Drug Release and Pharmacokinetic Evaluation of Novel Implantable Mometasone Furoate Matrices in Rabbit Maxillary Sinuses

Changcheng You, PhD[1], Ling-Fang Tseng, PhD[1], Alexander Pappas, PhD[1], Danny Concagh, MS[1], Yina Kuang, PhD[1]

[1] Lyra Therapeutics, Inc., Watertown, MA, USA

Corresponding Author:

Changcheng You, PhD, Lyra Therapeutics, Inc., 480 Arsenal Way, Watertown, MA 02472, US

Email: cyou@lyratx.com

Tel.: 617-393-4600

Keywords

Drug delivery, nasal implant, drug matrix, mometasone furoate, pharmacokinetics, chronic rhinosinusitis, bioresorbable, sustained release, corticosteroid, mucosa

This work was presented at the 66th Annual Meeting of the American Rhinologic Society, Boston, USA, September 12, 2020, as a poster presentation.

Abstract

Background: Intranasal corticosteroid sprays (INCS) used to treat chronic rhinosinusitis (CRS) are suboptimal due to limited penetration into the middle meatus, rapid clearance, and poor patient compliance. A bioresorbable drug matrix, developed with the XTreo™ drug delivery platform, may overcome the limitations of INCS by providing continuous dosing over several months.

Objective: To evaluate the *in vitro* drug release and *in vivo* pharmacokinetics of novel mometasone furoate (MF) matrices in a rabbit dorsal maxillary osteotomy model.

Methods: XTreo™ matrices were formulated to consistently elute MF for up to 6 months. Matrices were surgically placed bilaterally into the maxillary sinuses of New Zealand White (NZW) rabbits. Tissue and plasma MF concentrations were measured to assess the *in vivo* drug delivery. The *in vivo* and *in vitro* drug release kinetics of the matrices were quantified and compared to those of rabbits receiving daily Nasonex® MF nasal sprays.

Results: XTreo™ matrices self-expanded upon deployment to conform to the irregular geometry of the maxillary sinus cavities in the NZW rabbits. Sustained release of MF was demonstrated *in vitro* and *in vivo* for two MF matrices of distinct release durations and an *in vitro-in vivo* correlation (IVIVC) was established. Therapeutic levels of MF in local tissues were measured throughout the intended dosing durations. In contrast to the variable peaks and troughs of daily nasal sprays, sustained dosing *via* a single administration of MF matrices was confirmed by quantifiable plasma MF concentrations over the intended dosing duration.

Conclusion: The XTreo™ MF matrices provided targeted and efficient dosing to local sinus tissues that was superior to INCS. Sustained drug release was confirmed both *in vitro* and *in vivo*. The novel XTreo™ technology may provide precisely tuned, long-lasting drug delivery to sinus tissues with a single treatment.

Introduction

Chronic rhinosinusitis (CRS) is a common condition defined by symptomatic inflammation of the paranasal sinuses lasting longer than 12 weeks,[1,2] which significantly impacts the patients' quality of life.[3] CRS is highly prevalent, affecting approximately 4.9% to 12.5% of the US population,[4,5] 10.9% of the European population,[6] and 2.1% to 8.4% of the Asian population.[7] First-line treatment for CRS is medical management, which consists of topical intranasal corticosteroid spray (INCS) and may also include a short course of oral steroids in patients with severe nasal polyps.[8] The effectiveness of INCS is limited due to inefficient drug delivery to the inflamed mucosal tissues and/or poor compliance with the therapy.[9,10] Symptom improvement from oral steroids is short lived and their use is associated with systemic side effects.[11,12]

An ideal treatment for CRS would provide safe, local, and sustained delivery of an anti-inflammatory drug directly to the mucosal tissue with a single treatment to reduce nasal inflammation and secondarily improve patient symptoms. Local delivery targets the drug directly to the inflamed tissue and dramatically reduces side effects associated with systemic dosing of oral steroids.[1,2] A limited number of drug delivery implants have been approved for specific indications (*e.g.* post-surgical, recurrent polyposis). However, their treatment duration is limited, and the dose delivered to the mucosal tissue is inconsistent over the intended treatment duration. [13,14]

The XTreo™ drug delivery platform (developed by Lyra Therapeutics, Inc.) can deliver a consistent dose of a therapeutic agent over an extended period up to many months.[15] The XTreo™ matrix is a tubular elastomeric mesh comprised of biocompatible and bioresorbable materials that can be formulated for uniform and sustained release of a range of therapeutic agents directly to targeted tissues. Mometasone furoate (MF), a potent anti-inflammatory corticosteroid with high

glucocorticoid receptor affinity,[16] was formulated into the XTreo™ matrices to provide corticosteroid treatment directly to inflamed mucosal tissues due to CRS.

In this study, we investigated the *in vitro* drug dissolution of two XTreo™ MF matrices and their pharmacokinetics *in vivo* in a rabbit maxillary sinus model.

Materials and Methods

XTreo™ MF Matrices

The bioresorbable tubular rabbit matrices were fabricated from monofilament poly(L-lactide-co-glycolide) fibers and coated with an *in situ* formed elastomer and a bioresorbable formulation containing 390 µg of MF (XTreo-RF1) designed to deliver drug over 12 weeks *in vivo* and 2320 µg of MF (XTreo-RF2) over 24 weeks *in vivo*, respectively. The dimensions of these rabbit matrices are 8 mm in diameter and 5 mm in length, purposefully built to fit the rabbit maxillary sinuses.

