CLINICAL STUDY PROTOCOL

A PHASE 1 OPEN LABEL, RANDOMIZED, TWO-PERIOD, SINGLE AND MULTIPLE-DOSE, SAFETY, TOLERABILITY, PHARMACOKINETIC AND PHARMACODYNAMIC, STUDY OF AT-10 IN HEALTHY HUMAN SUBJECTS CONSIDERED AS EXTENSIVE AND POOR METABOLIZERS OF CYP2C19 BASED ON GENOTYPING

Protocol Number: CBCC/2019/003

Version: 1.0 (Amendment 3.0), 22/Apr/2021

SPONSOR	**CONTRACT RESEARCH ORGANIZATION**
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This study will be conducted in compliance with the Protocol, Good Clinical Practice (GCP) as set forth in the International Council on Harmonization (ICH) guidelines on GCP (ICH E6-R2) and applicable local regulatory requirements.	

1. STUDY INFORMATION

1.1. STUDY CONTACT INFORMATION DETAILS

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1.2. PROTOCOL SIGNATURE PAGE-SPONSOR

Protocol Title: A Phase 1 Open Label, Randomized, Two-Period, Single and Multiple-Dose, Safety, Tolerability, Pharmacokinetic and Pharmacodynamic, Study of AT-10 in Healthy Human Subjects considered as Extensive and Poor Metabolizers of CYP2C19 based on Genotyping.

We, on behalf of Ipca Laboratories Ltd, have read and understood this protocol amendment 3.0 hereby approve the same. We agree to comply with all requirements regarding the obligations of sponsor and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013 ICH-GCP (E6-R2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), New Drugs and Clinical Trials Rules, 2019 and ICMR's National Ethical guidelines for Biomedical and Health Research involving Human Participants (2017).

V.S. Raut 23/04/2021

Sponsor's authorized signatory Date

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1.3. PROTOCOL SIGNATURE PAGE – CRO

Protocol Title: A Phase 1 Open Label, Randomized, Two-Period, Single and Multiple-Dose, Safety, Tolerability, Pharmacokinetic and Pharmacodynamic, Study of AT-10 in Healthy Human Subjects considered as Extensive and Poor Metabolizers of CYP2C19 based on Genotyping.

I, on behalf of CBCC Global Research LLP have read and understood this protocol amendment 3.0 hereby approve the same. I agree to comply with all requirements regarding the obligations of sponsor and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013), and are consistent with the ICH-GCP (E6-R2) guidelines along with the local regulatory requirements of GCP for Clinical Research In India (2004, CDSCO), New Drugs and Clinical Trials Rules, 2019 and ICMR's National Ethical guidelines for Biomedical and Health Research involving Human Participants (2017).

Dr. Jignesh L. Patel Digitally signed by Dr. Jignesh L. Patel
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1.4. PROTOCOL SIGNATURE PAGE – Investigator

Protocol Title: A Phase 1 Open Label, Randomized, Two-Period, Single and Multiple-Dose, Safety, Tolerability, Pharmacokinetic and Pharmacodynamic, Study of AT-10 in Healthy Human Subjects considered as Extensive and Poor Metabolizers of CYP2C19 based on Genotyping.

I, the undersigned, have read and understood this protocol amendment 3.0 hereby agree to conduct the study in accordance with this protocol complying all requirements regarding the obligations of investigators and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013), and are consistent with the ICH-GCP (E6-R2) guidelines along with the local regulatory requirements of GCP for Clinical Research In India (2004, CDSCO), New Drugs and Clinical Trials Rules, 2019 and ICMR's National Ethical guidelines for Biomedical and Health Research involving Human Participants (2017).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than evaluation or conduct of the clinical investigation without the prior consent of Ipca Laboratories Ltd. I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

I further agree to ensure that all associates assisting in the conduct of this study are well informed regarding their obligations and confirm to conduct this study under my direction.

Dr.Aashutosh Patel

Digitally signed by Dr.Aashutosh Patel
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1.5 PROTOCOL SIGNATURE PAGE – Bioanalytical Investigator

Protocol Title: A Phase 1 Open Label, Randomized, Two-Period, Single and Multiple-Dose, Safety, Tolerability, Pharmacokinetic and Pharmacodynamic, Study of AT-10 in Healthy Human Subjects considered as Extensive and Poor Metabolizers of CYP2C19 based on Genotyping.

I, the undersigned, have read and understood this protocol amendment 3.0, and this study will be performed in compliance with the final protocol, ICH-GCP (E6-R2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), applicable principles of Good Laboratory Practices (GLP), relevant SOP's and applicable regulatory guidelines.

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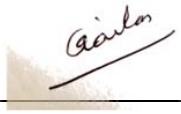
1.6 PROTOCOL SIGNATURE PAGE- Pharmacokinetic and Statistical Investigator

Protocol Title: A Phase 1 Open Label, Randomized, Two-Period, Single and Multiple-Dose, Safety, Tolerability, Pharmacokinetic and Pharmacodynamic, Study of AT-10 in Healthy Human Subjects considered as Extensive and Poor Metabolizers of CYP2C19 based on Genotyping.

I, the undersigned, have read and understood this final protocol amendment 3.0, and this study will be performed in accordance with ICH-GCP (E6-R2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), relevant SOP's and all other applicable regulatory guidelines.



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26.04.21

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2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

ACS	:	Acute Coronary Syndrome
ADP	:	Adenosine Diphosphate
AE	:	Adverse Event
ALT	:	Alanine Aminotransferase
ALP	:	Alkaline Phosphatase
ANOVA	:	Analyses of variance
AST	:	Aspartate Aminotransferase
AUC	:	Area Under the Curve
BLQ	:	Below Limit of Quantification
BMI	:	Body Mass Index
BUN	:	Blood Urea Nitrogen
CDSCO	:	Central Drugs Standard Control Organization
C_{max}	:	Maximum blood concentration
CLA	:	Central Licencing Authority
CNS	:	Central Nervous System
COA	:	Certificate of Analysis
CRF	:	Case Record/Report Form
CRO	:	Contract Research Organization
CYP	:	Cytochrome P450 enzymes
DCGI	:	Drug Controller General of India
EC	:	Ethics Committee
ECG	:	Electrocardiogram
FDA	:	Food and Drug Administration
GCP	:	Good Clinical Practice
GI	:	Gastrointestinal
GLP	:	Good Laboratory Practice
HBV	:	Hepatitis B Virus
hCG	:	Human Chorionic Gonadotropin
HCV	:	Hepatitis C Virus
HCT	:	Hematocrit
HDPE	:	High Density Polyethylene
HIV	:	Human Immunodeficiency Virus
ICF	:	Informed Consent Form
ICH	:	International Conference on Harmonization
ICMR	:	Indian Council of Medical Research
IPA	:	Inhibition Of Platelet Aggregation
IP	:	Investigational Product
K_2 EDTA	:	Di-Potassium Ethylene diamine tetra acetic acid
kg	:	Kilograms
LC-	:	Liquid Chromatography-Mass Spectrometry

MS/MS		
LLQ	:	Lower Limit of Quantification
LOQ	:	Limit of Quantification
LSMs	:	Least-Squares Means
MAD	:	Multiple Ascending Dose
MI	:	Myocardial Infarction
mg	:	Milligram
NDA	:	New Drug Application
NRV	:	Non-reportable Value
OTC	:	Over the Counter
OVIS	:	Online Volunteer Information System
PA	:	Posteroanterior
PD	:	Pharmacodynamics
PK	:	Pharmacokinetics
PI	:	Principal Investigator
PPI	:	Proton Pump Inhibitors
PT	:	Prothrombin Time
PTT	:	Partial Thromboplastin Time
RBCs	:	Red Blood Cells
RBS	:	Random Blood Sugar
RPR	:	Rapid Plasma Reagin
SAD	:	Single Ascending Dose
SAE	:	Serious Adverse Event
SAS	:	Statistical Analysis Software
SD	:	Standard Deviation
SOP	:	Standard Operating Procedure
$t_{1/2}$	:	The elimination or terminal half-life
T_{max}	:	Time of the maximum measured blood concentration
TTP	:	Thrombocytopenic Purpura
ULN	:	Upper Limit of Normal
UMC	:	Uppsala Monitoring Centre
VASP	:	Vasodilator-Stimulated Phosphoprotein Phosphorylation
WBCs	:	While Blood Cells
WHO	:	World Health Organization
WMA	:	World Medical Association

4 PROTOCOL SYNOPSIS

Protocol Title	A Phase 1 Open Label, Randomized, Two-Period, Single and Multiple-Dose, Safety, Tolerability, Pharmacokinetic and Pharmacodynamic, Study of AT-10 in Healthy Human Subjects considered as Extensive and Poor Metabolizers of CYP2C19 based on Genotyping.
Phase	Phase 1
Test Product	AT -10 (2-oxo-clopidogrel bisulfate) Tablets 10 mg, 30 mg or 40mg
Reference Product	Plavix®(Clopidogrel bisulfate) Tablets 75 mg and/or 300 mg
Route of Administration	Oral, on the morning of the each dosing day subjects will receive a dose of either test or reference product after a supervised overnight fasting of at least 10 hours.
No. of Subjects Planned	A sufficient number of subjects will be enrolled to ensure dosing of 40 healthy adult human subjects. Subjects who withdraw or are removed from the study will not be replaced.
Duration of Treatment	Each subject included in the study will receive a single loading dose followed by 5 daily doses (maintenance dose) of either AT -10 or Clopidogrel in Period 1 and then crossover to receive the other therapy (AT -10 or Clopidogrel) in Period 2. The two periods will be separated by washout period of at least 14 days from last dose of period 1 to first dose of period 2.
Study Duration	Considering the minimum washout period of at least 14 days, expected study duration of clinical phase is at least 27 days (excluding screening period) from the day of housing of period-I to the visit for the last study sample of period - II.
Objectives of the Study	The objectives of the study are as follows: **Primary:** • To determine the safety and tolerability of AT -10 compared to Clopidogrel administered orally to humans. • To compare the effect of AT -10 (loading and maintenance doses) Vs the approved doses of Clopidogrel (loading and maintenance doses) on platelet aggregation in poor and extensive metabolizers. • To confirm the AT -10 loading dose (PD equivalent dose to the Clopidogrel 300 mg) and the AT -10 maintenance dose (PD equivalent to the Clopidogrel 75 mg) given as a loading dose followed by 5 days of maintenance dose **Secondary:** • To determine the single and multiple dose pharmacokinetics (PK) of Clopidogrel, AT -10, and active metabolite MP-H4. *Note: It is important to note that AT-10 is an intermediate metabolite in the*

<table>
<tr><td></td><td>metabolic pathway of Clopidogrel to the active metabolite. Therefore, this study does not represent the first exposure of AT -10 to humans. It is, however the first direct administration of AT -10 to humans.</td></tr>
<tr><td>Study Design</td><td>This study is an open label, two-period, crossover study wherein each subject will receive a single loading dose followed by 5 daily doses (maintenance dose) of either AT-10 or Clopidogrel in Period 1 and then crossover to receive the other therapy (AT -10 or Clopidogrel) in Period 2.

40 subjects are planned to be randomized into the study. Out of this, 20 subjects would be extensive CYP2C19 metabolizers and 20 would be poor CYP2C19 metabolizers. The 20 extensive metabolizers will be randomized on a 1:1 basis into Groups 1 and 3. The 20 poor metabolizers will be randomized on a 1:1 basis into Groups 2 and 4. Subjects who withdraw or are removed from the study will not be replaced.

The dosing scheme is as follows:
<table>
<tr><th>Group & Sequence</th><th>Period 1</th><th>Period 2</th></tr>
<tr><td>Group 1
(n=10, extensive metabolizers)
Sequence 1</td><td>AT -10 40mg on Day 1
AT -10 10 mg on Days, 2, 3, 4, 5 & 6</td><td>Clopidogrel 300 mg on Day 1
Clopidogrel 75 mg on Days 2, 3, 4, 5 & 6</td></tr>
<tr><td>Group 2
(n=10, poor metabolizers)
Sequence 1</td><td>AT -10 40 mg on Day 1
AT -10 10 mg on Days, 2, 3, 4, 5 & 6</td><td>Clopidogrel 300 mg on Day 1
Clopidogrel 75 mg on Days 2, 3, 4, 5 & 6</td></tr>
<tr><td>Group 3
(n=10, extensive metabolizers)
Sequence 2</td><td>Clopidogrel 300 mg on Day 1
Clopidogrel 75 mg on Days 2, 3, 4, 5 & 6</td><td>AT -10 40 mg on Day 1
AT -10 10 mg on Days 2, 3, 4, 5 & 6</td></tr>
<tr><td>Group 4
(n=10, poor metabolizers)
Sequence 2</td><td>Clopidogrel 300 mg on Day 1
Clopidogrel 75 mg on Days 2, 3, 4, 5 & 6</td><td>AT -10 40 mg on Day 1
AT -10 10 mg on Days 2, 3, 4, 5 & 6</td></tr>
</table></td></tr>
<tr><td>Food and Fluid Restrictions</td><td>Fasting for at least 10 hours prior to dosing until at least 04 hours post-dose in each period after each dosing. Water will be restricted from at least 01 hour prior to dosing until at least 01 hours post-dose in each period (no fluid, except water given with dosing) after each dosing.</td></tr>
</table>

