Clinical Study Synopsis for Public Disclosure

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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***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim Pharma KG **Name of finished product:**		**Tabulated StudyReport**		**(For National Authority Use only)**
Name of active ingredient: Lefradafiban (BIBU 104 XX)		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**To:**	**Addendum No.:**
Report date: 10 December 1999	**Number:** 509.302	**Study period (years):** 1/1999-2/1999		

Title of study:	Influence of oral doses of 75 mg Clopidogrel on the pharmacodynamics and safety of Fradafiban after oral doses of 30 mg Lefradafiban tid over 8 days in healthy male subjects. An intra-individual, open trial.
Investigator:	[redacted]
Study centre (s):	Human Pharmacology Centre, Biberach, Germany
Publication (reference):	-
Clinical phase:	I
Objecti ves:	To assess the influence of 75 mg Clopidogrel on the pharmacodynamics and safety of 30 mg Lefradafiban tid
Methodology:	Platelet aggregation in platelet rich plasma
No. of subjects entered: **total:** **each treatment:**	 14 14
Diagnosis and main criteria for inclusion:	Healthy male subjects, aged 18 to 45 years
Test product: **dose:** **mode of admin.:** **batch no.:**	Lefradafiban in the presence of Clopidogrel 30 mg Lefradafiban tid, 75 mg Clopidogrel p.o. B970903, 800343
Duration of treatment:	8 days
Reference therapy 1: **dose:** **mode of admin.:** **batch no.:**	Lefradafiban without Clopidogrel 30 mg Lefradafiban tid p.o. B970903
Criteria for evaluation: **Efficacy:** **Safety:**	 Inhibition of platelet aggregation, fibrinogen receptor occupancy Adverse events, routine laboratory, urine test strips, bleeding time, fecal blood loss, PR, BP
Statistical methods:	Descriptive statistics for PD and PK parameters, investigation of relationships, confidence intervals for ratios with : without Clopidogrel

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SUMMARY CONCLUSIONS:

Efficacy results:

Not applicable

Pharmacodynamic results:

Lefradafiban (30 mg tid) inhibited platelet aggregation *ex vivo* in response to all stimuli. The maximal mean inhibition of ADP-induced platelet aggregation was 82 ± 12% (± SD; n = 12) 2 hours after administration on day 4. The trough of inhibition was 43 ± 15 % before the treatment on day 4 ($P<0.001$ versus control).

The combination of Lefradafiban with Clopidogrel (75 mg qd) inhibited ADP-induced platelet aggregation by 98 ± 6% two hours after and by 72 ± 16% before administration on the fourth day ($P<0.001$ versus control).

Treatment with 75 mg Clopidogrel alone for 4 days reduced ADP-induced platelet aggregation by up to 31 ± 31% ($P<0.01$ versus control). It did not affect platelet aggregation in response to collagen (2 to 10 µg/mL concentration) or TRAP. Only platelet aggregation induced by the weak stimulation with 1µg/mL collagen was reduced by up to 14 ± 17% two hours after the last Clopidogrel ingestion ($P<0.05$ versus control).

The maximal inhibition of platelet aggregation (% AUC) in response to the different stimuli is summarised in the following table as mean ± SD:

LEFRADAFIBAN TID / CLOPIDOGREL QD oral dose		Inhibition of Platelet Aggregation [%] induced by											
		ADP 20 µmol/L		collagen 1 µg/mL		collagen 2 µg/mL		collagen 5 µg/mL		collagen 10 µg/mL		TRAP 20 µmol/L	
		before	2 h p.a.	before	2 h p.a.	before	2 h p.a.	before	2 h p.a.	before	2 h p.a.	before	2 h p.a.
LEF 30mg (n=12)		43	82	60	95	43	82	35	66	34	57	39	71
day 4	± SD	15	12	21	13	10	17	9	10	8	10	13	15
LEF + CLO (n=12)		72	98	80	100	57	98	44	79	38	68	50	86
day 8	± SD	17	6	15	0	18	6	11	10	7	8	17	13
CLO 75mg (n=12)		22	31	8	14	3	5	2	2	2	2	1	3
day 12	± SD	21	31	13	17	9	12	11	10	8	6	8	10

Similar GP IIb/IIIa receptor occupancies (FRO) 2 hours after a 4-day treatment with Lefradafiban alone or in combination with Clopidogrel of 73 ± 8% and 76 ± 7%(mean ± SD; n=12) were measured, respectively. The maximal Fradafiban plasma levels were similar after treatment with Lefradafiban alone (178 ± 48 ng/ml) and its combination with Clopidogrel (203 ± 47 ng/ml). The maximal ADP receptor occupancy (ARO) was 58 ± 13% after Clopidogrel combined with Lefradafiban and 72 ± 11% (mean ± SD; n=12) after Clopidogrel alone.

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Pharmakokinetic results:

To investigate any potential effect of concomitant Clopidogrel intake on Lefradafiban pharmacokinetics relative Fradafiban bioavailability was derived from C_{2h} (near C_{max}) plasma concentration values and urinary excretion, Ae_{0-8}. A small (≤15 %), but statistically significant increase was found with C_{2h} values, whereas a small (≤27 %), but statistically significant decrease in Ae_{0-8} was observed. From historical group comparison with a previous trial with equal design no marked changes in model-free pharmacokinetic parameters as derived from standard non-compartmental analysis were found. From the results of this study it is concluded, that concomitant Clopidogrel intake has no remarkable effect on Lefradafiban pharmacokinetics.

Safety results:

Headache and gastrointestinal symptoms were reported most frequently but not considered drug related. Influenza like symptoms occurred frequently due to a wave of influenza before and during the study period. Twelve bleeding events were reported in 7 subjects, all of mild intensity. Occurrence of bleeding was during the Lefradafiban treatment in subjects no. [redacted], during the Lefradafiban plus Clopidogrel treatment in subjects no. [redacted] and post treatment in subject no. [redacted].

Conclusions:

This intra-individual comparison demonstrated that the antiaggregatory activity of oral treatment with Lefradafiban was further increased by the addition of Clopidogrel. The results provide a weak evidence against a more than additive effect of the combination of Lefradafiban with Clopidogrel on platelet inhibition but do not provide evidence for a subadditive effect of the combination.
The results of this study do not indicate a remarkable difference in Lefradafiban/Fradafiban pharmacokinetics after 4 days of concomitant 75 mg Clopidogrel qd dosing.
The trial does not exclude a slightly increased risk of bleeding with combined treatment of 30 mg Lefradafiban tid and 75 mg Clopidogrel qd as compared to either treatment alone.