In Vitro Cumulative Drug Release

In the *in vitro* kinetic drug release assessment, each MF matrix was placed individually in a medium of pH 7.4 phosphate buffered saline (PBS) with 2% sodium dodecyl sulphate (SDS) and gently agitated at 37 °C. The release media were refreshed periodically to maintain infinite drug sink conditions. The MF concentration in the release media was determined by high performance liquid chromatography with ultraviolet detection (HPLC-UV), which was used to calculate the cumulative drug release.

Animal Model

The New Zealand White (NZW) rabbits of approximately 3.0 - 4.0 kg in weight were used in the pharmacokinetic studies. The NZW rabbit maxillary sinus model is a well-established

surgical model for testing topical pharmaceuticals or local implants.[13,17,18] The experimental procedures were approved by the Testing Facility's Institutional Animal Care and Use Committee. All experiments were conducted in compliance with the relevant laws and regulations. Animals were tranquilized with subcutaneous (SC) acepromazine and anesthesia induced with intravenous propofol. Buprenorphine Slow Release (0.5 mg/kg, SC) was administered before surgery. In addition, Buprenorphine HCl (0.05 mg/kg, SC), Rimadyl/carprofen (4 mg/kg, SC), and Duplocillin (0.25 mL/kg, SC) were administered as pre-emptive analgesia and antimicrobial therapy. Appropriately sized skin incision was first performed to expose the left/right antral wall. Then, a dorsal maxillary osteotomy on each side was created in the front side of the maxillary sinus using a ~ 5 mm burr. The rabbit matrices were then placed in the left and right maxillary sinuses bilaterally through the surgical osteotomy *via* an applicator (OD = 3 mm). The periosteum and skin were closed with sutures.

In Vivo Pharmacokinetic Studies

Three *in vivo* pharmacokinetic (PK) studies were carried out with XTreo-RF1 and XTreo-RF2 rabbit matrices and a commercial INCS (Nasonex®, Merck). Blood collections were performed at baseline (T = 0) and various timepoints as summarized in Table 1. The plasma MF concentrations were measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS). The lower limit of quantification (LLOQ) for MF was determined to be 20 pg/mL (Study 1) or 10 pg/mL (Studies 2 and 3).

/Insert Table 1/

In Study 1, subgroups of animals (n = 4 for each timepoint) were sacrificed at 28, 60, and 90 days post-implantation to determine the amount of remaining MF on explanted XTreo-RF1 matrices and MF concentration in sinus tissues using either HPLC-UV or LC-MS/MS. In Study 2, the amount of remaining MF on the XTreo-RF2 matrices explanted at 168 days was measured using HPLC-UV. In Study 3, Nasonex® was administered daily to a group of 6 NZW rabbits for 28 consecutive days, while the MF matrices were placed bilaterally in the maxillary sinus cavities of another group of 6 NZW rabbits for 28 days. For dosing with Nasonex®, each rabbit received four sprays in each nostril (50 µg MF per spray), resulting in a total daily dose of 400 µg.

Results

Structure of XTreo™ Matrices

The rabbit matrix (8 mm x 5 mm) used in this study is a miniature version of the human matrix LYR-210 (13 mm x 10 mm) in development for the treatment of adult CRS patients (Figure 1A).[15] Both rabbit and human matrices are manufactured in a similar fashion and they are highly elastic and flexible with shape-memory properties. The engineered elastic properties of XTreo™ matrices allow for self-expansion from a constrained state when deployed from an applicator (Figure 1B). Moreover, these drug matrices can conform to irregularly shaped cavities, as demonstrated by the matrix adapting to the inner walls of a rabbit's maxillary sinus cavity (Figure 1C). These rabbit matrices have been found to stay in place without migration throughout the entire treatment duration (up to 24 weeks) due to their shape-memory properties.

/Insert Figure 1/

Tunable Drug Release Profiles of XTreo™ Matrices

To demonstrate the versatility of the XTreo™ drug delivery platform, two rabbit matrices carrying 390 µg MF (XTreo-RF1) and 2320 µg MF (XTreo-RF2) respectively were devised to release drug for different durations *in vitro* (Figure 2). The *in vitro* release duration of XTreo-RF2 is about two-fold longer than that of XTreo-RF1. Moreover, the XTreo-RF2 matrix exhibits a more linear drug release profile than that of XTreo-RF1 matrix and minimizes the early burst release commonly observed with other products.[13,14]

/Insert Figure 2/

In Vivo Assessment of XTreo-RF1 (Study 1)

The *in vivo* drug release profile of the XTreo-RF1 matrices was determined by measuring the remaining MF in the matrices explanted at different timepoints (Figure 3A). The *in vivo* drug release rate from XTreo-RF1 matrices is substantially slower than that obtained *in vitro*. An *in vitro-in vivo* correlation (IVIVC) analysis was performed on the XTreo-RF1 matrices *via* a direct comparison of its *in vitro* and *in vivo* drug release profiles (Figures 2 and 3A). A linear regression between the *in vitro* time and *in vivo* time for the same amount of drug released resulted in an IVIVC time scaling factor of 1.59 (*i.e.* $\text{Time}_{in\ vivo} = 1.59 \times \text{Time}_{in\ vitro}$) with a linear regression coefficient of R^2 = 0.9913, indicating that the *in vitro* testing condition is an accelerated drug release condition compared to the *in vivo* condition.

