CLINICAL STUDY REPORT

TAILORING OF PLATELET INHIBITION TO AVOID STENT THROMBOSIS

TOPAS-1
A Pharmacodynamic Phase II Study of Clopidogrel P2Y$_{12}$ Platelet Inhibition

EudraCT number:	2008-005491-27
UCR Protocol No.:	U-08-002
Investigational Product:	Clopidogrel
Sponsor:	**Uppsala Clinical Research Center (UCR)** University Hospital, SE-751 85 Uppsala, Sweden
Study initiation date:	First patient included 2009-03-03
Study completion date:	Last patient last visit 2010-03-01
Coordinating Investigator:	**Lars Wallentin**, MD, PhD Professor Cardiology UCR, University Hospital, SE-751 85 Uppsala, Sweden
Date of Report:	2011-01-13

The clinical trial was conducted, and essential documentation archived, in compliance with UCR SOPs and standards, which incorporate the requirements of the ICH Guideline for Good Clinical Practice.

SYNOPSIS

Name of Sponsor/Company: UCR, Uppsala Clinical Research Center	*(For National Authority Use only)*
Name of Finished Product: Plavix	
Name of Active Ingredient: Clopidogrel	
Title of Study: **T**ailoring **O**f **P**latelet inhibition to **A**void **S**tent thrombosis. TOPAS-1. A Pharmacodynamic Phase II Study of Clopidogrel $P2Y_{12}$ Platelet Inhibition	
Studied period (years): (date of first enrolment): 2009-03-03 (date of last completed): 2010-03-01	Phase of development: II

Objectives:

<u>The primary objective of the trial is</u>

• to establish a cut-off level of $P2Y_{12}$ inhibition measured with VerifyNow™ P2Y12 that separates patients with or without previous stent occlusion with acute clinical onset while on aspirin (Acetyl Salicylic Acid, ASA) and clopidogrel treatment within 6 months after coronary stenting for coronary artery disease.

The primary objective for the validation part in the trial is

• to verify the hypothesis that the platelet inhibitory response to clopidogrel is stable over time (in patients previously enrolled in the TABR trial)

<u>The secondary objectives in part 2 of the trial are</u>

1. to establish cut-off levels of $P2Y_{12}$ inhibition measured within 6 months after stenting for coronary artery disease with;

    • VerifyNow™ P2Y12 (PRU) in patients with experienced recurrent myocardial infarction after stenting

    • VerifyNow™ P2Y12 (PRU) in patients with experienced stent occlusion with acute clinical onset and/or recurrent myocardial infarction

    • VASP (PRI, %) in patients with experienced stent occlusion with acute clinical onset.

    • VASP (PRI, %) in patients with experienced recurrent myocardial infarction.

    • VASP (PRI, %) in patients with experienced stent occlusion with acute clinical onset and/or recurrent myocardial infarction

2. to evaluate the proportions of patients without stent thrombosis or recurrent myocardial infarction that will be above and below the established cut-off levels mentioned above

3. to analyse VerifyNow™ ASA in patients with experienced stent occlusion with acute clinical onset and/or recurrent myocardial infarction

4. to analyse biomarkers involved in coronary artery disease and the response to platelet inhibition in the study population

5. to analyse single nucleotide polymorphisms (SNP's) related to platelet function, cardiovascular risk, drug

uptake and metabolism

6. to evaluate the platelet inhibitory effect of clopidogrel in diabetic patients with acute stent occlusion and myocardial infarction

7. to evaluate angiographic predictors of stent thrombosis

Methodology:
Open, retrospective case-control trial comparing the pharmacodynamic response to clopidogrel in survivors with definite stent thrombosis or myocardial infarction (MI) on clopidogrel treatment within 6 months after coronary stenting versus matched controls without any of these events.

Number of patients (planned and analysed):A total number of 400 patients were initially planned to be enrolled (100 of them with stent thrombosis). Due to poor recruitment, a total of 156 patients were enrolled, 48 of them with stent thrombosis.

