Comparison of the Pharmacokinetics of Four Different Dose-Frequency Combinations of AMZ001 (Diclofenac Gel 3.06%) with Voltaren® (Diclofenac Gel 1%) in Healthy Subjects in a Phase 1 Study

Ahmed A. Kousba¹, Laetitia Delpy² and Dario Carrara²
¹MicroConstants Inc.; ²Amzell B.V.

PURPOSE
To evaluate how the steady state levels of AMZ001 applied one or two times daily compare to Voltaren® applied four times daily in healthy subjects.

OBJECTIVE(S)
1. Compare the pharmacokinetic (PK) exposure (Cmax and AUC0-24) of diclofenac (DCF) following four different dose-frequency combinations of AMZ001 with that of Voltaren®.
2. Compare the PK exposure of DCF among the four combinations of AMZ001.

METHODS (CONTINUED)
Treatment C. (N = 14 subjects) 4.6 g AMZ001 (141 mg of DCF-Na), applied as 2 pump actuations per knee once daily (QD) in the morning.

Treatment D. (N = 14 subjects) 4.6 g AMZ001 (141 mg of DCF-Na), applied as 2 pump actuations per knee once daily (QD) in the evening.

Treatment E. (N = 15 each) 9.2 g AMZ001 (282 mg of DCF-Na), applied as 2 pump actuations per knee twice daily (BID).

DCF PK was calculated using a non-compartmental analysis by validated pharmacokinetic software (WinNonlin Professional v 7.0).

The time to reach a steady state was assessed by linear regression analysis of the Ctrough. To establish the achievement of a steady state, the slope of the linear regression should be equal to the value of zero and the 95% confidence interval of the slope should include zero.

The comparison of the PK exposure of the four different dose-frequency combinations of AMZ001 (Treatments B through E) with Voltaren® (Treatment A) was performed using one-way ANOVA with a p value of significance set to <0.05 using GraphPad Prism v 5.01 (GraphPad Inc., CA). ANOVA was also used for the comparison of the PK exposure among the four AMZ001 treatments.

RESULT(S)
Following topical application of AMZ001 or Voltaren®, DCF was absorbed into the systemic circulation. Day 7 Tmax was 2-3x shorter than that of Day 1 for the QID and the BID and was similar to that of Day 1 for the QD (Table 1). There was no apparent difference in Days 1 and 7 DCF PK parameters (Cmax, Tmax and AUC0-24) following AMZ001 application in the evening and the morning. DCF exposure following 9.2 g AMZ001 gel was ~2x higher than that following 4.6 g AMZ001 gel. DCF exposure of Day 7 was higher than that of Day 1 for both AMZ001 and Voltaren® (Tables 1 and 2).

The steady state of DCF appeared to have been achieved in 3 to 4 days after AMZ001 or Voltaren® application. The mean values for DCF Cmax and AUC(0-24) on Days 1 and 7 following the AMZ001 in Treatments B, C, D and E were not significantly different from those following Voltaren in Treatment A (p > 0.05). The mean values for DCF Cmax on Days 1 and 7 and for AUC(0-24) on Day 1 following the AMZ001 in Treatments B, D and E were not significantly different from those following AMZ001 in Treatment C (p > 0.05). The mean values for DCF AUC(0-24) on Day 7 following the AMZ001 in Treatments B, D and E were significantly different from that of Treatment C. Using Dunnett’s multiple comparison post-hoc test showed that, only the mean for AUC(0-24) in Treatment E was significantly different from that of Treatment C.

CONCLUSION(S)
After seven days of treatment, the AUC0-24 for Voltaren® Gel was approximately the same as the AUC0-24 for AMZ001 administered with 1 pump BID, indicating similar exposure despite the difference in the number of applications (QID versus BID) and lower dose regimens (141 mg vs. 320 mg DCF applied).