/Insert Figure 3/

MF was present in the maxillary sinus tissue of the NZW rabbits throughout the 90-day duration (Figure 3B), confirming the ability of the XTreo™ drug matrices to deliver persistent dosing to local tissues over the entire treatment duration. Variability was observed from sample to sample, as commonly seen from tissue drug concentration measurements in animal models. The highest maxillary tissue concentrations of MF were detected at 60 days (range from 20.5 to 113.2

µg/g). At 90 days, the maxillary tissue concentrations of MF were generally about one order lower than the peak values with a single outlier of 37.4 µg/g, consistent with the change of drug release rate over time observed both *in vitro* and *in vivo*.

The peak plasma MF concentration was 141±29 pg/mL at 3 days post-implantation (Figure 3C). The plasma MF concentrations decreased to 81±9 and 56±6 pg/mL at 7 and 28 days after implantation, respectively. All plasma MF concentrations were below the LLOQ (20 pg/mL) at both 60 and 90 days post-implantation.

In Vivo Assessment of XTreo-RF2 (Study 2)

Plasma PK evaluation on the XTreo™ matrix carrying 2320 µg MF (XTreo-RF2) confirmed that MF is steadily released over at least 168 days (24 weeks), which was the last time point measured in the rabbit study (Figure 4A). The plasma MF concentration peaked at *ca.* 124±25 pg/mL at 24 hours post-bilateral implantation. Thereafter, the plasma concentrations gradually decreased over time and plateaued after 84 days with concentrations around 30 pg/mL. While the nominal daily dose of XTreo-RF2 is about 3 times that of XTreo-RF1, its C_{max} is comparable to that of XTreo-RF1, demonstrating the superiority of XTreo-RF2 in minimizing early burst release.

/Insert Figure 4/

XTreo-RF2 matrix softened over time upon implantation and showed loss of structural integrity during the removal procedure at 168 days. As expected, some matrices explanted at 168 days were partially covered with mucus. Neither animal safety nor drug release was impacted by the mucus over the 168-day study period. The HPLC-UV analysis on explanted XTreo-RF2 matrices at 168 days revealed that approximately 70% of the initially loaded drug was released *in*

vivo over the 168-day period. By assuming that the 70% released drug was proportionally absorbed into systemic circulation, the amount of drug absorbed after implantation of XTreo-RF2 was then calculated from the plasma PK data by the Wagner-Nelson method using the linear trapezoidal approach.[19,20] The calculated *in vivo* drug absorption was plotted as a function of time in Figure 4B. A linear relationship exists between the time *in vivo* and the time *in vitro* for a given fraction of absorbed or released drug. A time scaling factor of 1.57 (*i.e.* $\text{Time}_{in\ vivo} = 1.57 \times \text{Time}_{in\ vitro}$) is obtained from the linear regression analysis (R^2 = 0.9999), which is concordant with the value of 1.59 derived from the IVIVC analysis of XTreo-RF1.

Plasma PK Comparison Between XTreo-RF2 and Nasonex® (Study 3)

Plasma MF levels from XTreo-RF2 and Nasonex® were evaluated in a 28-day study to compare their pharmacokinetics. Plasma MF concentrations of the XTreo-RF2 matrices (2320 µg) peaked (106±26 pg/mL) at 24 hours after placement and remained stable beyond this time point until the end of the study (Figure 5), which are consistent with the values obtained from a separate study over the same period (Figure 4A). In comparison, the plasma drug concentrations of Nasonex® (400 µg, once daily) peaked within 15 to 30 minutes with high variability (C_{max} = 71 pg/mL at Day 1, 119 pg/mL at Day 14, and 56 pg/mL at Day 28) and approached the trough level (around or below LLOQ = 10 pg/mL) 2 hours after administration.

/Insert Figure 5/

Discussion

Despite the well demonstrated effectiveness of topical corticosteroids in reducing inflammation,[8] many CRS patients fail medical management using INCS, primarily due to the difficulty of INCS to reach inflamed tissues deep in the nasal cavity, short residency of the drug

on local tissues, and poor patient compliance to the dosage regimen.[9,10] An ideal corticosteroid product for treating CRS would be able to provide long-term, consistent drug delivery to local sinonasal tissues. Nasal corticosteroid-eluting implants may provide a strategy to achieve sustained daily drug dosing through a single administration. It is desired that a nasal implant can be devised with formulations that are tailorable through readily controllable drug release mechanisms and is able to stay in place to exert its function over time. Bioresorbable drug implants are of particular interest since they eventually degrade into non-toxic byproducts in the body and thus a surgical removal becomes optional or unnecessary once the drug is completely released.

