg bid and aspirin 81-100 mg for 2-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg and aspirin 81-100 mg for 2-4 weeks following ticagrelor LD of 180 mg at the time of PCI; or (c) clopidogrel maintenance dose (MD) 75 mg and aspirin 81-100 mg for 4-8 weeks following ticagrelor LD of 180 mg at the time of PCI	(a) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI; or (b) ticagrelor MD of 90 mg bid and aspirin 81-100 mg per day for 1-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-4 weeks (either directly or via clopidogrel loading dose [LD] of 300 mg or 600 mg) following ticagrelor LD of 180 mg at the time of PCI; or (c) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following ticagrelor LD of 180 mg at the time of PCI; or (d) based on investigator's judgement with at least 2 weeks continues use of clopidogrel MD and aspirin 81-100 mg per day before switching to prasugrel and maximum 8 weeks $P2Y_{12}$ inhibitors MD treatment (prasugrel is not allowed).
	34	The prasugrel MD dose for this study (3.75 mg)	The prasugrel MD dose for this study (3.75 mg once daily)
	34	The investigator's judgement	The investigator's discretion
	34	P2Y12 reactive unit (PRU)	P2Y12 reaction unit (PRU)

Section	Page	Old text	New text
	34	<<blank>>	Based on the investigator's discretion, patients will be offered to extend Period 2 up to maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI for an additional safety assessment of the same objectives.
	34	[…] during a longer Period 2 (+24 weeks)	[…] during a longer Period 2 (+24 weeks or optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI based on investigator's discretion).
8.0 Selection of study population	36	(a) clopidogrel maintenance dose (MD) of 75 mg and aspirin 81-100 mg for 4-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI; or (b) ticagrelor MD of 90 mg bid and aspirin 81-100 mg for 2-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg and aspirin 81-100 mg for 2-4 weeks following ticagrelor LD of 180 mg at the time of PCI; or (c) clopidogrel maintenance dose (MD) 75 mg and aspirin 81-100 mg for 4-8 weeks following ticagrelor LD of 180 mg at the time of PCI	(a) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI; or (b) ticagrelor MD of 90 mg bid and aspirin 81-100 mg per day for 1-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-4 weeks (either directly or via clopidogrel loading dose [LD] of 300 mg or 600 mg) following ticagrelor LD of 180 mg at the time of PCI; or (c) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following ticagrelor LD of 180 mg at the time of PCI; or (d) based on investigator's judgement with at least 2 weeks continues use of clopidogrel MD and aspirin 81-100 mg per day before switching to prasugrel and maximum 8 weeks $P2Y_{12}$ inhibitors MD treatment (prasugrel is not allowed).
8.1 Inclusion criteria	36	• clopidogrel maintenance dose (MD) of 75 mg and aspirin 81-100 mg for 4-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI	• clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI

Section	Page	Old text	New text
		• or ticagrelor MD of 90 mg bid and aspirin 81-100 mg for 2-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg and aspirin 81-100 mg for 2-4 weeks following ticagrelor LD of 180 mg at the time of PCI • or clopidogrel maintenance dose (MD) 75 mg and aspirin 81-100 mg for 4-8 weeks following ticagrelor LD of 180 mg at the time of PCI	• or ticagrelor MD of 90 mg bid and aspirin 81-100 mg per day for 1-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81 100 mg per day for 2-4 weeks (either directly or via clopidogrel loading dose [LD] of 300 mg or 600 mg) following ticagrelor LD of 180 mg at the time of PCI • or clopidogrel maintenance dose (MD) 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following ticagrelor LD of 180 mg at the time of PCI • or based on investigator's judgement with at least 2 weeks continues use of clopidogrel MD and aspirin 81-100 mg per day before switching to prasugrel and maximum 8 weeks $P2Y_{12}$ inhibitors MD treatment (prasugrel is not allowed)
8.2 Exclusion criteria	37	(5) Subject with hemoglobin <10.5 g/dL, or hematocrit < 30%	(5) Subject with hemoglobin <10.5 g/dL, or hematocrit < 30% at screening
	37	(6) Subject with severe left ventricular systolic dysfunction, EF < 35%	(6) Subject with severe left ventricular systolic dysfunction, EF < 35% within 3 months before baseline (visit 2)
	37	(10) Female pregnant or of child bearing potential, unless she has a negative serum pregnancy test at screening and agrees to use two methods of contraception during the study	(10) Female pregnant or of child bearing potential, unless she has a negative serum pregnancy test at screening and agrees to use at least one method of contraception during the study.
8.4 Efficacy and safety assessments	38	[…] and treatment week 28 (V5)	[…] , treatment week 28 (V5), and optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI (V6) based on investigator's discretion.
8.4.1.3	39	[…] previous clopidogrel MD 75 mg and/or ticagrelor MD 90 mg bid and aspirin 81-100 mg	[…] previous clopidogrel MD 75 mg once daily and/or ticagrelor MD 90 mg bid and aspirin 81-100 mg per day
8.4.1.6 Pregnancy test	39	[…] Blood pregnancy sampling will be obtained at screening and at visit 5 (week 28)	[…] Blood pregnancy sampling will be obtained at screening, at visit 5 (week 28), and optionally at visit 6

Section	Page	Old text	New text
			(maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) or early termination.
8.4.1.7 Procedure for clinical laboratory samples	40	[…] week 16 (visit 4) and week 28 (visit 5)	[…] week 16 (visit 4), week 28 (visit 5), optionally based on investigator's discretion at maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI (visit 6) or early termination.
	40	[…] from day 1 to week 28	[…] from day 1 to week 28 and optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
	40	P2Y12 reactive unit (PRU)	P2Y12 reaction unit (PRU)
8.4.1.8 Electrocardiogram, heart rate, blood pressure	41	[…] week 28 (V5)	[…] week 28 (visit 5), optionally based on investigator's discretion at maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI (visit 6) or early termination
8.4.1.9 Platelet function	41	P2Y12 reactive unit (PRU)	P2Y12 reaction unit (PRU)
	41	[...] clopidogrel 75 MD after 4 weeks screening	[…] clopidogrel 75 MD after maximum 4 weeks screening
8.4.2 Study procedures	44	<<blank>>	Optional treatment maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI (Visit 6, Day 365 - 28). End of Period 2 This visit is optional and will be based on investigator's discretion, and will be performed up to maximum overall 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, as the end of the Period 2. The following examinations/procedures will be performed: • Physical examination • Vital signs (including blood pressure) • Laboratory (hematology, biochemistry), serum pregnancy test (for women of childbearing potential) • Electrocardiogram • Recording of bleeding events

Section	Page	Old text	New text
			• Recording of major adverse cardiovascular events • Recording of all cause death • Recording of adverse events • Recording of concomitant medication
	45	[…] following investigators' judgement	[…] following investigators' discretion
8.4.3.1.1 Primary Variables	45	P2Y12 reactive unit (PRU)	P2Y12 reaction unit (PRU)
8.4.3.2 Period 2	46	PERIOD 2 (+24 weeks)	PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])
	46	[…] after 28-week MD treatment weeks	[…] after 28 MD treatment weeks or up to optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI.
8.4.3.2.2 Secondary variables	46	• Minor and clinically relevant bleeding events after 28 MD treatment weeks • Major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, stent thrombosis and revascularization after 28 MD treatment weeks • All cause deaths after 28 MD treatment weeks • Adverse events after 28 MD treatment weeks	• Minor and clinically relevant bleeding events after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) • Major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, stent thrombosis and revascularization after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) • All cause deaths after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) • Adverse events after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
8.5.2 Discontinuation or	47	[…] (same as for the week 28 visit, together with the platelet function tests if Visit 3 is not done) and	[…] (same as for the week 28 visit,) and determine the primary reason for the termination and where

Section	Page	Old text	New text
withdrawal of individual subjects		determine the primary reason for the termination and where possible the primary underlining reason, providing as much as detail as possible, and documenting the information on the eCRF.	possible the primary underlining reason, providing as much as detail as possible, and documenting the information on the eCRF. For subject who terminated before Visit 3, Platelet function tests have to be conducted during the early termination visit.
	47	(2) Noncompliance with investigational medicinal product (IMP) prasugrel MD + aspirin.	(2) Noncompliance with investigational medicinal product (IMP) prasugrel MD + aspirin. Period 1 compliance is defined as 80% compliance in the first 4 weeks with maximum 2 consecutive missed doses in the last week. Period 2 compliance is defined as 80% compliance in the 24 weeks (or up to 12 months, alternatively)
8.6.1 Treatment administered	48	Subjects will be treated with prasugrel 3.75 mg along with aspirin 81-100 mg during the study period.	Subjects will be treated with prasugrel 3.75 mg once daily along with aspirin 81-100 mg per day oral dose during the study period.
	48	The investigator's judgement	The investigator's discretion
8.6.2 Identify of Investigational product(s)	48	[…] The IMP will be identifiable by a unique identification number.	<<deleted>>
	48	Each card of investigational medication […]	Each box of investigational medication […]
8.6.3 Dosages and regimen	49	4 boxes of medication at Visit 3 (for 12 weeks of treatment ± 2 weeks), and the last 4 boxes of medication at Visit 4 (for 12 weeks of treatment ± 4 weeks).	4 boxes of medication at Visit 3 (for 12 weeks of treatment ± 2 weeks), 4 boxes of medication at Visit 4 (for 12 weeks of treatment ± 4 weeks), and the last 4 boxes of medication at Visit 5 (for up to maximum 12 months of treatment) for those patients proposed following investigator's discretion to the optional extension period.
	49	Subjects will be instructed to take the tablets orally per day at the same time.	Subjects will be instructed to take the tablets once daily oral dose at the same time.
	49	The investigator's judgement	The investigator's discretion
8.6.8 Treatment adherence	50	[…] At visit 3, 4, and 5	[…] At visit 3, 4, 5 and 6 (optional)
8.6.10 Drug accountability	51	[…] At visit 3, 4, and 5	[…] At visit 3, 4, 5 and 6 (optional)
	51	• Verifying that the log is completed with the drug	• Verifying that the log is completed with the drug lot/patient

Section	Page	Old text	New text
		lot/medication ID/ patient number used to document each dose.	number used to document each dose.
8.6.10 Drug accountability	51	<<compliance formula did not consider lost tablets>>	<<updated to account for lost tablets>>
9.6 Adverse event collection period	56	[…] treatment period 2 of +24 weeks	[…] treatment period 2 of +24 weeks (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
11.1.3 Efficacy analysis	60	P2Y12 reactive unit (PRU)	P2Y12 reaction unit (PRU)
	60	PERIOD 2 (+24 weeks)	PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])
	60	[…] after 28-week MD treatment	[…] after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
11.1.4.2.2	61	PERIOD 2 (+24 weeks)	PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])
	61	[…] after 28-week MD treatment	[…] after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
18.1 Schedule of Assessments	75		<<Updated>>