Housing	All subjects will be housed in the clinic facility from at least 11 hours prior to dosing until at least 24 hours post dose after administration of last maintenance dose in each study period.
Posture Restrictions	Subjects will remain seated upright for the initial 04 hours post-dose and only necessary movement will be allowed during this period. They will not be allowed to lie down except as directed by the physician and secondarily due to adverse events during this restriction period. Thereafter subjects will be allowed to ambulate freely during the remainder of the study.
Collection of blood samples for PK analysis	Blood samples (5 mL each) for PK analysis will be collected at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h (Day 2) after study drug administration on Days 1 and 6 in each period. On Days 3, 4 and 5 of each period only the pre-dose sample will be collected. The pre-dose (0.0 hour) blood sample shall be taken within 45 minutes prior to dosing on each dosing day in each period. All post-dose samples in each period will be collected within + 2 minutes (except 24 hour post dose time point for Day 1) of the scheduled time of blood sample collection. Note: In each period, 24 hour post dose sample of Day 1 will be considered as pre-dose sample of respective day.
Collection of blood samples for PD assessment	Blood samples (2.7 mL each) for PD assessment (ADP-induced platelet aggregation, 20µM ADP) will be taken pre-dose and 0.5, 2 and 6 hours post dose on each dosing day. Additionally, 24 hrs post dose sample on last dosing day of each period will be collected for assessing PD. All blood samples for PD assessment will be collected using sodium citrate vacutainers. (Note: The blood samples for aggregometry will be analyzed at the site.) The pre-dose (0.0 hour) blood sample shall be taken within 45 minutes prior to dosing on each dosing day in each period. All post-dose samples in each period will be collected within + 2 minutes of the scheduled time of blood sample collection.
Analytical methodology	Plasma samples will be assayed by a validated LCMS/MS method developed at Cliantha Research, Ahmedabad, which is specific for the determination of Clopidogrel, AT -10 (2-oxo-clopidogrel) and its metabolite MP-H4.
Criteria for Evaluation and statistical comparisons	**Pharmacodynamics:** Pharmacodynamic assessment will be performed using ADP-induced platelet aggregation in whole blood treated with sodium citrate as an anti-coagulant. ADP induced platelet aggregation will be assessed for change from baseline in each treatment group at each time point assessed on each dosing day (0.5, 2, and 6 hours post dose) and 24 hrs post dosing of last dosing day in each period. The change over time for each parameter will also be assessed. The data from Groups 1 and 3 will be combined in the analysis and Groups 2 and 4 will be combined in the analysis. The following assessments will also be performed and reviewed observationally to further assess the PD of AT -10:

	1. Liver function tests (ALT, AST, total bilirubin, and alkaline phosphatase) measured as part of clinical chemistry 2. Abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums Statistical comparison will be made between the change from baseline at each time point between the Groups 1 and 3 (extensive metabolizers) versus Groups 2 and 4 (poor metabolizers) for each treatment (AT -10 and Clopidogrel). The incidence of signs of bleeding from the abbreviated physical examination and the incidence of abnormal liver function tests (ALT, AST, total bilirubin, and alkaline phosphatase) will be tabulated for the treatment groups. The incidence of these events will not be formally tested and the comparison will be observational only. The observational comparisons will be made between the AT -10 and Clopidogrel in the extensive metabolizers and poor metabolizers. **Pharmacokinetics:** Pharmacokinetic parameters (AUC_t, AUC_{inf}, C_{max}, t_{max}, $t_{½}$, k_{el}, Cl/F, V_d/F) will be estimated following noncompartmental analysis of plasma concentration time-course data for Clopidogrel, AT -10 (2-oxo-clopidogrel), and MP-H4. PK parameters at steady-state will be estimated for Clopidogrel, AT-10 (2-oxo-clopidogrel), and MP-H4. Statistical comparison of the single-dose and multiple-dose PK parameters of peak (C_{max}) and total (AUC_t, AUC_{inf}) exposure for the AT-10 and MP-H4 will be made between the AT-10 and Clopidogrel dose groups; between and within metabolizer groups. Although this is not a bioequivalence study following PK comparison will be made: • PK comparisons will be made for AT -10 and MP-H4 from AT -10 treatment in extensive metabolizers versus Clopidogrel treatment in extensive metabolizers • PK comparisons will be made for AT -10 and MP-H4 from AT -10 treatment in poor metabolizers versus Clopidogrel treatment in poor metabolizers • PK comparisons will be made for AT -10 and MP-H4 from AT -10 treatments in extensive metabolizers versus AT -10 treatments in poor metabolizers. Other PK comparison will be made if deemed appropriate
Safety Assessment	Tolerability and safety will also be assessed. Safety assessments will include screening, pre-dose and post-dose vital signs, ECGs, clinical laboratory testing (hematology, blood chemistry, and urinalysis), documentation of AEs and clinical examinations. Coagulation parameters (PT and PTT) will also be assessed at screening, at housing during each period, at 8 hrs post-dose on each dosing day and at exit or early termination.

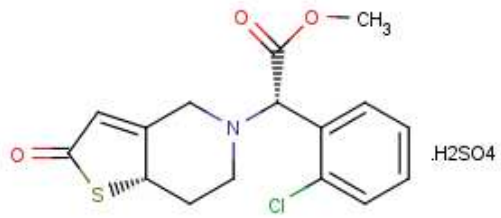
5 BACKGROUND INFORMATION

Investigational product: AT -10 (2-oxo-clopidogrel bisulfate)

Description:

Chemical Name: Methyl(2'S)-2'-[(7aS)-2-oxo-2H,4H,5H,6H,7H,7aH-thieno[3,2-c]pyridin-5-yl]-2'-(2-chlorophenyl)acetate bisulfate salt or (7aS,2'S)-2-oxoclopidogrel bisulfate salt

The chemical structure of AT-10 bisulfate is provided below.



2-Oxo-clopidogrel can exist in 4 chiral isomers: SS, SR, RR, and RS. In clopidogrel, 1 chiral carbon has S-configuration fixed, thus 2-oxo-clopidogrel metabolite of clopidogrel can exist in 2 chiral isomers (SS and SR). AT-10 is a single diastereomer (7aS,2'S-configuration) of 2-oxo-clopidogrel.

Cardiovascular diseases remain the leading cause of mortality worldwide. Of these deaths, more than 50% are secondary to coronary artery disease, with acute coronary syndrome (ACS) accounting for approximately 10% of all admissions presenting to emergency care physicians (Kontos, 2010). Platelets play a key role in the development of ACS, because plaque rupture is followed by platelet adhesion, activation, and aggregation, leading to thrombosis formation (Libby, 2001). Antiplatelet therapy is therefore the cornerstone of medical treatment in patients with ACS and is necessary in both the acute phase and long-term maintenance therapy (Menozzi, 2012). Antiplatelet agents, including the thienopyridine prodrugs, clopidogrel (Plavix®), Ticlopidine (Ticlid®), and Prasugrel (Effient®), inhibit platelet aggregation induced by ADP (Abell, 2011). While the use of clopidogrel has undoubtedly been a beneficial advance in the treatment of ACS with regard to both short and long term morbidity and mortality (Sabatine, 2005; Yusuf, 2001), it remains a treatment with several shortcomings.

It has been established that not all of the patients receiving clopidogrel benefit to the same extent, and it has been shown that patients with a poor metabolizer genotype for CYP2C19 are at increased risk of ischemic events (Menozzi, 2012). There is considerable heterogeneity in the activity of CYP450 enzymes in human populations and it has become apparent that a substantial minority of individuals (up to 14% in some series) have polymorphisms in CYP2C19 which cause impaired metabolism of clopidogrel (Contractor, 2012).

In human subjects, the CYP2C19 loss-of-function genotype is a major driver of H4 exposure, corresponding to lowered ADP-induced antiplatelet response (Gong, 2012). Recent findings suggest that CYP2C19 (but not PON1 or CYP3A4) is a mechanistic determinant of inter-patient antiplatelet

variability to clopidogrel therapy (Gong, 2012). Carriers of the reduced-function CYP2C19 alleles have lower levels of clopidogrel's active metabolite, show diminished platelet inhibition, and are at higher risk of major adverse cardiovascular events, including a threefold greater risk of stent thrombosis (Mega, 2009; Simon, 2009).

To overcome the limitations of clopidogrel associated with CYP2C19 metabolism, Ipca has developed AT-10, a prodrug that is metabolically converted, in one CYP-dependent step, to produce the active metabolite of the approved listed drug Plavix (clopidogrel bisulfate tablet, 300 mg; NDA 20839). A major advantage of the pro-drug AT-10 is its more efficient metabolism through one CYP-dependent step, as compared to the two-step process for clopidogrel involving several CYP450 isoenzymes. It is possible that AT-10 may provide a faster and more consistent inhibition of platelet function, thereby producing important clinical benefits for patients. The response to AT-10 may not be influenced by genetic CYP2C19 polymorphisms to the extent of its influence in clopidogrel, thus eliminating the need for characterization of clopidogrel responsiveness and thereby maintaining effectiveness in all patients, including those patients who are identified as CYP2C19 poor metabolizers. In light of promising data obtained from nonclinical and clinical studies, Ipca is pursuing the clinical development of AT-10 in Indian population for the reduction of atherothrombotic events in patients with a history of recent myocardial infarction (MI), recent stroke, established peripheral arterial disease, or for patients with ACS.

Mechanism of Action:

Clopidogrel is a prodrug, and its clinical efficacy appears to be a function of the amount of enzymatically derived active thiol metabolite formed (Frere, 2008; Pereillo, 2002). Clopidogrel is first metabolized to the intermediate metabolite 2-oxo-clopidogrel, which is next metabolized to a number of thiol metabolite stereoisomers, only one of which (H4) is active in vivo (Pereillo, 2002; Savi, 2000; Tuffal, 2011). Notably, both metabolic steps leading to H4 formation have been shown to be predominantly dependent on CYP2C19 and, to a lesser extent, CYP3A4 (Kazui, 2010). Recently,Gong, et al observed a strong correlation between H4 plasma exposure and platelet inhibition, demonstrating that individuals with highest exposure to H4 active metabolite have the greatest antiplatelet response (Gong, 2012).

Pre-clinical Studies:

Following pre-clinical studies have been conducted by Ipca with AT-10 so far;

A) Pharmacodynamic studies of AT-10

1. Inhibition of platelet aggregation in ex-vivo studies in wistar rats and cynomolgus monkeys.
2. PK-PD study in cynomolgus monkey
3. Antithrombotic activity in FeCl3 induced arterial thrombosis model in rats
4. P-Glycoprotein interaction study

B) Pharmacokinetic studies of AT-10

1. Mass balance and tissue distribution kinetics study in Cynomolgus monkeys
2. Drug metabolism studies in Clopidogrel in rat, dog, monkeys and humans hepatocytes

3. Enzyme Inhibition studies

C) Safety Pharmacology studies

1. Single dose acute toxicity study in Cynomolgus monkeys
2. 5 days repeat dose toxicity study in Cynomolgus monkeys
3. 28 days repeat dose toxicity study in Cynomolgus monkeys

D) Genotoxicity studies:

1. AMES Test (evaluated the mutagenic potential of AT-10 at different concentrations.
2. In-vitro Chromosomal aberration:
3. In vivo micronucleus assay

Clinical Studies:

Following clinical studies have been conducted by Ipca with AT-10 so far;

1. A phase 1, single ascending dose (SAD) and multiple ascending dose (MAD), PK-PD study in healthy human volunteers who were specifically genotyped for CYP2C19 (extensive metabolizers) - dose finding study.
2. Drug-drug interaction study with Omeprazole.
3. Study the effect of AT-10 in heavy smokers.

Note: All the above mentioned clinical studies were conducted in USA.

Phase 1 SAD and MAD study (Study number IPCA AT-10 2012-001):

Given that AT-10 is an intermediate metabolite in the metabolism of clopidogrel to the active metabolite, this study did not represent the first exposure of AT-10 to humans; rather, it represented the first direct administration of AT-10 to humans. This study was an open-label, single rising-dose crossover study in which each subject received a single dose of either AT-10 7.5 mg (Group 1) or clopidogrel 300 mg (Group 2) in Period 1, and then crossed over in Period 2 to receive the other drug as a single loading dose (clopidogrel 300 mg for Group 1 and AT 10 40 mg for Group 2) followed by 3 daily maintenance doses (clopidogrel 75 mg for Group 1 and AT 10 10 mg for Group 2). The primary objective of this study was to determine the safety and tolerability of AT-10. Additionally, this study was designed to determine the PK/PD equivalent doses of AT-10 to clopidogrel to be used in future studies.

This study met its primary objective and showed that AT-10 is safe and well-tolerated at each dose tested in the study. Safety findings from all 30 subjects did not show any clinically significant trends or abnormalities in LFTs, clinical chemistry, hematology, and coagulation. There were no deaths or serious AEs that occurred during the study. Most of the AEs were relatively minor in nature and were considered unrelated to study drug treatment. Results from vital signs and ECGs were unremarkable. Episodes of bleeding were very limited, with only 1 out of 30 subjects who had ecchymosis. No bleeding or other signs of bleeding (ie, petechia and bleeding gums), including ecchymosis, were reported in the remaining subjects. The PK/PD analyses were conducted in 29 of the 30 subjects, these

29 subjects completed the study and the objectives were met to determine PD equivalent doses between AT-10 and clopidogrel. Overall, the results of this study with the first administration of AT-10 in humans support the safe use of AT-10 at PD equivalent doses to clopidogrel.

Drug-drug interaction study with Omeprazole (Study number IPCA AT-10 2013-003):

This study was intended to assess the effect of coadministration of omeprazole with AT-10 and confirm that there is little to no effect of omeprazole on the pharmacokinetics and pharmacodynamics of AT-10. Omeprazole is a moderate CYP2C19 inhibitor (FDA, 2012; Yu, 2001), and administration of omeprazole with clopidogrel is contraindicated (Sanofi-Aventis US, 2011). Since the role of CYP2C19 in the metabolism of AT-10 is minimized or eliminated, coadministration of omeprazole was not expected to affect the pharmacokinetics or pharmacodynamics of AT-10 and therefore, administration of omeprazole and other compounds that inhibit CYP2C19 with AT-10 would not be contraindicated.

Therefore, the primary objective of the study was to compare the platelet aggregation effect of AT-10 (loading and maintenance doses) when coadministered with omeprazole (CYP2C19 inhibitor) and AT-10 without coadministered omeprazole in normal (also known as extensive) metabolizers for CYP2C19 (*1/*1 allele) based on genotyping. The secondary objectives were 1) To assess the effect of coadministration of omeprazole on the pharmacokinetics of AT-10 and MP-H4, 2) To determine the single-dose PK of AT-10 and MP-H4, 3) To determine the multiple-dose PK of AT-10 and MP-H4, and 4) To assess the safety and tolerability of AT-10 with and without coadministration of omeprazole.

