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ITC Commentary on Metformin Clinical Drug–Drug Interaction Study Design That Enables an Efficacy- and Safety-Based Dose Adjustment Decision

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Metformin drug–drug interaction (DDI) studies are conducted during development of drugs that inhibit organic cation transporters and/or multidrug and toxin extrusion proteins (OCTs/MATEs). Monitoring solely changes in systemic exposure, the typical DDI study endpoint appears inadequate for metformin, which is metabolically stable, has poor passive membrane permeability, and undergoes transporter-mediated tissue distribution and clearance. Evaluation of renal clearance, antihyperglycemic effects, and potentially lactate as an exploratory safety marker, can support rational metformin dose adjustment. The proposed DDI study design aims to adequately inform metformin dosing during comedication.

Metformin is a hydrophilic, metabolically stable drug with minimal passive membrane permeability, resulting in transporter-mediated distribution and clearance (Figure 1). Hepatic sinusoidal uptake by organic cation transporter (OCT) 1 is a key determinant of metformin distribution to the liver, the primary site of antihyperglycemic effect and rare serious toxicity, lactic acidosis. However, metformin is not cleared by the liver; it is cleared primarily by renal active tubular secretion via OCT2/MATE1/2-K (multidrug and toxin extrusion protein). Transporter-mediated disposition of metformin makes it susceptible to mechanistically atypical DDIs, with the potential to independently affect metformin pharmacokinetics, efficacy, or safety when coadministered with drugs that inhibit these transporters.

Metformin renal DDI studies have been conducted routinely during development of drugs that inhibit OCT2/MATE1/2-K since 2010–2012 per revision of draft DDI guidances issued by regulatory authorities, including the European Medicines Agency (EMA) and US Food and Drug Administration (FDA). The endpoint suggested in these guidances, change in systemic drug exposure, has been most commonly used to-date for metformin DDI studies. This sole endpoint is uniquely inappropriate for evaluating DDI effect on metformin because of its transporter-mediated distribution and clearance. Consequently, dose-adjustment decisions for metformin based solely on systemic exposure changes may not be appropriate, because systemic exposure may not represent the DDI effect at the site of action. That is, metformin pharmacodynamics may change independently of systemic pharmacokinetics, because distribution to the hepatic site of action is mediated by OCT1, which can be subject to independent modulation during...

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DDIs. Metformin DDIs can be mechanistically complex, as changes in metformin pharmacodynamics can be unexpected based on observed (or lack of) changes in systemic pharmacokinetics. Specifically, altered hepatic exposure and antihyperglycemic effect despite unaltered systemic pharmacokinetics, and vice versa (i.e., unaltered hepatic exposure and response during increased systemic exposure), have been reported.2–6 This commentary proposes a metformin clinical DDI study design that enables a rational dose adjustment decision for metformin when coadministered with OCT/MATE inhibitors.

**METFORMIN DDI STUDY DESIGN**

Compared with most pharmacokinetic DDI studies, metformin DDI studies are unique in that both pharmacokinetic and pharmacologic endpoints are needed to enable rational dose adjustment. Such studies should examine three metformin endpoints: 1) systemic pharmacokinetics, 2) renal clearance, and 3) antihyperglycemic effects (i.e., oral glucose tolerance test (OGTT)). The metformin effect on blood lactate concentrations may also be evaluated to assess potential for lactic acidosis, although this approach is not clinically validated.

The OGTT is administered as a 75-g glucose dose 1–3 hours post metformin administration. This effect endpoint is reported as reduction of glucose area under the concentration–time curve (AUC), which requires a crossover glucose AUC determination following an OGTT administered in the absence of metformin. This design enables examination of the metformin antihyperglycemic effect acutely in healthy volunteers. The OGTT is a favored marker of the metformin antihyperglycemic effect because it is easily administered, and effects can be observed after a single metformin dose. Finally, this approach evaluates potential alterations in overall antihyperglycemic effect, not only at the level of the liver (largest contributor to metformin response), but also in the intestine and skeletal muscle, although the latter should not be mechanistically attributed to OCT1/2 and MATE1/2-K modulation, because they involve additional transporters.7 Other endpoints have shortcomings. First, because metformin does not elicit hypoglycemia in healthy volunteers, fasting blood glucose is not appropriate for these individuals. Second, although the metformin effect could be measured as reductions in fasting blood glucose or hemoglobin A1c in diabetic patients, neither are practical in the context of a DDI study due to large patient (vs. healthy volunteers) numbers required for robust measurement of a variable biomarker (fasting blood glucose) or long study durations necessary to detect changes in hemoglobin A1c. Third, because metformin is not an insulin secretagogue, insulin is not an appropriate biomarker.

