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ORIGINAL RESEARCH

Population Pharmacokinetic-Pharmacodynamic (popPK/PD) Relationship of Orismilast, A Potent and Selective PDE4B/D Inhibitor, in Atopic Dermatitis

Richard B. Warren · Anne Weiss · Jakob Felding · Morten O. A. Sommer

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ABSTRACT

***Introduction*:** Orismilast is a novel oral selective inhibitor of phosphodiesterase 4B and 4D subtypes (PDE4B/D) in clinical development for treatment of atopic dermatitis (AD) and other inflammatory skin conditions. Herein, we describe a pharmacokinetic/pharmacodynamic (PK/PD) analysis comparing predicted exposure data of orismilast and apremilast in AD patients and place these data in the context of their IL-13 secretion data generated in a human whole-blood assay.

***Methods*:** A PK/PD assessment of orismilast and apremilast in AD was performed. In a human whole blood assay, the levels needed to inhibit IL-13 production were measured for orismilast and apremilast head-to-head. These data were then contextualized with simulated exposure of clinically relevant doses of the two drugs.

***Results*:** The analysis shows that orismilast has potential to significantly inhibit IL-13 production at all three clinical doses trialed in AD (20 mg bid, 30 mg bid, and 40 mg bid) as the drug has a predicted $C_{average}$ plasma concentration exceeding the IL-13 IC_{90} value of the human whole-blood assay and a predicted C_{min} above the IL-13 IC_{50} value. Apremilast, in contrast, is predicted to reach $C_{average}$ plasma concentrations below the IL-13 IC_{50} value for both doses (30 mg bid and 40 mg bid) and only exceeding the IL-13 IC_{50} value at peak concentrations for the highest dose.

***Conclusion*:** The outcome of the analysis supports the observed clinical effect of orismilast in patients with AD and could explain the lack of efficacy of apremilast in the same indication.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD) is a common chronic inflammatory skin condition that negatively impacts AD patients' quality of life. Various drugs are used for treatment of AD; however, a safe and effective oral treatment is still an important unmet need. Orismilast is an orally available PDE4B/D selective inhibitor in clinical development that has demonstrated improved

R. B. Warren (✉)
Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester NIHR Biomedical Research Centre, The University of Manchester, Salford, Manchester M6 8HD, UK
e-mail: richard.warren@manchester.ac.uk

A. Weiss · J. Felding · M. O. A. Sommer
UNION Therapeutics A/S, Hellerup, Denmark

M. O. A. Sommer
Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark (DTU), Lyngby, Denmark

effect in pre-clinical models and clinical studies compared to apremilast. This analysis compared predicted exposures of orismilast and apremilast in relation to data from a human whole-blood assay measuring IL-13 release. The authors reported that orismilast has potential to block IL-13 secretion more efficiently compared to apremilast at therapeutically relevant doses, supporting the observed clinical effect of orismilast in patients with AD and lack of efficacy of apremilast in the same indication. It highlights the strength of using drug exposure in relation to whole-blood derived data when performing pharmacokinetic/pharmacodynamic (PK/PD) assessments instead of comparing dose and biochemical data.

Keywords: Atopic dermatitis; Pharmacokinetics; Pharmacodynamics; Orismilast; PDE4

Key Summary Points
Why carry out this study?
This study was conducted to increase our understanding of the different clinical outcomes in patients with atopic dermatitis when treated with orismilast compared to apremilast.
It highlights the strength of using drug exposure in relation to whole blood derived data when performing pharmacokinetic/pharmacodynamic (PK/PD) assessments.
What was learned from the study?
The presented PK/PD analysis supports the observed clinical effect of orismilast in patients with AD and lack of efficacy of apremilast for the same indication.
These results indicate that orismilast is a distinct drug with a superior PK/PD profile for treatment of atopic dermatitis compared to apremilast and will guide the dose selection of orismilast in future studies.

INTRODUCTION

The currently available immunosuppressive drugs for oral treatment of atopic dermatitis (AD), including cyclosporine, abrocitinib, baricitinib, and upadacitinib, all require monitoring for serious adverse events such as nephrotoxicity or infections, tuberculosis, thrombosis, cancer, and major adverse cardiovascular events [1]. A safe and effective alternative, therefore, remains a significant unmet need for patients with moderate-severe AD.