To achieve these objectives, an open-label, 2-period, crossover study was performed in which each subject received 5 daily doses of AT-10 (a loading dose of 40 mg on the first day followed by a maintenance dose of 10 mg for 4 consecutive days) with or without omeprazole (80 mg) in Period 1 and then crossed over to receive the same doses of AT-10 with the opposite omeprazole status in Period 2; there was an omeprazole lead-in period of 4 days prior to Day 1 and Day 20 of dosing with AT-10 (as of Day 1 for Group 1 and Day 20 for Group 2, omeprazole was co-administered with the same 40 mg of AT-10 with 240 mL of water). A total of 24 subjects were enrolled in the study: 12 subjects in Group 1 and 12 subjects in Group 2. Two subjects (Subjects 307 and 312), both in Group 2, were withdrawn from the study after failing their drug/breath alcohol tests at check in (Day 5). These subjects did not receive any study medication. No major protocol deviation occurred.

Pharmacodynamic analysis of patients receiving both AT-10 and omeprazole showed that coadministration of AT 10 with omeprazole decreased the effect of AT-10 treatment on percent inhibition of platelet aggregation (%IPA) significantly (40–50% decrease after the loading dose and 20–50% decrease over the course of 4 days of maintenance doses). However, the %IPA effect after the coadministration of AT 10 with omeprazole and after the treatment with clopidogrel is similar. Additionally, co-administration of AT-10 with omeprazole resulted in decrease in platelet reactivity index by 75% after loading dose on day 1 and approx 40% on day 5.

To study the effect of AT-10 in heavy smokers (Study number IPCA AT-10 2013-005):

This study was intended to assess the effect of smoking in normal CYP2C19 metabolizers on the pharmacodynamics and pharmacokinetics of AT-10 compared to clopidogrel. AT-10 is a prodrug that is

metabolically converted, in one CYP-dependent step, to produce the active metabolite of the approved listed drug Plavix® (clopidogrel bisulfate tablet, 300 mg; NDA 20839). The metabolic activation of clopidogrel is a two-step process and is most often described involving CYP2C19, but other CYP450 isoenzymes also play a role such as CYP1A2, which is induced by cigarette smoking.

The primary objective of the study was to compare the inhibition of platelet aggregation effect of AT-10 (loading and maintenance doses) to the FDA-approved doses of clopidogrel (loading and maintenance doses) in heavy smokers (CYP2C19 normal metabolizers with *1/*1 alleles as per genotyping). The secondary objectives were to assess the safety and tolerability of AT-10 compared to clopidogrel in heavy smokers that are normal metabolizers, and to evaluate the impact of heavy smoking on the PK/PD of clopidogrel and AT-10 in comparison to the PK/PD of non-smokers utilizing data from previous studies conducted by Ipca.

To achieve these objectives, an open-label, 2-period, crossover study was performed. In Period 1 of the crossover study each subject received a single loading dose of AT 10 (40 mg) or clopidogrel (300 mg) followed by 4 daily maintenance doses of the same therapy (AT-10 10 mg or clopidogrel 75 mg). In Period 2, the subjects crossed over to receive the other therapy (clopidogrel or AT-10). Each group was divided into 2 cohorts of 6 in order to accommodate the clinical logistics of the trial.

The results from this study demonstrate that AT-10 administered in heavy smokers is safe and well-tolerated. Addressing the primary objective, the pharmacodynamic analyses showed that AT-10 was generally similar to clopidogrel in its ability to inhibit platelet aggregation as evidenced by %IPA and %PRI assays (VASP). Therefore, the PD results suggest that AT-10 will provide clinically beneficial therapy in heavy smokers since there is no impact observed on %IPA using AT-10 with regard to smoking status. Finally, when compared to a similar study in non-smokers, AT-10 showed similar effects in smokers and non-smokers, while clopidogrel appeared to have higher exposure and enhanced inhibition of platelet aggregation in smokers. AT 10 was found to be safe and well tolerated in this study.

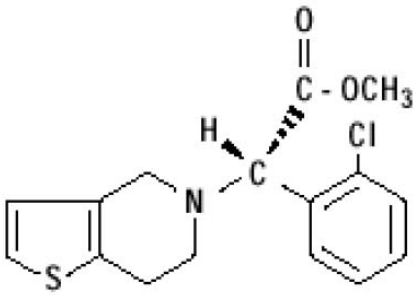
Conclusion:

Based on the results of nonclinical and clinical studies conducted so far, AT-10 was found to be safe, well tolerated and effective drug. And hence in order to further confirm its efficacy and safety in target populations and to overcome the limitations of existing drug i.e. Clopidogrel, further evaluation of AT-10 in Indian population is worth exploring.

Reference Product: Clopidogrel Bisulfate Tablet

Description:
Chemical Name: Hydrogen sulfate;hydron;methyl (2S)-2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetate

The chemical structure of Clopidogrel bisulfate is provided below.



Mechanism of Action:

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets.

Pharmacodynamics:

Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GP IIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Consequently, platelets exposed to clopidogrel's active metabolite are affected for the remainder of their lifespan (about 7 to 10 days). Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Plavix. Repeated doses of 75 mg Plavix per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg Plavix per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Geriatric Patients

Elderly (≥75 years) and young healthy subjects had similar effects on platelet aggregation.

Renally Impaired Patients

After repeated doses of 75 mg Plavix per day, patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) and moderate renal impairment (creatinine clearance from 30 to 60 mL/min) showed low (25%) inhibition of ADP-induced platelet aggregation.

Hepatically Impaired Patients

After repeated doses of 75 mg Plavix per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects.

Gender

In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women.

Pharmacokinetics:

Clopidogrel is a prodrug and is metabolized to a pharmacologically active metabolite and inactive metabolites.

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Effect of food

Plavix can be administered with or without food. In a study in healthy male subjects when Plavix 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by less than 9%. The active metabolite AUC0-24 was unchanged in the presence of food, while there was a 57% decrease in active metabolite Cmax. Similar results were observed when a Plavix 300 mg loading dose was administered with a high-fat breakfast.

Metabolism

Clopidogrel is extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. Cytochromes first oxidize clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.

The Cmax of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose. Cmax occurs approximately 30 to 60 minutes after dosing. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: 4-fold the dose results in 2.0-fold and 2.7-fold the Cmax and AUC, respectively.

Elimination

Following an oral dose of 14C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The half-life of the active metabolite is about 30 minutes.

Drug Interactions:

Effect of other drugs on Plavix

Clopidogrel is metabolized to its active metabolite in part by CYP2C19.

CYP2C19 inducers
Since clopidogrel is metabolized to its active metabolite partly by CYP2C19, use of drugs that induce the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel.

Rifampin strongly induces CYP2C19 resulting to both an increase level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, avoid concomitant use of strong CYP2C19 inducers

Concomitant use of strong inducers of CYP2C19 results in increased plasma concentration of the active metabolite of clopidogrel and an increase in platelet inhibition.

Rifampin: Coadministration of rifampin 300 mg twice daily for 7 days with 600 mg loading dose of clopidogrel in healthy adults increased the mean AUC and Cmax of clopidogrel's thiol metabolites by 3.8-fold. Mean inhibition of platelet aggregation at 4 hours post-dose was 34% higher in the presence of rifampin compared to clopidogrel administered alone.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
Coadministration of Plavix and NSAIDs increases the risk of gastrointestinal bleeding.

Warfarin (CYP2C9 Substrates)
Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of Plavix with warfarin increases the risk of bleeding because of independent effects on hemostasis.
However, at high concentrations *in vitro*, clopidogrel inhibits CYP2C9.

SSRIs and SNRIs

Since selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.

CYP2C19 inhibitors

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition

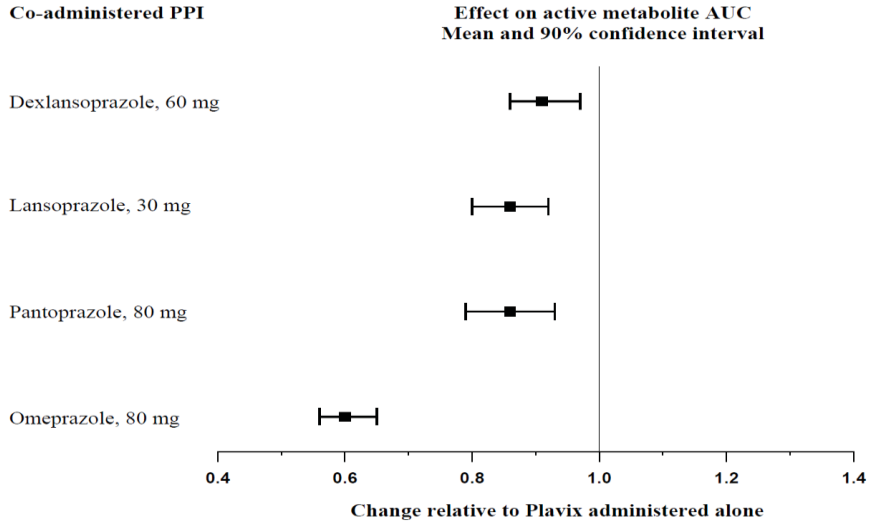
Concomitant use of certain inhibitors of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.

Omeprazole or Esomeprazole

Avoid concomitant use of Plavix with omeprazole or esomeprazole. In clinical studies, omeprazole was shown to reduce significantly the antiplatelet activity of Plavix when given concomitantly or 12 hours apart. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with Plavix. Dexlansoprazole, lansoprazole, and pantoprazole had less effect on the antiplatelet activity of Plavix than did omeprazole or esomeprazole.

Proton pump inhibitors (PPI)

The effect of proton pump inhibitors (PPI) on the systemic exposure to the clopidogrel active metabolite following multiple doses of Plavix 75 mg evaluated in dedicated drug interaction studies is presented in below figure: Exposure to Clopidogrel Active Metabolite Following Multiple Doses of Plavix 75 mg Alone or with Proton Pump Inhibitors (PPIs)



Pharmacodynamic and pharmacokinetic parameters measured in these studies showed that the interaction was highest with omeprazole and least with dexlansoprazole.

Opioids

As with other oral P2Y12 inhibitors, coadministration of opioid agonists delay and reduce the absorption of clopidogrel, presumably because of slowed gastric emptying, resulting in reduced exposure to its metabolites. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring coadministration of morphine or other opioid agonists.

Coadministration of 5 mg intravenous morphine with 600 mg loading dose of clopidogrel in healthy adults decreased the AUC and Cmax of clopidogrel's thiol metabolites by 34%. Mean platelet aggregation was higher up to 2 to 4 hours with morphine coadministration.

Effect of Plavix on other drugs

In vitro studies have shown that the glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C8. Concomitant administration of repaglinide with Plavix increased the systemic exposure to repaglinide ($AUC_{0\text{-}inf}$) by 5.1-fold following the loading dose (300 mg) and by 3.9-fold on day 3 of the maintenance dose (75 mg) of Plavix

Repaglinide (CYP2C8 Substrates)

The acyl-β-glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C8. Plavix can increase the systemic exposure to drugs that are primarily cleared by CYP2C8, thereby needing dose adjustment and appropriate monitoring.

Plavix increased repaglinide exposures by 3.9-fold to 5.1-fold. Avoid concomitant use of repaglinide with Plavix. If concomitant use cannot be avoided, initiate repaglinide at 0.5 mg before each meal and do not exceed a total daily dose of 4 mg. Increased frequency of glucose monitoring may be required during concomitant use.

Adverse Events:

The following serious adverse reactions are reported in prescribing information of Clopidogrel bisulfate (Plavix®):

- Bleeding
- Thrombotic thrombocytopenic purpura

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions and durations of follow up, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Plavix has been evaluated for safety in more than 54,000 patients, including over 21,000 patients treated for 1 year or more. The clinically important adverse reactions observed in trials comparing Plavix plus aspirin to placebo plus aspirin and trials comparing Plavix alone to aspirin alone are discussed below.

Bleeding

CURE

In CURE, Plavix use with aspirin was associated with an increase in major bleeding (primarily gastrointestinal and at puncture sites) compared to placebo with aspirin (see Table 1). The incidence of intracranial hemorrhage (0.1%) and fatal bleeding (0.2%) were the same in both groups. Other bleeding events that were reported more frequently in the clopidogrel group were epistaxis, hematuria, and bruise. The overall incidence of bleeding is described in below table (CURE Incidence of Bleeding Complications (% patients)).

Event	Plavix (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)
Major bleeding †	3.7 ‡	2.7 §
Life-threatening bleeding	2.2	1.8
Fatal	0.2	0.2
5 g/dL hemoglobin drop	0.9	0.9
Requiring surgical intervention	0.7	0.7
Hemorrhagic strokes	0.1	0.1
Requiring inotropes	0.5	0.5
Requiring transfusion (≥4 units)	1.2	1.0
Other major bleeding	1.6	1.0
Significantly disabling	0.4	0.3
Intraocular bleeding with significant loss of vision	0.05	0.03
Requiring 2-3 units of blood	1.3	0.9
Minor bleeding ¶	5.1	2.4

* Other standard therapies were used as appropriate.
† Life-threatening and other major bleeding.
‡ Major bleeding event rate for Plavix + aspirin was dose-dependent on aspirin: <100 mg = 2.6%; 100-200 mg = 3.5%; >200 mg = 4.9%
Major bleeding event rates for Plavix + aspirin by age were: <65 years = 2.5%, ≥65 to <75 years = 4.1%, ≥75 years = 5.9%
§ Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg = 2.0%; 100-200 mg = 2.3%; >200 mg = 4.0%
Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, ≥65 to <75 years = 3.1%, ≥75 years = 3.6%
¶ Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin or low molecular weight heparin (LMWH), and the rate of bleeding in these patients was similar to the overall results.

COMMIT

In COMMIT, similar rates of major bleeding were observed in the Plavix and placebo groups, both of which also received aspirin (below table: Incidence of Bleeding Events in COMMIT (% patients)).

