INTRODUCTION

A single-dose oral granule formulation of secnidazole 2 g (SOLOSEC™), a 5-nitroimidazole antibiotic, has been developed and approved in the US as a treatment for bacterial vaginosis. Secnidazole has demonstrated in vitro antimicrobial activity against many anaerobic Gram-negative and Gram-positive bacterial species, while sparing Lactobacillus species.1,2 Previous clinical studies have demonstrated a robust tolerability profile, with an efficacy similar to metronidazole, which is given as a week-long regimen. In addition, secnidazole can be administered with or without a meal.3,4 These characteristics and the single-dose regimen have the potential to
improve treatment adherence, which could lead to improved clinical outcomes for women with bacterial vaginosis (BV).

Secnidazole shares the same mechanism of action (MOA) as other 5-nitroimidazoles, although it is not completely understood. 5-7 Reduction of the nitro-group by nitroreductases leads to DNA strand breakage that decreases the stability and integrity.8,9 The low reduction potential of the nitro-group contributes to the selectivity of 5-nitroimidazoles against anaerobic organisms.5,10,11 While previous studies have focused on the MOA, pharmacokinetic properties, and activity against anaerobes of 5-nitroimidazoles, and secnidazole in particular, there have been few reports that characterize the in vitro metabolism and drug-drug interaction potential mediated by cytochrome P450 (CYP) enzymes.1,5,10,11

Metabolism by the CYP family of enzymes is frequently the principal means of metabolism for many pharmaceuticals.12 Some human CYP enzymes are polymorphic with a significant percentage of a demographic population exhibiting a deficiency for a specific enzyme (eg CYP2C19 and CYP2D6). Other human CYP enzymes are known to be induced by certain environmental exposures or therapies (eg CYP2A6 and CYP3A4). As a result, adverse effects can arise if a person is a poor metabolizer phenotype or if a CYP inhibitor is added to their therapeutic regimen. In addition, it is important to know if certain therapeutics may have an alcohol-drug interaction, for instance, due to inhibition of human aldehyde dehydrogenase 2 (ALDH2), a major enzyme catalyzing a rate-limiting step in alcohol elimination.13 Alcohol is metabolized by several processes or pathways. The most common of these pathways involves two enzymes—alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH2). First, ADH metabolizes alcohol to acetaldehyde. Then, in a second step, acetaldehyde is further metabolized down to another, less active byproduct called acetate, which is then broken down into water and carbon dioxide for easy elimination. The toxic effects of altered ethanol metabolism are due to a build up of acetaldehyde, via inhibition of ALDH2. These toxic effects, hypothesized to be a result of inhibition of ALDH2, have been reported in the literature and patient labeling instructions for metronidazole, another oral nitroimidazole compound. This toxicity limits patient use and restricts the ingestion of alcohol while patients are receiving a course of treatment with metronidazole.14 In order to inform patient labeling for secnidazole, the in vitro investigation of a potential alcohol interaction was performed. The objectives of these studies were to investigate the metabolism of secnidazole by CYP enzymes and determine whether secnidazole is a CYP inhibitor. In addition, secnidazole was investigated as a potential inhibitor of human ALDH2.

2 | MATERIALS AND METHODS

2.1 | Preparations of enzymes and secnidazole

Commercially available human plasma (Bioreclamation), Corning® Gentest™ pooled human liver microsomes, Corning® Gentest™ Supersomes™ (cDNA-Expressed CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5), Corning® Gentest™ Human CryoHepatocytes, Corning® Gentest™ Hepatocyte Medium supplemented with glutamine, gentamicin, and fungizone, and without supplemented growth factor or serum, and Corning® Gentest™ and Plating Medium were purchased from Corning Life Sciences (http://www.corning.com) and used in assays to measure metabolism and inhibition. All P450 enzyme products contained cDNA-expressed cytochrome b5, except CYP1A2 and CYP2D6. Recombinant human ALDH2 was purchased from Raybiotech and used in assays for direct and time-dependent inhibition. Secnidazole (SYM-1219) was obtained from Symbiomix Therapeutics, a Division of Lupin Pharmaceuticals. Secnidazole has a solubility of approximately 30 mg/mL in distilled water. All test solution solubilities used within these experiments were visually verified. Stable-labeled CYP probe substrate and metabolite internal standards were obtained from Corning.

