A Novel Oral 3D-Printed Delayed- and Extended-Release Tofacitinib (T19) for the Treatment of Rheumatoid Arthritis and Related Inflammatory Diseases

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Introduction

Patients with inflammatory diseases, such as rheumatoid arthritis (RA), frequently continue to suffer from morning symptoms despite treatment with conventional therapies [1,2]. Routine morning administration of tofacitinib results in peak drug concentrations several hours (around 12 noon) after peak cytokine release and disease symptoms. A product designed to be taken at bedtime and exhibiting a delayed and extended release profile that releases tofacitinib late in the night providing maximum tofacitinib concentrations in the early morning hours, could provide an enhanced opportunity to address morning symptoms.

Objective

T19 is a novel, three-dimensionally (3D) printed tablet being developed for delayed- and extended- release (DR/ER) of tofacitinib and engineered to provide peak tofacitinib concentrations concurrent with the circadian rhythm of early morning endogenous cytokine release and disease symptoms. The current study was designed to characterize the pharmacokinetics of T19 and evaluate the single-dose relative bioavailability of T19 compared to Xeljanz XR in healthy participants.

Methods

T19 was manufactured by "Melt Extrusion Deposition (MED®)" 3D printing technology (**Figure 1**). A total of 24 participants were enrolled in the Phase I, randomized, open-label, single-dose, three-period, three-sequence crossover study to compare the pharmacokinetics (PK) between T19 and the reference listed drug (LD, Xeljanz XR). Participants were randomized 1:1:1 to receive two formulations of T19 (Z001101 & Z001091; designed to provide differing degrees of delayed release) or LD in the three sequences (**Table 1**). T19 was administered orally at bedtime (approximately 22:00) following a standard dinner at approximately 18:00. Following dinner, the participants remained fasted for 4 hours before the administration of T19. Xeljanz XR was administered orally in the morning after an overnight fast of at least 10 hours. There was a minimum 4-day washout period between treatments.

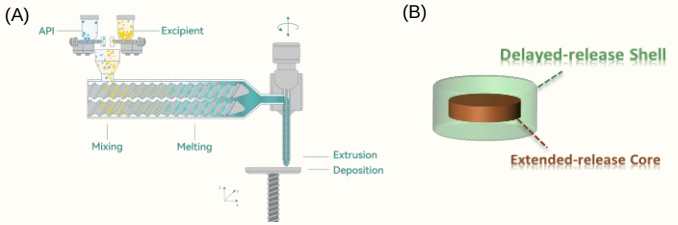

Figure 1 (A) Melt Extrusion Deposition (MED) Process; (B) Schematic Drawing of 3D structure of T19

Table 1 Study Workflow and Participant Randomization

Period	Group A	Group B	Group C
Period 1	Xeljanz XR	T19 (Z001091)	T19 (Z001101)
Period 2	T19 (Z001091)	T19 (Z001101)	Xeljanz XR
Period 3	T19 (Z001101)	Xeljanz XR	T19 (Z001091)

Results

Following administration of T19 and LD, both formulations of T19 exhibited a delayed time of maximum plasma concentration (T_{max}), as compared to the LD. Under fasting conditions, the median T_{max} was 5.5 - 6.0 h with a range of 3.0 - 10.0 h for T19, whereas the median T_{max} was 4.5 h (2.5 - 5.0 h) for the LD. The T_{max} of the T19 formulations was significantly different as compared to the LD (Wilcoxon signed-rank test, p <0.001). There was no statistical difference in relative bioavailability between either of the T19 formulations as compared to the LD, demonstrating that the exposure of T19 was similar to that of LD. The area under the concentration-time curve (AUC_{inf}) and maximum plasma concentration (C_{max}) of T19 were within the desired bioequivalence range relative to LD (**Table 2**).

Table 2 Relative Bioavailability Analysis of T19 versus Xeljanz XR

Parameter (Unit)	T19 (Z001091) / Xeljanz XR		T19 (Z001101) / Xeljanz XR	
	Ratio of Adjusted Geometric Means (%)	90% CI for Ratio	Ratio of Adjusted Geometric Means (%)	90% CI for Ratio
C_{max} (ng/mL)	130.89	(113.49, 150.95)	116.95	(104.92, 130.35)
AUC_{0-t} (ng·h/mL)	104.24	(100.79, 107.81)	105.60	(102.02, 109.31)
AUC_{0-inf} (ng·h/mL)	104.04	(100.81, 107.38)	105.46	(102.03, 109.38)

Other than a delay in drug release (T_{max}), the PK profile of T19 was superimposable with the LD, including exhibiting similar PK parameter estimates for drug absorption and elimination (**Figure 2**).

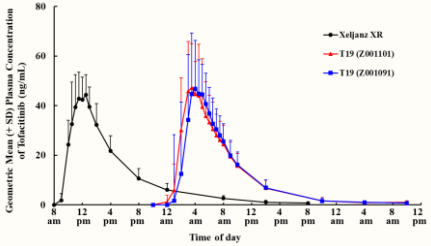

Figure 2 Geometric mean (+SD) Plasma Concentration of Tofacitinib-Time Curves for T19 and Xeljanz XR after Single Dose Administration

Conclusions

This study demonstrated that T19 exhibited delayed- and extended-release properties, while being bioequivalent as compared to the LD. The T19 formulation provided early morning peak plasma concentrations when morning symptoms are most present. The bioequivalence of T19 and LD (AUC and C_{max}) suggests a potential pharmacokinetic bridge between the products and a basis for a 505(b)(2) application for T19, providing a potential therapeutic option for patients with morning symptoms.

References

[1] Ursini F, et al. Pharmaceutics. 2021 Nov 2;13(11):1832.
[2] Cutolo M, et al. Ann Rheum Dis. 2008 Jul;67(7):905-8.

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