Blood lactate is most useful as an exploratory safety marker when studied with the highest metformin clinical dosing regimen (ideally 850 mg t.i.d., although 1,000 mg b.i.d. may be more practical to enable sampling over a 12-hour vs. 8-hour dosing interval). The recommendation to use the highest clinical dose of metformin is unusual in the context of a DDI study, where generally the lowest dose is used to ensure safety when systemic exposure is increased. However, this approach is considered safe with study period durations ≤1 week, and for metformin, the most aggressive dosing regimen is needed to determine whether ultimately a dose limitation may be warranted because of increased likelihood of lactic acidosis. However, blood lactate is difficult to measure, has not yet been clinically validated, and may not show a response in this context. Furthermore, lactate response may be correlated with the antihyperglycemic effect.

The proposed evaluation of metformin DDI involves a unique three-way crossover design (Figure 2). The three study periods are 1) new molecular entity (NME) alone, 2) metformin alone, and 3) metformin with NME. The first period is necessary to characterize any independent effects of the NME on antihyperglycemic response. If this endpoint is impacted during coadministration (third period), these data enable understanding whether observed changes are due to altered metformin disposition, dual response, or a combination of both. If NME antihyperglycemic effects can be ruled out with existing blood glucose and/or hemoglobin A1c data, a traditional two-period study may suffice.

The DDI should be evaluated with steady-state metformin alone and with the NME at clinically relevant steady-state concentrations (typically, 1 week of dosing per period, unless the NME has a long half-life, requiring dosing for at least five half-lives) (Figure 2a). Alternatively, metformin DDIs can be evaluated with acute metformin (Figure 2b), although it is not known presently whether acute metformin DDI results can be extrapolated to the steady-state situation, or whether acute metformin dosing is sufficient for assessment of lactate response.
Metformin is available in immediate- and extended-release formulations; immediate-release formulation is generally recommended, as it is the most commonly used, unless the intent is to study extended-release metformin for specific comedication with this formulation.

The number of subjects needed to describe a metformin DDI with adequate precision must consider the two pharmacokinetic endpoints (systemic exposure and renal clearance) and two effect endpoints (glucose and potentially lactate), which is uniquely complex relative to routine DDI study designs. For pharmacokinetic endpoints, a study to conclude no-effect could target the standard bioequivalence boundaries for systemic exposure and renal clearance ratios (0.8–1.25), with specific subject numbers driven by metformin pharmacokinetic variability. In terms of antihyperglycemic effect, the metformin dose is titrated in 500-mg increments, and a therapeutic dose is typically 1,500 mg. As such, a threshold change in antihyperglycemic effect is defined as a 500-mg dose adjustment, with preliminary conservative OGTT no-effect boundaries of 0.75–1.33. Current understanding of lactate is insufficient to define no-effect boundaries. For drugs likely to alter either the pharmacokinetic or pharmacodynamic endpoints more than the proposed no-effect criteria, the precision of the study should be sufficient to justify subsequent dosing recommendations.

**MODELING AND SIMULATION IN METFORMIN DDI STUDY DESIGN**
A physiologically based PK model for metformin has been proposed and verified to a limited extent. Confidence in this approach is limited due to the complex interplay of multiple transporters and difficulties in validating model-predicted changes in tissue exposure. However, the availability of well-designed metformin clinical DDI data that include effect measurements, as well as emerging metformin tissue pharmacokinetic data from clinical imaging studies, could allow refinement and verification of these models to achieve a verified model that could be used to prospectively guide future metformin DDI studies.