2.0 Summary

Name of Sponsor(s): Daiichi Sankyo Taiwan Ltd.	**Compound:** Prasugrel 3.75 mg
Title of Protocol: Phase IV, non-comparative, open label, multicenter, 28-week switching study of prasugrel maintenance dose from clopidogrel in patients with acute coronary syndrome (ACS) who underwent a percutaneous coronary intervention (PCI) in Taiwan	
Study Number: CS747S-B-A4003	**Phase:** 4
Study design: Phase IV, non-comparative, open label, multicenter, 28 weeks (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) switching study.	
28-WEEK (OPTIONALLY UP TO A MAXIMUM 12 MONTHS OF $P2Y_{12}$ INHIBITOR TREATMENT AFTER ACS UNDERWENT PCI) SWITCHING STUDY: **PERIOD 1 (4-weeks)** **Primary objective:** To assess the antiplatelet effect of prasugrel on $P2Y_{12}$ reaction unit (PRU) value assessed with VerifyNow® from baseline to the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD. **Secondary objectives:** To assess the antiplatelet effect and safety of prasugrel from baseline to the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD. The antiplatelet effect assessments will include percentage of High on-Treatment Platelet Reactivity (HTPR) and percentage of platelet inhibition. The safety assessments will include major, minor and clinically relevant bleeding events, major adverse cardiovascular events (MACE), all cause deaths and adverse events. **PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])** **Primary objective:** To assess the safety of prasugrel on major bleeding events from baseline to the end of the 28-week MD treatment period, after switching from clopidogrel MD to prasugrel MD. **Secondary objectives:** To assess the safety of prasugrel from baseline to the end of the 28-week prasugrel MD treatment, or the maximum 12-month of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI. The safety assessments will include minor and clinically relevant bleeding events, major adverse cardiovascular events (MACE), all cause deaths and adverse events.	
Exploratory objectives: Exploratory objectives will include the association CYP2C19 genotyping for subjects (targeted 100 subjects) who have signed the pharmacogenomic informed consent separately.	
Subject Population:	
Number of Subjects: 200 enrolled	**Number of sites:** Appr. 10 sites in Taiwan
Dose Levels: Prasugrel 3.75 mg once daily.	**Route of Administration:** Oral

Duration of Treatment: Maximum 12 months of $P2Y_{12}$ inhibitor treatment per subject	**Period of Evaluation:** Screening of 4 weeks MD treatment of 28 weeks (Period 1 of 4 weeks + Period 2 of additional 24 weeks) Optional MD treatment of up to a maximum overall 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI (Period 1 of 4 weeks + Period 2 of up to a maximum overall 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) Safety follow-up (patients with AEs at the last treatment)

The reference population will consist of patients with percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS).

Main Criteria for Inclusion:

(1) Subject who has provided signed informed consent.
(2) Subject of either sex aged ≥ 20 years old at the informed consent date
(3) Subject's weight of at least 50 kg at the time of screening
(4) Subject with previous diagnosis of ACS (unstable angina [UA], non-ST elevation myocardial infarction [NSTEMI], or ST elevation myocardial infarction [STEMI]) who has underwent PCI and was treated with either:
- clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI
- or ticagrelor MD of 90 mg bid and aspirin 81-100 mg per day for 1-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-4 weeks (either directly or via clopidogrel loading dose [LD] of 300 mg or 600 mg) following ticagrelor LD of 180 mg at the time of PCI
- or clopidogrel maintenance dose (MD) 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following ticagrelor LD of 180 mg at the time of PCI
- or based on investigator's judgement with at least 2 weeks continues use of clopidogrel MD and aspirin 81-100 mg per day before switching to prasugrel and maximum 8 weeks $P2Y_{12}$ inhibitors MD treatment (prasugrel is not allowed)

Main Criteria for Exclusion:

(1) Subject with active bleeding or significant increase of risk of hemorrhage such as severe hepatic insufficiency, peptic ulcer present, proliferative diabetic retinopathy, antecedents of severe systemic bleeding, gastrointestinal bleeding, macrohematuria, intraocular hemorrhage, hemorrhagic stroke, or intracranial bleeding), or other antecedents of bleeding diathesis or coagulopathy.
(2) Subject with any transient ischemic attack [TIA] within 3 months before the informed consent date, or any ischemic stroke within 3 months before the informed consent date, or any previous hemorrhagic stroke.
(3) Subject with known allergies or hypersensitivity to prasugrel, aspirin, or any of their excipients.
(4) Subject with significant hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg) at either the time of screening or baseline assessment
(5) Subject with hemoglobin <10.5 g/dL, or hematocrit < 30% at screening
(6) Subject with severe left ventricular systolic dysfunction, EF < 35% within 3 months before baseline (visit 2)
(7) Subject is under hemodialysis
(8) Subject with evidence of severe hepatic disease, or any of the following: serum alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 3 times the upper limit of normal (ULN) laboratory reference range; or bilirubin ≥ 2 times the ULN of laboratory reference range at screening.
(9) Subject with any other results of clinical laboratory tests at the time of screening that are judged by the investigator that could be detrimental to the Subject or could compromise the study

(10) Female pregnant or of child bearing potential, unless she has a negative serum pregnancy test at screening and agrees to use at least one method of contraception during the study.
(11) Subject currently enrolled in, or discontinued within the last 30 days prior to baseline from, a clinical study involving an off-label use of an investigational drug or device, or concurrently enrolled in a non-observational clinical study or any other type of medical research judged not to be scientifically or medically compatible with this study.
(12) Subject who has previously completed or withdrawn from this study.
(13) Subject with evidence of significant active neuropsychiatric disease, alcohol abuse or drug abuse, in the investigator's opinion
(14) Subject who is unreliable and unwilling to make him/herself available for the duration of the study and who will not abide by the research unit policy and procedure and study restrictions.

Endpoints

PERIOD 1 (4 weeks)

Primary endpoint:

Mean change in the $P2Y_{12}$ reaction unit (PRU) value assessed with VerifyNow® from baseline to the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD.

Secondary variables:

Efficacy (antiplatelet effect):

- Percentage of High on-Treatment Platelet Reactivity (HTPR) defined as PRU > 235.
- Percentage of platelet inhibition at the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD.

Safety:

- Major bleeding events (non-coronary artery bypass grafting [CABG] thrombolysis in myocardial infarction (TIMI) major) after 4 MD treatment weeks.
- Minor and clinically relevant bleeding events after 4 MD treatment weeks
- Major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, stent thrombosis and revascularization after 4 MD treatment weeks
- All cause deaths after 4 MD treatment weeks
- Adverse events after 4 MD treatment weeks

PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])

Primary endpoint:

Major bleeding events (non-coronary artery bypass grafting [CABG] thrombolysis in myocardial infarction (TIMI) major) after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI.)

Secondary variables:

Safety:

- Minor and clinically relevant bleeding events after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
- Major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, stent thrombosis and revascularization after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
- All cause deaths after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
- Adverse events after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)

EXPLORATORY

Association CYP2C19 genotyping for subjects (targeted 100 subjects) who have signed the pharmacogenomic informed consent form separately.

Main Criteria for Evaluation and Analysis:

PERIOD 1 (4 weeks)

Primary variable:

Mean change in the $P2Y_{12}$ reaction unit (PRU) value assessed with VerifyNow® from baseline to the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD will be analyzed with a paired t-test model. Mean changes will be presented with their corresponding 95% confidence interval.

Secondary variables:

Percentage of High on-Treatment Platelet Reactivity (HTPR) defined as PRU > 235 will be summarized with their corresponding 95% confidence interval.

Percentage of platelet inhibition at the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD will be obtained together with its 95% confidence interval.

Incidence of events after 4 MD treatment weeks (major bleeding events, minor or clinically relevant bleeding events, major adverse cardiovascular events) will be summarized with their corresponding 95% confidence interval, including median times to events as per Kaplan-Meier estimates.

Percentage of all cause deaths and adverse events after 4 MD treatment weeks will be summarized with their corresponding 95% confidence interval.

PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])

Primary variable:

Incidence of major bleeding events (non-coronary artery bypass grafting [CABG] thrombolysis in myocardial infarction (TIMI) major) after 28 MD treatment period (optionally maximum 12-month P2Y12 inhibitor treatment period after ACS underwent PCI) will be summarized with their corresponding 95% confidence interval, including median times to events as per Kaplan-Meier estimates.

Secondary variables:

Incidence of events (minor or clinically relevant bleeding events, major adverse cardiovascular events) after 28 MD treatment weeks up to maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion, will be summarized with their corresponding 95% confidence interval, including median times to events as per Kaplan-Meier estimates.

Percentage of all cause deaths and adverse events after 28 MD treatment weeks (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion) will be summarized with their corresponding 95% confidence interval.

EXPLORATORY VARIABLES

Association of primary and secondary variables with CYP2C19 genotype will be evaluated. Similar analysis to the described above may be obtained per genotype subgroups when appropriate for the size of the subgroup.

Sample size Justification: A total of 200 subjects will be enrolled to have 170 completed subjects in the study (expected drop-out rate of 15%).

The proposed total sample size of 170 completed subjects will allow to estimate a mean PRU value with a precision of around 10% and a confidence level of 95%, considering a standard deviation of 70 (Han-Young Jin, 2014).

The probability that 1 or more adverse reactions (or other events) will occur in a sample of 170 subjects with an anticipated incidence rate of 0.01 is 0.82%. So this sample achieves a power of 82% to find adverse events with incidences close to 0.01. This sample size will also permit enough power to detect a statistically significant reduction of the $P2Y_{12}$ ($\neq$ 0), considering an effect size around 0.40 (μ=30, SD=70) (Han-Young Jin, 2014), using a significance level of 0.05 and a two-sided one-sample t-test.	
Interim analysis: No interim analysis is planned; however, the Period 1 analyses (both primary and secondary) will be analyzed separately per protocol.	
Study schedule and anticipated date of completion	May-Jul 2018: EC/IRB/Health Authorities submission Nov 2018 - Aug 2020: Recruitment and treatment period Sep-Oct 2020: Database lock Jan-Feb 2021: Clinical Study Report

3.0 Table of contents

Page

4.0 List of abbreviations and definition of terms

Abbreviation	Description
ACS	Acute Coronary Syndrome
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
bid	Bis in Die (Latin: twice a day)
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Grafting
CM	Concomitant Medication
CRF/eCRF	Case Report Form / electronic CRF
CRO	Clinical Research Organization
CSR	Clinical Study Report
CVD	Cardiovascular Disease
DHM	Data Handling Manual
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EoS	End of Study Visit
FAS	Full Analysis Set
GCP	Good Clinical Practice
GP	GlycoProtein
HTPR	High on-Treatment Platelet Reactivity
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHD	Ischemic Heart Disease
IMP	Investigational Medicinal Product
INN	International Non-proprietary Name
IRB	Institutional Review Board
ISF	Investigator's Study File

Abbreviation	Description
ITT	Intention-to-Treat
KM	Kaplan and Meier
LD	Loading Dose
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MD	Maintenance Dose
MI	Myocardial Infarction
NHI	National Health Insurance
NSTEMI	Non-ST Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PI	Package Insert
POC	Point Of Care
PP	Per-Protocol
PRU	$P2Y_{12}$ Reaction Unit
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
STEMI	ST Elevation Myocardial Infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TIA	Transient Ischemic Attack
TIMI	Thrombolysis In Myocardial Infarction
ULN	Upper Limit of Normality
WHO	World Health Organization

5.0 Introduction

5.1. Background

Cardiovascular diseases (CVD) are the leading cause of death in the Western world[1-3]. The global number of deaths from CVD has increased during the past decade by 12.5%, with CVD now accounting for approximately one third of all deaths globally[2]. Ischemic heart disease (IHD) is the leading component of the global CVD burden, followed by stroke and heart failure.