2.2 | Metabolism of secnidazole in human liver microsome (HLM) and by human cytochrome P450 isoforms

Incubations with HLMs were carried out in a 0.1 mol/L potassium phosphate buffer (1.3-mmol/L NADP+, 3.3-mmol/L glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, 3.3-mmol/L MgCl2, pH 7.4) at 37°C for all metabolism experiments, unless noted otherwise. Time course and HLM protein concentration dependence of metabolite production were measured using substrate concentrations or 100 and 5100-μmol/L HLM protein concentrations of 0.5, 1.0, and 1.5 mg/mL, and a time course of 0, 30, 60, and 90 minutes. Aliquots (0.2 mL) were removed at four time points quenched with 0.1-mL acetonitrile and frozen (−20°C) for analysis by high-performance liquid chromatography (HPLC) with radiochemical detection. Blank incubations (acetonitrile added prior to HLM addition) were performed for the highest and lowest substrate concentrations. The samples were frozen at −20°C for analysis by HPLC with radiochemical detection. Additional incubations were conducted with HLM in the presence or absence of chemical (2-μmol/L ketoconazole, CYP3cide) and monoclonal antibody inhibitors (anti-CYP2B6 monoclonal antibody). The metabolism of secnidazole was initially measured using cDNA-expressed human CYP enzymes (Supersomes). CYP isoforms were incubated with secnidazole (1 μmol/L) and aliquots (50 μL) were removed at 0, 5, 10, 20, and 30 minutes, quenched with stop solution (200 μL of acetonitrile plus an internal standard), and placed on ice. Samples were vortexed and centrifuged, diluted with ddH2O, and then analyzed with LC-MS/MS. Response curves were measured relative to the zero-minute time point. Positive control substrates for each enzyme were assayed using the conditions described above, except for CYP2A6. The positive control for CYP2A6 was determined in a 0.2-mL reaction mixture with 0.2-mmol/L coumarin substrate in 50-mmol/L potassium phosphate buffer (pH 7.4) at 37°C for 20 minutes. The reaction was terminated with acetonitrile/0.5 mol/L Tris base (80%/20%; v/v), and
fluorescence with excitation at ~390 nm and emission at ~460 nm. Assays with CYP2A6 were run in triplicate. Additional experiments were carried out with radiolabeled secnidazole (Figure 1) at concentrations of 200 and 6400 µmol/L for 0, 30, 60, and 90 minutes. 14C-secnidazole was manufactured by Perkin Elmer with a specific activity of 20.8 mCi/mmol and purity of >99%. The enzyme amounts were chosen to achieve twice the enzyme activity present per unit volume (unless stated otherwise) in the pooled human liver microsomal incubations.

2.3 | Inhibition of human cytochrome P450 enzyme isoforms by secnidazole

Direct and time-dependent inhibition by secnidazole of human CYP enzyme isoforms was measured in HLMs using probe substrates selective for each CYP isoform. The human CYP enzyme isoforms were evaluated and the probe substrates were: CYP1A2/phenacetin (40 µmol/L), CYP2A6/coumarin (1.5 µmol/L), CYP2B6/bupropion (80 µmol/L), CYP2CB/amodiaquine (1.5 µmol/L), CYP2C9/diclofenac (5 µmol/L), CYP2C19/(S)-mephenytoin (40 µmol/L), CYP2D6/dextromethorphan (5 µmol/L), CYP2E1/chlorzoxazone (60 µmol/L), CYP3A4/midazolam (3 µmol/L), and CYP3A4/testosterone (50 µmol/L). For direct inhibition assays, reaction mixtures contained eight concentrations of test article (0, 10, 30, 100, 300, 1000, 3000, and 5000 µmol/L), microsomal protein, an NADPH-regenerating system (1.3-mmol/L NADP⁺, 3.3-mmol/L glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, 3.3-mmol/L magnesium chloride), and one concentration of probe substrate (at or near the Kₘ) in 100-mmol/L potassium phosphate buffer (pH 7.4). Reactions were stopped by addition of 100-µL stop solution (0.1% formic acid in acetonitrile containing a stable isotope-labeled internal standard) and placement on ice. For time-dependent inhibition, following preincubation of secnidazole (0, 10, 30, 100, 300, 1000, 3000, and 5000 µmol/L) with HLM and an NADPH-regenerating system for 30 minutes, an aliquot was diluted 10× (5× for CYP2C19 only) into a prewarmed secondary reaction mixture (400 µL final volume) containing NADPH-regenerating system and one concentration (≥4× the Kₘ) of probe substrate and incubated for a further 5 or 10 minutes, depending on the CYP isoform. The reaction was then quenched with 100-µL stop solution (0.1% formic acid in acetonitrile containing a stable isotope-labeled internal standard) and placed on ice. The probe substrate metabolites were analyzed by LC-MS/MS as previously described and described below. All assays were conducted in duplicate. Catalytic activities were calculated using standard curves for each metabolite based on peak area ratios (analyte/internal standard).