Type of bleeding	Plavix (+ aspirin) (n=22961)	Placebo (+ aspirin) (n=22891)	p-value
Major* noncerebral or cerebral bleeding**	0.6	0.5	0.59
Major noncerebral	0.4	0.3	0.48
Fatal	0.2	0.2	0.90
Hemorrhagic stroke	0.2	0.2	0.91
Fatal	0.2	0.2	0.81
Other noncerebral bleeding (non-major)	3.6	3.1	0.005
Any noncerebral bleeding	3.9	3.4	0.004

* Major bleeds were cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.

** The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for Plavix + aspirin by age were: <60 years = 0.3%, ≥60 to <70 years = 0.7%, ≥70 years = 0.8%. Event rates for placebo + aspirin by age were: <60 years = 0.4%, ≥60 to <70 years = 0.6%, ≥70 years = 0.7%.

CAPRIE (Plavix vs. Aspirin)

In CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2.0% in those taking Plavix vs. 2.7% in those taking aspirin; bleeding requiring hospitalization occurred in 0.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for Plavix compared to 0.5% for aspirin.

Other bleeding events that were reported more frequently in the Plavix group were epistaxis and hematoma.

Other Adverse Events

In CURE and CHARISMA, which compared Plavix plus aspirin to aspirin alone, there was no difference in the rate of adverse events (other than bleeding) between Plavix and placebo.

In CAPRIE, which compared Plavix to aspirin, pruritus was more frequently reported in those taking Plavix. No other difference in the rate of adverse events (other than bleeding) was reported.

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of Plavix. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP), acquired hemophilia A

- Gastrointestinal disorders: colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastric/duodenal ulcer, diarrhea
- General disorders and administration site condition: FeverHepato-biliary disorders: Acute liver failure, hepatitis (non-infectious), abnormal liver function test
- Immune system disorders: Hypersensitivity reactions, anaphylactoid reactions, serum sickness, insulin autoimmune syndrome, which can lead to severe hypoglycemia

- Musculoskeletal, connective tissue and bone disorders: myalgia, arthralgia, arthritis
- Nervous system disorders: Taste disorders, headache, ageusia
- Psychiatric disorders: Confusion, hallucinations
- Respiratory, thoracic and mediastinal disorders: Bronchospasm, interstitial pneumonitis, eosinophilic pneumonia.
- Renal and urinary disorders: Increased creatinine levels
- Skin and subcutaneous tissue disorders: Maculopapular, exfoliative or erythematous rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, lichen planus, generalized pruritusVascular disorders: Vasculitis, hypotension

WARNINGS AND PRECAUTIONS:

Diminished Antiplatelet Activity in Patients with Impaired CYP2C19 Function

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19.

The metabolism of clopidogrel can also be impaired by drugs that inhibit CYP2C19, such as omeprazole or esomeprazole. Avoid concomitant use of Plavix with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of Plavix.

General Risk of Bleeding

Thienopyridines, including Plavix, increase the risk of bleeding.

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days). Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.
Use of drugs that induce the activity of CYP2C19 would be expected to result in increased drug levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution, avoid concomitant use of strong CYP2C19 inducers.

Discontinuation of Plavix

Discontinuation of Plavix increases the risk of cardiovascular events. If Plavix must be temporarily discontinued (e.g., to treat bleeding or for surgery with a major risk of bleeding), restart it as soon as possible. When possible, interrupt therapy with Plavix for five days prior to such surgery. Resume Plavix as soon as hemostasis is achieved.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP, sometimes fatal, has been reported following use of Plavix, sometimes after a short exposure (<2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever.

Cross-Reactivity among Thienopyridines

Hypersensitivity including rash, angioedema or hematologic reaction has been reported in patients receiving Plavix, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines.

6 STUDY OBJECTIVES AND RATIONALE

6.1 STUDY OBJECTIVES

Primary:

- To determine the safety and tolerability of AT -10 compared to Clopidogrel administered orally to humans.
- To compare effect of AT -10 (loading and maintenance doses) Vs approved doses of Clopidogrel (loading and maintenance doses) on platelet aggregation in poor and extensive metabolizers.
- To confirm the AT -10 loading dose (PD equivalent dose to the Clopidogrel 300 mg) and the AT -10 maintenance dose (PD equivalent to the Clopidogrel 75 mg) given as a loading dose followed by 5 days of maintenance dose

Secondary:

- To determine the single and multiple dose pharmacokinetics (PK) of Clopidogrel, AT -10, and active metabolite MP-H4.

6.2 RATIONALE

Requirement of conducting this study:

The growing body of literature implicating CYP2C19 loss-of-function alleles in adverse clopidogrel responses prompted the USFDA to ask the application holder to implement a boxed warning on the clopidogrel package insert stating, “Effectiveness of Clopidogrel bisulfate depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Consider use of another platelet $P2Y_{12}$ inhibitor in patients identified as CYP2C19 poor metabolizers”. Hence there is a well-established relationship exist between CYP2C19 deficient pharmacogenomic populations and drug response, that results in diminished effectiveness in poor metabolizers.

To overcome the limitations of clopidogrel associated with CYP2C19 metabolism, Ipca has developed AT-10, a prodrug that is metabolically converted, in one CYP-dependent step, to produce the active metabolite of the approved listed drug Plavix (clopidogrel bisulfate tablet, 300 mg; NDA 20839). A major advantage of the pro-drug AT-10 is its more efficient metabolism through one CYP-dependent step, as compared to the two-step process for clopidogrel involving several CYP450 isoenzymes. It is possible that AT-10 may provide a faster and more consistent inhibition of platelet function, thereby producing important clinical benefits for patients. The response to AT-10 may not be influenced by genetic CYP2C19 polymorphisms to the extent of its influence in clopidogrel, thus eliminating the need for characterization of clopidogrel responsiveness and thereby maintaining effectiveness in all patients, including those patients who are identified as CYP2C19 poor metabolizers as well. So in order to explore the PK-PD and safety profile of AT-10 in Indian population the current study has been proposed.

Selection of AT-10 doses for this study:

It is important to note that AT-10 is an intermediate metabolite in the metabolic pathway of Clopidogrel to the active metabolite. Therefore, this study does not represent the first exposure of AT-10 in humans. It does, however, represent the first direct administration of AT-10 to humans. The highest single dose planned for AT-10 is 40 mg and the highest single dose planned for Clopidogrel is 300 mg.

Further, in the nonclinical toxicology studies in primates conducted by Ipca, the no adverse effect level has been determined to be 150 mg/kg (48 mg/kg human equivalent dose) resulting in a 72-fold safety margin for the AT-10 40 mg dose.

The PD potency of AT-10 was thought to be between 4 and 10 times greater than that of Clopidogrel. This was based on the nonclinical studies that have been completed and the amount of AT-10 exposure that results from a dose of Clopidogrel. Specifically, in a rodent model, PD indicated that AT-10 is approximately 10 times more potent than Clopidogrel. In a primate model, the PK exposure observed with AT-10 was approximately 4 times higher than that observed with Clopidogrel when adjusted for dose. Further, when the metabolic fate of Clopidogrel is assessed, it is estimated that approximately 8 – 10% of the administered dose of Clopidogrel is metabolized into AT-10. Based on these data, the effective loading dose of AT-10 was expected to be between 30 and 75 mg and the effective maintenance dose was expected to be between 7.5 and 20 mg.

Further, the 40 mg loading dose and 10 mg maintenance doses of AT-10 for this study has been selected based on a pharmacodynamically similar dose to the clopidogrel 300-mg loading dose and the clopidogrel 75-mg maintenance dose. This dose was determined from our earlier conducted study entitled “A Phase 1, Randomized, Single-Ascending and Multiple-Dose Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of AT 10 in Healthy Subjects Considered Extensive Metabolizers of CYP2C19 Based on Genotyping.” (*1/*1 alleles) (Protocol Number IPCA AT-10 2012-001).

Selection of duration of therapy:

As per PIL of Plavix, dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Plavix. Repeated doses of 75 mg Plavix per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg Plavix per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Further, since AT 10 (2-oxo-clopidogrel) is one of the metabolite in the biotransformation pathway of clopidogrel that leads to the active metabolite MPH4, it is anticipated that multiple dose study that includes a single loading dose of AT-10 followed by five (5) daily doses of the maintenance dose of AT-10 compared to the approved loading and maintenance doses of Plavix® (Clopidogrel) would be sufficient as the steady state is being reached by Day 6.

Rational for study population:

As significant amount (>35%) of Indian population either lacks CYP2C19 enzyme or have reduced-function genes which may results in lower response to Clopidogrel when administered at recommended dose. (Umamaheswaran G, et al.2014) there exists a need of drug(s) which required less degree of metabolism by CYP2C19 enzyme but still gives a desired therapeutic action at lower dose covering entire population (poor as well as extensive metabolizers). Hence, we feel that further evaluation of AT-10 in Indian population is worth exploring.

7 STUDY DESIGN

7.1 Design

This study is an open label, two-period, crossover study wherein each subject will receive a single loading dose followed by 5 daily doses (maintenance dose) of either AT-10 or Clopidogrel in Period 1 and then crossover to receive the other therapy (AT -10 or Clopidogrel) in Period 2.

40 subjects are planned to be randomized into the study. Out of this, 20 subjects would be extensive CYP2C19 metabolizers and 20 would be poor CYP2C19 metabolizers. The 20 extensive metabolizers will be randomized on a 1:1 basis into Groups 1 and 3. The 20 poor metabolizers will be randomized on a 1:1 basis into Groups 2 and 4. Subjects who withdraw or are removed from the study will not be replaced.

The dosing scheme is as follows:

Group & Sequence	Period 1	Period 2
Group 1 (n=10, extensive metabolizers) Sequence 1	AT -10 40mg on Day 1 AT -10 10 mg on Days, 2, 3, 4, 5 & 6	Clopidogrel 300 mg on Day 1 Clopidogrel 75 mg on Days 2, 3, 4, 5 & 6
Group 2 (n=10, poor metabolizers) Sequence 1	AT -10 40 mg on Day 1 AT -10 10 mg on Days, 2, 3, 4, 5, & 6	Clopidogrel 300 mg on Day 1 Clopidogrel 75 mg on Days 2, 3, 4, 5 & 6
Group 3 (n=10, extensive metabolizers) Sequence 2	Clopidogrel 300 mg on Day 1 Clopidogrel 75 mg on Days 2, 3, 4, 5, & 6	AT -10 40 mg on Day 1 AT -10 10 mg on Days 2, 3, 4, 5 & 6
Group 4 (n=10, poor metabolizers) Sequence 2	Clopidogrel 300 mg on Day 1 Clopidogrel 75 mg on Days 2, 3, 4, 5, & 6	AT -10 40 mg on Day 1 AT -10 10 mg on Days 2, 3, 4, 5 & 6

8 POPULATION / SAMPLE SIZE

This is the first administration of AT-10 in Indian population. The sample size chosen is not based on a statistical calculation of PD effect or PK variability, but rather on the number of subjects deemed necessary to assess the safety and tolerability of AT-10 in humans, establish the PK parameters of AT-10 in humans, and to generate proof-of-concept data (evaluate the set objectives) on the pharmacodynamic effect of AT- 10.

40 Healthy male and / or female subjects of ages 18-45 years (both ages inclusive) will be enrolled in the study.

- Group 1: n=10, Healthy male and / or female subjects who are extensive (normal) metabolizers
- Group 2: n=10, Healthy male and / or female subjects who are poor metabolizers
- Group 3: n=10, Healthy male and / or female subjects who are extensive (normal) metabolizers
- Group 4: n=10, Healthy male and / or female subjects who are poor metabolizers

The site will carry out general screening with CYP2C19 based genotyping, so that site will have database of volunteers in sufficient number who are extensive (normal) metabolizers and poor metabolizers.

8.1 ENTRY CRITERIA

8.1.1 Inclusion Criteria

Subjects will be considered eligible for the study based on the following criteria:

1) Subjects who are willing to provide voluntary informed consent and are willing to participate in the study.
2) Normal healthy human adult male and/or female subjects between 18-45 years (both ages inclusive) of age.
3) Body Mass Index of 18.50 to 29.90 kg/m^2 (both inclusive).
4) No evidence of underlying disease during the pre-study screening, medical history, clinical examination and laboratory investigations performed within 28 days prior to commencement of the study.
5) Subject classified as extensive (normal) metabolizer (*1/*1) or poor metabolizer (*2/*2, *2/*3, *3/*3) based on CYP2C19 allele 1 and 2, 3 and 17 genotyping.
6) Pre-study screening laboratory tests are either normal or within acceptable limits or are considered by the Investigator to be of no clinical significance with respect to participation in the study.
7) Negative test results for alcohol, drugs of abuse, Beta hCG test (for female subjects only) and who is negative or non-reactive for antibodies to HIV 1 and 2, hepatitis B & C and RPR at the time of screening.
8) 12-lead ECG recording within normal or within acceptable limits or as considered by the Investigator to be of no clinical significance with respect to his/her participation in the study.
9) Normal chest X-ray taken within 6 month of enrollment.

10) Subjects who are available for the entire study period and are capable of understanding and communicating with the investigators and clinical study facility staff.
11) Subject must agree to use an acceptable method of contraception at least 48.00 hours prior to dosing of IP, during the study & for 07 days after study completion.

