T1530-13-83

# Mass Balance, Metabolic Disposition, and Pharmacokinetics of [$^{14}$C]Etrasimod Following Oral Administration to Healthy Male Volunteers

Caroline A. Lee, D. Alexander Oh, Yong Tang, Anthony Blackburn, Steve Bloom, Christopher H. Cabell, Kye Gilder, and John S. Grundy

Arena Pharmaceuticals, Inc., San Diego, CA

**CONTACT INFORMATION:** clee@arenapharm.com

aaps PharmSci 360®

Advancing Pharmaceutical Sciences, Careers, and Community

## PURPOSE

- Etrasimod (APD334) is a once-daily, oral, sphingosine 1-phosphate (S1P) receptor modulator that selectively targets $S1P_1$, $S1P_4$, and $S1P_5$ receptors[1–3]
- S1P receptor modulators reduce lymphocyte egress from lymph nodes, thereby decreasing circulating lymphocytes and subsequent tissue inflammation and damage[1]
- Etrasimod is in clinical development for the treatment of immune-mediated inflammatory disorders, such as ulcerative colitis, Crohn's disease, and atopic dermatitis

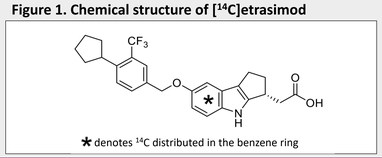
## OBJECTIVE

- We evaluated the mass balance, disposition, pharmacokinetics (PK), metabolite profile, and safety and tolerability of [$^{14}$C]etrasimod administered to healthy male subjects

## METHODS

- An open-label, single oral-dose study in healthy male subjects (N = 8). Following an overnight fast, subjects received 2 mg of [$^{14}$C]etrasimod (~100 µCi; **Figure 1**) administered as an oral solution via syringe
- Whole blood, plasma, urine, and feces samples were collected for up to 336 hrs post-dose
- Mass balance was determined based on recovery of radioactivity in the excreta
- Plasma concentrations of etrasimod (via validated LC-MS/MS assay), whole blood and plasma concentrations of total radioactivity, and associated PK parameters were determined
- The Hamilton method was implemented to create individual subject plasma pools (0–312 hrs), which were combined to create a single cross-subject plasma pool for quantitative metabolite profiling
- Urine and fecal samples from each subject were pooled across the collection period of 0–168 hrs (urine) and 0–240 hrs (feces) to create individual subject pools
- Quantitative metabolite profiling of the evaluated sample pools was conducted by liquid chromatography (LC) with fraction collection and offline radioactivity detection of collected fractions by accelerator mass spectrometry (AMS; plasma only) or TopCount™ microplate scintillation counter (feces and urine)
- Metabolite identification was performed via LC- high resolution mass spectrometry (LC-HRMS)

**Figure 1. Chemical structure of [$^{14}$C]etrasimod**




* denotes $^{14}$C distributed in the benzene ring

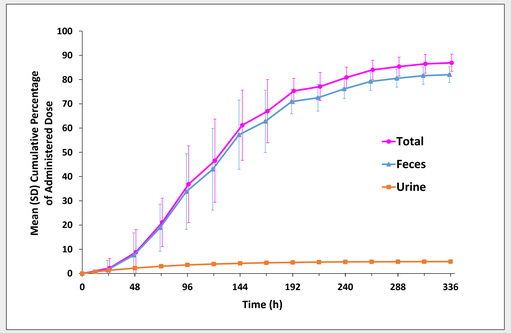
## RESULTS

- All eight subjects completed the study, and the administered study drug was generally well tolerated

### Excretion and Mass Balance of Radioactivity in Excreta

- By 336 hrs post-dose, a mean of 86.9% of the total administered radioactive dose was recovered in the excreta and found predominantly in the feces (82.0%), with relatively little excreted into urine (4.9%) (**Figure 2**)