2.4 | Analytical instruments and conditions

LC-MS/MS was performed as previously described. Briefly, ABI/MDS Sciex 4000 Q TRAP™ and ABI/MDS Sciex 4000 LC/MS systems were used along with CTL LEAP autosamplers. Following separation of samples on a Waters® Symmetry® C18 column, standard curves were prepared.

Liquid scintillation counting was performed using a Zorbax SB C18, 4.6 × 250 mm, 5 micron column. The mobile phase used was 0.15% KH₂PO₄, pH 3.2:CH₃CN (9:1, v/v), with a flow rate of 1.2 mL/min.

2.5 | Data analysis

The IC₅₀ values for inhibition assays were determined by nonlinear regression using XLfit software (IDBS Inc) based on the Hill equation:

\[
\text{Fit} = \frac{V_{\text{max}} \times [\text{secnidazole}]^n}{[\text{secnidazole}]^n + K_{m}^{n}}
\]

where Fit is the fraction of control activity, Kᵢᵢ = IC₅₀ is the inhibitor concentration associated with 50% inhibition, [secnidazole] is the concentration µmol/L, Vₘₐₓ is the activity in the vehicle-only samples, representing 100% activity, and n is the Hill coefficient.

2.6 | Reversible inhibition of human aldehyde dehydrogenase 2 (ALDH2) by secnidazole

Activity of human ALDH2 was monitored indirectly by oxidation of propionaldehyde to propionic acid, based on the method of Parajuli et al. This reaction results in the formation of

FIGURE 1  Chemical structure of secnidazole. The asterisk indicates the location of the 14C in the labelled material
β-nicotinamide adenine dinucleotide (NADH), which can be monitored by fluorescence. Two mixes were prepared. Mix 1 contained 2 × NAD+ (100 μmol/L) in 0.1 mol/L N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid sodium salt (BES) buffer (pH 7.4) and mix 2 contained 2× enzyme/substrate in 0.1 mol/L BES buffer. The final concentrations of enzyme and substrate were 1.25 μg/mL (estimated to be 23 nmol/L) and 0.1-μmol/L propionaldehyde, respectively. To prepare plate containing test compound, to the first column of the 96-well plate, 72 μL of mix 1 was added, followed by 50 μL of mix 1 supplemented with 4% DMSO to columns 2 through 10. Then, 3 μL of 50× upper concentration of the test or control compound dissolved in DMSO was added to column 1. The test compound was diluted serially at 1:3 through column 8 with the final 25 μL discarded. Column 10 served as the solvent-only control. The reaction was initiated by adding 50 μL of mix 2 to each well. The fluorescence of NADH was measured with excitation/emission wavelength settings of 350/465 nm, respectively. Readings were taken at 4-minute intervals out to 24 minutes. Assays were conducted in duplicate.

3 | RESULTS

3.1 | Metabolism of secnidazole by human cytochrome P450 enzyme isoforms: reaction phenotyping

There was no evidence of secnidazole metabolism in human plasma in vitro. The first experiment, conducted with a concentration of 1-μmol/L secnidazole, did not demonstrate conclusive evidence of any metabolism of secnidazole in cDNA-expressed enzymes. In a second experiment, two metabolites, M1 and M2, were observed in incubations of 100 and 5100-μmol/L 14C-secnidazole with HLM. Incubations were conducted with cDNA-expressed enzymes to identify enzymes capable of generating M1 and M2. At a substrate concentration of 200 μmol/L, the formation of M1 was observed in incubations with CYP3A4 and CYP3A5, and occurred in a time-dependent and HLM protein concentration-dependent manner (Table 1, Figure 2).

