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: Boehringer Ingelheim Pharma KG		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Not applicable				
Name of active ingredient: Ibuprofen		**Page:**	**Number:**	
Ref. to Documentation:	**Volume: I of II**	**Page: 1**	**to PK I 113**	**Addendum No.:**
Report date: 21 April 1999	**Number:**	**Study period (years):** September – October 1998		

Title of study:	An open two-way cross-over study to evaluate the relative bioavailability of Ibuprofen enantiomers after single p.o. administration of 200 mg syrup (T) compared with 200 mg standard Brufen® syrup (R).
Investigator:	[redacted]
Study centre(s):	Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma KG, F.R.G.
Publication (reference):	None
Clinical phase:	I
Objectives:	Pharmacokinetics, safety and tolerability
Methodology:	Single doses, open, randomised, period-balanced, within – subject two-way cross-over
No. of subjects entered:	
total:	24
each treatment:	Ibuprofen syrup (T): 24; Brufen® syrup (R): 24
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 21 – 50 years, Broca-Index: ±20 %
Test product:	Ibuprofen syrup (T)
dose:	200 mg (10 ml)
mode of admin.:	oral
batch no.:	F 4760
Duration of treatment:	One day at each formulation
Reference therapy:	Brufen® syrup (R)
dose:	200 mg (10 ml)
mode of admin.:	oral
batch no.:	2T
Criteria for evaluation:	
Efficacy:	Not applicable
Safety:	Blood pressure, pulse rate, ECG, laboratory parameters, adverse events
Pharmacokinetics:	C_{max}, $AUC_{(0-\infty)}$, t_{max}, $t_{1/2}$, λ_z, $AUC_{(0-t(last))}$, MRT_{tot}, Cl/f and Vz/f
Statistical methods:	descriptive analysis, 90% confidence intervals for pharmacokinetic parameters

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SUMMARY - CONCLUSIONS:

29 healthy male volunteers were screened for this open two-way cross-over trial; 24 of them were considered eligible (median age 32.5 years; median body weight 82.5 kg) and treated with a single dose of 200 mg Ibuprofen syrup and 200 mg Brufen® syrup on two separate study days.

Efficacy:

Not applicable

Safety and tolerability:

Exposure to either Ibuprofen 200 mg formulation did not reveal any clinically relevant drug-induced change of blood pressure, pulse rate or ECG recordings in supine position. Furthermore, no drug dependent alterations were observed in the standard laboratory evaluation (haematology, urinalysis and clinical chemistry). Four of 24 treated subjects reported five adverse events (two on Ibuprofen, two on Brufen® syrup, one during the washout period of Brufen® syrup). Two adverse events were of mild and three adverse events were of moderate intensity.
All adverse events were judged not to be drug related by the investigator.
All treated subjects completed the study.

Pharmacokinetics:

R- and S-Ibuprofen enantiomers plasma concentrations were determined by means of a validated HPLC assay with UV detection (assay precision within ± 7.3%, assay accuracy within ± 4.8%). The C_{max} was reached after app. 1 hour for both test [T] and reference [R] formulations. Geometric means C_{max} (%gCV) values were 8.88 (25.2) [T] vs. 8.17 (18.9) [R] µg/ml for R-Ibuprofen and 8.37 (24.8) [T] vs 8.18 (19.2) [R] µg/ml for S-Ibuprofen. The 90% confidence intervals for C_{max} of R-Ibuprofen ranged from 99% to 119% with a point estimate of 109%, whilst the 90% confidence intervals for S-Ibuprofen ranged from 94% to 111% with a point estimate of 102%. The geometric mean $AUC_{0-\infty}$ (%gCV) values were also comparable and reached 23.07 (23.2) [T] vs. 20.49 (24.6) [R] µg•h/ml for R-Ibuprofen and 31.16 (27.3) [T] vs. 30.70 (25.9) [R] µg•h/ml for S-Ibuprofen, respectively. The 90% confidence intervals for $AUC_{0-\infty}$ of R-Ibuprofen ranged from 104% to 122% with a point estimate of 113%, whilst the 90% confidence intervals for S-Ibuprofen ranged from 96% to 107% with a point estimate of 101%. In summary, 90% confidence intervals for both C_{max} and $AUC_{0-\infty}$ were within the bioequivalence limits of 80-125%.

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SUMMARY - CONCLUSIONS: (continued)

		R-Ibuprofen				S-Ibuprofen			
		Ibuprofen syrup, 200mg		Brufen® syrup, 200mg		Ibuprofen syrup, 200mg		Brufen® syrup, 200mg	
		mean (%CV)	gmean (%gCV)	mean (%CV)	gmean (%gCV)	mean (%CV)	gmean (%gCV)	mean (%CV)	gmean (%gCV)
C_{max}	[µ/ml]	9.14 (24.2)	8.88 (25.2)	8.31 (19.6)	8.17 (18.9)	8.61 (24.1)	8.37 (24.8)	8.33 (19.9)	8.18 (19.2)
$AUC_{0-\infty}$	[µg•h/ml]]	23.67 (23.5)	23.07 (23.2)	21.08 (24.9)	20.49 (24.6)	32.25 (27.1)	31.16 (27.3)	31.70 (26.6)	30.70 (25.9)
t_{max}	[h]	# 0.75	§ 0.5-2.5	# 0.75	§ 0.25-2.0	# 0.75	§ 0.5 – 3.0	# 1.125	§ 0.25-2.0
λ_z	[h^{-1}]	0.425 (34.6)	0.400 (36.6)	0.484 (32.7)	0.457 (36.8)	0.351 (14.9)	0.347 (14.5)	0.367 (18.4)	0.361 (18.9)
$t_{½}$	[h]	1.84 (36.7)	1.73 (36.6)	1.62 (38.8)	1.52 (36.8)	2.02 (13.9)	2.00 (14.5)	1.95 (18.9)	1.92 (18.9)
MRT_{tot}	[h]	2.51 (18.0)	2.47 (17.9)	2.39 (18.8)	2.36 (17.8)	3.49 (17.0)	3.45 (16.6)	3.47 (15.5)	3.43 (16.0)
CL/f	[ml/min]	74.04 (22.5)	72.24 (23.2)	83.66 (24.5)	81.34 (24.6)	--*	--*	--*	--*
V_z/f	[l]	11.72 (45.8)	10.83 (40.2)	11.36 (35.8)	10.68 (37.4)	--*	--*	--*	--*

#: median, §: range
Source data: cf. Appendix 15.9.3.3, TABLEs 11,12 and TABLEs 15,16
* Calculation not applicable, due to unidirectional chiral inversion of R- to S-Ibuprofen *in-vivo*

Conclusions:

Both Ibuprofen formulations were equally well tolerated after 200 mg oral doses and pharmacokinetic bioequivalence was demonstrated in this trial.