Inhibition of phosphodiesterase 4 (PDE4) has been validated as a therapeutic strategy for topical treatment of mild-moderate AD based on the launch of crisaborole and the successful Ph3 studies reported on topical administration of roflumilast [2, 3]. Apremilast is a marketed orally dosed PDE4 inhibitor that was trialed in moderate-severe AD. Further development for AD was, however, discontinued because of lack of efficacy based on patients achieving Static Physician's Global Assessment-Acute Signs (sPGA-A) response at Week 12 (apremilast 30 mg: 3.4%; 40 mg: 14.3% and 6.3% in the placebo group) [4]. Administration of apremilast doses beyond 40 mg bid does not seem feasible and has not been tested in patient studies because of dose-limiting adverse events [5]. Orismilast is a PDE4B/D selective inhibitor with improved potency compared to apremilast in various pre-clinical models [6]. Furthermore, Phase 2b data on orismilast in psoriasis (IASOS) indicated a deeper response for this indication compared to apremilast based on the proportion of patients achieving PASI90 (orismilast 20 mg: 24.1%; 30 mg: 22.0%; 40 mg: 28.3%; placebo: 8.3%; $p<0.05$ for 20 and 40 mg doses), which is numerically greater than for apremilast (30 mg: 9.8% vs placebo: 0.4%, $p<0{\cdot}05$) [7]. Recently, we reported clinical data on orismilast from a 16-week Phase 2b study in patients with AD, and although not all endpoints reached statistical significance, more patients achieved an Investigator's Global Assessment (IGA) of 0/1 at Week 16 in the orismilast groups compared to placebo (orismilast 20 mg: 26.3%; 30 mg: 24.3%; 40 mg: 30.9%; placebo: 9.5%; $p<0.05$

for 20 and 40 mg doses) [8]. These data suggest that the clinical relevance of selective PDE4B/D inhibition with orismilast has potential to offer a convenient, novel oral therapy to treat psoriasis and AD.

AD is a heterogenous disease involving interactions among a dysregulated type 2 immune response, skin microbiome dysbiosis, and a disrupted barrier function [9]. Multiple factors contribute to the defective immune-mediated response in AD; however, IL-13 has been reported to be a crucial cytokine involved in the disease pathogenesis [10]. IL-13 is a central driver of type-2 T-helper inflammation, overexpressed in lesional skin of AD patients, and is involved in modification of the skin microbiome and reduction of epidermal barrier protein expression [11]. In addition, tralokinumab and lebrikizumab, which are monoclonal antibodies that specifically target IL-13, have been approved for AD [12].

The aim of the current report is to provide a PK/PD assessment of orismilast and apremilast in AD by contextualizing the levels needed to inhibit IL-13 production in human whole blood with simulated clinical exposures of the two drugs. The analysis will assist in understanding the reported outcomes of their respective Phase 2 AD trials and guide the dose selection of orismilast in future AD studies.

METHODS

IL-13 Concentration in Human Whole Blood

Fresh human whole blood ($n = 8$) collected in heparin tubes from healthy donors was sourced from Tissue Solutions. Whole blood was plated (100 µl/well) in duplicates in white flat-bottomed 96-well plates and stimulated with lipopolysaccharide (LPS, 1 µg/ml, 50 µl/well) for 24 h (at approximately 37 °C and 5% CO_2) in the presence or absence of orismilast (MW: 510.29 g/mol) or apremilast (MW: 460.5 g/mol) using eight concentrations. Cultures were carried out in technical duplicates. Neat cell culture supernatants (50 µl/well) were analyzed using the Procartaplex Luminex IL-13 assay kit according to manufacturer's instruction. LDH-Glo® storage buffer was added to 1 µl of the neat supernatant, and the LDH-Glo® cytotoxicity assay was performed according to the supplier's instructions. No cytotoxicity was observed at the tested concentrations. Visualization and statistical analysis were conducted using GraphPad Prism. Three donors had a majority of data points below the limit of quantification; one each showed a non-response in the two treatment groups and were thus excluded from the data analysis. An asymmetric five-parameter curve was fitted to the data using least square regression as the fitting method to estimate the concentration needed to inhibit 50% of IL-13 levels (IC_{50}) relative to the maximum response achieved with each drug. Using the hillslope coefficient, the concentration needed to inhibit 90% of IL-13 levels (IC_{90}) was calculated.