**PHARMACOGENETIC CONSIDERATIONS**
Transporters that mediate metformin renal clearance (OCT2, MATE1, and MATE2-K) and hepatic distribution (OCT1 and MATE1) exhibit a relatively high prevalence of polymorphisms, including functionally deficient phenotypes. For example, up to 9% of Caucasians exhibit an OCT1 null phenotype. Pharmacogenetic variability in metformin pathways raises an important question whether and how it should be considered in DDI study design. Based on currently available information, it is premature to make specific pharmacogenetic recommendations, as there is no evidence suggesting that incorporating pharmacogenetic recruitment criteria would be helpful in evaluating metformin DDIs. Instead, crossover design studies are emphasized. Nevertheless, genotyping study subjects would be prudent to help explain outlier individuals, and over time, help support a potential value (or

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**Figure 2** Generic scheme of the proposed metformin DDI study design (a). The depicted study sequence is arbitrary, and ideally an equal number of subjects would be randomized into possible study sequence combinations. Alternatively, metformin DDIs can be evaluated with acute metformin administration (b). A recent famotidine DDI study used this acute metformin design, where a single 1,000-mg metformin dose was followed by an 850-mg dose 12 hours later. The depicted design assumes q.d. dosing of the NME for 1 week, which can be abbreviated if clinically relevant steady-state can be achieved faster as exemplified in the famotidine DDI study. Note that it is not known whether acute metformin DDI results can be extrapolated to the steady-state situation, or whether acute metformin dosing is sufficient for assessment of lactate response. NME, new molecular entity; OGTT, oral glucose tolerance test; PK, pharmacokinetics; CL, renal clearance. Black arrows denote metformin administration; green arrows denote NME administration intended for q.d. dosing.
lack thereof) for genotype-based metformin DDI study design, as well as improve the understanding of the impact of individual and combined covariates causing changes in metformin PK and PD.

VALUE OF PROPOSED DESIGN TO INFORM METFORMIN DOSING

The following case study illustrates the value of the proposed metformin DDI study design in dose adjustment recommendations. An OCT2-inhibitor NME increased metformin systemic exposure 2.45-fold; no other endpoints were measured. The US product labeling recommended limiting coadministered metformin to the lowest clinical dose out of concerns for increased lactic acidosis potential. The rationale for this recommendation was that the DDI study supported metformin safety only with 500 mg b.i.d., where metformin systemic exposure during coadministration approximated the highest approved dose regimen (850 mg t.i.d.). Furthermore, the pharmacologic relevance of the observed DDI was impossible to explain in the prescribing information solely based on the change in systemic exposure. Therefore, it was recommended to monitor the metformin effect when starting and discontinuing the comedication. Finally, the pharmacokinetics of this DDI are puzzling because the metformin half-life was not increased, as would be expected for an inhibitor of renal clearance via OCT2; however, as this parameter was not obtained, it is unknown whether renal clearance was decreased as expected and was the sole reason for the increased systemic exposure. If the DDI study additionally assessed renal clearance and metformin effect as proposed, an improved understanding of the DDI and its consequences may have been obtained to support a dosing recommendation.

Another recent metformin DDI study illustrates the value of the proposed design in characterizing a complex metformin DDI, which would have been overlooked in a traditional protocol due to unchanged metformin systemic exposure.2,3 Famotidine enhanced the antihyperglycemic effects of metformin within the first 30 minutes after administration. The study evaluated the independent antihyperglycemic effects of famotidine to rule out a potential PD interaction. Famotidine increased both metformin oral absorption and renal clearance to the same extent, such that systemic exposure was unaltered, but elucidation of these pharmacokinetic changes was possible only because both urinary metformin recovery and renal clearance were obtained. A similarly complex interaction including increased metformin antihyperglycemic effect was observed with the MATE2-K inhibitor nizatidine; in this case, increased metformin half-life was attributed to increased volume of distribution rather than reduced renal clearance.4

CONCLUDING REMARKS

Due to its extremely hydrophilic nature and transporter-mediated tissue distribution/clearance, metformin requires a nontraditional DDI study protocol that examines its effect (OGTT) and renal clearance in addition to systemic exposure. The proposed study protocol is specific to the labeling of OCT/MATE inhibitor NMEs for coadministration with metformin. Results from these studies should not be extrapolated to other drugs. Conversely, while other probe drugs or biomarkers (e.g., creatinine) may provide a qualitative assessment of the potential for an effect on the renal clearance of metformin, they are unlikely to be informative for the distribution to the liver and resulting efficacy and safety of metformin.

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CONFLICT OF INTEREST

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