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The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: A1900832
Title: A Pharmacokinetic Study to Evaluate the Rate and Extent of Absorption of Paracetamol from Two Formulations in an Indian Population.
Rationale: Panadol Advance is a new fast dissolving formulation of paracetamol that has faster disintegration and plasma absorption compared to standard paracetamol tablets. GSK Asia Pvt. Ltd., India plans to launch Crocin Advance, which is the same formulation as Panadol Advance in India. In order to get Crocin Advance registered in India, the current study was designed to assess bioequivalence between Crocin Advance and Panadol Advance in fasted state
Phase: 4
Study Period: 20th April 2010 – 19th May 2010
Study Design: This was a randomised, open label, single dose, two way crossover study, in healthy male subjects. The study was conducted with 2 treatment sessions in a residential treatment phase
Centres: 1, India
Indication: Relief of fever, headache and other minor aches and pains
Treatment: After overnight fasting for at least 10 hours, single dose of Paracetamol 500 mg [Test product (A) or Reference product (B)] was administered orally to each subject in sitting posture, with 240 mL of water at ambient temperature, in each treatment session, as per the randomisation schedule **Test (A)** Crocin Advance(Paracetamol 500mg) **Reference (B)** Panadol Advance (Paracetamol 500mg)
Objectives: Primary Objective: To establish bioequivalence between Crocin Advance & Panadol Advance by assessing AUC0-t, AUC0-inf, and Cmax Secondary Objectives: • To compare Tmax of Crocin Advance with Panadol Advance. • To assess the frequency of adverse events (AEs) in both treatment arms during the study
Primary PK Variables: AUC0- t: area under the paracetamol time curve from zero to the final sample time AUC0 - inf: area under the paracetamol concentration-time curve from zero extrapolated to infinity Cmax: maximum paracetamol concentration
Secondary PK Variables: Tmax: time of maximum plasma concentration.
Statistical Methods: AUC0-inf, AUC0-t, Cmax and Tmax were calculated for each subject for each treatment. A linear mixed effects model was used to analyze the logarithmically transformed (natural log) primary endpoints (AUC0-inf, AUC0-t and Cmax) using PROC MIXED of SAS. The model included factors for subjects, as a random effect and formulation (treatment) and period as fixed effects. The residual variance from the model was used to construct 90% confidence intervals for the difference between the Test and the Reference treatment mean ratios. These were then back-transformed (antilogged) to obtain point estimates and confidence intervals for the ratio of the treatment geometric means. Tmax was analyzed using non-parametric method of Wilcoxon Signed Rank test. Median differences among formulations were presented with 95% confidence interval for the median difference calculated using method of Hodges and Lehman. Bioequivalence was concluded as the 90% confidence intervals for the treatment mean ratios for all three

primary pharmacokinetic parameters Cmax, AUC0-t and AUC0-inf lie completely within the range 80.00-125.00. The method of two one-sided t-test procedures was used for each of the primary endpoints, as recommended by Indian BA/BE guidelines and the US FDA guidelines for equivalence testing.

Study Population: 30 healthy human adult male volunteers

	Overall	
Number of Subjects:	30	
Planned, N	30	
Randomised, N	30	
Completed, N (%)	28(93.3)	
Total Number Subjects Withdrawn, N (%)	2 (6.7)	
Withdrawn for other reasons, N (%) lost to follow up	2(6.7)	
Demographics	**Overall**	
	Test (A)	**Reference (B)**
N	30	
Females: Males	0:30	0:30
Mean Age, years (SD)	26.0,(4.51)	26.0,(4.51)
Asian - Central / South Asian Heritage, N (%)	30(100%)	30(100%)

Primary PK Results:

Pharmacokinetic Parameters of Paracetamol from Test (A)

	C_{max} (ng/mL)	**AUC_{0-t} (ng.h/mL)**	**AUC_{0-inf} (ng.h/mL)**
N#	30	30	30
Mean	10790.558	30341.151	33219.772
SD	3959.8582	6461.2556	8142.7274
CV%	36.70	21.30	24.51
Geometric Mean	10147.275	29690.252	32306.003

Pharmacokinetic Parameters of Paracetamol from Reference (B)

	C max (ng/mL)	**AUC0-t (ng.h/mL)**	**AUC0-inf (ng.h/mL)**
N#	30	30	30
Mean	10673.393	30939.490	33511.265
SD	3762.9501	7526.4247	8882.7040
CV%	35.26	24.33	26.51
Geometric Mean	10058.595	30114.139	32467.732

Summary of Bioequivalence Parameters of Paracetamol

	N#	**LS Mean**		**LSMR**	**90% CI for LSMR**
		Test (A)	**Reference (B)**		
C_{max} (ng/mL)	30	10147.275	10058.595	100.88	(89.12, 114.20)
AUC_{0-t} (ng.h/mL)	30	29690.252	30114.139	98.59	(96.05, 101.20)
AUC_{0-inf} (ng.h/mL)	30	32306.003	32467.732	99.50	(97.91, 102.17)

Note: # - Intention to Treat Population; Test (A) - Crocin Advance tablet (500 mg paracetamol); Reference (B) -Panadol Advance tablet (500 mg paracetamol)

Secondary PK Results:

Parameter	Median		Hodges-Lehman Estimator for B-A	95% CI	*p*-value
	Reference (B)	Test (A)			
T_{max} (hrs)	0.500	0.460	0.0000	(-16, 17)	0.5185

Note: # - Intention to Treat Population; Test (A) - Crocin Advance tablet (500 mg paracetamol); Reference (B) -Panadol Advance tablet (500 mg paracetamol)

Safety Results: All subjects who received the study treatment in either study period were considered evaluable for the safety population.

Treatment wise incidence of AE's

Body system/Adverse Event	Test (A)	Reference (B)
Fever		01
Headache		01
Sore Throat		01
Elevated ALT - 59 U/L	01	
Clinically significant abnormality in urine report - Blood (10 Ery/µL) 1+	01	
Elevated ALT-100 U/L		01
Elevated AST– 89 U/L		01
Elevated GGTP – 95 U/L		01

Test (A) - Crocin Advance tablet (500 mg paracetamol); Reference (B) -Panadol Advance tablet (500 mg paracetamol)

Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication]
No SAE occurred on either treatment.

Conclusion:

- The least square mean ratio (LSMR) for Paracetamol Cmax (measured data) was 100.88 with 90% CI of (89.12, 114.20)
- The LSMR for Paracetamol AUC0-t (measured data) was 98.59 with 90% CI of (96.05, 101.20)
- The LSMR for Paracetamol AUC0-inf (measured data) was 99.5 with 90% CI of (97.91, 102.17)
- The Difference in Tmax (Hodges-Lehmann Estimator for B-A) was 0.0000 with 95% CI of (-16, 17)
- The 90% CI of LSMR for Cmax, AUC0-t and AUC0-inf of Test to the Reference product were within the acceptable limits of 80.00 to 125.00 and also there was no difference among the formulations with respect to Tmax.
- Based on above results obtained in this study, Test product (A) was bioequivalent to Reference product (B), in healthy human adult male subjects under fasting conditions.
- Based on evaluation of adverse events, clinical laboratory evaluation, vital signs, physical examinations and enquiry of well being, it was concluded that both the Test and Reference products were tolerated well and were safe.

Publications: This section to be updated once the data have been published