8.1.2 Exclusion Criteria

Subjects will be excluded from the study based on the following criteria:

1) Known allergic to Clopidogrel, AT-10 or any component of the formulation and to any other related class of drug.
2) History or presence of significant cardiovascular, respiratory, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, musculoskeletal, neurological or psychiatric disease.
3) Female subjects who are nursing mothers\lactating women.
4) History/presence of significant alcohol dependence (abuse) or drug abuse within the past 1 year.
5) History of chronic smoking (more than 10 units per day of cigarettes, bidis, or any other form) or chronic consumption of tobacco products.
6) History/presence of significant Asthma, urticaria or other allergic type reactions after taking any medication.
7) History/presence of clinically significant illness within 04 weeks before the start of the study.
8) History of clinically relevant allergy (except for untreated, asymptomatic, seasonal allergies at time of dosing) or any allergic reactions to any drugs.
9) History of vascular collapse.
10) Subjects scheduled for surgery any time during study or within 07 days after study completion.
11) History of difficulty in donating blood.
12) Subjects who have unsuitable veins for repeated vein puncture.
13) Subjects who have donated blood or loss of blood 50 ml to 100 ml within 30 days or 101 ml to 200 ml within 60 days or > 200 ml within 90 days (excluding volume drawn at screening for this study) prior to first dose of study medication.
14) Subjects who have received a known investigational drug within ten elimination half-life of the administered drug prior to first dose of study medication or who have participated in a clinical drug study or bioequivalence study within 90 days prior to the first dose of study medication, whichever is greater; or subjects who have not completed sufficient days of no participation in clinical study as indicated by the investigator / institute of the last study participation as reflected in OVIS.
15) Subjects who have taken prescription medication or OTC products (including vitamins and natural products) within 14 days prior to dosing of IP, including topical medication.
16) Use of any medication known to alter hepatic enzyme activity within 28 days prior to the initial dose of study medication (e.g. Omeprazole or other proton pump inhibitors).
17) Reported or documented use of aspirin or its derivatives, including patches, creams, rubs, sprays, or non-steroidal anti-inflammatory drug(s) within the last 14 days.
18) Subject who was hospitalized within 28 days prior to administration of the study medication.
19) History of difficulty in swallowing.

20) Subjects with known increased risks of bleeding (eg, frequent nose bleeding, recent trauma, surgery or other pathological condition), including known history of bleeding dyscrasias such as Von Willebrand, Hemophilia A or B, or any other type of bleeding disorder.
21) Any abnormal laboratory value or physical finding which may interfere with the interpretation of test results or cause a health hazard for the volunteer if he / she participates in the study.
22) Evidence of skin lesions on forearm or signs of vein puncture on the forearm suggestive of recent donation or participation in clinical trial.
23) Platelet count outside the normal range at screening or housing for Period 1.
24) Subject has a condition the Investigator believes would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk.

8.2 DISCONTINUATION AND WITHDRAWAL CRITERIA

- Subjects are free to withdraw from the study at any time without stating any reason.
- The investigator can withdraw a subject from the particular period or from the study if:
  1. The subject suffers from significant inter current illness or undergoes surgery during the study.
  2. The subject experiences an AE, when withdrawal would be in the best interest of the subject or subject experiences SAE will be withdrawn from the study unconditionally.
  3. The subject fails to comply with the requirements of the protocol.
  4. The subject tests positive for alcohol and/or drugs of abuse during the time of study period.
  5. The subject is found positive for Pregnancy test or becomes pregnant during the study.
  6. It is necessary to further protect the health of the subject or the integrity of the study.
  7. Any subject cross participates in other clinical study.
  8. The subject is found to hide important medical history which in opinion of Principal Investigator may compromise study objectives or his/her safety during participation in this study
  9. In Principal Investigator's opinion it is not in the subject's best interest to continue or any other justifiable reason, which should be adequately documented.
  10. Sometimes, though rarely, the sponsor may stop the study.

Note:

1) No additional subjects will be enrolled to replace dropouts
2) Any subject who vomits within 2 hours after administration of study drug, the PK blood sampling for that period will be stopped and PK data will not be evaluated for PK; however, the pharmacodynamic assessments should be conducted. Vomiting early after administration of the test medication may decrease the bioavailability of the test drug. However, the subject may continue with subsequent periods (if any) of the study.
3) The final report will include reasons for withdrawal.
4) If any subject is withdrawn or dropped-out, subject's shall be requested for end of study safety assessment to ensure subject's safety. Subject withdrawal during the study shall be handled as per applicable SOPs with adequate documentation.

8.3 DATA COLLECTION AND FOLLOW-UP FOR DISCONTINUED SUBJECTS

Investigator should try to obtain the reason, if subject withdraws his/her consent. Reason for withdrawal from the study shall be documented, whenever possible. Post-study safety follow-up shall be performed for all prematurely discontinued subjects as per discretion of the investigator. For all discontinued subjects, data collected till the time of discontinuation shall be reported in CRF. Safety data shall be collected for all discontinued subjects, who are discontinued due to an adverse event (AE) or serious adverse event (SAE). In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If the subject is discontinued due to an event, he/she should be given an appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

9 STUDY SCHEDULE AND PROCEDURES

Procedure	Screening	Study Periods (Period 1 and 2)			End of study safety assessment
		Housing	Day 1 to 6	Day 7	
Informed Consent	√				
Inclusion Exclusion Criteria check		√			
Demographics and medication, medical History	√				
Vital Signs	√	√	√	√	√
Clinical Examination	√	√		√	√
CYP2C19 genotyping	√				
Haematology	√	√		√	√
Biochemistry	√	√			√
Serology	√				
Liver function tests	√	√		√	√
Urine analysis	√	√			√
Coagulation parameters	√	√	√	√	√
Urine pregnancy test and beta hCG test (only for female subjects)	√	√			√
12 Lead ECG	√	√			√
Chest X-ray	√				
Urine drug screen for drugs of abuse	√	√			
Breath alcohol test	√	√			
IP Administration			√		
PK Blood Sampling			√	√	
PD Blood Sampling			√	√	
Abbreviated physical examination	√	√	√	√	√
Meal		√	√		
Discharge				√	
Monitoring and capturing of AE/SAE		√	√	√	√

9.1 SCREENING (DAY -28 TO -1)

- Written informed consent will be taken from the subject. No study related procedure will be conducted prior to obtaining written informed consent.
- CYP2C19 genotyping for classifying the subject as extensive (normal) metabolizer (for group 1 and 3) or poor metabolizer (for group 2 and 4) and informed consent during screening will be obtained from the volunteer before genotyping.
- Assessment of subject eligibility as per Inclusion and Exclusion criteria.
- Demographics (Such as Height, Weight, BMI, Age, Sex, Race, Ethnicity etc.)
- Clinical examination (including abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums)
- Vital signs (including sitting blood pressure, pulse rate, respiratory rate and oral body temperature) after sitting for at least 3 minutes
- Prior medical history
- Medication history- The medication history of the subject must be recorded of at least 8 weeks prior to the screening visit.
- 12-Lead ECG
- Chest X-ray: X-ray done within 6 months of first dosing will be considered
- Clinical laboratory investigations (Hematology, Biochemistry including liver function tests, Serology)
- Coagulation parameters (PT and PTT) test
- Urine analysis (including urine pregnancy test)
- Beta hCG test (only for female subjects)
- Urine drug screen for drugs of abuse
- Breath Alcohol test

The site will carry out general screening with CYP2C19 based genotyping, so that site will have database of volunteers in sufficient number who are extensive (normal) metabolizers and poor metabolizers.

9.2 STUDY PERIOD

Housing (both periods) (Day (-1)):

- Evaluation as per inclusion/exclusion criteria
- A baseline 12-lead ECG will be performed.
- Clinical laboratory investigations (Hematology, Biochemistry including liver function tests)
- Urine analysis
- Coagulation parameters (PT and PTT) test
- Vital sign assessment (blood pressure, pulse rate, oral temperature, respiratory rate)
- Clinical examination (including abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums)
- Urine pregnancy test and beta hCG test (only for female subjects)
- Urine drug screen for drugs of abuse

- Breath alcohol test
- Monitoring and capturing of AE/SAE

Day 1 (both periods):

- Cannulation
- IP administration as per randomization
- PK blood sampling
- PD blood sampling
- Vital signs examination
- Abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums
- Coagulation parameters (PT and PTT) test at 8 hr
- Meal at appropriate time (lunch, evening snacks, dinner)
- Monitoring and capturing of AE/SAE

Day 2 (both periods):

- IP administration
- PK blood sampling
- PD blood sampling
- Vital signs examination
- Abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums
- Coagulation parameters (PT and PTT) test at 8 hr
- Meal at appropriate time (lunch, evening snacks, dinner)
- Monitoring and capturing of AE/SAE

Day 3 (both periods):

- IP administration
- PK blood sampling
- PD blood sampling
- Vital signs examination
- Abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums
- Coagulation parameters (PT and PTT) test at 8 hr
- Meal at appropriate time (lunch, evening snacks, dinner)
- Monitoring and capturing of AE/SAE

Day 4 (both periods):

- IP administration
- PK blood sampling
- PD blood sampling
- Vital signs examination

- Abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums
- Coagulation parameters (PT and PTT) test at 8 hr
- Meal at appropriate time (lunch, evening snacks, dinner)
- Monitoring and capturing of AE/SAE

Day 5 (both periods):

- IP administration
- PK blood sampling
- PD blood sampling
- Vital signs examination
- Abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums
- Coagulation parameters (PT and PTT) test at 8 hr
- Meal at appropriate time (lunch, evening snacks, dinner)
- Monitoring and capturing of AE/SAE

Day 6 (both periods):

- Cannulation
- IP administration
- PK blood sampling (Serial)
- PD blood sampling
- Vital signs examination
- Abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums
- Coagulation parameters (PT and PTT) test at 8 hr
- Meal at appropriate time (lunch, evening snacks, dinner)
- Monitoring and capturing of AE/SAE

Day 7 (both periods):

- Last PK and PD blood sampling
- Safety assessment as follow
  - ✓ Clinical laboratory test (Hematology, Liver function test, Coagulation parameters (PT and PTT))
  - ✓ Vital sign assessment (blood pressure, pulse rate, oral temperature, respiratory rate)
  - ✓ Clinical examination (including abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums)
- Discharge from the facility
- Monitoring and capturing of AE/SAE

End of Study Safety Assessment / Early Termination procedures:

- Safety assessment as follow

- Clinical laboratory test (Hematology, Biochemistry, Liver function test, Coagulation parameters (PT and PTT))
- Urine analysis
- Urine pregnancy test and beta hCG test (only for female subjects)
- Vital sign assessment (blood pressure, pulse rate, oral temperature, respiratory rate)
- Clinical examination (including abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums)
- 12 lead ECG
- Monitoring and capturing of AE/SAE
- The subjects will then be discharged from the study center.

9.2.1 HOUSING

In both periods, subjects will be housed in the clinical study facility for at least 11.00 hours before administration of the IP and will continue to remain in the clinical study facility for at least 24.00 hours after administration of the last maintenance dose of IP.

A washout period of at least 14 days will be maintained between the study periods.

The subjects will be housed in a batch of not more than 18 subjects. Only one gender subject will be housed in one clinical ward. The study will be conducted in batches of subjects as per availability of subjects.

An example: Following may be the suggested plan of clinical conduct of study for various groups in different batches.

Group	Day 1-7	Day 8-14	Day 21-27	Day 28-34	Day 1-7	Day 8-14	Day 21-27	Day 28-34
Group-1 Males	P-I		P-II					
Group-2 Males	P-I		P-II					
Group-1 Females		P-I		P-II				
Group-2 Females		P-I		P-II				
Group-3 Males					P-I		P-II	
Group-4 Males					P-I		P-II	
Group-3 Females						P-I		P-II
Group-4 Females						P-I		P-II

P-I = Period 1, P-II = Period 2

9.2.2 INVESTIGATIONAL PRODUCT ADMINISTRATION

The randomization will be generated of #40 subjects for each type of metabolizers i.e. extensive and poor, and it will be for each gender group i.e. #20 for each male and female respectively for each type of metabolizers. Total 04 randomization schedule will be prepared. Each randomization schedule should be containing 20 subjects (10 subjects for each sequence). This randomization approach will help in achieving near to equal proportionate distribution of the treatment across the study and between the gender.

As per randomization, IP will be administered as per below scheme on day 1, 2, 3, 4, 5 and 6 in each period. Subjects will be fasting overnight for at least 10.00 hours before IP administration. IP will be administered orally in sitting posture with 240 ± 2 mL of water at room temperature.

Group & Sequence	Period 1	Period 2
Group 1 (n=10, extensive metabolizers) Sequence 1	AT -10 40mg on Day 1 AT -10 10 mg on Days, 2, 3, 4, 5 & 6	Clopidogrel 300 mg on Day 1 Clopidogrel 75 mg on Days 2, 3, 4, 5 & 6
Group 2 (n=10, poor metabolizers) Sequence 1	AT -10 40 mg on Day 1 AT -10 10 mg on Days, 2, 3, 4, 5, & 6	Clopidogrel 300 mg on Day 1 Clopidogrel 75 mg on Days 2, 3, 4, 5 & 6
Group 3 (n=10, extensive metabolizers) Sequence 2	Clopidogrel 300 mg on Day 1 Clopidogrel 75 mg on Days 2, 3, 4, 5, & 6	AT -10 40 mg on Day 1 AT -10 10 mg on Days 2, 3, 4, 5 & 6
Group 4 (n=10, poor metabolizers) Sequence 2	Clopidogrel 300 mg on Day 1 Clopidogrel 75 mg on Days 2, 3, 4, 5, & 6	AT -10 40 mg on Day 1 AT -10 10 mg on Days 2, 3, 4, 5 & 6

Note: In all the periods, IP administration will be done by trained study personnel delegated by the investigator and will be reviewed by quality control / quality assurance personnel. Investigator will be available at site during IP administration. Subjects will be asked to swallow the tablet as a whole without being chewed, crushed or bitten. The time of dosing on Day 01 will be the reference time for all subsequent dosing. Dose 02 to Dose 06 will be administered at an interval of 24 hours of previous dose.

After IP administration, a mouth check will be done. It will be done by thorough check of the oral cavity using a flashlight and tongue depressor immediately after dosing followed by hand check. A 'Tear off' label will be affixed to the CRF to confirm IP administration with correct allocated IP. The actual time of IP administration will be recorded in the CRF.

9.2.3 SUBEJCT IDENTIFICATION AND COMPLIANCE

Subjects will be provided with a subject identity card with photo when any protocol related study procedure is going to be carried out. Before each dosing, trained study personnel on duty will confirm the subject's identity with the ID-card and the Subject ID mentioned on the IP label, biological fluid collection unit (if any) and the CRF.