Platelets are an essential component of blood coagulation and are responsible for maintaining primary hemostasis under conditions of blood flow. When an arterial blood vessel is injured, platelets adhere to and aggregate at the vessel wall to initiate primary hemostasis as well as promoting secondary hemostasis to stop bleeding[4]. In dysfunctional blood vessels (due to plaque formation, inflammation, or lipid deposition), however, platelets become activated and platelet aggregation may cause excessive thrombus formation and vascular occlusion, resulting in myocardial infarction (MI) or stroke.

Percutaneous coronary intervention (PCI), usually with stenting, has become the standard treatment for acute coronary syndromes (ACS). During this procedure, trauma commonly occurs to the arterial endothelium that, among other effects, causes the activation and aggregation of platelets. Because platelet aggregation may lead to coronary thrombosis in a patient already vulnerable to it, antiplatelet agents are essential adjunctive therapies in patients with ACS undergoing PCI[5-7]. Even though stent thrombosis is a rare event, it is a severe or fatal complication and is associated with high mortality rates[8].The goal of antiplatelet therapy is to provide maximal protection against thrombosis without increasing the risk of bleeding. Aspirin, thienopyridines, and glycoprotein (GP) IIb/IIIa inhibitors are the mainstays of antiplatelet therapy in patients undergoing PCI. Dual antiplatelet therapy consisting of aspirin and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) is state-of-the-art therapy in ACS patients undergoing PCI for prevention of ischemic adverse events[9, 10]. However, a significant proportion of patients do not respond adequately to uniform antiplatelet treatment. These ‘non-responders’ have an increased risk for stent thrombosis, stroke, and other ischemic complications.

There are several methods for platelet function testing (PFT), which differ with regard to the underlying detection principle, agonists, and sample material used for testing[4]. The VerifyNow® system (Accumetrics, Inc., San Diego, CA, USA) is one of the most user-friendly point-of-care (POC) platelet function test systems because it produces rapid results at the patient bed-site. It consists of an instrument and disposable single-use cartridges that contains the biochemical reagents, agonists and fibrinogen coated beads required to perform the specific assay[11]. After the citrated tube is inserted into the cartridge, whole blood is mixed with the platelet agonists and the fibrinogen-coated beads by the movement of an electromagnetic driven steel ball. When the antiplatelet drug does not appropriately exhibit its inhibitory effect, the platelets become activated by the specific agonist. As a result, the activated platelets bind to fibrinogen-coated beads, cause agglutination and fall out of the solution. The VerifyNow instrument measures the light absorbance through the sample 16 times per second. Both the rate and extent of platelet-induced agglutination over a fixed period of time are measured and a proprietary algorithm is used to report the values in reaction units. The VerifyNow platform has currently three types of single-

use, disposable cartridges that can be used to monitor different antiplatelet drugs: aspirin, clopidogrel and glycoprotein (GP) IIb/IIIa therapy.

5.2. Study Rationale

Prasugrel, a third-generation thienopyridine, has demonstrated a rapid and more predictable antiplatelet effect, partially overcoming the problems of poor response and delayed onset of action of Clopidogrel[12-14]. Prasugrel represents a treatment of choice for patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS)[15, 16] (Class 1 recommendation), especially in the context of STEMI, where early administration of potent antiplatelet agents, together with mechanical reperfusion therapies, have dramatically improved the outcome[17-19]. However, in the daily activity, clinicians face the decision of switching from clopidogrel to prasugrel at high risk of clinical events. Recent studies[19, 20] indicate that switching from clopidogrel to prasugrel in patients undergoing non-emergent coronary stent implantation seems to be tolerated with no overt signs of increased bleeding.

Therefore, the current study is designed to assess the efficacy of prasugrel on platelet function 4 weeks after switching from clopidogrel MD to prasugrel MD. In order to better assess the mid-term safety, the study will include a second period until 28-week MD to assess bleeding events, major adverse cardiovascular events (MACE), and all cause deaths. Based on investigator's discretion, the study will offer this second period until maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI to assess bleeding events, major adverse cardiovascular events (MACE), and all cause deaths.

6.0 Study Objectives and Endpoints

6.1. Objectives

6.1.1 PERIOD 1 (4 weeks)

6.1.1.1 Primary Objective

To assess the antiplatelet effect of prasugrel on $P2Y_{12}$ reaction unit (PRU) value assessed with VerifyNow® from baseline to the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD.

6.1.1.2 Secondary Objective(s)

To assess the antiplatelet effect and safety of prasugrel from baseline to the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD. The antiplatelet effect assessments will include percentage of High on-Treatment Platelet Reactivity (HTPR) and percentage of platelet inhibition. The safety assessments will include major, minor and clinically relevant bleeding events, major adverse cardiovascular events (MACE), all cause deaths and adverse events.

6.1.2 PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])

6.1.2.1 Primary Objective

To assess the safety of prasugrel on major bleeding events from baseline to the end of the 28-week MD treatment period (optional maximum 12-month $P2Y_{12}$ inhibitor treatment period after ACS underwent PCI), after switching from clopidogrel MD to prasugrel MD.

6.1.2.2 Secondary Objective(s)

To assess the safety of prasugrel from baseline to the end of the 28-week MD treatment period (optional maximum 12-month $P2Y_{12}$ inhibitor treatment period after ACS underwent PCI), after switching from clopidogrel MD to prasugrel MD. The safety assessments will include minor and clinically relevant bleeding events, major adverse cardiovascular events (MACE), all cause deaths and adverse events.

6.1.3 Exploratory

Exploratory objectives will include the association CYP2C19 genotyping for subjects (targeted 100 subjects) who have signed the pharmacogenomic informed consent form separately.

6.2. Endpoints

6.2.1 PERIOD 1 (4 weeks)

6.2.1.1 Primary Endpoint

The primary endpoint will be the mean change in the $P2Y_{12}$ reaction unit (PRU) value assessed with VerifyNow® from baseline to the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD.

6.2.1.2 Secondary Endpoint(s)

Efficacy (antiplatelet effect):

- Percentage of High on-Treatment Platelet Reactivity (HTPR) defined as PRU > 235.
- Percentage of platelet inhibition at the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD.

Safety: Incidence of:

- Major bleeding events (non-coronary artery bypass grafting [CABG] thrombolysis in myocardial infarction (TIMI) major) after 4 MD treatment weeks.
- Minor and clinically relevant bleeding events after 4 MD treatment weeks
- Major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, stent thrombosis and revascularization after 4 MD treatment weeks
- All cause deaths after 4 MD treatment weeks
- Adverse events after 4 MD treatment weeks

6.2.2 PERIOD 2 (+ 24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])

6.2.2.1 Primary Endpoint

The primary endpoint will be the incidence of major bleeding events (non-coronary artery bypass grafting [CABG] thrombolysis in myocardial infarction (TIMI) major) after 28 MD treatment weeks or up to maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI.

6.2.2.2 Secondary Endpoint(s)

Safety: Incidence of:

- Minor and clinically relevant bleeding events after 28 MD treatment weeks or up to maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI
- Major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, stent thrombosis and revascularization after 28 MD treatment weeks, or up to maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI

- All cause deaths after 28 MD treatment weeks or up to maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)
- Adverse events after 28 MD treatment weeks or up to maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI)

6.2.3 Exploratory Endpoint(s)

The association CYP2C19 genotyping for available subjects (targeted 100 subjects) who have signed the pharmacogenomic informed consent form separately.

7.0 Investigational Plan

7.1. Overall Study Design and Plan: Description

This phase 4 study is designed as multicenter, non-comparative, open label, 28-week (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion) switching study in subjects with a previous diagnosis of Acute Coronary Syndrome (ACS) who had underwent Percutaneous Coronary Intervention (PCI) and were treated with either (a) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI; or (b) ticagrelor MD of 90 mg bid and aspirin 81-100 mg per day for 1-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-4 weeks (either directly or via clopidogrel loading dose [LD] of 300 mg or 600 mg) following ticagrelor LD of 180 mg at the time of PCI; or (c) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following ticagrelor LD of 180 mg at the time of PCI; or (d) based on investigator's judgement with at least 2 weeks continues use of clopidogrel MD and aspirin 81-100 mg per day before switching to prasugrel and maximum 8 weeks $P2Y_{12}$ inhibitors MD treatment (prasugrel is not allowed).

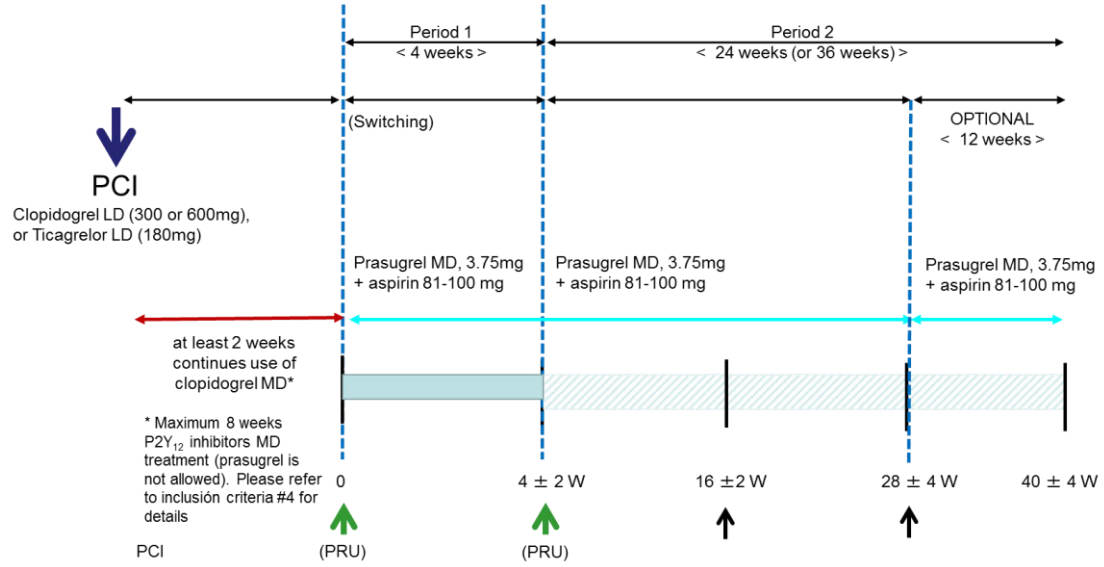
Eligible subjects will receive open-label prasugrel MD 3.75 mg once daily and aspirin 81-100 mg per day. The investigator's discretion will be followed for deciding on aspirin dosing as far as continuing the dual antiplatelet therapy (DAPT) may increase the risk of gastrointestinal bleeding; therefore adverse events management related to aspirin doses will be managed as per the investigator's criteria for this and any other criteria based on medical judgement.

After signing the study informed consent, subjects will enter a flexible screening period based on the investigator's discretion (lasting up to a maximum of 4 weeks). Key inclusion / exclusion criteria will be verified to determine subject eligibility at the screening.

There is Period 1 of 4-week prasugrel MD treatment period, starting on Day 1, followed by a Period 2 of +24-week prasugrel MD treatment (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI), and thereafter a safety follow-up for patients with AEs at the last treatment. For early termination, all the assessments of the treatment week 28 visit (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion) should be performed, if possible, including the safety follow-up for AEs at the last treatment.

A schematic of the study design is included in Figure 1 and the schedule of assessments is listed in Appendix 18.1.