XTreo™ is a versatile, bioresorbable, and biocompatible drug delivery platform for sustained and highly controlled delivery of drugs to local target tissues. It can be manufactured into various dimensions and braid patterns for use in various anatomies. Its elasticity, flexibility, and self-expanding properties allow the XTreo™ drug matrix to adapt to irregularly shaped cavities, providing conformity and optimal tissue contact.[21] Furthermore, the elastomeric design of the XTreo™ drug matrix allows it to dynamically expand over time as inflammation resolves and/or tissues remodel, ensuring continuous apposition to the surrounding tissue for the duration of treatment to facilitate effective drug delivery.[15] Drug delivery in the current matrix system was engineered to be driven by diffusion-dominated kinetics with tunable drug release durations, as exemplified by XTreo-RF1 and XTreo-RF2. Since the XTreo™ drug delivery system is compatible with a wide range of therapeutic agents such as antibiotics and steroidal or non-steroidal anti-inflammatory drugs, it has the potential to provide optimized topical treatment for CRS as well as other ear, nose, and throat (ENT) related diseases.

Through the *in vitro* drug release and *in vivo* pharmacokinetic studies on XTreo-RF1 and XTreo-RF2 matrices that have distinct release profiles (Figure 2), a meaningful IVIVC has been

established with a time scaling factor of about 1.6, deduced from both *in vivo* drug release and systemic absorption. The *in vitro* release profiles can therefore be used to predict the *in vivo* drug release and absorption accordingly, which is useful in guiding formulation changes in various stages of drug product development and providing insights for future related studies. The difference between the *in vitro* and *in vivo* drug release rates may stem from the different environment to which the matrices were exposed. The *in vitro* drug release evaluation was performed by submerging matrices in a release medium that provided infinite drug sink conditions at 37 °C. In the PK studies, however, the matrices were placed in the maxillary sinuses of rabbits, where the matrices were exposed to a moist versus submerged environment with slightly lower temperatures.[22] There, dissolution of the drug by the surrounding sinus mucus determines the *in vivo* release rate from the matrices, which was anticipated to be slower than that *in vitro*. While the current IVIVC provides a mathematical model to predict the *in vivo* drug release and absorption behavior of MF matrices in the rabbit model, it may not necessarily be equivalent to what occurs in humans due to their anatomical differences and the distinct pharmacokinetics of MF in these two species. Further exploration of an IVIVC in human would need to be confirmed independently.

It has been demonstrated that the XTreo™ MF matrix is superior to the conventional INCS with respect to continuous dosing to local tissue. The latter are usually associated with much lower tissue drug concentrations that are eliminated within a short period of time.[23] Sustained drug delivery directly targeting local tissues has been proven for XTreo-RF1. The observed MF concentrations in rabbit maxillary sinus tissue (2 – 100 µg/g) in our study are comparable to that of the report of a 30-day MF implant in the same animal model,[13] both are considerably higher than the tissue concentrations (e.g. tens to hundreds ng/g) that resulted from the administration of

INCS at a clinically relevant dose.[23] Furthermore, these tissue MF concentrations are several orders higher than the half maximal effective concentrations (EC50) for transexpression of transcription factors, such as activator protein-1 (AP-1) and nuclear factor-kappa B (NF-κB), through which glucocorticoids primarily exert their anti-inflammatory effects.[24,25] The previously reported 30-day MF implant released 90% of its drug load within the first 13 days and the maxillary tissue concentrations of MF peaked during the 7- to 13-day time frame. In the present study, about 90% of the loaded drug was released at 90 days and maxillary tissue concentrations were observed through 90 days, indicating that XTreo-RF1 can deliver MF to the local tissues in a more effective and sustained manner.

Controlled and sustained drug delivery is also confirmed in the plasma PK studies of XTreo™ matrices. The XTreo-RF1 matrix showed quantifiable plasma MF concentrations for a minimum of 28 days, while plasma MF were measurable from the XTreo-RF2 matrix throughout the 168-day study period, further supporting sustained drug treatment for extended periods can be achieved from a single administration. The low levels of drug exposure did not cause systemic toxicity as assessed via the animal health, clinical pathology panels, and cortisol levels, as well as the absence of any matrix-related adverse events. It has been shown that minor systemic effect like serum cortisol reduction was only associated with very high plasma MF concentrations (e.g. 149 to 195 pg/mL) that were resulted from inhaled MF at a dose of 1600 µg/day in human patients.[26]

Besides being swallowed, two aspects of absorption may be involved in the intranasal administration of a lipophilic corticosteroid (*e.g.* MF): (1) topical absorption at the target site to bind with the glucocorticoid receptors that determines therapeutic efficacy and (2) systemic absorption.[27] It has been well established that MF undergoes rapid and extensive first-pass

metabolism following oral administration and its corresponding systemic bioavailability is < 1%.[28] It is likely that the major portion of MF in systemic circulation comes from absorption through the extensively vascularized nasal mucosa. The systemic absorption and receptor binding rate constants for intranasally administered MF are comparable to each other as demonstrated by a PK model.[29] In this context, the systemic exposure may be an appropriate surrogate for nasal/sinus exposure to MF. The transient plasma MF concentration of Nasonex® may be attributed to the rapid mucociliary clearance of intranasal sprays,[30,31] suggesting a limited availability of the sprayed drug to the local nasal tissue. For instance, it was reported that about 50-60% MF is cleared from the nasal cavity 10-15 minutes after administration of MF nasal sprays due to mucociliary transport.[32,33] Patel *et al.* assessed the tissue PK and plasma PK of a fluticasone propionate-eluting nasal implant in a rabbit model. Their data showed that the drug concentrations in sinus tissues are positively correlated with the plasma drug concentrations.[18] In this regard, a certain level of systemic exposure could be an indirect indication of active drug delivery to the local sinus tissues for this type of drug matrix