### Table 1 Percent of peak area for metabolite (M) formation from incubation of secnidazole with cDNA-expressed enzymes

| P450 isoform | 200-μmol/L secnidazole | 6400-μmol/L secnidazole |
|--------------|-------------------------|--------------------------|
|              | M1 | M2 | M3 | M4 | M5 | M1 | M2 | M3 | M4 | M5 |
| CYP1A2       | 0.84% | – | – | – | – | – | – | – | – | – |
| CYP2A6       | 0.48% | – | – | – | – | – | – | – | – | – |
| CYP2B6       | 0.72% | – | – | – | – | – | – | – | – | – |
| CYP2C8       | 0.95% | – | – | – | – | – | – | – | – | – |
| CYP2C9       | 0.68% | – | – | – | – | – | – | – | – | – |
| CYP2C19      | 0.51% | – | – | – | – | – | – | – | – | – |
| CYP2D6       | 0.57% | – | – | – | – | – | – | – | – | – |
| CYP2E1       | 0.58% | – | – | – | – | – | – | – | – | – |
| CYP3A4       | 1.93% | 1.30% | 2.92% | 0.57% | – | – | – | – | – | – |
| CYP3A5       | 2.09% | 1.83% | 11.94% | 0.96% | 2.98% | 1.26% | 2.22% | – | – | – |
| Buffer       | 0.59% | – | – | – | – | – | – | – | – | – |
| Insect control | 0.46% | – | – | – | – | – | – | – | – | – |

Abbreviation: –, not detected.
incubations of 6400-μmol/L 14C-secnidazole, CYP2B6, in addition to CYP3A4, and CYP3A5 formed M1. (Table 1, Figure 2). Results demonstrated that CYP3A4 and CYP3A5 were the only two enzymes that generated a significant amount of M1 at 200 and 6400 μmol/L of 14C-secnidazole, which was well above the background peak area in buffer and insect control (Table 1). Background peak area was attributed to a small radiochemical impurity.

The formation of M2 was also time- and HLM protein concentration-dependent (data not shown). Metabolite 2 was observed for CYP3A4 and CYP3A5 when incubated with 200 and 6400 μmol/L concentrations of secnidazole (Table 1, Figure 2). The rate of M1 and M2 formation was linear with substrate concentration, indicating that the K_m was >6400 μmol/L for both metabolites. Formation of metabolite 3, M4, and M5 was observed only in incubations with CYP3A5, and only at the higher concentration of secnidazole (6400 μmol/L). Metabolite 3, M4, and M5 were not observed in incubations with HLM, probably because of the low abundance of CYP3A5 in HLM.

3.2 | Inhibition of human cytochrome P450 enzyme isoforms by secnidazole

Direct inhibition by secnidazole was only observed for CYP2C19 and CYP3A4. The measured IC_{50} values for these two enzymes ranged from 3722 to 4306 μmol/L. The IC_{50} values measured for all other enzymes were >5000 μmol/L (Table 2). Similarly, the IC_{50} values measured for the time-dependent inhibition was >500 μmol/L for all enzymes in the presence or absence of NADPH (Table 2) indicating the absence of time-dependent inhibition.

3.3 | Reversible inhibition of ALDH2 by secnidazole

In the reversible inhibition assay, the IC_{50} value calculated for secnidazole was 503 μmol/L (Table 3). However, it is likely that the true IC_{50} value for secnidazole is higher due to the signal quenching of NADH fluorescence observed in earlier experiments, which tracked
apparent inhibition response. The positive control daidzin had an observed IC_{50} of 4.7 μmol/L that is comparable with the literature-reported value of 8.7 μmol/L, and demonstrating that the assay was functioning properly (Table 3).

### 3.4 | Time-dependent inhibition of ALDH2 by secnidazole

In the time-dependent inhibition assay, secnidazole was preincubated with ALDH2 enzyme and NAD+ from 1 to 24 minutes. Whereas preincubation with secnidazole at 10 or 100 μmol/L exhibited little or no time-dependent inhibition; the positive control DEAB yielded substantial time- and concentration-dependent inhibition of ALDH2 compared with secnidazole (Table 4). As with the reversible inhibition assay, concentrations above 100 μmol/L were not evaluated since secnidazole quenches fluorescence at those concentrations.