Whenever blood sample collection, vital signs examination and meal activities are scheduled at same time, the order of activity followed will be blood sample collection, meal and vital signs examination.

9.2.4 RESTRICTIONS

Subjects will be instructed/restricted/prohibited as follows:

- Not to consume tobacco containing products (smoking, tobacco chewing, gutkha etc.) and xanthine containing food and beverages, (chocolates, tea, coffee or cola drinks) for at least 48.00 hours (02 days) prior to administration of investigational product in till last blood sample collection of the study.
- To abstain from consuming alcohol, grapefruit or its juice and cranberry juice for at least 48.00 hours (02 days) prior to administration of investigational product till last blood sample collection of the study.
- Not to consume any medication (including over-the-counter products), and recreational drugs such as Marijuana, Cocaine, Heroin, Amphetamine etc., 14 days preceding administration of IP till last blood sample collection of the study. This restriction includes vitamins taken as nutritional supplements for non-therapeutic indication. If concomitant medication is required in the above mentioned period, the subjects will be treated accordingly, and a decision to continue or discontinue the subjects will be made by the Principal Investigator, based on (a) the time the medication was administered, (b) pharmacology and pharmacokinetic interaction of concomitant medication with the IP.
- Male subjects will be advised to use adequate contraception and avoid fathering a child while receiving the Investigational Product during study. Use of hormone replacement therapy and use of androgens or anabolic steroids is not allowed in the study.
- Female subjects of child bearing potential should practice adequate contraception at least 48.00 hours (02 days) prior to administration of investigational product till end of study. Study-acceptable methods of contraception are double-barrier methods, which include combination of any 2 of the following: diaphragm, condom, copper intrauterine device, sponge, or spermicide. For female subjects, a partner's use of condoms, partner's vasectomy, or spermicide alone, are not study-acceptable methods of birth control but should be used in addition to female contraception for additional protection against conception.
- No subject may take medication during the time of sample collection or during the washout period between drug administrations.

Restriction of Drinking Water and Washroom Access:

- Drinking water will be restricted from 1 hour pre-dose until 1-hour post each dose (except during administration of the drug) in each study period unless clinically indicated. Drinking water will be allowed ad libitum at all other times.
- Subjects will be restricted from going to washroom/toilet till 01.00 hour after each dose in each study period, In case of exigencies the subject may be accompanied by the custodian/study personnel.

Posture restriction:

- In each study period, subjects will remain in sitting position for at least 04.00 hours post-dose, unless medically necessary due to adverse event or procedurally required. In these cases it will not be considered as protocol deviation. Subjects will be allowed to do normal routine activity avoiding strenuous physical activity during the entire housing period of the study.

9.2.5 DISTRIBUTION OF MEALS

On each housing day, subjects will be provided with standardized lunch, evening snacks and dinner at appropriate time (e.g. at 4, 8 and 12 hr of IP administration).

9.2.6 PHARMACOKINETIC BLOOD SAMPLE COLLECTION

Blood samples (5 mL each) for PK analysis will be collected at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after study drug administration on Days 1 and 6 in each period. On Days 3, 4 and 5 in each period only the pre-dose sample will be collected.

The pre-dose (0.0 or 24.00 hour) blood sample shall be taken within 45 minutes prior to dosing on each dosing day in each period. All post-dose samples in each period will be collected within + 2 minutes of the scheduled time of blood sample collection.

Note:
In each period, 24 hour post dose sample of Day 1 will be considered as pre-dose sample of respective day.

PK blood samples will be collected through an indwelling intravenous cannula placed in a forearm vein or dorsal aspect of hand of the subjects. Intravenous indwelling cannula will be kept in situ as long as possible (up to 12 h) by injecting 0.3 mL of normal saline (to prevent cannula from clogging) and 0.3 mL of normal saline diluted blood will be discarded prior to collection of the next PK sample. In case the indwelling cannula is blocked or does not function properly or it must be removed for practical reasons, then if necessary re-cannulation procedures will be performed and particular blood sample may be collected by direct vein puncture. A blood sample of (1×3.0 mL) will be collected to perform Beta hCG test (for female subjects) at screening. Extra blood sample may be collected for repeat laboratory test(s), if required, at the discretion of the investigator.

Total volume of blood drawn will not exceed 551.4 mL+ 10 mL per male subject and 563.4 mL + 10 mL per female subject for the entire study.

Description	Blood loss for male subjects	Blood loss for female subjects
Blood withdrawn for screening	20	20
Blood loss for the samples of period I and II (for PK)	290	290

Blood loss for the samples of period I and II (for Pharmacodynamic blood sample (Aggregometry))	135	135
Discarded blood of normal saline	14.4	14.4
Blood withdrawn for post study laboratory assessment	12	12
Blood withdrawn for serum pregnancy test (for female subjects only)	-	12
Blood withdrawn for coagulation parameters and other laboratory tests at housing of both period and discharge of period I	80	80
Total blood loss for the study*	**551.4**	**563.4**
*Note: Based on Investigator discretion additional blood sample (up to 10 mL) may be collected for additional tests/repeats, sample clots, sample spillage or any other justifiable reason, if deemed necessary.		

Extra blood sample may be collected for repeat laboratory test(s), if required, at the discretion of the investigator.

9.2.7 SAMPLE PROCESSING AND SHIPMENT TO BIOANALYTICAL SITE

A separate bioanalytical lab manual will be prepared for sample management. The manual will include procedures to be followed for sample processing at clinical site, sample shipment from clinical site to bioanalytical site and sample storage conditions to be followed at clinical and bioanalytical site.

10 TREATMENT OF SUBJECT

10.1 DESCRIPTION OF INVESTIGATIONAL PRODUCT

	Test product
Active Ingredient	AT-10
Dosage form	Tablet
Strength	10 mg, 30 mg or 40 mg
Marketed / Distributed / Supplied by:	Manufactured by Ipca Laboratories Ltd. India
Note: For administration of 40mg dose, one tablet of 10mg and one tablet of 30mg may be used.	

	Reference product (Plavix)
Active Ingredient	Clopidogrel
Dosage form	Tablet
Strength	75 mg and/or 300 mg
Marketed / Distributed / Supplied by:	Distributed by Bristol-Myers Squibb / Sanofi Pharmaceuticals Partnership, Bridgewater, NJ
Note: For administration of 300 mg dose, 4 tablets of 75mg may be used.	

The Batch no./Lot no., Mfg. date, Re-test date, and other details of the drug will be mentioned in the final Clinical Study report.

10.2 SUPPLY AND ACCOUNTABILITY OF INVESTIGATIONAL PRODUCTS

- The Sponsor shall supply sufficient quantities of the IPs for the study conduct and properly labeled according to the applicable requirements.
- It is the responsibility of the Sponsor to ensure that appropriate Investigational Product identification, assay testing and dissolution profiles for the test(s) are provided to CBCC Global Research LLP clinical study centre before the start of the clinical study.
- The Investigational Products will be received by the Principal Investigator or Clinical Investigator or Research Pharmacist or a suitable designate from the concerned department along with Certificate of Analysis (COA)
- The investigational products will be supplied in an appropriate package deemed to maintain the integrity of the product.
- Records will be made of the receipt and dispensing of clinical supplies to provide complete accountability of all supplies.
- The supplies will be stored with appropriate labeling at specified storage conditions as per label instructions or as per COA or as per any written storage instructions provided by the sponsor in pharmacy accessible only to the pharmacist or authorized personnel.
- All the investigational products shall be issued and used in accordance with the protocol and it is the investigator's responsibility to ensure that an accurate record of the investigational product issued and returned is maintained.

- Batch number / lot number, manufacturing date, manufactured by / distributed by/manufactured for investigational product(s) will be included in the final report.

10.3 DISPENSING AND LABELING OF INVESTIGATIONAL PRODUCTS

The dispensing of the investigational products will be done as specified in the relevant SOP by pharmacist as per dispensing plan. For each subject a single dose of test product will be placed in an individually labeled HDPE container.

The HDPE container label and a duplicate 'tear off' label for the subject CRF will essentially bear at least the below mentioned details:

- Cautionary statement "For Clinical Research Use Only"
- Protocol No.
- Subject ID.
- Day and Period
- Pharmaceutical Dosage form
- Name of active ingredient and strength
- Number of units
- Specified Storage Conditions

The 'tear off' label will be affixed on to the subject's CRF to confirm correct allocation of the Investigational Products during dosing.

10.4 IP RETENTION

After the completion of the study, all the remaining investigational products will be retained as per instruction of the sponsor.

10.5 CONCOMITANT MEDICATION

Subjects will not be permitted to take any prescription medicine or Over the Counter (OTC) products (including vitamins and products from natural origin e.g. St. John's Wort) within 14 days prior to IP administration in Period 01 and during the course of the study. If the Principal Investigator or Clinical Investigator considers that, some medication is essential for the well-being of the subject, it may be given and if any of the subjects takes any medication during the course of the study, they must inform the Principal Investigator or Clinical Investigator. The decision to withdraw a subject from the study will be taken by the Principal Investigator based on the possible interference of the drug with the study or analysis, and on the continuing health of the subject. All occasions of non-study drug intake will be recorded.

11 ASSESSMENTS

11.1 SAFETY ASSESSMENTS

Subject Screening

Medical history and demographic data including sex, age, body weight (Kg), and height (cm), habits will be recorded during a general screening of subjects that is organized within 28 days prior to study start. Each subject will undergo a complete general clinical examination followed by CYP2C19 genotyping (to classify the subject as extensive (normal) metabolizer (for group 1 and 3) or poor metabolizer (for group 2 and 4)) and laboratory tests for hematology, clinical bio-chemistry, serology, urine analysis, serum pregnancy test (for female subjects) and test for alcohol (in breath), drugs of abuse. Tests for alcohol (in breath) and drugs of abuse will also be done before housing of each period. Only medically healthy subjects with clinically acceptable laboratory profiles, chest X- ray (PA-view) and 12-lead ECG will be enrolled into the study.

Clinical / Diagnostic Laboratory Tests

Clinical / Diagnostic Laboratory tests to be done during the screening are tabulated below:

<table>
<tr><th colspan="3">Clinical / Diagnostic Laboratory Tests at Screening</th></tr>
<tr><td colspan="3">• CYP2C19 allele 1, and 2, 3 and 17 genotyping (to classify the subject as extensive (normal) metabolizer (for group 1 and 3) or poor metabolizer (for group 2 and 4))</td></tr>
<tr><td>Hematology
▪ Hemoglobin
▪ Hematocrit
▪ Total and differential leukocyte count
▪ Red blood cell count
▪ Platelet count</td><td>Clinical bio-chemistry
▪ Total Cholesterol
▪ Triglycerides
▪ Random Blood Sugar (RBS)
▪ Creatinine
▪ Sodium
▪ Potassium
▪ Chloride
▪ Urea</td><td rowspan="2">Urine analysis
▪ Color
▪ Transparency
▪ pH
▪ Specific Gravity
▪ Blood in urine
▪ Proteins
▪ Glucose
▪ Ketone
▪ Bilirubin
▪ Urobilinogen
▪ Microscopic Examination
▪ Pregnancy Test (for female volunteer only)
▪ Urine Drug of Abuse Screen (for Morphine, Marijuana, Phencyclidine, Amphetamine, Cocaine, and Benzodiazepine)</td></tr>
<tr><td>▪ Coagulation parameters (PT and PTT) test</td><td>Liver Function and Other Enzyme Tests
▪ Total Bilirubin
▪ Total protein
▪ Albumin
▪ Creatinine Kinase
▪ Alanine Aminotransferase (ALT)
▪ Aspartate Aminotransferase (AST)
▪ Alkaline Phosphatase (ALP)</td></tr>
<tr><td colspan="2">Serology
▪ Human Immunodeficiency Virus (HIV) 1 and 2
▪ Hepatitis B
▪ Hepatitis C
▪ Rapid Plasma Reagent (RPR)</td><td>Others
▪ Beta hCG test (for female subjects)</td></tr>
<tr><td colspan="2">Chest X-ray (PA view)</td><td>12-lead Electrocardiogram (ECG)</td></tr>
</table>

Clinical / Diagnostic Laboratory tests to be done during housing (both period) are tabulated below:

<table>
<tr><th colspan="3">Clinical / Diagnostic Laboratory Tests at housing of both periods</th></tr>
<tr><td>Hematology
▪ Hemoglobin
▪ Hematocrit
▪ Total and differential leukocyte count
▪ Red blood cell count
▪ Platelet count</td><td>Clinical bio-chemistry
▪ Total Cholesterol
▪ Triglycerides
▪ Random Blood Sugar (RBS)
▪ Creatinine
▪ Sodium
▪ Potassium
▪ Chloride
▪ Urea</td><td rowspan="2">Urine analysis
▪ Color
▪ Transparency
▪ pH
▪ Specific Gravity
▪ Blood in urine
▪ Proteins
▪ Glucose
▪ Ketone
▪ Bilirubin
▪ Urobilinogen
▪ Microscopic Examination
▪ Pregnancy Test (for female volunteer only)
▪ Urine Drug of Abuse Screen (for Morphine, Marijuana, Phencyclidine, Amphetamine, Cocaine, and Benzodiazepine)</td></tr>
<tr><td>▪ Coagulation parameters (PT and PTT) test</td><td>Liver Function and Other Enzyme Tests
▪ Total Bilirubin
▪ Total protein
▪ Albumin
▪ Creatinine Kinase
▪ Alanine Aminotransferase (ALT)
▪ Aspartate Aminotransferase (AST)
▪ Alkaline Phosphatase (ALP)</td></tr>
<tr><td colspan="2">Beta hCG test (for female subjects)</td><td>12-lead Electrocardiogram (ECG)</td></tr>
</table>

Clinical / Diagnostic Laboratory tests to be done on Day 1 to 6 (both periods) are tabulated below:

Clinical / Diagnostic Laboratory Tests on Day 1 to 6 (both periods)
▪ Coagulation parameters (PT and PTT) test at 8 hr