Conclusions

XTreo™ is a versatile platform for targeted and sustained drug delivery, which can be designed for optimized tissue contact while maintaining underlying tissue function through its open cell design. This novel polymer-drug composite has broad application as it is compatible with a wide range of drugs and can be customized to release those therapeutic agents for various controlled durations. Here, XTreo™ drug matrices have been developed and formulated to release MF for up to 24 weeks *in vivo* and conform to the sinus anatomy, maintaining persistent tissue contact for continuous drug delivery throughout the intended treatment duration. The controlled and consistent release of MF from XTreo™ bioresorbable matrices was demonstrated both *in vitro*

and *in vivo,* and an IVIVC was established accordingly. Therapeutically efficacious MF concentrations were measured in the local sinus tissues, while low levels of MF were detected in plasma, demonstrating that the XTreo™ matrices can maximize the therapeutic effect to the immediately contacted tissues while potentially eliminating systemic side effects. Unlike INCS, the MF matrices provide a continuous dose of MF over several months from a single administration, as demonstrated in this study and a previously reported phase 1 clinical study.[15] Thus, XTreo™ MF matrices enable a novel therapeutic approach for CRS by providing optimal and continuous targeted drug dosing to inflamed sinonasal tissues.

Acknowledgments

We would like to thank Stephanie Webber, Allison Gartung, Maria Palasis, and Corinne Noyes for useful discussion in preparing this manuscript.

Author Contributions

Conceived, designed, and wrote the manuscript: CY, YK, DC. Analyzed the data: CY, LFT, AP.

Declaration of Conflicting Interests

Potential conflict of interest: C.Y., L.F.T., A.P., D.C., and Y.K. were employees of Lyra Therapeutics at the time of this work. All authors have stock options in Lyra Therapeutics.

References

1. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology.* 2020; 58(suppl S29):1-464.
2. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol.* 2021; 11(3):213-739.
3. Rudmik L, and Smith TL. Quality of life in patients with chronic rhinosinusitis. *Curr Allergy Asthma Rep.* 2011; 11(3):247-252.
4. Bhattacharyya N. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. *Ann Otol Rhinol Laryngol.* 2011; 120(7):423-427.
5 Hamilos DL. Chronic rhinosinusitis: Epidemiology and medical management. *J Allergy Clin Immunol.* 2011; 128(4):693-707.
6. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe – an underestimated disease. A GA^{2}LEN study. *Allergy.* 2011; 66(9):1216-1223.
7. Zhang Y, Gevaert E, Lou H, et al. Chronic rhinosinusitis in Asia. *J Allergy Clin Immunol.* 2017; 140(5):1230-1239.
8. Rudmik L, and Soler ZM. Medical therapies for adult chronic sinusitis: A systematic review. *J Am Med Assoc.* 2015; 314(9):926-939.
9. Moeller W, Schuschnig U, Meyer G, et al. Ventilation and aerosolized drug delivery to the paranasal sinuses using pulsating airflow - a preliminary study. *Rhinology.* 2009; 47(4):405-412.
10. Nabi S, Rotenberg BW, Vukin I, et al. Nasal spray adherence after sinus surgery: Problems and predictors. *J Otolaryngol Head Neck Surg.* 2012; 41(suppl 1):S49-S55.
11. Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: Two different approaches to treat nasal polyps. *J Allergy Clin Immunol.* 2010; 125(5):1069-1076.
12. Vaidyanathan S, Barnes M, Williamson P, et al. Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: A randomized trial. *Ann Intern Med.* 2011; 154(5):293-302.
13. Li PF, Downie D, and Hwang PH. Controlled steroid delivery via bioabsorbable stent: Safety and performance in a rabbit model. *Am J Rhinol Allergy.* 2009; 23(6):591-596.
14. Ow R, Gropp E, Clutter D, et al. Steroid-eluting sinus implant for in-office treatment of recurrent polyposis: a pharmacokinetic study. *Int Forum Allergy Rhinol.* 2014; 4(10):816-822.
15. Douglas RG, Psaltis AJ, Rimmer J, et al. Phase 1 clinical study to assess the safety of a novel drug delivery system providing long-term topical steroid therapy for chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2019; 9(4):378-387.
16. Winkler J, Hochhaus G, and Derendorf H. How the lung handles drugs: pharmacokinetics and pharmacodynamics of inhaled corticosteroids. *Proc Am Thorac Soc.* 2004; 1(4):356–363.
17. Perez AC, Buzatto GP, de Picole Dantas I, et al. Review of experimental models: sinusitis in rabbits. *Braz J Otorhinolaryngol.* 2014; 80(5):435-440.
18. Patel VS, Walgama E, Psaltis A, et al. Biocompatibility and pharmacokinetics of fluticasone-eluting sinus implant in a rabbit model. *Am J Rhinol Allergy.* 2017; 31(6):382-388.
19. Wagner JG and Nelson E. Kinetic analysis of blood levels and urinary excretion in the absorptive phase after single doses of drug. *J Pharm Sci.* 1964; 53(11): 1392-1403.
20. Emami J. In vitro-in vivo correlation: from theory to applications. *J Pharm Pharmaceut Sci* 9:31-51, 2006.
21. Sharma U, Concagh D, Core L, et al. The development of bioresorbable composite polymeric implants with high mechanical strength. *Nat Mater.* 2017; 17(1):96-103.
22. Perko D. Temperature measurements in the maxillary sinus of rabbits. *Rhinology.* 1991; 29(3):185-192.
23. Bonsmann U, Bachert C, Delank KW, et al. Presence of fluticasone propionate on human nasal mucosal surface and human nasal tissue over a period of 24 h after intranasal application. *Allergy.* 2001; 56(6):532-535.
24. Roumestan C, Henriquet C, Bousquet J, et al. Fluticasone propionate and mometasone furoate have equivalent transcriptional potencies. *Clin Exp Allergy.* 2003; 33(7):895-901.
25. Dirks NL, Li S, Huth B, et al. Transexpression and transactivation potencies of inhaled glucocorticoids. *Pharmazie.* 2008; 63(12):893-898.
26. Affrime MB, Kosoglou T, Thonoor CM, et al. Mometasone furoate has minimal effects on the hypothalamic-pituitary-adrenal axis when delivered at high doses. *Chest.* 2000; 118(6):1538-1546.