Figure 1. Study figure



7.2. Discussion of Study Design, including the Choice of Control Groups

This trial is designed as a phase 4, multicenter, non-comparative, open label, 28 weeks (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) switching study in subjects with a previous diagnosis of Acute Coronary Syndrome (ACS) who had underwent Percutaneous Coronary Intervention (PCI) and were treated with either (a) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI; or (b) ticagrelor MD of 90 mg bid and aspirin 81-100 mg per day for 1-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-4 weeks (either directly or via clopidogrel loading dose [LD] of 300 mg or 600 mg) following ticagrelor LD of 180 mg at the time of PCI; or (c) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following ticagrelor LD of 180 mg at the time of PCI; or (d) based on investigator's judgement with at least 2 weeks continues use of clopidogrel MD and aspirin 81-100 mg per day before switching to prasugrel and maximum 8 weeks $P2Y_{12}$ inhibitors MD treatment (prasugrel is not allowed).

The prasugrel MD dose for this study (3.75 mg once daily) has been selected based on the package insert DSTW 201803-03, Daiichi Sankyo Taiwan Ltd. The investigator's discretion will be followed for deciding on aspirin dosing as far as continuing the dual antiplatelet therapy (DAPT) may increase the risk of gastrointestinal bleeding; therefore adverse events management related to aspirin doses will be managed as per the investigator's criteria for this and any other criteria based on medical judgement.

The $P2Y_{12}$ reaction unit (PRU) assessed with VerifyNow® has been selected for the evaluation of the study primary endpoint because this is one of the most user-friendly point-of-care (POC) platelet function test systems because it produces rapid results at the patient bed-site[(11)], and the VerifyNow platform consists on a validated tool which has currently three types of single-use,

disposable cartridges that can be used to monitor different antiplatelet drugs: aspirin, clopidogrel and glycoprotein (GP) IIb/IIIa therapy. The PRU will be assessed immediately before dosing as that will assess the steady state which is the most appropriate approach for a maintenance dose. For clopidogrel assessment, Day 1 (before prasugrel switch dosing) is selected as being the last day of clopidogrel 75 MD after 4 weeks screening (suggested test timing for clopidogrel 75 mg ≥ 6 days of maintenance)[21]. For prasugrel assessment, Week 4 is selected as being the last day of prasugrel 3.75 mg MD after 4 weeks treatment Period 1 (suggested test timing for prasugrel 5 mg ≥ 5 days on maintenance)[21].

The study has been designed with 2 periods: the first one to assess the platelet function after 4 weeks, and a longer period up to 28 weeks for a mid-term safety assessment of bleeding events, major adverse cardiovascular events (MACE), and all cause deaths. Based on the investigator's discretion, patients will be offered to extend Period 2 up to maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI for an additional safety assessment of the same objectives.

The study sample size is based on the expected PRU change from baseline after 4 weeks of treatment based on a previously published reference[22]. We consider the antiplatelet effect of prasugrel in PRU value assessed with VerifyNow® can be observed within 4 weeks which is a valid recall period, assessing other safety endpoints during a longer Period 2 (+24 weeks; or optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI based on investigator's discretion). The selected sample size will be also enough for an 82% probability that 1 or more adverse reactions (or other events) will occur with an anticipated incidence close to 0.01.

8.0 Selection of study Population

The subject population will comprise male and female subjects of any race, aged at least 20 years at screening, with a previous diagnosis of ACS, NSTEMI, STEMI or UA, a weight of at least 50 Kg at the time of screening, and having underwent PCI and previously treated with either (a) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI; or (b) ticagrelor MD of 90 mg bid and aspirin 81-100 mg per day for 1-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-4 weeks (either directly or via clopidogrel loading dose [LD] of 300 mg or 600 mg) following ticagrelor LD of 180 mg at the time of PCI; or (c) clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following ticagrelor LD of 180 mg at the time of PCI; or (d) based on investigator's judgement with at least 2 weeks continues use of clopidogrel MD and aspirin 81-100 mg per day before switching to prasugrel and maximum 8 weeks $P2Y_{12}$ inhibitors MD treatment (prasugrel is not allowed). Prior to any and all study-specific examinations, subjects will be informed as to the extent and nature of their study participation and will be given the opportunity to provide their written informed consent.

Approximately 10 active study sites in Taiwan will include a total of 200 subjects in order to have at least 170 completed subjects.

Both inclusion and exclusion criteria will be assessed during the screening period (see Section 8.1 and Section 8.2, respectively). Corresponding information should be provided in the eCRF.

8.1. Inclusion Criteria

Subjects will be eligible for inclusion into the study only if all of the following criteria are met:

(1) Subject who has provided signed informed consent.

(2) Subject of either sex aged ≥ 20 years old at the informed consent date

(3) Subject's weight of at least 50 kg at the time of screening

(4) Subject with previous diagnosis of ACS (unstable angina [UA], non-ST elevation myocardial infarction [NSTEMI], or ST elevation myocardial infarction [STEMI]) who has underwent PCI and was treated with either:

- clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following clopidogrel loading dose (LD) of 300 mg or 600 mg at the time of PCI
- or ticagrelor MD of 90 mg bid and aspirin 81-100 mg per day for 1-4 weeks and switching to clopidogrel maintenance dose (MD) of 75 mg once daily and aspirin 81-100 mg per day for 2-4 weeks (either directly or via clopidogrel loading dose [LD] of 300 mg or 600 mg) following ticagrelor LD of 180 mg at the time of PCI
- or clopidogrel maintenance dose (MD) 75 mg once daily and aspirin 81-100 mg per day for 2-8 weeks following ticagrelor LD of 180 mg at the time of PCI

- or based on investigator's judgement with at least 2 weeks continues use of clopidogrel MD and aspirin 81-100 mg per day before switching to prasugrel and maximum 8 weeks $P2Y_{12}$ inhibitors MD treatment (prasugrel is not allowed)

8.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria are met:

(1) Subject with active bleeding or significant increase of risk of hemorrhage such as severe hepatic insufficiency, peptic ulcer present, proliferative diabetic retinopathy, antecedents of severe systemic bleeding, gastrointestinal bleeding, macrohematuria, intraocular hemorrhage, hemorrhagic stroke, or intracranial bleeding), or other antecedents of bleeding diathesis or coagulopathy.

(2) Subject with any transient ischemic attack [TIA] within 3 months before the informed consent date, or any ischemic stroke within 3 months before the informed consent date, or any previous hemorrhagic stroke.

(3) Subject with known allergies or hypersensitivity to prasugrel, aspirin, or any of their excipients.

(4) Subject with significant hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg) at either the time of screening or baseline assessment

(5) Subject with hemoglobin <10.5 g/dL, or hematocrit < 30% at screening

(6) Subject with severe left ventricular systolic dysfunction, EF < 35% within 3 months before baseline (visit 2)

(7) Subject is under hemodialysis

(8) Subject with evidence of severe hepatic disease, or any of the following: serum alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 3 times the upper limit of normal (ULN) laboratory reference range; or bilirubin ≥ 2 times the ULN of laboratory reference range at screening.

(9) Subject with any other results of clinical laboratory tests at the time of screening that are judged by the investigator that could be detrimental to the Subject or could compromise the study

(10) Female pregnant or of child bearing potential, unless she has a negative serum pregnancy test at screening and agrees to use at least one method of contraception during the study.

(11) Subject currently enrolled in, or discontinued within the last 30 days prior to baseline from, a clinical study involving an off-label use of an investigational drug or device, or concurrently enrolled in a non-observational clinical study or any other type of medical research judged not to be scientifically or medically compatible with this study.

(12) Subject who has previously completed or withdrawn from this study.

(13) Subject with evidence of significant active neuropsychiatric disease, alcohol abuse or drug abuse, in the investigator's opinion

(14) Subject who is unreliable and unwilling to make him/herself available for the duration of the study and who will not abide by the research unit policy and procedure and study restrictions.

8.3. Prior and Concomitant Therapy

Any medication or therapy given in addition to the study medication is defined as concomitant medication/therapy (CM) and is to be thoroughly documented in the eCRF together with any previous medication administered within 4 weeks prior to the date of the informed consent signature until end of study. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Sponsor.

At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

To the extent possible, the dose of any CM required for chronic diseases should be kept as constant as possible throughout the study. Any changes in administration of any CM must be recorded by the investigator in the relevant eCRF page.

Subjects must be instructed to consult first with the investigator prior to take any other medication, including over-the-counter products. The investigator contact the medical monitor for questions regarding episodic use.

8.4. Efficacy and Safety Assessments / Variables

The schedule of assessments is described in the Appendix 18.1.

Subject recruitment for the study is competitive through all sites. Subject data must be entered – after written informed consent is obtained– into the eCRF system as soon as possible, including demographic data. Data/results from screening should be added upon availability.

Subjects not entered in the eCRF are not considered as enrolled in the study.

Study visits are categorized according to the following schedule: pre-treatment screening visit (V1), treatment Day 1 (V2), treatment week 4 (V3), treatment week 16 (V4), treatment week 28 (V5), and optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI (V6) based on investigator's discretion. The activities planned for all study visits are described in this section.

8.4.1 Description of study procedures

8.4.1.1 Informed Consent

Subject Informed Consent should be obtained prior to the subject entering into the study and before any study specific assessment and/or procedures are performed (see Section 12.3).

A unique subject identification number (subject number) will be assigned to each subject at the time of screening; this subject number will be used throughout the study.

8.4.1.2 Demographics

Demographic information will be collected at screening, including age, gender and race.

8.4.1.3 Medical history and previous medication

Medical history, including LD treatment during the PCI (clopidogrel LD 300 mg or 600 mg; or ticagrelor LD 180 mg), previous clopidogrel MD 75 mg once daily and/or ticagrelor MD 90 mg bid and aspirin 81-100 mg per day and stent type (BMS and/or DES), will be checked and recorded during the screening. Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that stopped at or prior to Screening (time of informed consent). Ongoing conditions are considered concurrent medical conditions.

All relevant previous medication, including all ongoing medication and medication of the last 4 weeks before screening, should be recorded in the eCRF too.

8.4.1.4 Physical examination

Complete physical examination will be performed at all study visits. Physical examinations will consist of the following body systems: (1) general appearance; (2) extremities; (3) skin; (4) head and neck; (5) eyes, ears, nose and throat; (6) lungs and chest; (7) heart/ cardiovascular; (8) neurological; (9) abdomen / gastrointestinal; (10) liver; (11) musculoskeletal; and (12) other. Each system should be assessed as normal or abnormal and in this last case if that is clinically relevant or not.

8.4.1.5 Vital signs

Vital signs (height [only once at screening], weight, BMI, heart rate and blood pressure) will be assessed at all study visits.

8.4.1.6 Pregnancy test

Blood pregnancy sampling will be obtained at screening, at visit 5 (week 28), and optionally at visit 6 (maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) or early termination.

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued and returned to the study site. In addition, any

pregnancies in the partner of a male subject during the study or for 4 weeks after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication or within 4 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form.

If the female subject, or female partner of a male subject, agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time the subject/female partner of the subject became pregnant and provide details of treatment the subject received.

All pregnancies from subjects on active study drug will be followed up to final outcome, using the pregnancy form ("EXPOSURE IN UTERO REPORTING FORM"). The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs outlined in Section 9.7.

8.4.1.7 Procedure for Clinical Laboratory Samples

Blood sampling for local assessment will be obtained at screening (visit 1), Day 1 (visit 2), week 4 (visit 3), week 16 (visit 4), week 28 (visit 5), optionally based on investigator's discretion at maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI (visit 6) or early termination. All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be provided by the site and archived in the trial master file (TMF). There is no need for fasting conditions for the analyses; but the same fasting or fed conditions should remain the same for all the blood samples obtained and analyzed at the same site for all their corresponding patients. Blood samples obtained from day 1 to week 28 and optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI will be taken before prasugrel MD + aspirin administration of each corresponding visit.