Clinical / Diagnostic Laboratory tests to be done on Day 7 (at discharge in both periods) are tabulated below:

Clinical / Diagnostic Laboratory Tests on Day 7 (at discharge in both periods)
Hematology ▪ Hemoglobin ▪ Hematocrit ▪ Total and differential leukocyte count ▪ Red blood cell count ▪ Platelet count
Liver Function and Enzyme Tests ▪ Total Bilirubin ▪ Total protein ▪ Albumin ▪ Creatinine Kinase ▪ Alanine Aminotransferase (ALT) ▪ Aspartate Aminotransferase (AST) ▪ Alkaline Phosphatase (ALP)
▪ Coagulation parameters (PT and PTT) test

Clinical / Diagnostic Laboratory tests done on end of study safety analysis (at discharge of period 2) are tabulated below:

<table>
<tr><td colspan="3">Clinical / Diagnostic Laboratory Tests at End Of Study Safety Analysis (at discharge of period 2)</td></tr>
<tr><td>Hematology
▪ Hemoglobin
▪ Hematocrit
▪ Total and differential leukocyte count
▪ Red blood cell count
▪ Platelet count</td><td>Clinical bio-chemistry
▪ Total Cholesterol
▪ Triglycerides
▪ Random Blood Sugar (RBS)
▪ Creatinine
▪ Sodium
▪ Potassium
▪ Chloride
▪ Urea</td><td rowspan="2">Urine analysis
▪ Color
▪ Transparency
▪ pH
▪ Specific Gravity
▪ Blood in urine
▪ Proteins
▪ Glucose
▪ Ketone
▪ Bilirubin
▪ Urobilinogen
▪ Microscopic Examination
▪ Pregnancy Test (for female volunteer only)</td></tr>
<tr><td>▪ Coagulation parameters (PT and PTT) test</td><td>Liver Function and Other Enzyme Tests
▪ Total Bilirubin
▪ Total protein
▪ Albumin
▪ Creatinine Kinase
▪ Alanine Aminotransferase (ALT)
▪ Aspartate Aminotransferase (AST)
▪ Alkaline Phosphatase (ALP)</td></tr>
<tr><td colspan="2">Beta hCG test (for female subjects)</td><td>12-lead Electrocardiogram (ECG)</td></tr>
</table>

Note:

1) Urine pregnancy test (for female subjects) will be performed by using pregnancy kit.
2) If a chest X-ray (PA-view) was taken for the subject within 06 months prior to the IP administration, the same will be considered.

If required, any of the laboratory blood and urine tests as mentioned above may be repeated once with a fresh sample, at the discretion of the Investigator, for confirmation.

All subjects who receive at least one dose of the study drug will be included in the safety analysis.

Vital Signs & Wellbeing:

Vital signs (sitting blood pressure, pulse rate, respiratory rate and oral temperature) and wellbeing will be assessed at following time-point.

- Screening
- Housing (both periods)
- Day 1 to 6 (both periods): Pre-dose, 03.00, 06.00 and 10:00 hours of IP administration
- Day 7 at Discharge (both periods)

All these vital signs and well-being assessment will be completed within ±01.00 hour of the scheduled time so as not to interfere with scheduled blood sampling times or meals. The actual time of measurement will be recorded in the CRF.

Abbreviated Physical Examination:

Abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums will be carried out as a part of clinical examination at screening, housing, discharge and end of study safety assessment as well as on day 1 to 6 (both periods) at 2, 4, 8, 12 hr of IP administration.

11.2 PHARMACODYNAMIC EFFECT ASSESSMENTS

Pharmacodynamic effect will be assessed by whole blood impedance or optical platelet aggregometry using ADP as an agonist. Blood sample for aggregometry will be collected at pre-dose and at 0.5, 2, 6 hr of IP administration on day 1 to 6 (both periods) and additionally at 24 hrs post dose sample on last dosing day of each period in sodium citrate tube. The pre-dose (0.0 hour) blood sample shall be taken within 45 minutes prior to dosing on each dosing day in each period. Blood samples will be collected as per procedure similar to pharmacokinetic blood sample collection (section 9.2.6 Pharmacokinetic Blood Sample Collection). (Note: The blood samples for aggregometry will be analyzed at the site.)

For aggregometry, 2.7 mL blood sample will be collected and processed. Preferably, the blood should be drawn with a minimum of trauma or stasis at the venipuncture site and preferred needle size is between 19 and 21 gauge.

Aggregometry will be carried-out after stimulation with 20 µM of ADP. All analyses will be performed by trained personnel. Aggregation curves will be recorded and analyzed.

12 SUBJECT SAFETY

12.1 ASSESSING, RECORDING AND ANALYZING SAFETY PARAMETERS

12.1.1 Adverse Events

As per Indian GCP guidelines, adverse event (AE) is 'Any untoward medical occurrence (including a symptom / disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human subject that does not necessarily have a relationship with the treatment being given'.

As per ICH-GCP (E6 R2) guidelines, adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

All AEs must be graded for severity and relationship to IP. All AEs will be followed to adequate resolution.

All AEs including local and systemic reactions not meeting the criteria for "serious adverse events" should be captured on the pre-defined CRF AE pages. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product and time of resolution/stabilization of the event. All AEs occurring while in the study must be documented appropriately regardless of relationship.

Severity of event
For evaluating severity, following classification will be used to quantify intensity:

Table: Severity classification of adverse event

Mild	Adverse event which is asymptomatic or with mild symptoms; clinical or diagnostic observations only; and intervention not indicated.
Moderate	Adverse event which requires minimal, local or noninvasive intervention; limits age-appropriate instrumental activities of daily living e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.
Severe	Adverse events which are medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living e.g. bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Significant changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed.

The occurrence of adverse event can be classified as follow.
Single episode: Adverse event occurred as one episode
Intermittent: Adverse event is reoccurring after some clinically significant gap / pause
Continuous: Adverse event is occurring continuously without interruption

Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to investigational products

Causality assessment of adverse events shall be done as per WHO-UMC system. Causality assessment is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and all available information about the adverse event. The causality assessment can be done by classifying the association of the adverse event with the IP as definite / certain, probable / likely, possible or unlikely.

Definite / Certain: Following are the criteria to classify the adverse event causality as definite / certain.

- Having plausible time relationship to IP intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

Probable / Likely: Following are the criteria to classify the adverse event causality as probable / likely.

- Having reasonable time relationship to IP intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

Possible: Following are the criteria to classify the adverse event causality as possible.

- Having reasonable time relationship to IP intake
- Could also be explained by disease or other drugs
- Information on IP withdrawal may be lacking or unclear

Unlikely: Following are the criteria to classify the adverse event causality as unlikely.

- Having time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

During initial reporting, the causality assessment may be reported as conditional / unclassified or unassessible / unclassifiable because of non-availability of required information; however, it can be revised later on once required information are made available.

Conditional / Unclassified: Following are the criteria to classify the adverse event causality as conditional / unclassified.

- More data for proper assessment needed, or
- Additional data under examination

Unassessible / Unclassifiable: Following are the criteria to classify the adverse event causality as unassessible / unclassifiable.

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

If AE is ongoing at a visit, please follow the subject till the event get resolved or condition gets stabilized.

12.1.2 Serious Adverse Event or Serious Adverse Drug Reaction

As per ICH-GCP (E6, R2), ICMR and Indian GCP guidelines, serious adverse event (SAE) or serious adverse drug reaction is any medical occurrence that at any dose:

No.	Description
1	Results in death
2	Is life threatening
3	Requires inpatient hospitalization or prolongation of existing hospitalization
4	Results in persistent or significant disability/incapacity
5	is a congenital anomaly or birth defect
6	Requirement of intervention to prevent permanent impairment or damage

Any other important medical event that may not result in death, or is life threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic broncho-spasm requiring intensive treatment in an emergency room or at home, blood dyscarsias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs will be recorded on the appropriate SAE form.

12.1.3 Abnormal Laboratory Values or Abnormal Clinical Findings

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Abnormal laboratory values or abnormal clinical findings at the time of screening will be considered as medical history and not AE. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have

returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Abnormal lab values observed during study or in post study safety analysis should be reported as an adverse event if-

- The test result is accompanied by an associated symptom or clinical sign.
- The test result requires an additional diagnostic exam or medical/surgical intervention.
- The test result leads to a change in the study drug dose or study discontinuation, introduction of a significant concomitant drug treatment or other therapy.
- The test result is considered by the principal investigator/clinical investigator or by the sponsor as an adverse event.

12.2 ADVERSE EVENT DOCUMENTATION

All adverse events that are reported will be properly documented on the adverse event reporting form. In particular the information required will include: a full description of the event, date and time of onset, date and time of reporting, date and time of dosing, description of the severity of the event, any treatment or diagnostic steps taken in relation to the event, description of the outcome of the event, judgment by the physician of any relationship of the event to the Investigational Product or procedures.

A summary of the recorded adverse events capturing all the necessary details will be forwarded to the sponsor's pharmacovigilance department at pharmacovigilance.mumbai@ipca.com on resolution of the adverse event.

12.3 REPORTING OF SERIOUS ADVERSE EVENTS

All the serious adverse events should be reported by Investigator to the Ethics Committee and through CBCC Global Research LLP to the CLA and the Sponsor or his representative within 24.00 hours of their occurrence. The report of SAE of death after due analysis to be forwarded within 14 days of occurrence. The reporting of SAE from investigator and sponsor shall be done as per New Drugs and Clinical Trials Rules 2019 as tabled below.

Reporting SAE (including permanent disability or any other injury other than death)			
Particular	***From***	***To***	***Timelines***
Initial	Investigator	CLA, Sponsor / its Representative, EC	24 hr of occurrence
With Due Analysis	Investigator	CLA, Chairperson of EC, Head of Institute	14 days of reporting
With Due Analysis	Sponsor / its Representative	CLA, Chairperson of EC, Head of Institute	14 days of reporting

Reporting SAE (Death)			
Particular	***From***	***To***	***Timeline***
Initial	Investigator	CLA, Sponsor / its Representative, EC	24 hr of occurrence
With Due Analysis	Investigator	CLA, Head of Institute	14 days of knowledge of occurrence
With Due Analysis	Sponsor / its Representative	CLA, Head of Institute	14 days of knowledge of occurrence

In case the Investigator fails to report any serious adverse event with in the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the CLA along with the report of the serious adverse event.

12.4 DCGI NOTIFICATION

CBCC Global Research LLP on behalf of sponsor shall notify the DCGI, by submission of any SAE(s) [as per regulatory requirement of India] associated with the use of the drug as soon as possible but not later than 14 days.

The Investigator will report all serious adverse events (including death, irrespective of the reason) to the applicable local regulatory authority, Sponsor, Ethics Committee and Head of institution within 24 hours of occurrence. The notification to the applicable local regulatory authority, Sponsor, Independent Ethics Committee and Head of institution has to be followed by a serious adverse event report (including death, irrespective of the reason) as per the required timelines of applicable regulatory requirements. The Sponsor and Ethics Committee will inform to the applicable regulatory authorities as per the required timelines, as applicable. The written report will include a detailed description of the observed symptoms, laboratory tests and treatment of the event. Subject demographic information, subject history, concomitant medication and date/time of occurrence and report of the event must also be clearly stated. The Investigator will judge the possible causal relationship between the event and the investigational medicinal product. The study may be suspended or terminated depending on the seriousness of the adverse effects encountered during the study.

12.5 EXPOSURE IN UTERO DURING CLINICAL STUDIES

If a subject becomes pregnant during study then she will be discontinued from the study and will be followed until the outcome of the pregnancy is known (e.g., delivery, elective termination, or spontaneous abortion). If subject becomes pregnant within 07 days after administration of last dose of study medication will be followed until the outcome of the pregnancy is known (e.g., delivery elective termination, or spontaneous abortion). The investigator should make every effort to follow the subject until completion of the pregnancy. The Investigator must notify sponsor and ethics committee within 24.00 hours of first identification of the occurrence of pregnancy. Although pregnancy is not technically an AE or SAE, if the outcome of pregnancy meets the criteria for immediate classification as a SAE i.e., post-partum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly,

including that in an aborted foetus, the investigator will follow the procedure for reporting SAEs.

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13 BIOANALYTICAL PROCEDURES

Plasma samples will be assayed by a validated LCMS/MS method developed at Cliantha Research, Ahmedabad, which is specific for the determination of Clopidogrel, AT -10 (2-oxo-clopidogrel) and its metabolite MP-H4.

All available samples will be analyzed. Concentration values of the subject withdrawn/dropped out will be presented in a separate table. All concentration values below the limit of quantification will be set to zero for all pharmacokinetic and statistical evaluation. However, the concentration below the limit of quantification will be reported as Below Limit of Quantification (BLQ) in the concentration table. Any missing sample will be reported as “M” and Non-reportable concentration values will be reported as “NRV”.

The criteria for repeat analysis, as defined in the respective in-house procedure will be followed. Incurred sample reanalysis will be performed as per Cliantha Research, Ahmedabad, In-house SOP standard).

14 DATA HANDLING AND DATA ANALYSIS

14.1 SOURCE DOCUMENTS

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents and data records include, but are not limited to, clinical pharmacology records, clinical and office charts, laboratory notes, memoranda, patient's memory aid (diaries) or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, and patient files and records kept at the pharmacy, laboratories and medico-technical departments involved in the clinical study.

The study site will maintain appropriate medical and research records for this study, in compliance with ICH E6 guidelines and Indian GCP guidelines along with the regulatory and institutional requirements for the protection of confidentiality of subject. Sponsor and EC will have access to records. The study site will permit authorized representatives of the sponsor(s), EC and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

14.2 DATA COLLECTION

Study specific paper case record form (CRF) will be designed by CBCC Global Research LLP and used to document the subject's data during the course of the study. The investigator will ensure that all data are entered promptly, legibly, completely and accurately. The CRF along with subjects 12-lead ECG recording, chest X-ray (PA view), lab reports etc. will serve as source documents.