Population Pharmacokinetic Model of Orismilast When Dosed in Modified-Release Tablets

Pharmacokinetic profiles of orismilast dosed as modified-release tablets were simulated from internal analyses using PK data from 366 subjects from two phase 1 studies (healthy Caucasian and Chinese volunteers) and two Phase 2b studies [a psoriasis study (IASOS, NCT05190419) and atopic dermatitis study (ADESOS, NCT05469464)]. All studies were conducted in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and the Declaration of Helsinki, with approval of national independent ethics committees. All patients provided written informed consent before any study-related activities, and the study protocol was approved by the relevant local institutional review boards and independent ethics committees. Briefly, a population pharmacokinetic model was established using a two-compartment model and population mean parameters (e.g., clearance, volume of distribution, absorption coefficients, and lag time).

The following PK parameters at steady state were derived from the final model for 20,

30, and 40 mg bid: $C_{\text{average-ss}}$ (derived from AUC_{τ}/12 h), $C_{\text{max-ss}}$, and $C_{\text{min-ss}}$ were calculated for atopic dermatitis patients and are presented for normal weight (BMI < 30 kg/m^2). Furthermore, a pharmacokinetic profile was simulated for individuals with normal weight (60 kg–100 kg) following administration of 20 mg bid orismilast. Plasma concentrations at steady state between the 10th and 11th dose were visualized.

Apremilast Predictive Exposure Based on Final Population Pharmacokinetic Model When Dosed Orally

Plasma concentrations in female atopic dermatitis patients were simulated using population mean parameters from the FDA-approved final population pharmacokinetic model of apremilast in psoriasis patients, as shown in Table 1 [13]. Interindividual variability of the parameters has not been published; hence, variability of plasma concentrations could not be calculated.

A one-compartment model and a dosing interval of 12 h for 11 doses bid of 30 mg and 40 mg (steady state) were used with the following ordinary differential equations:

$$\frac{dA}{dt}[1] = -K_a[1] \quad (1)$$

$$\frac{dA}{dt}[2] = K_a \cdot A[1] - \left(\frac{CL}{V}\right) \cdot A[2] \quad (2)$$

A is absorption, K_a is the absorption rate constant, 1 is the first compartment, and 2 is the second compartment; CL = clearance, V = volume of distribution.

The following PK parameters were calculated in the last dosing interval after the simulated bid administration: $C_{\text{average-ss}}$, $C_{\text{max-ss}}$, and $C_{\text{min-ss}}$. The average concentration was calculated by dividing the area under the curve (trapezoidal estimation) by the dosing interval (12 h). Simulations were carried out in R using the *PKPDsim* package.

Table 1 Population pharmacokinetic parameters of apremilast from the final PK model for Otezla® in psoriasis

Parameter	Geometric mean
CL/F (l/h)	9.26
If other disease or missing	1.09x
V_c/F (l)	118
K_a (1/h)	1.84

For the clearance (CL/F), we applied the indicated factor and used 10.09 l/h. V_C/F = Volume of distribution in central compartment/bioavailability, K_a = absorption coefficient

Plasma Exposure Profile Regarding IL-13

Table 2 Effect of orismilast and apremilast on IL-13 in a human whole blood assay

IL-13 in human whole blood	Orismilast	Apremilast
IC_{50}	8 nM (4 ng/ml)	881 nM (405 ng/ml)
IC_{90}	49 nM (25 ng/ml)	163 μM (74 μg/ml)

Concentration needed to inhibit 50% (IC_{50}) and 90% (IC_{90}) of IL-13 levels using least square regression as fitting method for orismilast and apremilast

Whole Blood Assay

The predicted plasma concentration profile and pharmacokinetic parameters of apremilast and orismilast were plotted regarding the respective relative IC_{50} and/or IC_{90} from the IL-13 whole blood assay. As the in vitro IL-13 potency was assessed in whole blood, adjustments for protein binding and cellular penetrations were not considered. Although the distribution ratio is not publicly available for apremilast, the large volume of distribution, exceeding the volume of total body water, suggests that apremilast is extensively distributed from plasma into tissues.