| TABLE 2 Summary of direct and time-dependent inhibition by secnidazole |
|---------------------------------------------------------------|
| P450 Isoform       | Direct inhibition | Time-dependent inhibition |<|<|<|<|
|                   | Positive control | IC_{50} a | Positive control | IC_{50} (+NADPH)b | IC_{50} (−NADPH)b |
| CYP1A2             | 7,8-Benzoflavone | >5000     | Furafylline      | >500             | >500             |
| CYP2A6             | Tranylcypromine  | >5000     | 8-Methoxypsoralen| >500             | >500             |
| CYP2B6             | Ketoconazole     | >5000     | Ticlopidine      | >500             | >500             |
| CYP2C8             | Montelukast      | >5000     | Gemfibrozil      | >500             | >500             |
| CYP2C9             | Sulfaphenazole   | >5000     | Tienilic acid    | >500             | >500             |
| CYP2C19            | S-Benzylpirvinol | 3873      | S-Fluoxetine     | >1000            | >1000            |
| CYP2D6             | Quinidine        | >5000     | Paroxetin        | >500             | >500             |
| CYP2E1             | Chlormethiazole  | >5000     | Diethylthiocarbamate| >500          | >500             |
| CYP3A4/Midazolam   | Ketoconazole     | 3722      | Azamulin         | >500             | >500             |
| CYP3A4/Testosterone| Ketoconazole     | 4306      | Azamulin         | >500             | >500             |

aIC_{50} value after a 30-min preincubation calculated based on inhibitor concentrations in the secondary incubation. The concentration of test article in the preincubation step was 5- to 10-fold higher than the concentrations in the secondary incubation, which were used to calculate the IC_{50} value. Therefore, the test article was evaluated as a time-dependent inhibitor at concentrations up to 5000 μmol/L.

### DISCUSSION AND CONCLUSIONS

These studies characterize the results of an in vitro investigation of the potential drug-drug and alcohol-drug interactions of secnidazole. Previous descriptions of the metabolism of secnidazole and its ability to induce or inhibit the activity of CYP isoforms have been limited in scope, or have not been the focus of any study. The study conducted here was part of a larger therapeutic program for the development of SOLOSEC™, a single-dose oral granule formulation containing 2 g of secnidazole recently approved in the US for the treatment for bacterial vaginosis. Here we report on the in vitro metabolism of secnidazole and inhibitory activity in CYP isoforms. In addition, the inhibitory potential of secnidazole on ALDH2 was investigated. The CYP enzyme involvement in the metabolism of secnidazole was also investigated in order to examine the potential of secnidazole to be subject to drug-drug interactions.

Secnidazole was found to be slowly metabolized in HLMs where there was ≤1% conversion to metabolites after a 90-min
incubation with 1.5 mg/mL of protein. In total, five metabolites were observed when human CYP isoforms were incubated with secnidazole. The main metabolites, M1 and M2, generated through incubations with HLM were also generated by cDNA-expressed CYP3A4 and CYP3A5. Incubation with CYP3A4 and CYP3A5 at 200 μmol/L of secnidazole led to the formation of metabolites M1 and M2 in nearly equal concentrations. However, in the presence of 6400-μmol/L secnidazole, M1 was formed in much higher concentrations when incubated with CYP3A5 (Table 1). In addition, at 6400-μmol/L secnidazole, three other metabolites, M3, M4, and M5 were observed following incubation with CYP3A5 (Table 1). Previous studies of secnidazole metabolism had reported a single oxidized hydroxyethyl metabolite that forms in the liver.1,6 That oxidized hydroxyethyl metabolite may correspond to metabolite M1 in this study as it is formed more prevalently than any of the other metabolites (Figure 2), although metabolite identification was not an objective of this study.1,6 To date, there is no evidence of pharmacological activity reported for any metabolite associated with secnidazole.1

The concentrations of secnidazole used in this study are much greater than those used in clinical studies of the pharmacokinetic properties of single-dose secnidazole 2 g.1 In those studies, C_max ranged between 18 and 25 μmol/L, which is 8- to 11-fold lower than the concentrations that led to the observable formation of metabolites M1 and M2, and 256- to 356-fold lower than the concentrations that led to the observable formation of metabolites M3, M4, and M5 (Table 1).6 Using such high concentrations in these in vitro studies was necessary in order to increase the likelihood of observing the formation of the secnidazole metabolites. Based on these results and the minimal formation of metabolites in vitro even at very high secnidazole concentrations, our experiments suggest that secnidazole metabolites are not likely present in any significant concentration under clinically relevant conditions. This is consistent with results that have previously been reported for secnidazole indicating that minimal metabolite formation in plasma as cumulative urinary excretion of free and conjugated secnidazole was found to be approximately 50%.18 The omission of metabolite identification as part of this body of work may be considered a limitation of these studies as the full metabolic characterization of compounds typically involves the identification of all metabolites formed. Given the very low percentage of metabolites formation vs secnidazole concentrations in our studies, we did not pursue the identification of the metabolites any further. As the development of secnidazole may continue for other indications and dosing regimens, this metabolite identification may be revisited.

