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***.

3. SYNOPSIS AND TRIAL ABSTRACT

3.1 SYNOPSIS

Name of company: BI Pharma KG		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Lefradafiban				
Name of active ingredient: (3S,5S)-5-[(4'-methoxycarbonylamidino-4-biphenylyl)oxymethyl]-3-[(methoxycarbinyl)methyl]-2-pyrrolidinone)		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**to**	**Addendum No.:**
Report date: 14 January 1999	**Number:** 509.119	**Study period (years):** 4/1998 –7/1998		

Title of study:	Influence of 40 mg Pantoprazole per day on the pharmacokinetics of Fradafiban after multiple oral doses of 20 mg Lefradafiban tid as acid free tablet and sachet over 5 days in healthy subjects. A 4-way crossover randomized open trial.	
Investigator:	[redacted]	
Study centre(s):	Human Pharmacology Centre, Boehringer Ingelheim Pharma KG, Biberach	
Publication (reference):	n.a.	
Clinical phase:	I	
Objectives:	To assess the absorption of 20 mg Lefradafiban in two formulations, each under physiological conditions and with 40 mg Pantoprazole.	
Methodology:	4-way cross-over, randomized, open	
No. of subjects entered:		
Total:	12	
Each treatment:	12	
Diagnosis and main criteria for inclusion:	Healthy male subjects, age 18 to 60 years	
Test product:	Lefradafiban, acid free tablet/double chamber sachet	Pantoprazole, tablet
Dose:	20 mg Lefradafiban tid	40 mg q.d.
Mode of admin.:	p.o.	p.o.
Batch no.:	9980033 / 9960298	197272
Duration of treatment:	5 days per period (4 periods)	
Reference therapy:	Lefradafiban, acid free tablet / double chamber sachet	
Dose:	20 mg	
Mode of admin.:	p.o.	
Batch no.:	9980033 / 9960298	

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Criteria for evaluation:

Efficacy: n.a.

Primary endpoints: $AUC_{ss,13}$, $C_{max,ss,13}$, $C_{pre,ss,13}$, $Ae\%_i$ (i=1,...,13).
Secondary endpoints: $C_{pre,i}$ (i=1,4,7,10,11,12), $C_{2h,i}$ (i=10,11,12), $t_{1/2}$, $\%Swing_i = (C_{2h,i}-C_{pre,i}) / C_{pre,i} * 100\%$ (i=10,11,12), $\%PTF_{13} = (C_{max,ss,13}-C_{pre,ss,13})\cdot * 8h / AUC_{ss,13} * 100\%$, $AUC_{fluc,13} = (AUC_{above,13} - AUC_{below,13}) / AUC_{above,13}$ of Fradafiban; FRO

Safety: Pulse rate, systolic and diastolic blood pressure, laboratory, adverse events

Statistical methods: Descriptive statistics, analysis of variance, incidence of poor absorption events, 90% confidence intervals for ratios between treatments of pharmacokinetic parameters of Fradafiban

SUMMARY – CONCLUSIONS:

Efficacy results: not applicable

Pharmacodynamic/ -kinetic results:
Steady state geometric mean plasma concentration-time and %FRO profiles of all treatments exhibited only minor differences. Only the treatment AFT+Pantoprazole showed a significantly lower profile. The AFT showed a 27% higher bioavailability as compared to the sachet. Co-treatment with Pantoprazole decreased the bioavailability (Ae(0-168)) of the tablet by 30% and increased the bioavailability of the sachet by 13%. Inter-individual variability with respect to model-free pharmacokinetic parameters was higher in the treatments with the acid-free tablet, especially under co-treatment of Pantoprazole (median gCV = 38.02%), but was still in an acceptable range for a solid formulation in comparison to a solution.
Average steady state %FRO values of all treatments were still within the accepted range of 50-80%, defining the presumed lower limit of efficacy and the upper limit in terms of safety (risk for bleeding).