RESULTS

A whole blood assay using LPS stimulation was carried out to investigate the impact on IL-13 levels upon addition of orismilast or apremilast. Following 24 h incubation, the relative IC_{50} of orismilast and apremilast was 8 nM and 881 nM (Table 2), respectively, demonstrating a 100 times higher potency of orismilast than of apremilast in this assay.

To establish a pharmacodynamic-pharmacokinetic relationship, we then estimated the plasma exposure of orismilast in atopic dermatitis patients in the ADESOS study based on the final population pharmacokinetic model of orismilast. Exposure at steady state was simulated following 20, 30, and 40 mg bid as trialed in the ADESOS study. At all three therapeutic doses of orismilast, the predicted plasma concentrations (C_{max} and $C_{average}$) were higher than the IL-13 IC_{50} and IC_{90} values (Fig. 1A), whereas the predicted C_{min} was comparable to the IL-13 IC_{50} value. The systemic exposure and peak concentration increased dose proportionally, and no additional benefit in terms of pharmacodynamic target coverage was seen with doses > 20 mg bid orismilast in AD patients.

As previously reported, a weight-based dosing regimen could be anticipated for future trials with oral orismilast [7]. A dose of 20 mg bid orismilast in normal weight patients (60 kg–100 kg) would serve as reference for dose adjustments because of the observed PD target saturation using this dose. Therefore, dose adjustments (e.g., obese, adolescents,