All laboratory values outside the normal range must be evaluated and assessed by the investigator for clinical relevance and in this case, they should be recorded in the eCRF as adverse events.

The clinical analyses will be performed in a local laboratory (including hematology, biochemistry and pregnancy testing). An extra blood sample will be obtained at visit 3 (week 4) once during the whole study for the pharmacogenomic central laboratory examination for patients who sign the pharmacogenomic informed consent form separately.

The following parameters will be assessed:

- Platelet function: $P2Y_{12}$ reaction unit (PRU, also to derive the platelet reactivity [HTPR]), platelet inhibition (%). (See Section 8.4.1.9)
- Hematology: White Blood Cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, Red Blood Cells (RBC), Hemoglobin, Hematocrit, Platelet Count.

- Biochemistry: Total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, LDL cholesterol. The estimated glomerular filtration rate (eGFR) will be calculated following the CKD-EPI Creatinine Equation (2009)[23, 24].

8.4.1.8 Electrocardiogram, heart rate, blood pressure

A 12-lead ECG will be performed locally at screening (visit 1), treatment week 4 (visit 3), treatment week 28 (visit 5), optionally based on investigator's discretion at maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI (visit 6) or early termination. Additional ECGs may be performed at the discretion of the investigator during any follow-up. The findings and any abnormality will be recorded in the eCRF as either medical history (findings at screening) or adverse events (any further finding or change from screening). Standard ECG parameters will be recorded in the eCRF (heart rate, RR, QT, QTc following both Bazzett's and Fridericia's methods).

8.4.1.9 Platelet function

$P2Y_{12}$ reaction unit (PRU) with the VerifyNow®, High on-treatment Platelet Reactivity (HTPR), and percentage of platelet inhibition will be assessed at Day 1 (pre-dosing) and treatment week 4 (visit 3). The PRU will be assessed immediately before dosing as that will assess the steady state which is the most appropriate approach for a maintenance dose. For clopidogrel assessment, Day 1 (before prasugrel switch dosing) is selected as being the last day of clopidogrel 75 MD after maximum 4 weeks screening (suggested test timing for clopidogrel 75 mg $\geq$ 6 days of maintenance)[21]. For prasugrel assessment, Week 4 is selected as being the last day of prasugrel 3.75 mg MD after 4 weeks treatment Period 1 (suggested test timing for prasugrel 5 mg $\geq$ 5 days on maintenance)[21].

8.4.1.10 Bleeding Events

Major, minor and clinically relevant bleeding events will be assessed at all study visits after the first prasugrel MD treatment.

8.4.1.11 All cause deaths

All cause deaths will be assessed at all study visits after the first prasugrel MD treatment.

8.4.2 Study Procedures

Screening assessments (Visit 1, Day -28 to Day -1)

Subjects will be screened for enrolment within 4 weeks prior to the start of prasugrel MD. Subjects will be screened in accordance with predefined entrance criteria as described in Sections 8.1 and 8.2. See Section 8.5.1 for the procedure for documenting screen failures.

Procedures to be completed at screening include:

- Subject information/Informed consent signed and dated.
- Demographics
- Assessment of inclusion / exclusion criteria.
- Medical history and previous medication
- Physical examination
- Vital signs (including blood pressure)
- Laboratory (hematology, biochemistry), serum pregnancy test (for women of childbearing potential)
- Electrocardiogram
- Determination of subject eligibility
- Recording of adverse events

Treatment Day 1 (Visit 2)

This visit will be performed on the 1st prasugrel MD administration (Day 1). The following examinations/procedures will be performed:

- Confirmation of inclusion / exclusion criteria.
- Confirmation of subject eligibility
- Physical examination
- Vital signs (including blood pressure)
- Laboratory (platelet function) to be done immediately before first dose of prasugrel MD + aspirin administration of Day 1
- Laboratory (hematology, biochemistry)
- Recording of bleeding events
- Recording of major adverse cardiovascular events
- Recording of all cause death
- Study drug dispensing (prasugrel 3.75 mg)
- Recording of adverse events
- Recording of concomitant medication

Treatment week 4 (Visit 3, Day 28 ± 14). End of Period 1

This visit will be performed 4 weeks after the 1st prasugrel MD administration, as the end of the Period 1. The following examinations/procedures will be performed:

- Physical examination
- Vital signs (including blood pressure)
- Laboratory (hematology, biochemistry)
- Laboratory (platelet function) to be done immediately before the daily dose of prasugrel MD + aspirin administration of Visit 3
- Blood sample for CYP2C19 genotyping (before prasugrel MD + aspirin administration of Visit 3)
- Electrocardiogram
- Recording of bleeding events
- Recording of major adverse cardiovascular events
- Recording of all cause death
- Study drug dispensing (prasugrel 3.75 mg)
- Recording of adverse events
- Recording of concomitant medication

Treatment week 16 (Visit 4, Day 112 ± 14)

This visit will be performed 16 weeks after the 1st prasugrel MD administration. The following examinations/procedures will be performed:

- Physical examination
- Vital signs (including blood pressure)
- Laboratory (hematology, biochemistry)
- Recording of bleeding events
- Recording of major adverse cardiovascular events
- Recording of all cause death
- Study drug dispensing (prasugrel 3.75 mg)
- Recording of adverse events
- Recording of concomitant medication

Treatment week 28 (Visit 5, Day 196 ± 28). End of Period 2

This visit will be performed 28 weeks after the 1st prasugrel MD administration, as the end of the Period 2. The following examinations/procedures will be performed:

- Physical examination

- Vital signs (including blood pressure)
- Laboratory (hematology, biochemistry), serum pregnancy test (for women of childbearing potential)
- Electrocardiogram
- Recording of bleeding events
- Recording of major adverse cardiovascular events
- Recording of all cause death
- Recording of adverse events
- Recording of concomitant medication

Optional treatment maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI (Visit 6, Day 365 - 28). End of Period 2

This visit is optional and will be based on investigator's discretion, and will be performed up to maximum overall 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, as the end of the Period 2. The following examinations/procedures will be performed:

- Physical examination
- Vital signs (including blood pressure)
- Laboratory (hematology, biochemistry), serum pregnancy test (for women of childbearing potential)
- Electrocardiogram
- Recording of bleeding events
- Recording of major adverse cardiovascular events
- Recording of all cause death
- Recording of adverse events
- Recording of concomitant medication

Early Termination

In case of an early termination after 1st prasugrel MD administration and before treatment at visit 5 (week 28), the same procedures planned for the treatment at visit 5 (week 28) should be performed.

Unscheduled Visit

Unscheduled visits may be arranged following investigators' discretion for adverse event findings identified either at the end of study or during the follow-up period. The examinations/procedures may include:

- Physical examination
- Vital signs
- Laboratory (hematology, biochemistry), serum pregnancy test (for women of childbearing potential)
- Electrocardiogram, heart rate, blood pressure
- Recording of adverse events
- Recording of concomitant medication

Telephone Contacts

Sites will maintain telephone contacts with subjects during the study as reminders for the study logistics, including the safety assessment during follow-up.

8.4.3 Efficacy Variables

8.4.3.1 PERIOD 1 (4 weeks)

8.4.3.1.1 Primary Variables

The primary variable will be the mean change in the $P2Y_{12}$ reaction unit (PRU) value assessed with VerifyNow® from baseline to the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD.

8.4.3.1.2 Secondary Variables

Secondary variables of the period 1 will assess both efficacy and safety:

Efficacy (antiplatelet effect):

- Percentage of High on-Treatment Platelet Reactivity (HTPR) defined as PRU > 235.
- Percentage of platelet inhibition at the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD.

Safety:

- Major bleeding events (non-coronary artery bypass grafting [CABG] thrombolysis in myocardial infarction (TIMI) major) after 4 MD treatment weeks.
- Minor and clinically relevant bleeding events after 4 MD treatment weeks.
- Major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, stent thrombosis and revascularization after 4 MD treatment weeks.

- All cause deaths after 4 MD treatment weeks.
- Adverse events after 4 MD treatment weeks.

8.4.3.2 PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])

8.4.3.2.1 Primary Variables

The primary variable will be the incidence of major bleeding events (non-coronary artery bypass grafting [CABG] thrombolysis in myocardial infarction (TIMI) major) after 28 MD treatment weeks or up to maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI.

8.4.3.2.2 Secondary Variables

Secondary variables of the period 2 will assess just safety in terms of the incidence of:

- Minor and clinically relevant bleeding events after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI).
- Major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, stent thrombosis and revascularization after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI).
- All cause deaths after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI).
- Adverse events after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI).

8.4.4 Exploratory Variables

The association CYP2C19 genotyping for available subjects (targeted 100 subjects) who have signed the pharmacogenomic informed consent form separately will be assessed as exploratory analysis.

8.5. Removal of Subjects from Therapy or Assessment

8.5.1 Screening failures

Subjects who signed the informed consent form and performed screening activities (either completely or partially) but not having started the 1st prasugrel MD treatment are considered screening failures.

If the subject is found to be not eligible at this visit, the investigator should complete the eCRF for screening visit only.

The primary reason for screen failure should be recorded in the eCRF using the following categories:

- AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal, <specify reason>.
- Study termination.
- Other, <specify reason>.

Subject numbers assigned to subjects who fail screening should not be reused.

8.5.2 Discontinuation or Withdrawal of Individual Subjects

If a subject having received the 1st prasugrel MD treatment terminates the study prematurely for any reason, all attempts should be made by the investigator to perform the procedures for the early termination visit (same as for the week 28 visit) and determine the primary reason for the termination and where possible the primary underlining reason, providing as much as detail as possible, and documenting the information on the eCRF. .

For subject who terminated before Visit 3, Platelet function tests have to be conducted during the early termination visit.

The primary reason for discontinuation or withdrawal of the subject from the study should be noted using the following categories:

(1) Adverse Event (AE). The subject has experienced an adverse event that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the adverse event or pre-treatment adverse event.

(2) Noncompliance with investigational medicinal product (IMP) prasugrel MD + aspirin.

Period 1 compliance is defined as 80% compliance in the first 4 weeks with maximum 2 consecutive missed doses in the last week.

Period 2 compliance is defined as 80% compliance in the 24 weeks (up to 12 months, alternatively)

(3) Major protocol deviation. The subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health, or a major protocol deviation occurred at the site.

(4) Withdrawal of consent. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the case report form (eCRF). Subjects may withdraw from the study at any time at their own request without giving reasons and without any disadvantageous consequences for their subsequent medical care.

(5) Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

(6) Other.

In the case of study termination by the sponsor, institutional review board (IRB), independent ethics committee (IEC), or regulatory agency, reason for withdrawal should be captured as Other, Study Termination.

If the subject is found to be pregnant during the study, the subject must be withdrawn immediately. The reason for withdrawal should be "major protocol deviation" unless there was a complication of the pregnancy which led to withdrawal, in which case the reason for withdrawal should be "adverse event(s)". The procedure is described in Section 9.7.

8.6. Treatments

8.6.1 Treatments Administered

Subjects will be treated with prasugrel 3.75 mg once daily along with aspirin 81-100 mg per day oral dose during the study period.