27. Szefler SJ. Pharmacokinetics of intranasal corticosteroids. *J Allergy Clin Immunol*. 2001; 108(suppl 1):S26-S31.
28. Crim C, Pierre LN, Daley-Yates PT. A review of the pharmacology and pharmacokinetics of inhaled fluticasone propionate and mometasone furoate. *Clin Ther*. 2001; 23(9):1339-1354.
29. Rygg A, Hindle M, and Longest PW. Linking suspension nasal spray drug deposition patterns to Pharmacokinetic profiles: A proof-of-concept study using computational fluid dynamics. *J Pharm Sci.* 2016; 105(6):1995-2004.
30. Derendorf H, and Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. *Allergy*. 2008; 63(10):1292-1300.
31. Gizurarson S. The effect of cilia and the mucociliary clearance on successful drug delivery. *Biol Pharm Bull.* 2015; 38(4):497-506.
32. Emanuel IA, Blaiss MS, Meltzer EO, et al. Nasal deposition of ciclesonide nasal aerosol and mometasone furoate aqueous nasal spray in allergic rhinitis patients. *Am J Rhinol Allergy*. 2014; 28(2):117-121.
33. Shah SA, Berger RL, McDermott J, et al. Regional deposition of mometasone furoate nasal spray suspension in humans. *Allergy Asthma Proc.* 2015; 36(1):48-57.

Table 1. Blood collection schedule for measuring plasma MF concentrations

Study	Drug	Blood Collection Time
1	XTreo-RF1	T = 0, 1 hour, 6 hours, 1 day, 3 days, 7 days, 28 days, 60 days, and 90 days (n = 4 for each timepoint)
2	XTreo-RF2	T = 0, 1 hour, 3 hours, 6 hours, 1 day, 3 days, 7 days, 14 days, 28 days, 56 days, 84 days, 112 days, 140 days, and 168 days (n = 12 for each timepoint)
3	Nasonex®	T = 0 (all animals, n = 6), 15 min, 30 min, 1 hour, 2 hours, 4 hours, 8 hours, and 24 hours (alternating n = 3 animals to minimize blood loss in each animal) on Days 1, 14 and 28
	XTreo-RF2	T = 0 (all animals, n = 6), and 15 min, 30 min, 1 hour, 2 hours, 4 hours, 8 hours (alternating n = 3 animals to minimize blood loss in each animal), 1 day, 2 days, 3 days, 5 days, 7 days, 14 days, 21 days, and 28 days (all animals, n = 6)