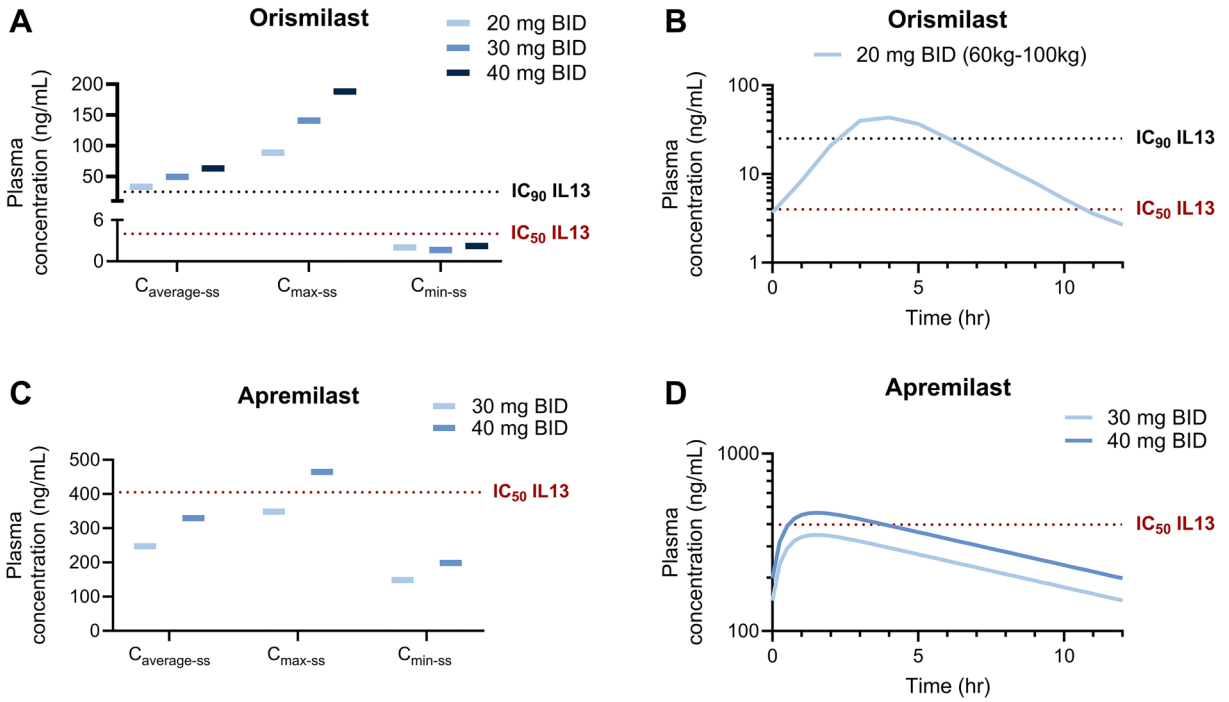

Fig. 1 Pharmacokinetic-pharmacodynamic relationship of oral apremilast and orismilast in atopic dermatitis. **A** Model-derived pharmacokinetic (PK) parameters, average ($C_{average}$), maximum (C_{max}), and minimum concentration (C_{min}) of orismilast at steady state in atopic dermatitis patients in the ADESOS study (< BMI 30 kg/m^2) set in relation to the IC_{50} and IC_{90} of IL-13 inhibition measured in human whole blood. **B** Simulated orismilast exposure at steady state in individuals with a bodyweight of 60–100 kg following administration of 20 mg bid oral orismilast based on the final Population PK (PopPK) model. **C**, **D** Predicted plasma concentrations of apremilast at steady state in atopic dermatitis patients following 30 mg bid and 40 mg bid based on the final PopPK model of Otezla® relative to IC_{50} of IL-13 inhibition in human whole blood. Medians are displayed in all panels

etc.) should match the exposure of 20 mg bid in a normal weight group with orismilast concentrations at steady state above the IL-13 IC_{50} for 80% and above the IL-13 IC_{90} for 25% of the time within a dosing interval (Fig. 1B).

In the absence of published pharmacokinetic data of the two doses of apremilast trialed in the Phase 2 study in atopic dermatitis patients, we simulated the plasma concentration profile of apremilast following 30 mg bid and 40 mg bid. We predicted the exposure of apremilast at steady state in atopic dermatitis patients following 11 twice-daily doses based on the reported PopPK model for psoriasis patients (Fig. 1C, D). Considering the exposure of the highest clinical dose of apremilast (40 mg bid) in the context of the IL-13 whole blood data indicates that apremilast insufficiently covers IL-13 at steady state as the peak plasma concentration (C_{max}) of apremilast is just above the IC_{50} IL-13 value, whereas the average concentration ($C_{average}$) is below the IL-13 IC_{50} value (Fig. 1C). Furthermore, apremilast concentrations are only above IL-13 IC_{50} for 2.5 h with 40 mg bid (Fig. 1D). At no time point in the dosing interval of either apremilast dose was the concentration high enough to reach IL-13 IC_{90}.

DISCUSSION

Topically applied PDE4 inhibitors have been used to treat AD since the launch of crisaborole in 2017. An orally available PDE4 inhibitor has, in contrast, not yet been approved for AD. While orally dosed apremilast (pan-PDE4 inhibitor) failed to demonstrate efficacy in a Phase 2 study [4], orismilast (PDE4B/D selective inhibitor) showed encouraging data in the ADESOS Phase 2b study after oral administration [8]. We hypothesize this difference in clinical effect is based on how effectively these two drugs inhibit production of key cytokines, including IL-13. To investigate this hypothesis, we profiled orismilast and apremilast head-to-head in a human whole-blood assay, measuring IL-13 release, and investigated how the respective in vitro potencies relate to the predicted systemic exposure of each drug using therapeutically trialed doses. To the best of our knowledge, IL-13 human whole blood data have not previously been reported for the two drugs.