Secnidazole was observed to directly inhibit CYP2C19 (IC_{50} = 3873 μmol/L) and CYP3A4 (IC_{50} = 3722 and 4306 μmol/L; Table 2). Measured IC_{50} values were >5000 μmol/L for all other CYP isoforms (Table 2). Although there was some clear concentration-dependent inhibition at higher concentration with some of the CYP isoforms—notably CYP2A6, CYP2B6, and CYP2D6—there was no evidence of time-dependent inhibition for any of the enzymes (Table 2). These results are the first reported observation of inhibition from secnidazole. While some imidazole-based drugs are known to be inhibitors of CYPs, the IC_{50} value for secnidazole inhibition is much greater and likely not a clinically significant result.17 In addition, the R value calculations were conducted according to the FDA Guidance for Industry: In Vitro Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020) to determine the need for clinical drug interaction studies. The calculations for all CYPs were below the cut-off value of R = 1.02 and R_{1-gut} ≥ 11, indicating that clinical drug interaction studies were not required.

Secnidazole has an apparent IC_{50} of 503 μmol/L for direct inhibition of human ALDH2. In addition, there was no identifiable evidence of time-dependent inhibition of ALDH2 by secnidazole (Table 4). The range of secnidazole and the accuracy of the observed measurements at the high end of the range were limited by quenching of the fluorophore with secnidazole. However, the function of the assay was confirmed using the positive control DEAB, which yielded an IC_{50} value of 4.7 μmol/L that is comparable to the literature-reported value of 8.7 μmol/L.16 Furthermore, there was no observed metabolism or inhibition of CYP2E1, which is also known to mediate alcohol-drug interactions (Tables 1 and 2).19 Together, these results suggest that under the reported conditions, secnidazole is not likely to have a clinically meaningful alcohol-drug interaction.

The metabolic drug interaction profiles described here for secnidazole compare favorably to those that have been

| Preincubation time | Solvent vehicle | 0.2-μmol/L DEAB | 2-μmol/L DEAB | 10-μmol/L secnidazole | 100-μmol/L secnidazole |
|-------------------|-----------------|-----------------|---------------|---------------------|----------------------|
| 0.5               | 98              | 96              | 67            | 104                 | 91                   |
| 1                 | 101             | 87              | 45            | 103                 | 89                   |
| 2                 | 102             | 76              | 33            | 101                 | 92                   |
| 3                 | 114             | 63              | 29            | 104                 | 92                   |
| 4                 | 108             | 60              | 27            | 101                 | 92                   |
| 8                 | 112             | 39              | 23            | 110                 | 102                  |
| 16                | 121             | 29              | 16            | 113                 | 97                   |
| 24                | 136             | 33              | 15            | 131                 | 104                  |
reported for another widely used nitroimidazole, metronidazole. Metronidazole, administered as a multi-day regimen, is associated with potential alcohol-drug interactions,20,21 and patients are directed to refrain from alcohol consumption during its use.14 In addition, metronidazole may interact with a wide range of medications, including oral contraceptives, that inhibit or induce CYP isoenzymes where secnidazole does not.22-24 Taken together with the favorable efficacy data in clinical studies,4,25-27 these metabolic drug interaction findings suggest that a single-dose oral secnidazole regimen provides a compelling alternative for treating women with BV.

4.1 | Conclusions

Secnidazole is slowly metabolized in HLMs and forms at least two metabolites through low, nonsaturable rates of metabolism. CYP3A4 and CYP3A5 were the major contributors to metabolism. These results are the first reported observation of the metabolism and drug-drug interaction profile for secnidazole and demonstrate that the agent does not have any potential for clinically relevant drug interactions. Furthermore, secnidazole does not exhibit inhibition of ALDH2 or CYP2E1, and is not metabolized by CYP2E1, suggesting it does not have a clinically meaningful alcohol-drug interaction.

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AUTHOR CONTRIBUTIONS

The authors have contributed as detailed here: Conceptualization, HP. Resources, NA and GK. Writing—original draft preparation, HP. Writing—review and editing, HP, NA, and GK. Supervision, NA and GK. Project administration, NA.

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