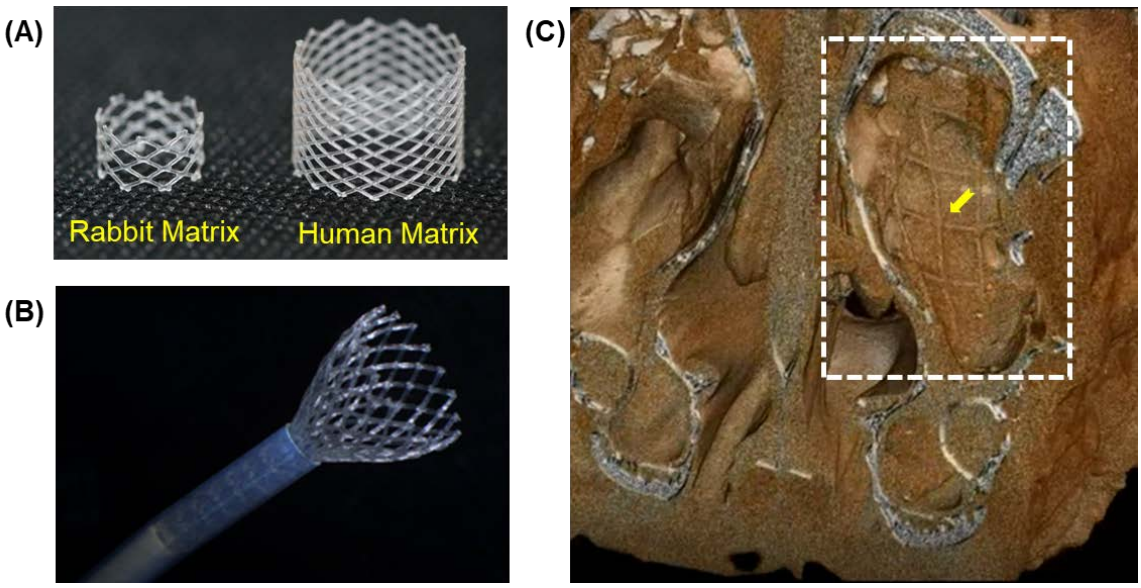

Figure 1. Structural characteristics of the XTreo^{TM} MF matrices: (A) Comparison of rabbit and human MF matrices. (B) MF matrix self-expands from a constrained state when deployed from an applicator. (C) Microcomputed tomography (µCT) image of the rabbit MF matrix conformed to the irregular geometry of the rabbit maxillary sinus cavity (dashed rectangle). The arrow points to the drug matrix structure.

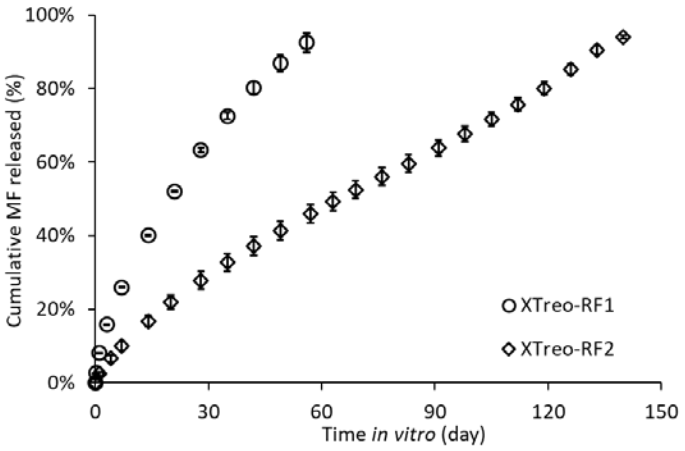

Figure 2. Cumulative *in vitro* MF release profiles of two rabbit MF matrices with different release durations.