The investigator's discretion will be followed for deciding on aspirin dosing as far as continuing the dual antiplatelet therapy (DAPT) may increase the risk of gastrointestinal bleeding; therefore adverse events management related to aspirin doses will be managed as per the investigator's criteria for this and any other criteria based on medical judgement.

Daiichi Sankyo Taiwan Ltd. will supply the IMP consisting of:

- Prasugrel 3.75 mg tablets

8.6.2 Identity of Investigational Product(s)

Experimental treatment:

Product Name:	Prasugrel
Drug substance:	Prasugrel hydrochloride
Pharmaceutical Form:	Tablets containing prasugrel hydrochloride 3.75 mg
Administration route:	Oral use
Dosage:	Once daily administration
Manufacturer:	Daiichi Sankyo Propharma Co., Ltd.

The IMP will be supplied as two blisters included in one medication box. The supplies will contain a surplus of tablets to cover the treatment period and visit windows. The IMP should be stored at room temperature (≤ 25ºC).

Each box of investigational medication will be labelled with pertinent study information and country-specific regulatory caution statements in the country-specific language (Chinese).

8.6.3 Dosages and Regimen

Each subject who qualifies for the study will receive aspirin 81-100 mg per day and tablets of study medication: prasugrel MD 3.75 mg once daily during the study period. Subjects will receive 2 boxes of medication at Visit 2 (for 4 weeks treatment period ± 2 weeks), 4 boxes of medication at Visit 3 (for 12 weeks of treatment ± 2 weeks), 4 boxes of medication at Visit 4 (for 12 weeks of treatment ± 4 weeks), and the last 4 boxes of medication at Visit 5 (for up to maximum 12 months of treatment) for those patients proposed following investigator's discretion to the optional extension period.

Subjects will be instructed to take the tablets once daily oral dose at the same time. The first dose is to be taken the day 1 when study medication has been dispensed to the subject. Based the PRU assessment should be done immediately before the prasugrel MD + aspirin administration, the investigator will give instructions to the subject for the most appropriate timing for the daily tablets to be taken on the dates of the visits where the PRU is assessed.

The investigator's discretion will be followed for deciding on aspirin dosing as far as continuing the dual antiplatelet therapy (DAPT) may increase the risk of gastrointestinal bleeding; therefore adverse events management related to aspirin doses will be managed as per the investigator's criteria.

The investigator or designee must instruct the subject to bring each of their study medication containers (boxes) to each clinic visit, regardless of whether the study medication boxes are empty.

8.6.4 Packaging and Labelling

IMP manufacture will be performed according to Good Manufacturing Practice (GMP) standards and according to the currently valid version of the respective national laws applicable at Taipei, Taiwan. Identity and stability of the substance for the duration of the study are ensured and documented through Certificates of Analyses.

Products' labelling will show at least the following information:

- Name and address and contact phone of Sponsor and CRO.
- Trial reference code.
- Pharmaceutical dosage form, route of administration and quantity of dosage units.
- The number of the IMP, batch number and expiry date.
- The statement "for clinical trial use only".
- The statement "keep out of the reach of children".
- The medication number and the Patient Number.
- Storage conditions.
- Name, principal investigator.

If applicable, local or country specific requirements regarding labelling of the medication boxes are also to be considered.

8.6.5 Storage and Disposition of Study Drug

At each study site, the investigator is responsible for the correct storage and handling of the IMP. The IMP must be stored in a place with access limited to the investigator and/or especially authorized personnel of the local study team only, i.e. study nurse or study coordinator.

The temperature of the storage area must be monitored and documented. The investigator is required to inform the responsible monitor immediately in cases of deviation of the storage temperature from the required range (room temperature ≤ 25ºC). Furthermore adherence to the storage conditions will be checked routinely by the monitor during the on-site visits.

8.6.6 Method of Assigning Subjects to Treatment Groups

Not applicable as being a non-randomized study.

8.6.7 Blinding

Not applicable as being an open-label study.

8.6.8 Treatment Adherence

The IMP will be self-administered by the subjects as once daily oral tablets in the morning. At visit 3, 4, 5 and 6 (optional), subjects will return any empty and non-used treatments providing information to study personnel regarding their compliance with study medication. Compliance will be monitored by study personnel at the site by using the source documents and will be recorded in the eCRF.

Every visit after baseline will be used for dispensing new medication and collecting used medication in order to closely promote the treatment adherence.

8.6.9 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to the individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s).

SAEs associated with overdose should be reported according to the procedure outlined in Section 9.7.1.

In the event of drug overdose, the subject should be treated symptomatically.

8.6.10 Drug Accountability

The investigator or designee must document the receipt, dispensing, and return of IMP supplies and materials provided for this study in specific accountability forms included in the investigator's study file (ISF). The scanned copy of drug accountability forms will be retrieved from the study site by the responsible monitor, and the investigator will retain the original ones. Documentation of drug accountability for individual subjects will be captured in the eCRF.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, they should acknowledge the receipt of the shipment (by signing the packing list and faxing or emailing per instructions provided on the form). If there are any discrepancies between the packing list and the actual product received, Linical must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed with the drug lot/patient number used to document each dose.
- Verifying that all containers used/assigned are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

Residual medication (complete blisters and boxes) must be returned to the sponsor, who will be responsible for accountability and destruction. If the site is responsible for destruction, the process must be done once the accountability is verified by the study monitor. The investigator is not permitted to dispense any study medication to persons not taking part in the study. Non-used drug will be returned to the center at visits 3, 4, 5, and 6 (optional), and compliance for prasugrel will be assessed as:

$$\text{Compliance (\%)} = \frac{(\text{Tablets dispensed}) - (\text{Tablets lost}) - (\text{Tablets returned})}{\text{Total number of days between visits}} \times 100$$

9.0 Adverse Events (AEs)

9.1. Definitions

9.1.1 Adverse Event

An adverse event (AE) is defined as any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom or disease, temporally associated with the use of a medicinal product, regardless of its nature, intensity, seriousness, or presumed relationship (causality) to the product or experimental procedure used.

Adverse Events will be collected since the informed consent signature, and all adverse events which occur after the first study medication intake and within 14 days after the treatment stop date will be considered as treatment emergent adverse events (TEAEs).

Each TEAE will be evaluated for duration, intensity, and relationship to (or association with) the study treatment (or other causes). Additionally, the actions taken (e.g., administration of treatment) and the resulting outcome of the adverse event will be indicated on the eCRF. All adverse events will be followed up until resolved or as clinically required.

Only subjects with an ongoing AE at the last study visit will be followed-up for safety reasons until the event is resolved or stabilized.

Any AE, which remains unresolved after completion of the trial, requires detailed evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence is found.

If a worsening of any pathological condition that the subject had before the start of the study or medical problems that are present prior to the start of treatment but worsen during treatment occur, these must be considered as a new adverse event and will require a complete evaluation and the relevant explanation in the case report form.

9.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the event term recorded captures the change in the condition (e.g., “worsening of…”).
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g., “worsening of…”).
- If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., “worsening of…”).

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., “worsening of…”).
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., “worsening of…”).

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

9.1.3 Serious Adverse Event

Serious adverse events are defined as any untoward medical occurrence that at any dose:

- result in subject's death.
- are life-threatening.
- result in permanent or significant disability/incapacity.
- cause hospital admission or prolong hospital stay.
- result in congenital anomalies or birth defects.
- medically important condition that may jeopardize the subject or may require intervention to prevent any of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

NOTE: The term "life-threatening" in the definition of "serious" refers to any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the event as it

occurred, i.e., it does not include an event that, had it occurred in a more severe form, might have caused death.

An overnight stay in the hospital that is only due to transportation, organization or accommodation problems and without medical background does not need to be handled/documented as a SAE. Hospitalizations due to surgical procedures for pre-existing conditions that have been planned before enrolment of the subject are not considered SAEs.

9.1.4 Unexpected Adverse Event

Any adverse event, which is not described in the Reference Safety Information (RSI) of the package insert (PI) in nature, severity or frequency is unexpected. Expectedness will be assessed in relation to the RSI of the PI. For details, please check the corresponding prasugrel / aspirin package inserts.

9.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse reaction related to the treatment that is both unexpected and serious.

9.2. Adverse Event Severity

Severity of adverse events will be classified according to the following criteria:

Mild	Discomfort noted, but no disruption of normal daily activity.
Moderate	Discomfort sufficient to reduce or affect normal daily activity.
Severe	Inability to work or perform normal daily activity

9.3. Relationship to Study Drug

The causal relationship of an adverse event with the study medication will be established based on the following definitions:

Related	The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, concomitant medications). The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
Not related	The AE does not follow a reasonable temporal sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, concomitant medications).

Any subject who is withdrawn from the study because of an AE will be followed until the outcome of the event is determined, and the investigator will prepare a written summary of the event and document the available follow-up information on the eCRF.

9.4. Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

9.5. Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

9.6. Adverse Event Collection Period

Adverse events will be collected throughout the whole study period (screening of 4 weeks, treatment period 1 of 4 weeks, treatment period 2 of +24 weeks (optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI), and safety follow-up if needed).

9.7. Adverse Event Reporting

All adverse events occurring during the trial must be documented in the CRF. This applies not only to those adverse events supposedly related to the study medication, but also to any undesired experience, whether or not a causal relationship is suspected.

For this, the CRF includes a specific section for collecting information related to the adverse events. In addition, for the serious adverse events, a standard Serious Adverse Event report form will be included.

9.7.1 Serious Adverse Events

All serious adverse events will be reported by the investigator to the monitor responsible for the clinical trial or to the Pharmacovigilance Manager at Linical within 24 hours after their knowledge. A Serious Adverse Event report form, with the minimal information related to the event, should be made available to the Pharmacovigilance Manager at Linical within 24 hours:

- a serious adverse event term (verbatim)
- an identifiable reporting source (at least name, site name, address and telephone number of the reporting investigator),
- suspected investigational medicinal product,
- an identifiable subject
- criterion of seriousness of the adverse event,
- the mandatory administrative information,
- Relationship with the study drug and a posible cause for the event

LINICAL

All notifications calls will be made to Linical Safety department:

PPD

Rosa de Lima, 1-bis – EDIFICIO ALBA

28290 Las Matas (Madrid), Spain

PPD

Reporting of serious adverse events using the Serious Adverse Event report form does not exempt from the need to complete all information relating to such adverse events in the specific eCRF section.

9.7.2 Non Serious Adverse Events

Non-serious adverse events will be documented in the specific section for reporting in the eCRF that will be submitted to Daiichi Sankyo Taiwan Ltd. once the participation of the subject in the clinical trial is completed.

10.0 Protocol Deviations

10.1. Protocol Deviations

Generally, a protocol deviation is not imperative for subject withdrawal. Before the statistical analysis begins, the protocol deviations must be taken into account for the population analysis. The mandatory withdrawal reasons will be considered as major protocol deviations. Other protocol deviations will be classified as minor protocol deviations. Additionally, the following major protocol deviations will be considered:

1) Violation of one of the inclusion/exclusion criteria after enrolment into the study.
2) Treatment incorrectly administered, or overdose.

Any protocol deviation must be recorded in the eCRF.

10.2. Procedure for protocol amendments

Any amendment to this protocol involving a substantial change may be made as an amendment or addendum in writing. In order to be formalized, it is necessary to obtain the agreement of all the responsible people who signed the original protocol.

Amendments that can result in substantial changes in the original protocol must be submitted and approved by the IRB/IEC.