The current analysis, focusing on AD patients, shows that orismilast has a predicted $C_{average}$ which exceeds the IL-13 IC_{90} value of the human whole blood assay and a C_{min} above the IL-13 IC_{50} value, suggesting a pronounced inhibition of IL-13 production for all three clinical doses. Apremilast, in contrast, is predicted to reach $C_{average}$ plasma concentrations below the IL-13 IC_{50} value for both doses and only exceeds the IL-13 IC_{50} value at peak concentrations for the highest dose. The difference between the two drugs is also reflected in the time above their respective IL-13 IC_{50} values at steady state. The plasma concentration of the lowest orismilast dose (20 mg bid) is above the IC_{50} value ~ 80% of the time (~ 10 h out of 12.5 h) and, importantly, on par with the IC_{50} value for the remaining ~ 20%. The plasma concentration of apremilast, however, is only above the IC_{50} value ~ 20% of the time (2.5 h out of 12.5 h) for the highest dose but below the IC_{50} value at all time points for the lower dose. These data indicate that the limited benefit of apremilast in AD is due to insufficient coverage of IL-13 with the concentration reached using the highest dose. In contrast, orismilast exposure following 20 mg dosing achieved a superior PD coverage, which could explain the higher efficacy in AD compared to apremilast, although this conclusion is limited by an indirect comparison between trials with different outcome measures.

Based on the presented data for orismilast, a 20 mg bid dose should be sufficient to deliver efficacy in AD, and a limited benefit is apparent for the higher doses in normal weight patients (60 kg–100 kg), in line with the lack of dose-response observed in the ADESOS study. However, future studies in larger populations need to be conducted to verify a favorable benefit-risk profile using this dose.

A key strength of this analysis is the use of human whole blood IL-13 data of orismilast and apremilast generated using the same assay conditions [14]. In addition, in vitro potency data were used in combination with predicted clinical exposure bridging the pre-clinical potencies

to exposure in AD patients and supporting the observed difference in clinical efficacy of the two drugs in AD. One key limitation of the analysis is that it is only based on IL-13. AD is a complex disease, and IL-13 is not the only important player. However, IL-13 is a key cytokine in AD as demonstrated by the two anti-IL13 antibodies marketed for AD treatment [10, 12]. In addition, our analysis did not include biologics, such as the widely used tralokinumab, lebrikizumab, and dupilumab, because of the substantial difference in their interference with the IL-13 biology, challenging the interpretation of a direct comparison. A PDE4 inhibitor reduces the production of IL-13, whereas dupilumab blocks IL-13 signaling and tralokinumab/lebrikizumab removes IL-13 from the circulation altogether. Finally, PDE4 inhibitors have a broad mechanism of action and reduce other cytokines than IL-13, which could contribute to efficacy in AD [15].

Another limitation is the lack of PK data of apremilast in AD subjects; however, using the FDA-approved population pharmacokinetic model of apremilast is a robust approach to estimate exposure in this patient population.

CONCLUSION

The present analysis integrating IL-13 human whole blood data of orismilast and apremilast with predicted exposures of the two drugs supports the observed clinical effect of orismilast, and lack of efficacy for apremilast, in patients with AD. It also highlights the strength of using drug exposure in relation to whole blood-derived data when performing PK/PD assessments in place of comparing dose and biochemical data. Our analysis shows that orismilast is a distinct drug with a superior PK/PD profile for treatment of atopic dermatitis compared to apremilast. Finally, orismilast could potentially be a safe oral alternative to the launched biologics in AD. However, Phase 3 studies need to be conducted to confirm the potential of orismilast.

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Data Availability. The data that support the study findings are included in this published article.

Declarations

Conflict of Interest. Richard B. Warren has received research grants from AbbVie, Almirall, Amgen, Celgene, Janssen, Lilly, LEO Pharma, Novartis, Pfizer, and UCB and consulting fees from AbbVie, Almirall, Amgen, Arena, Astellas, Avillion, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, DiCE, GlaxoSmithKline, Janssen, Lilly, LEO Pharma, Novartis, Pfizer, Sanofi, Sun Pharma, UCB, and UNION Therapeutics. Richard B. Warren is Editor-in-Chief of Dermatology and Therapy. Richard B. Warren was not involved in the selection of peer reviewers for the manuscript or any of the subsequent editorial decisions. Anne Weiss and Jakob

Felding are employees of UNION Therapeutics. Morten O.A. Sommer is an employee and board member of and shareholder in UNION Therapeutics.

Ethical Approval. This study was conducted in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and the Declaration of Helsinki and with the approval of national independent ethics committees. All patients provided written informed consent before any study-related activities were carried out, and the study protocol was approved by the relevant local institutional review boards and independent ethics committees. Written patient consent for publication was obtained.

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