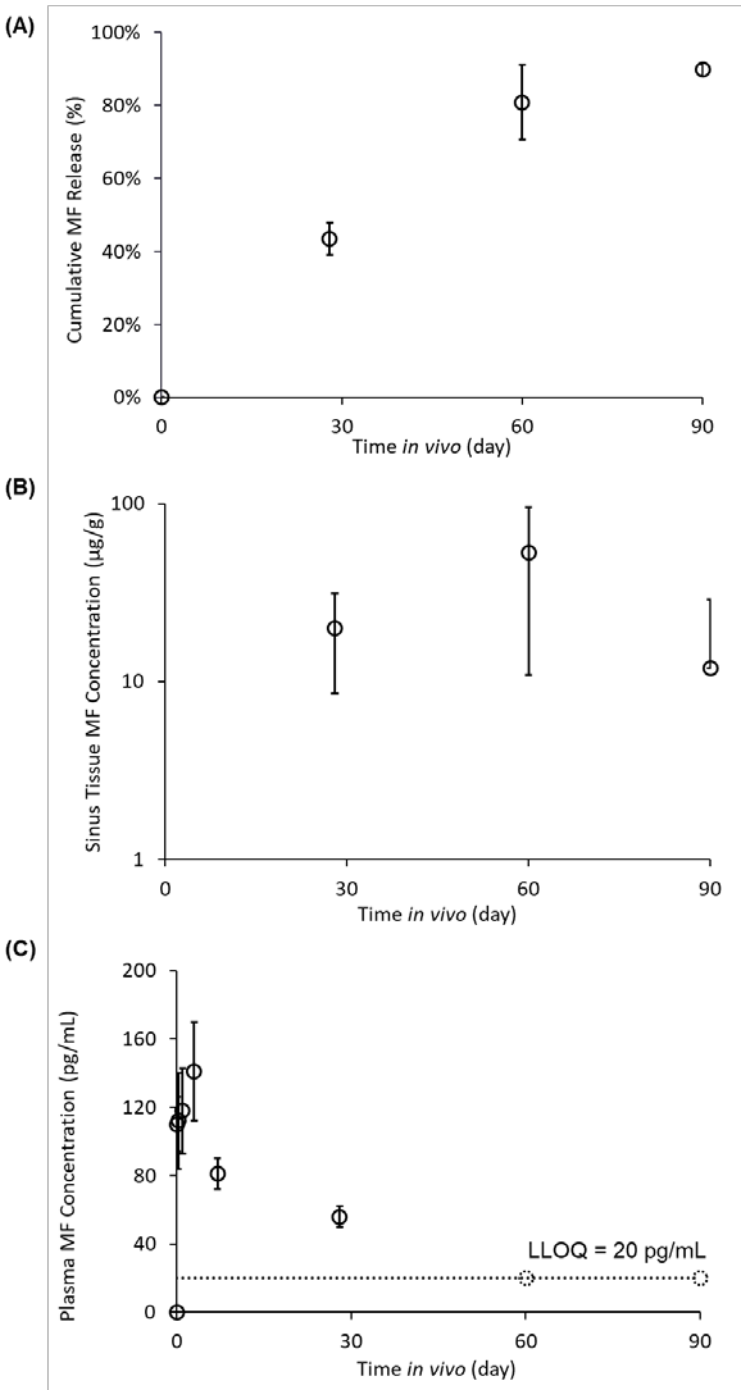

Figure 3. Assessment of a 390 µg MF rabbit matrix (XTreo-RF1): (A) *in vivo* drug release profile, (B) MF concentration in maxillary sinus tissue, and (C) Plasma MF concentration. The dotted line in panel (C) represents the lower limit of quantification (LLOQ) of MF in plasma (20 pg/mL).

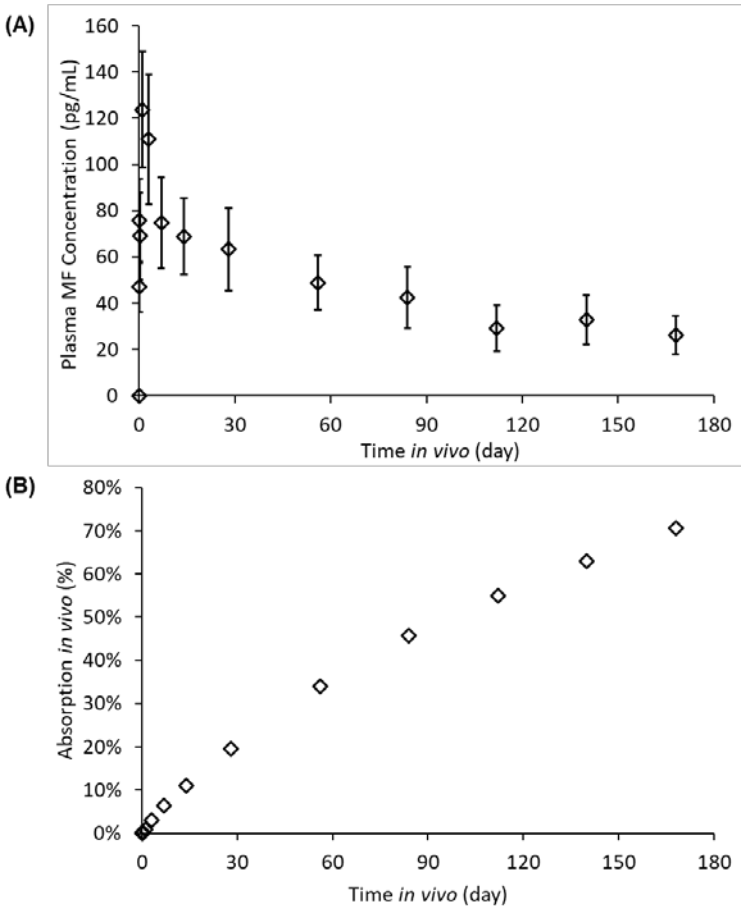

Figure 4. Assessment of a 2320 µg MF rabbit matrix (XTreo-RF2): (A) Plasma MF concentrations and (B) the calculated *in vivo* drug absorption profile.

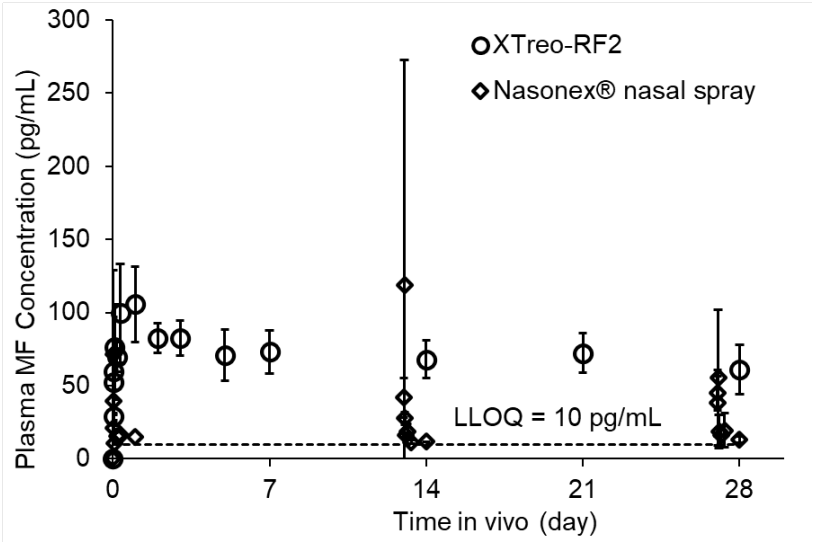

Figure 5. Plasma PK profiles of once daily Nasonex® MF nasal sprays (400 µg/day) and bilaterally placed XTreo-RF2 drug matrices (2320 µg) in a NZW rabbit model.