11.0 Statistical Methods and Determination of Sample Size

11.1. Statistical and analytical plans

The statistical analysis will be performed by the Department of Biostatistics of Linical, using SAS®[(25)] version 9.4 or later.

Statistical significance will be assessed for two-sided probability values < 0.05.

All descriptive variables will be tabulated. Quantitative variables will be described showing their number of available and missing observations, mean, median, standard deviation (SD), the range (minimum and maximum) and the first and third quartiles. Frequency and percentage will describe qualitative variables. Missing values will be tabulated with their frequency but will not be included in the calculation of percentages.

The main population for both the efficacy (antiplatelet effect) and the safety analysis will be the safety population (SAF), defined as all the subjects who have received at least one dose of study treatment. A Per Protocol (PP) population, defined as all the subjects of the safety population who do not perform any major protocol deviation

Full details of the statistical analysis will be given in a Statistical Analysis Plan (SAP) which will be prepared, approved and signed before the database closure, and so before the subjects' evaluability assessment.

Any deviation from the original SAP will be included and reported in the clinical study report (CSR).

11.1.1 Data Sets Analyzed

The safety population (SAF) will be defined as all subjects who have received at least one dose of the study treatment.

The per protocol population (PP) will be defined as all subjects in the SAF who do not experience a major protocol deviation.

11.1.2 Demographic and Other Baseline Characteristics

Baseline characteristics (gender, age, race, weight, height, body mass index, blood pressure, heart rate) for the safety population will be summarized descriptively.

Categorical data will be summarized with absolute and relative frequencies (percentage), and numerical data will be summarized with the number, mean, median, standard deviation (SD), the range (minimum and maximum), and the first and third quartiles (if applicable).

11.1.3 Efficacy Analyses

11.1.3.1 Primary Efficacy Analyses

11.1.3.1.1 PERIOD 1 (4 weeks)

Mean change in the $P2Y_{12}$ reaction unit (PRU) value assessed with VerifyNow® from baseline to the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD will be analyzed with a paired t-test model. Mean changes will be presented with their corresponding 95% confidence interval.

11.1.3.1.2 PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])

Period 2 will include just safety analyses.

11.1.3.2 Secondary Efficacy Analyses

11.1.3.2.1 PERIOD 1 (4 weeks)

Percentage of High on-Treatment Platelet Reactivity (HTPR) defined as PRU > 235 will be summarized with their corresponding 95% confidence interval.

Percentage of platelet inhibition at the end of the 4-week MD treatment period, after switching from clopidogrel MD to prasugrel MD will be obtained together with its 95% confidence interval.

11.1.3.2.2 PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])

Period 2 will include just safety analyses.

11.1.4 Safety Analyses

11.1.4.1 Primary Safety Analysis

11.1.4.1.1 PERIOD 1 (4 weeks)

Period 1 will include just efficacy analyses (antiplatelet effect) as primary endpoint.

11.1.4.1.2 PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])

Incidence of major bleeding events (non-coronary artery bypass grafting [CABG] thrombolysis in myocardial infarction (TIMI) major) after 28 MD treatment weeks (optional maximum 12-month $P2Y_{12}$ inhibitor treatment after ACS underwent PCI) will be summarized with their corresponding 95% confidence interval, including median times to events as per Kaplan-Meier estimates.

11.1.4.2 Secondary Safety Analysis

11.1.4.2.1 PERIOD 1 (4 weeks)

Incidence of events after 4 MD treatment weeks (major bleeding events, minor or clinically relevant bleeding events, major adverse cardiovascular events) will be summarized with their corresponding 95% confidence interval, including median times to events as per Kaplan-Meier estimates.

Percentage of all cause deaths and adverse events after 4 MD treatment weeks will be summarized with their corresponding 95% confidence interval.

11.1.4.2.2 PERIOD 2 (+24 weeks [optionally up to a maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI, based on investigator's discretion])

Incidence of events after 28 MD treatment (optional maximum 12-month $P2Y_{12}$ inhibitor treatment period after ACS underwent PCI) (minor or clinically relevant bleeding events, major adverse cardiovascular events, stent thrombosis and revascularization) will be summarized with their corresponding 95% confidence interval, including median times to events as per Kaplan-Meier estimates.

Percentage of all cause deaths and adverse events after 28 MD treatment (optional maximum 12-month $P2Y_{12}$ inhibitor treatment period after ACS underwent PCI) will be summarized with their corresponding 95% confidence interval.

11.1.5 Exploratory Analyses

Association of primary and secondary variables with CYP2C19 genotype will be evaluated. Similar analysis to the described above may be obtained per genotype subgroups when appropriate for the size of the subgroup.

11.1.6 Other Analyses

No other analyses are planned.

11.2. Determination of sample size

A total of 200 patients will be enrolled to have 170 completed patients in the study (expected drop-out rate of 15%).

The proposed total sample size of 170 completed patients will allow to estimate a mean PRU value with a precision of around 10% and a confidence level of 95%, considering a standard deviation of 70 (Han-Young Jin, 2014).

The probability that 1 or more adverse reactions (or other events) will occur in a sample of 170 patients with an anticipated incidence rate of 0.01 is 0.82%. So this sample achieves a power of 82% to find adverse events with incidences close to 0.01.

This sample size will also permit enough power to detect a statistically significant reduction of the $P2Y_{12}$ ($\neq 0$), considering an effect size around 0.40 (μ=30, SD=70)[22], using a significance level of 0.05 and a two-sided one-sample t-test.

11.3. Randomization Methods

Not applicable as being a non-randomized study.

11.4. Interim Analysis

No interim analysis is planned; however, the Period 1 analyses (both primary and secondary) will be analyzed once the last patient has completed the 4-week treatment period.

11.5. Handling of dropouts or missing data

As a general approach, no missing data imputation is planned for the study; however, it will be further concreted in the Statistical Analysis Plan (SAP).

11.6. Multiple Comparisons/ Multiplicity

No adjustments for multiplicity of assessments will be considered.

11.7. Examination of subgroups

No specific subgroup of patients analysis is planned; however, it will be further concrerted in the Statistical Analysis Plan (SAP).

12.0 Ethics

12.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The participating centers have their IRB/IEC (or an IRB/IEC tutoring them) established and authorized by the respective authorities, whose composition is available to them and is not shown here.

The Principal Investigator at each site is responsible for obtaining IRB/IEC approval for the final protocol, informed consent form and patient information sheet, any advertisements to recruit subjects, and documents to be handed out to the subjects at the next available meeting.

Written approval of these documents must be obtained from the committee before any subject is enrolled at a site.

When in accordance with local regulations IRB/IEC submission and interaction can be also covered by the assigned CRO.

Each investigator will also be responsible for complying with ethical standards for clinical trials as per local and European laws and regulations, during the study.

12.2. Ethical Conduct of the Study

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki (18th World Medical Assembly, 1964) and its last revision (Fortaleza, October 2013)[(26)], the ICH Harmonized Tripartite Guideline for GCP and local laws and regulations of the country where the study is performed (Taiwan).

12.3. Subject Information and Consent

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject.

It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope and possible consequences of the clinical study have been explained in a form understandable to them.

The investigator will provide the subject with an information form on the product and the study characteristics that should be read to and/or discussed with the subject in an understandable way. In this document, the subjects willing to consent to participate in this study will be informed of the nature, extent, design and conduct of the study and their consent will be obtained in writing prior to inclusion to the study schedule. Subjects will be given the opportunity to ask questions and will be informed of their right to withdraw from the study at any time, for any reason.

After reading the informed consent document, the subject must give consent in writing. The consent must be confirmed at the time of consent by the personally dated signature of the subject and the personally dated signature of the person conducting the informed consent discussions. A copy of the subject information sheet and the signed consent forms must be given to the subjects. The original signed consent will be retained in the investigator's site file.

The principal investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The investigator will not include in the study any subject without previously obtaining written consent from the subject.

12.4. Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

12.5. Insurance Policy

Daiichi Sankyo Co. Ltd. will obtain liability insurance, in accordance with the national requirements established in the laws of Taiwan, which covers health impairments resulting from medications and/or substances/investigational products administered in the course of this study for which the subject has given his/her written informed consent to participate.

13.0 Source Documents and Case Report Form Completion

13.1. Source Documents

According to the guidelines on Good Clinical Practice, the Monitors Team must check the electronic case report form (eCRF) entries against the source documents, except for the pre-identified source data directly recorded in the eCRF.

During the study, the investigator will maintain adequate records for the study, including medical records, records detailing the progress of the study for each subject, laboratory reports, eCRFs, signed informed consent forms, drug disposition records, AE reports, and information regarding subject discontinuation and completion of the study.

The Informed Consent Form will include a statement by which the subject allows the Sponsor's duly authorized personnel, the IRB/IEC, and the regulatory authorities to have direct access to source data which supports the data on the eCRF (e.g., subject's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

The process for source data verification will be documented in the monitoring plan.

13.2. Case Report Forms

The investigator must keep a written or electronic file for each subject that participates in the clinical trial. In that file, the subjects' demographic and medical data, especially: name, birthday, gender, medical history, diseases and concomitant drug, physical examination and clinical signs, observed adverse events, etc. should be recorded. It must be possible, in any moment, to identify the subject with his/her personal file. The period that the subject participates in the clinical trial must be clearly specified. The data collection will be done using the Electronic Data Capture (EDC) market leader tool from Medidata® called RAVE®. The RAVE® platform has been validated according to the highest industry standards and practices. The InForm® software uses a secure web browser to provide access to clinical study data and management of the clinical study process.

All documentation will be transcribed to an electronic CRF (eCRF). Any created documentation, especially the files that would be created by the technicians, must be filed. This includes the results of laboratory tests, ECGs, etc. These documents must be identified with the subject number, date of making and study code, in order to specify clearly the subject to whom this document belongs, and to identify the participants.

The main objective is to get the most complete files of each candidate.

Any result obtained during the study development will be reported in the subject's electronic case report form, and if it is used, the serious adverse event form must be sent to Daiichi Sankyo Taiwan Ltd.

The investigator will guarantee that all the documents sent to Daiichi Sankyo Taiwan Ltd., including the eCRF and other type of documents, do not contain any mention to the name of the subject. It is an investigator's duty to guarantee adequate filing and storage of the study documentation after the end of the study as specified in the Guidelines for Good Clinical Practice.

All the original files must be kept as much as possible following the hospital rules, research institutes or local regulation, but for at least 25 years according to the legislation in force.

All the eCRFs must be completed in its entirety. Any correction or amendment will be corrected by the investigator and the previous value recorded in the audit trail of the EDC system along with the reason and date of the change.

The eCRF is considered an official document, and it must be available for the Health Authorities.

Additional information on the data management and quality process is included in Section 13.0 and Section 15.0.

13.3. Monitoring

Representatives of Sponsor must be allowed to visit all study site locations periodically to assess the data quality and study integrity. They will review study records on site and will compare them with source documents. They will also discuss the conduct of the study with the Investigator, and will verify that the facilities remain compliant with the study requirements.

14.0 Data Quality Assurance

For the purpose of ensuring compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements, the sponsor's Quality Assurance department (or authorized representatives) may conduct on site audits of all aspects of the clinical study either during the study or after the study has been completed. The investigator/institution will permit study related monitoring, audits, IRB/IEC review and regulatory inspection(s) by providing direct access to source documents.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

As soon as the Investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate at this inspection.

The confidentiality of the data verified and the anonymity of the subjects should be respected during these inspections.