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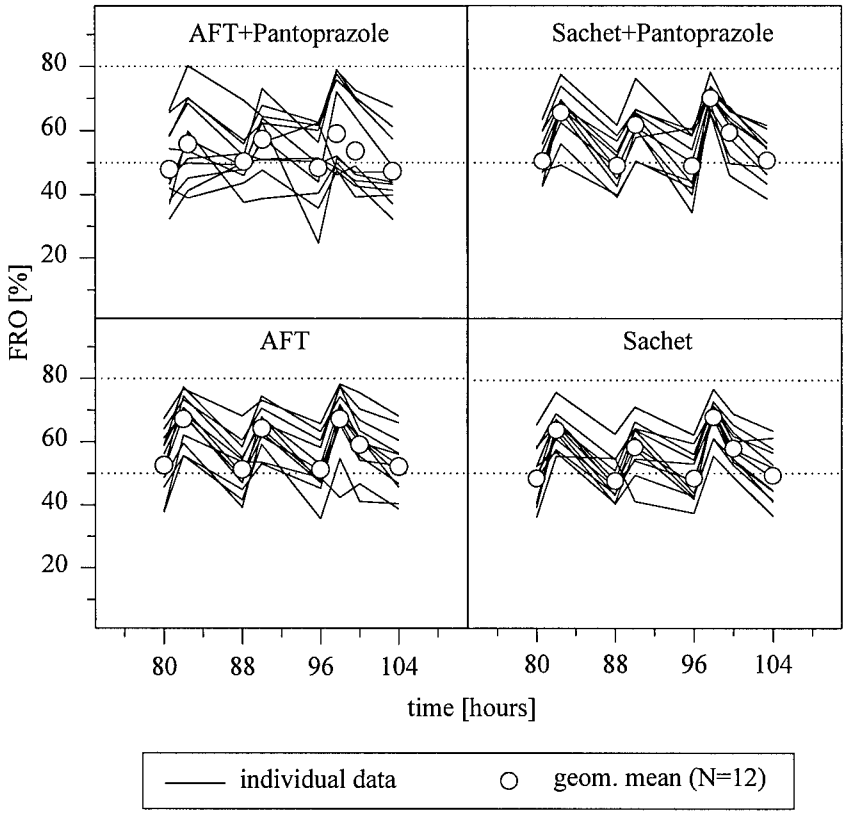

With regard to individual profiles there were a significant number of poor absorption events in 7 out of 12 subjects in the treatment AFT+Pantoprazole resulting in individual "peak" %FRO values below the anticipated lower limit of efficacy (50 %FRO). Since poor absorption events occurred more frequently in subjects ≥ 35 years, it is anticipated that Pantoprazole has a more pronounced effect in this age group.
With the 20 mg dose a significant number of individual "trough" %FRO values below 50% were

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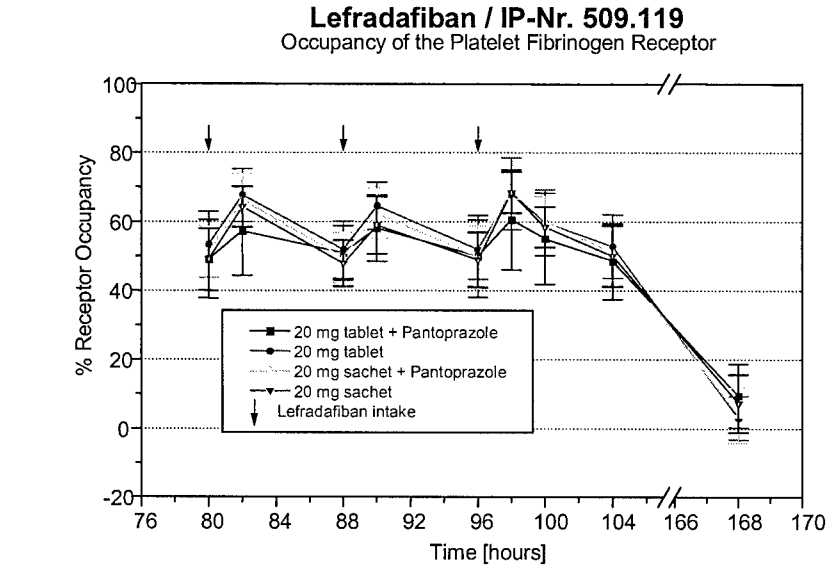
observed in all treatments. Therefore the 20 mg dose has to be considered as sub-optimal for both, the tablet and the solution prepared from the two-compartment sachet.



Safety results:
Lefradafiban given as acid-free tablet was well tolerated. Seven subjects reported at least 1 adverse event. Pain, especially headache, was observed most frequently but not considered drug related. Bleeding events, 2 (lip bleed, gingival bleed) of mild and 1 (large haematoma at puncture site) of moderate intensity, occurred in 3 subjects during treatment.

Conclusions:
The results of this study support the switch from the two-compartment sachet to the acid-free tablet for use in phase III clinical trials. For the 20 mg dose, however, anacidic gastric conditions, e.g. due to subject age or co-medication, may result in an increased number of individual %FRO values

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below 50%.
The performance of the trial was a burden for the subjects due to the long duration of the 4-way crossover and the multiplicity of blood sampling.