Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product:				
Name of active ingredient: BIWH 3		**Page:**	**Number:**	
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Report date: 15 April 2005	**Number:** U05-1429	**Study period (dates):** 03 June - 22 August 2003		

Title of study:	Pharmacokinetics and Pharmacodynamics of BIWH 3: a randomised, placebo-controlled, double blind dose escalation study (0.02, 0.06, 0.2, 0.6, and 2.0 µg/kg intravenous over one hour) in healthy Duffy positive vs. Duffy negative male volunteers
Investigator:	[redacted]
Study center(s):	[redacted], Austria
Publication (reference):	Not applicable
Clinical phase:	I
Objectives:	To compare the pharmacokinetic and pharmacodynamic effects of escalating dosages of BIWH 3 in Duffy positive vs. Duffy negative healthy male volunteers: plasma levels of monocyte chemotactic protein-1 (MCP-1) and markers of leukocyte, coagulation, platelet and endothelial activation were quantified; to examine the safety of BIWH 3 in this setting
Methodology:	Randomised (2:1-4:1, active:placebo), double blind, placebo controlled within each dose group, dose escalation trial, at a single centre
No. of subjects:	
total	36
each treatment:	In each of the first two dose levels, 3 Duffy positive subjects were enrolled (randomization: 2 active: 1 placebo). In each of the subsequent cohorts, 5 Duffy positive subjects were enrolled (randomization: 4 active: 1 placebo) and 5 Duffy negative subjects were enrolled (randomization: 4 active: 1 placebo)
Diagnosis and main criteria for inclusion:	Healthy male subjects, age 18 to 50 years
Test product:	BIWH 3 vial
dose:	escalating dosages of BIWH 3: 20 ng/kg-2µg/kg
mode of admin.:	iv infusion over 1 hour
batch no.:	
Duration of treatment:	one hour
Reference therapy:	placebo
dose:	equal volume of PBS with 0.02% Tween (placebo)
mode of admin.:	iv infusion over 1 hour
batch no.:	

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Criteria for evaluation:

Efficacy: **Primary Endpoint**: Time vs. concentration profiles of MCP-1 in Duffy positive vs. Duffy negative volunteers, compared to baseline values
Secondary Endpoints: PD-variables: monocyte surface activation: CD11b, (ICAM-1) CD54 expression, CCR2b (chemokine receptor for MCP-1); platelet activation: soluble P-selectin; endothelial activation: soluble E-selectin inflammation: mRNA of IL-1; coagulation: prothrombin fragment (F_{1+2})

Safety: Safety and tolerability of BIWH 3 in terms of incidence and severity of adverse events. Changes from baseline in vital signs (pulse rate, systolic & diastolic blood pressure, ECG) and laboratory variables including serum chemistry, differential blood counts with platelets, and CRP-levels.

Statistical methods: Descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy results:

All 36 subjects enrolled were male between 20 and 45 years old. Fifteen were Duffy negative (all Black) and 21 were Duffy positive (all White).

Following a 1-hour intravenous infusion, plasma concentrations rose above baseline MCP-1 levels in a dose proportional manner. Plasma concentrations declined very rapidly with a half-life of about 0.4-0.5 hours. There was virtually no excretion of BIWH 3 in urine.

Infusion of BIWH 3 greatly enhanced the number of circulating monocytes, particularly in dose groups 4 and 5. Concomitantly, there was an apparently dose-dependent effect on ICAM-1 (CD54) expression with maximal effect seen at the end of BIWH 3 infusion. At the same time CD11b expression and CCR2b expression slightly decreased, the former two possibly characterizing a different monocyte population in the circulation.

The Duffy negative subjects reached the t_{max} slightly earlier than the Duffy positive subjects; the difference was only between 10 and 20 minutes on average. However, there were no significant differences in C_{max} and AUC, hence, the Duffy status did not appear to be an important factor for the pharmacokinetics of BIWH 3. Therefore, the initially suggested scavenging effect of the Duffy antigen receptor is much less pronounced as compared to Duffy knock out animals.

In addition, none of the PD variables suggests that the tested dosages of BIWH 3 have prominent effects on endothelial/platelet activation, coagulation or inflammation.

In summary infusion of BIWH 3 markedly increased circulating monocytes at dosages of 0.6 and 2.0 µg/kg. This is consistent with its proposed mechanism of action, which is indicated by the name “monocyte chemotactic protein”.

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Safety results:	The infusion with BIWH 3 was well tolerated by all subjects without any exception. There was no evidence for adverse effects of BIWH 3, except for possible decreasing trends on platelets and total protein. There was no evidence for adverse cardiovascular reactions caused by BIWH 3.
Conclusions:	BIWH 3 has a dose dependent PK-profile. In contrast to knock out animals, the role of the Duffy antigen in scavenging MCP-1 is limited in humans. This study unequivocally showed that the primary mechanism of action of BIWH 3 is to attract monocytes into the circulation at the tested dosages. BIWH 3 is excellently tolerated up to 2.0 µg/kg administered as intravenous infusion.