The study will be conducted with an electronic case report form with a qualified single data entry performed by the investigators with controlled and restricted access. Additional information on the data management will be provided in a specific document (Data Handling Manual [DHM]). A full data validation plan will be performed and described in this DHM which should be approved before the data entry process starts.

The database quality will be assessed before the database closure; and only when the Statistical Analysis Plan (SAP) is approved and the populations are determined, the database will be locked and moved to Statistics to perform the statistical analysis and prepare the Clinical Study Report (CSR).

Additional information on the data management process is included in Section 16.0.

15.0 Practical Issues

15.1. Early Termination of the Study

The sponsor can prematurely terminate or suspend the study. Study sites will be closed upon study completion.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance.

Reasons for discontinuation of the study may include but are not limited to the following:

- The risks and benefits of the study are re assessed.
- The incidence of AEs constitutes a potential health hazard.
- New scientific data on the investigational medication do not justify a continuation of the clinical study.
- Serious and/or persistent non adherence to the protocol, GCP, and/or applicable regulatory requirements by an investigator/institution occurs.
- Subject enrolment is unsatisfactory.
- The IRB/IEC or other regulatory authority decides to terminate or suspend approval for the investigation or investigator.

Additionally, the sponsor has the right to terminate the study for any reason at any time.

If the study is prematurely terminated or suspended for any reason, the investigator has to inform the subjects and assure appropriate follow up for the subjects. The sponsor should promptly inform the investigators or institutions and the regulatory authorities of the termination or suspension and the reasons for the termination or suspension within the timeframes referred to in applicable regulations. The IRB/IEC should also be informed promptly and provided the reasons for the termination or suspension by the sponsor or by the investigator or institution as specified by the applicable regulatory requirements.

The last visit of the last patient (LPLV) indicates the end of the study and that end of study will be communicated to the IRBs/IECs and the regulatory authorities of each participating country. Last visit of the last subject at each site/country also indicates the end of the study for that site/country.

15.2. Publication Policy

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and

review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.2.1 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Daiichi Sankyo Taiwan Ltd. will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study. Daiichi Sankyo Taiwan Ltd. contact information, along with investigator's city, and recruiting status will be registered and available for public viewing.

15.2.2 Clinical Trial Results Disclosure

Daiichi Sankyo Taiwan Ltd. will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Daiichi Sankyo Taiwan Ltd. Policy/Standard, applicable laws and/or regulations.

16.0 Data Management Procedures

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

16.1. Review and Confirmation of Case Report Forms

Electronic case report forms will be filled directly by the investigators.

Prior to obtaining the clean file, checks of consistency of inclusion/non-inclusion criteria, clinical assessment, visit dates, compliance, concomitant treatment, adverse event, withdrawal information and efficacy evaluation (antiplatelet effect) will be performed.

Data query forms will be generated to the investigator in order to clarify the data inconsistencies through the source data verification.

16.2. Database production and verification

16.2.1 Data Management Plan

A validation plan is set-up according to the protocol requirements, which describes the validation rules to be applied, in addition to the SAE reconciliation process between the clinical database and the safety database (Argus). Actions that should be taken in case of data abnormalities are detailed. In case of missing values, out of range values, data inconsistencies or values that fail logical checks, correction forms (queries) are edited and transmitted to the investigator for clarification.

16.2.2 Database

A database will be created in order to collect all clinical and other data from the clinical trial. The data management will take place at the Data Management Department of Linical.

16.2.3 Database access

Access to the database will be restricted to the investigators, data managers and clinical monitors. Any entry in the database will be traceable through its identification and date. Audit trail of data changes will be assured.

16.2.4 Quality and consistency controls

The investigators will enter the clinical data in the electronic case report form.

Prior to obtaining the clean file, checks of consistency of inclusion/exclusion criteria, clinical assessment, visit dates, compliance, concomitant treatment, adverse event, withdrawal information and efficacy evaluation (antiplatelet effect) will be performed.

16.2.5 Data queries

Data query forms will be generated to the investigator in order to clarify the data inconsistencies through the source data verification.

Only then and after all detected errors, inconsistencies or doubts cleared, will the database be declared a clean file and protected accordingly.

16.2.6 Clean File

A clean file will be created and registered, to which further changes will be disallowed. A document with the eligibility of subjects will be generated.

16.2.7 Data coding

Coding will be carried out according to standard dictionaries partly by program and then validated and completed by a medical doctor according to the Linical dictionaries. The latest available version of the following dictionaries will be used:

- Concomitant treatments: WHO DRUG
- Adverse Events: MedDRA

All case report forms and data checking records will be retained as permanent records of the study.

17.0 Reference List

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459-544. Epub 2016/10/14.
2. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. Journal of the American College of Cardiology. 2017;70(1):1-25. Epub 2017/05/22.
3. World Health Organization. Global Health Estimates 2015: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2015. Genevva: World Health Organization,; 2016. Available from: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.
4. Lenk E, Spannagl M. Platelet Function Testing-Guided Antiplatelet Therapy. Ejifcc. 2013;24(3):90-6. Epub 2013/02/01.
5. Fitzgerald DJ, Roy L, Catella F, FitzGerald GA. Platelet activation in unstable coronary disease. The New England journal of medicine. 1986;315(16):983-9. Epub 1986/10/16.
6. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (2). The New England journal of medicine. 1992;326(5):310-8. Epub 1992/01/30.
7. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). The New England journal of medicine. 1992;326(4):242-50. Epub 1992/01/23.
8. Ge J, Yu H, Li J. Acute Coronary Stent Thrombosis in Modern Era: Etiology, Treatment, and Prognosis. Cardiology. 2017;137(4):246-55. Epub 2017/05/05.
9. Damman P, van 't Hof AW, Ten Berg JM, Jukema JW, Appelman Y, Liem AH, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: comments from the Dutch ACS working group. Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2017;25(3):181-5. Epub 2016/12/15.
10. NHI - National Health Insurance Administration - Ministry of Halth and Welfare. NIH chapter 2: Cardiovascular-renal drugs. 2018 [April 2018]; Available from: https://www.nhi.gov.tw/english/.
11. Accumetrics Inc. VerifyNow-PRU Test package insert. San Diego, CA.2007.
12. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. Journal of the American College of Cardiology. 2007;49(14):1505-16. Epub 2007/04/10.
13. Armero S, Camoin Jau L, Omar Ait Mokhtar O, Mancini J, Burignat-Bonello C, Tahirou I, et al. Intra-individual variability in clopidogrel responsiveness in coronary artery disease patients under long term therapy. Platelets. 2010;21(7):503-7. Epub 2010/07/31.
14. Wallentin L, Varenhorst C, James S, Erlinge D, Braun OO, Jakubowski JA, et al. Prasugrel achieves greater and faster P2Y12receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. European heart journal. 2008;29(1):21-30. Epub 2007/12/07.
15. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial

Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European heart journal. 2014;35(37):2541-619. Epub 2014/09/01.

16. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2015;10(9):1024-94. Epub 2014/09/05.
17. De Luca G, Verdoia M, Schaffer A, Suryapranata H, Parodi G, Antoniucci D, et al. Switching from high-dose clopidogrel to prasugrel in ACS patients undergoing PCI: a single-center experience. Journal of thrombosis and thrombolysis. 2014;38(3):388-94. Epub 2014/03/25.
18. Parodi G, De Luca G, Bellandi B, Comito V, Valenti R, Marcucci R, et al. Switching from clopidogrel to prasugrel in patients having coronary stent implantation. Journal of thrombosis and thrombolysis. 2014;38(3):395-401. Epub 2014/03/25.
19. Verdoia M, Barbieri L, Suryapranata H, De Luca G. Switching from Clopidogrel to Prasugrel in patients undergoing PCI: A meta-analytic overview. Platelets. 2016;27(2):93-104. Epub 2015/05/15.
20. Rollini F, Franchi F, Angiolillo DJ. Switching P2Y12-receptor inhibitors in patients with coronary artery disease. Nature reviews Cardiology. 2016;13(1):11-27. Epub 2015/08/19.
21. Accriva Diagnostics. VerifyNow(R) System: Reference guide 2016. Available from: http://www.accriva.com/uploads/literature/mvn0005_verifynow_pocket_guide_01.pdf.
22. Jin HY, Yang TH, Choi KN, Seo JS, Jang JS, Kim DK, et al. Randomized Comparison of the Platelet Inhibitory Efficacy between Low Dose Prasugrel and Standard Dose Clopidogrel in Patients Who Underwent Percutaneous Coronary Intervention. Korean circulation journal. 2014;44(2):82-8. Epub 2014/03/22.
23. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;55(4):622-7. Epub 2010/03/27.
24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009;150(9):604-12. Epub 2009/05/06.
25. SAS Institute. Base SAS 9.4 procedures guide : statistical procedures. Fourth edition. ed2015. 559 pages p.
26. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-4. Epub 2013/10/22.

18.0 Appendices

18.1. Schedule of Assessments

Period 1 → Period 2 →

VISITS Week	V1 Screening	V2 Day 1	V3 Week 4	V4 Week 16	End of Study Early Termination[9]	
					V5 Week 28	OPTIONAL V6 Maximum 12 months of $P2Y_{12}$ inhibitor treatment after ACS underwent PCI
Study days (allowed deviation days in brackets)	**D-28 to D-1**	**D1**	**D28 (± 14)**	**D112 (± 14)**	**D196 (± 28)**	**D365 (-28)**
Informed consent	X					
Demographics	X					
Inclusion and exclusion criteria	X	X				
Medical history	X					
Physical examination	X	X	X	X	X	X
Vital signs (including blood pressure)	X	X	X	X	X	X
Pregnancy test	X				X	X
Safety laboratory tests	X	X[2]	X[2]	X[2]	X[2]	X[2]
Blood sample for CYP2C19 genotyping			X[1]			
Electrocardiogram	X		X		X	X
$P2Y_{12}$ reaction unit (PRU)		X[3]	X[4] [9]			
HTPR		X[3]	X[4] [9]			
Platelet inhibition (%)		X[3]	X[4] [9]			
Major bleeding events		X	X	X	X	X
Minor and clinically relevant bleeding events		X	X	X	X	X
Major adverse cardiovascular events (MACE)		X	X	X	X	X
All cause death		X	X	X	X	X
Prasugrel Maintenance Dose (MD) + aspirin		X	X	X	X	X
Pre-treatment adverse events[5] [6]	X	X[6]				
Treatment emergent adverse events[5] [7]		X[7]	X	X	X[8]	X[8]
Previous medication	X					
Concomitant medication		X	X	X	X	X

(1) Patients who signs the pharmacogenomic informed consent form separately will preserve a blood sample for CYP2C19 genotyping
(2) Safety lab sample to be done before prasugrel MD + aspirin administration of each corresponding visit.
(3) PRU to be done immediately before prasugrel MD + aspirin administration on Day 1
(4) PRU to be done immediately before prasugrel MD + aspirin administration on Visit 3 (Week 4)
(5) Adverse Events will be collected since the informed consent signature until last study visit
(6) Pre-treatment adverse events will be considered since signature date to the date of 1st MD prasugrel administration (until pre-dosing)
(7) Treatment emergent events will be considered since 1st MD prasugrel administration (post-dosing) until last MD prasugrel administration + 14 days
(8) Safety follow-up will be extended for patients with AEs at the last visit until the event is resolved or stabilized
(9) For subject who terminated before Visit 3, Platelet function tests have to be conducted during the early termination visit