14.3 PHARMACOKINETIC PARAMETERS AND ANALYSIS

Pharmacokinetic parameters (AUCt, AUCinf, Cmax, tmax, t½, kel, Cl/F, Vd/F) will be estimated following noncompartmental analysis of plasma concentration time-course data for Clopidogrel, AT -10 (2-oxo-clopidogrel), and MP-H4. PK parameters at steady-state will be estimated for Clopidogrel, AT -10(2-oxo-clopidogrel), and MP-H4. Statistical comparison of the single-dose and multiple-dose PK parameters of peak (Cmax) and total (AUCt, AUCinf) exposure for the AT-10 and MP-H4 will be made between the AT-10 and Clopidogrel dose groups; between and within metabolizer groups. Additionally, geometric means will be calculated for AUCt, AUCinf, and Cmax. Analyses of variance (ANOVA) will be performed on the ln-transformed PK parameters AUCt, AUCinf, and Cmax. Each ANOVA will include calculation of least-squares means (LSMs), the differences between adjusted means, and the standard error associated with these differences. Ratios of means will be calculated using the LSM for Lntransformed AUCt, AUCinf, and Cmax. Although this is not a bioequivalence study, statistical comparison of the PK of AT-10 and MP-H4 between the AT-10 and Clopidogrel dose groups will be performed.

Although this is not a bioequivalence study following PK comparison will be made:

- PK comparisons will be made for AT -10 and MP-H4 from AT -10 treatment in extensive metabolizers versus Clopidogrel treatment in extensive metabolizers
- PK comparisons will be made for AT -10 and MP-H4 from AT -10 treatment in poor metabolizers versus Clopidogrel treatment in poor metabolizers
- PK comparisons will be made for AT -10 and MP-H4 from AT -10 treatments in extensive metabolizers versus AT -10 treatments in poor metabolizers.

The 90% confidence interval of the relative mean (geometric least square mean) of AT -10 and MP-H4 from AT -10 treatment versus Clopidogrel treatment for Ln-transformed Pharmacokinetic parameters Cmax, AUCt, AUC(0-inf) will be computed. Other PK comparison will be made if deemed appropriate.

C_{max}	Maximum measured plasma concentration over the time span specified
T_{max}	Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value
AUC_{0-t}	Area under the concentration-time curve from time zero to the last sample with quantifiable concentration calculated using the linear trapezoidal method
AUC_{0-inf}	Total area under the concentration-time curve from time zero extrapolated to infinity
$t_{½}$	The terminal elimination half-life calculated by ln2/Kel
K_{el}	The elimination rate constant
% AUC_Extrapolation	It is the percentage of extrapolated area under the plasma concentration versus time curve from the last measurable concentration to infinity. It will be calculated as $\{(AUC_{0-inf} - AUC_{0-t}) / AUC_{0-inf}\}$ X 100

Actual time of blood sample collection will be used for pharmacokinetic calculation. All concentration values below the Limit of Quantification (LOQ) will be set to "zero" for all pharmacokinetic and statistical calculations. Any missing concentration will be reported as "Missing" and will not be included for pharmacokinetic and statistical analysis.

14.4 PHARMACODYNAMIC EFFECT ANALYSIS

ADP induced platelet aggregation will be assessed for change from baseline in each treatment group at each time point assessed on each dosing day (0.5, 2 and 6 hours post dose) and 24 hrs post dosing of last dosing day in each period. The change over time for each parameter will also be assessed.

Platelet inhibition will be calculated as per below formula.

Platelet Inhibition = (1 – Residual Impedance / Baseline Impedance) × 100

The results will be reported as either residual platelet aggregation, measured as maximal amplitude of impedance (ohms), or platelet inhibition. The data from treatment groups 1 and 3 will be combined in the

analysis and similarly for treatment group 2 and 4 will be combined in the analysis. Statistical comparison will be made between the change from baseline at each time point between the treatment groups 1 and 3 (extensive metabolizers) versus treatment groups 2 and 4 (poor metabolizers) for each treatment (AT -10 and Clopidogrel). If applicable, as clinical phase of study will be conducted in group of volunteers not more than 18, volunteer group effect will also be analyzed statistically.

The incidence of signs of bleeding from the abbreviated physical examination and the incidence of abnormal liver function tests (ALT, AST, total bilirubin, and alkaline phosphatase) will be tabulated for the treatment groups. The incidence of these events will not be formally tested and the comparison will be observational only. The observational comparisons will be made between the AT -10 and Clopidogrel in the extensive metabolizers and poor metabolizers.

Additionally, the relationship between the PK of MP-H4 and pharmacodynamic measurements will be addressed using population PK-PD analysis.

15 ETHICAL AND REGULATORY STANDARDS

15.1 ETHICAL PRINCIPLES, LAWS AND REGULATIONS

The clinical study will be conducted as per the principles and requirements of Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, 2013), and are consistent with the ICH-GCP (E6-R2) guidelines along with the local regulatory requirements of GCP for Clinical Research In India (2004, CDSCO), New Drugs and Clinical Trials Rules 2019 and all applicable amendments (Drug and Cosmetics Rules, 1945) and ICMR's National Ethical guidelines for Biomedical and Health Research involving Human Participants (2017).

15.2 ETHICS COMMITTEE

Protocol (protocol amendment, if applicable) and associated documents will be reviewed by Ethics Committee (EC), Registered with CDSCO, for the formal approval of the study conduct. The decision of the EC signed by its chairman / designed person of EC with EC composition, concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. If requested, a progress report during the study and a summary of the study at the end of the clinical study will be sent to the EC. The study will not commence until the committee has approved the final version of the protocol.

15.3 INFORMED CONSENT PROCESS

The investigator or a person designated by the investigator, and under the investigator's responsibility, should completely inform the subjects and/or their families describing this study and providing sufficient information to them for making an informed decision about their participation in this study.

All the subjects should be informed to the complete extent possible about the study, in language and terms they are able to understand. Consent form must be EC approved and the subject will be provided the consent in vernacular language of his /her choice(s).

Prior to subject's participation in this study, the written informed consent form must be signed, name filled in and personally dated by the subject / impartial witness (along with subject's thumb impression in case when he/she is illiterate) and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the subject.

Subjects may be paid an adequate (EC approved) participation fee on account of their participation in the study. In case of withdrawal of a subject before completion of the study, subject will be paid compensation corresponding to the extent of participation and any controversy pertaining to this will be forwarded to EC and the decision of EC will be final as well as binding on both the subjects and CBCC Global Research LLP.

As per New Drugs and Clinical Trials Rules 2019, audio-video recording of the informed consent process is not applicable for this study.

15.4 SUBJECT AND DATA CONFIDENTIALITY

Subject confidentiality along with the information disclosed/provided/produced by the sponsor during the clinical study, including, but not limited to, the clinical study protocol, the CRFs, ICFs and results are strictly held in trust by the sponsor, sponsor's authorized personnel, investigator and their staff members, CBCC and its staff. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records maintained by the investigator and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

However, the submission of this clinical study protocol and other necessary documentation to the ethics committee (EC) is expressly permitted, the EC members having the same obligation of confidentiality.

16 RECORD RETENTIONS

It is the responsibility of Sponsor to make arrangements for safe and secure custody of all study related documents and material for a period of 15 years after the completion of the study. These documents should be retained for a longer period of time, if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator / institution as to when these documents no longer need to be retained. The Bioanalytical, data will be archived at Bioanalytical site.

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17 STUDY MONITORING, AUDITING AND INSPECTING

17.1 RESPONSIBILITIES OF INVESTIGATORS

The investigator(s) is responsible to perform the clinical study in compliance and accordance with this clinical study protocol, ICH E6 guidance and all other applicable guidelines and regulations. The investigator is also responsible to provide reliable data and all information requested by the clinical study protocol (with the help of CRF, or other appropriate mode of communication) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by sponsor/sponsor representatives.

17.2 RESPONSIBILITIES OF SPONSORS

The sponsor of this clinical study is responsible for taking all reasonable steps to ensure the proper conduct of the protocol as regards ethics, clinical study protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main role of the clinical monitoring team is to help the investigator and the sponsor in maintaining a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical study.

17.3 AUDITING AND INSPECTING

The investigator will permit study-related monitoring, audits and inspections by the EC, the sponsor, government regulatory bodies and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator agrees to allow the auditors or 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. The confidentiality of the data verified and the protection of the subjects should be respected during these inspections.

The investigator will ensure the capacity for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, study documents etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and quality assurance offices. As soon as the investigator is notified of a future inspection by the authorities, he/she will inform the sponsor and authorize the sponsor to participate in these inspections. Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the investigator to the sponsor.

17.4 QUALITY CONTROL AND QUALITY ASSURANCE

The Principal Investigator by careful planning, assigning responsibilities to well qualified study personnel, through continuous review, verifies and maintains desired level of quality in the study process.

Review will be carried out by the QA department to confirm that deviations if any, from approved protocol or SOPs are adequately documented.

The bioanalytical and statistical site will be responsible for quality assurance audit of bioanalytical and statistical data.

18 ADMINISTRATIVE PROCEDURES

The investigator must maintain confidentiality of all study related documents, and take measures to prevent accidental or premature destruction of these documents. The retention of the study related documents is depicted in the present protocol. The trial master file will be maintained by the CRO.

18.1 PROTOCOL AMENDMENTS

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Sponsor, CDSCO where required, and the EC.

Notwithstanding the need for approval of formal protocol amendments, the investigator is responsible to take any immediate action required for the safety of any subject included in this study, even if this action represents a violation of the protocol. In such cases Sponsor should be notified of this action and the EC should be informed as soon as possible.

18.2 PROTOCOL DEVIATIONS AND VIOLATIONS

According to FDA Inspectional Manual, the term "Protocol Deviation" is "A protocol deviation/violation that is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change". A protocol deviation or violation is any noncompliance with the requirements of clinical study protocol, SOPs, ICH-GCP-E6 guidelines and New Drugs and Clinical Trials Rules 2019 (CDSCO) guidelines. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations or violation, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the CRO to observe vigilance to identify and report deviations immediately upon identification of the protocol deviation. All deviations from the protocol must be addressed in study subject source documents. A completed copy of the protocol deviation form must be maintained in the regulatory file, as well as in the subject's source document. Protocol deviations must be sent to the EC, if required, per their guidelines. The investigator / staff is responsible for adhering to EC requirements.

18.3 INSURANCE COMPENSATION

The sponsor will ensure that a liability insurance policy covering this clinical study in accordance with local laws and requirements will be made available prior to first subject enrollment. A copy of the insurance certificate will be provided to the EC.

CBCC will execute insurance on behalf of Sponsor and will ensure it's in effect throughout the study duration. The insurance will cover CBCC's liabilities for professional indemnity in the current study.

In the case of an injury occurring to the subject during the study, free medical management will be provided to the subjects as long as required or till such time it is established that the injury is not related to the clinical study, whichever is earlier.

18.4 INDEMNITY AGREEMENT AND STUDY FINANCES

Sponsor will undertake to maintain an appropriate clinical study insurance and indemnity policy.

Deviation from the study Protocol-Especially the prescription of a dose other than that scheduled in the study Protocol, other modes of administration, other indication, and longer treatment periods – are not permitted and shall not be covered by the Insurance.

18.5 PREMATURE DISCONTINUATION OF THE STUDY

Sponsor on the basis of new information regarding safety or efficacy, reserves the right to terminate the investigational site or this clinical study at any time. Reasons for termination include, but not limited to, following:

a) Unacceptable safety issues
b) If the investigator has received from the sponsor all investigational products, means and information necessary to perform the clinical study and has not included any subject after a reasonable period of time mutually agreed upon, site can be prematurely closed.
c) The site can be prematurely closed if there is an event of breach by the investigator of the fundamental obligation under this agreement, including but not limited to breach of the clinical study protocol, breach of the applicable laws and regulations or breach of the applicable guidelines for GCP.
d) Additionally,
    a. EC can terminate the study for the safety of subjects and major violations of ethical considerations.
    b. Subsequent review of serious, unexpected, and related AEs by the medical monitor, EC, the sponsor(s), or local regulatory authorities may also result in suspension of further study interventions/administration of study product at a site. The study sponsor(s) retain the authority to suspend additional enrollment and study interventions/administration of study product for the entire study, as applicable.

18.6 PROPERTY RIGHTS AND DATA PROTECTION

All information, documents and investigational product provided by the sponsor or its assignee are and remain the sole property of the sponsor. The investigator shall not mention any information or the product in any application for a patent or for any other intellectual property rights. All the results, documents and inventions, which arise directly or indirectly from the clinical study in any form, shall be the exclusive property of the sponsor. Any investigator involved with this study is obliged to provide the sponsor with complete test results and all data derived from the study. The sponsor may use or exploit

all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical study.

The data collected during the entire study will be included in the sponsor database and shall be treated in compliance with the SOPs prepared according to applicable laws and regulations. When archiving or processing the data, sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

18.7 CLINICAL STUDY REPORT

A final clinical study report will be prepared according to the ICH E3 guideline on structure and content of Clinical Study Report. A Final Clinical Study Report will be prepared regardless of whether the study is completed or prematurely terminated. The final report will be prepared according to the eCTD (electronic Common Technical Document) format.

The study report will include reports on the bioanalytical phase and data analysis phase of the study. The report will contain data regarding the analytical methodology and the chromatography (including at least 20% of the serially/randomly selected subject chromatograms), the pharmacokinetic calculations, the statistical analysis of the data, and a clinical report along with raw data. The deviations from the protocol will be documented as protocol deviations and presented in the final report.

18.8 PUBLICATION POLICY

It is the responsibility of Sponsor to register this study in an acceptable registry. On the basis of the statistical and clinical evaluation of the pooled results across the study centers, a clinical study report will be prepared by CBCC. This can form the basis of a manuscript for publication in a peer-reviewed journal. The sponsor will hold the right to publish the results of present study at any time. An investigator may seek permission to publish results of the study from the sponsor. If published the subject's identity will not be revealed.

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20 APPENDICES

20.1 INFORMED CONSENT DOCUMENTS