Diagnosis and main criteria for inclusion:
Stent thrombosis or myocardial infarction

Inclusion criteria:
Patient group 1 – validation part.

Patients fulfil inclusion criteria if they provide signed informed consent and have previously been randomised to clopidogrel treatment in the TABR study.

Patient groups 2 and 3

Patients must fulfil the following inclusion criteria to be included:

1. Provide signed written informed consent.
2. Male or female patients above 18 years old.
3. Previous PCI and coronary stenting for coronary artery disease
4. Previous (after coronary stenting) or current dual antiplatelet treatment (ASA 75 mg once daily (o.d) and clopidogrel 75 mg o.d). All patients need to be on treatment with ASA 75 mg once daily at least seven days prior to enrollment.

and experienced one of the following alternatives:

5. a) Stent thrombosis within 6 months of PCI while on dual antiplatelet treatment.

or

b) Experienced MI within 6 month after coronary stenting while on dual antiplatelet treatment.

or

c) No experience of stent thrombosis or MI for at least 6 months and until visit 1 (matched control)

Test product, dose and mode of administration, batch number:
Plavix 600 mg

Duration of treatment: One single oral loading dose of 600 mg clopidogrel if patient not on daily maintenance dose of clopidogrel 75 mg.

Reference therapy, dose and mode of administration, batch number: Not applicable.

Criteria for evaluation:
Efficacy:
Pharmacodynamic assessment of platelet activity with vasodilator-stimulated phosphoprotein (VASP) and point-of-care testing with Verify*Now*® P2Y12.

Safety:
SAE and AE reporting from informed consent until the last study visit.

Statistical methods:

The primary objective was addressed by defining a cut-off level of the primary variable below which no more than 10 % of the patients with definite stent thrombosis are found. This was performed by presenting the one-sided 95 % confidence limit for the 10th percentile of the distribution. The confidence interval was calculated by using bootstrapping method.

The secondary objectives concerning evaluation of the cut-off levels for the measures with VASP and for the measurements of platelet inhibition with VerifyNow™ were performed by calculating the one-sided 95% confidence limit for 10^{th} percentile and one-sided 95% confidence limit for the 30^{th} percentile. The groups of patients evaluated were those with acute clinical onset of definite stent thrombosis and patients with the recurrent myocardial infarction.

Analyses using receiver-operation characteristic (ROC) curves were used to examine the predicted abilities of the VASP and VerifyNow™ P2Y12 assays. The optimal cut-off was defined as the value corresponding to the Youden index of the ROC curve.

The sensitivity, specificity, positive predicated values (PPV) and negative predicted values (NPV) were calculated based on cut-off levels.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:
The mean $P2Y_{12}$ reaction units (PRU) was higher (246.8 ± 75.9 vs. 200.0 ± 82.7, p=0.001) in ST patients compared to controls. The cut-off level defined as the proportion of controls below the 10^{th} percentile of $P2Y_{12}$ inhibition distribution in patients with ST was ≥123 PRU. The optimal cut-off for ST was ≥222 PRU (area under the curve 0.69, p<0.0001) in a receiver operating characteristics (ROC) analysis, which was identical to the cut-off level defined as the proportion of controls below the 30^{th} percentile of $P2Y_{12}$ inhibition distribution in patients with ST. The cut-off level resulted in 70.2% sensitivity and 67.3% specificity. There was no significant difference in mean PRU but a higher device-reported % inhibition (45.1 ± 23.8 vs 32.1 ± 23.2, p=0.04) in patients with MI compared to controls. Results with the VASP-P assay were not related to the occurrence of ST or MI.

SAFETY RESULTS:
Clopidogrel and ASA were both well tolerated in all treatment groups with a limited number of expected side-effetcs.

CONCLUSION:
Stent thrombosis was associated with high on-clopidogrel platelet reactivity measured with Verify*Now*™. Spontaneous MI in stented patients on clopidogrel treatment was not. There was, however, a substantial overlap in clopidogrel platelet reactivity response between patients with and without on-treatment ST.

Date of the report: 13 January 2011