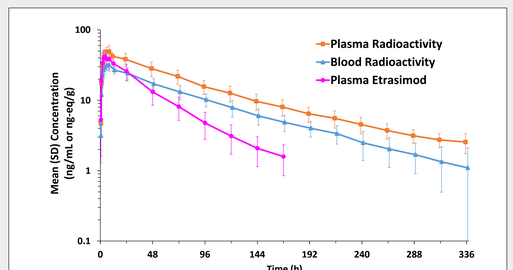
**Figure 2. Cumulative excretion of radioactivity in urine and feces**




### Etrasimod and Total Radioactivity Concentration-Time Profiles

- The mean plasma concentration-time profile for total radioactivity was higher than that for the parent drug etrasimod (**Figure 3**)

**Figure 3. Plasma etrasimod and blood or plasma total radioactivity concentration-time profiles in healthy subjects following a single 2-mg oral dose of [$^{14}$C]etrasimod[a]**




[a]Etrasimod concentration reflects a 1.55 correction factor to capture [$^{14}$C]etrasimod that is not measured by LC-MS/MS assay (detects non-radiolabel etrasimod)

### Etrasimod and Total Radioactivity Pharmacokinetic Parameters in Plasma and Whole Blood

- Peak concentrations ($C_{max}$) of etrasimod and total radioactivity (radiolabeled components) in plasma and/or whole blood were typically reached between 4 and 7 hours (**Table 1**)
- Etrasimod geometric mean plasma $C_{max}$ and $AUC_{0-\infty}$ values accounted for 83% and 40%, respectively, of corresponding total radioactivity plasma values
- Mean half-life of total radioactivity in plasma was 2.4-fold longer than etrasimod
- Etrasimod oral plasma clearance was low relative to human hepatic blood flow
- PK exposure parameters of etrasimod and total radioactivity showed moderate interindividual variability

**Table 1. Pharmacokinetic parameters of etrasimod and total radioactivity in plasma and/or whole blood**

| Parameter | Plasma Etrasimod (N = 8) | Plasma Total Radioactivity (N = 8) | Whole Blood Total Radioactivity (N = 8) |
|---|---|---|---|
| $C_{max}$ (ng/mL or ng-eq/g) | 41.5 (22.7) | 49.9 (18.9) | 33.0 (14.8) |
| $t_{max}$ (h)[a] | 4.0 (3.0, 8.0) | 6.0 (6.0, 8.0) | 7.0 (6.0, 8.0) |
| $AUC_{0-168}$ (ng·h/mL or ng-eq·h/g) | 1740 (31.4) | 3550 (21.4) | 2220 (20.3) |
| $AUC_{0-312}$ (ng·h/mL or ng-eq·h/g) | N/A | 4210 (22.4) | 2620 (22.1) |
| $AUC_{0-\infty}$ (ng·h/mL or ng-eq·h/g) | 1820 (32.6) | 4580 (22.4) | 2810 (23.5) |
| $t_{1/2}$ (h)[b] | 37.8 (3.2) | 89.0 (8.5) | 78.0 (10.8) |
| CL/F (L/h) | 1.10 (33.3) | N/A | N/A |
| $V_z$/F (L) | 59.6 (26.0) | N/A | N/A |
| $C_{max}$ plasma etrasimod / total radioactivity ratio | N/A | 0.83 (18.4) | N/A |
| $AUC_{0-\infty}$ plasma etrasimod / total radioactivity ratio | N/A | 0.40 (12.5) | N/A |
| $AUC_{0-\infty}$ Blood / Plasma Total Radioactivity Ratio | N/A | N/A | 0.6 (3.6) |

Geometric mean (SD) results are presented unless otherwise noted.
[a] median (minimum, maximum); [b]arithmetic mean (SD).
$AUC_{0-\infty}$= area under the concentration-time curve from time 0 to infinity; $AUC_{0-t}$ = area under the concentration-time curve from time 0 to the last quantifiable concentration; CL/F = apparent plasma clearance after oral administration; $C_{max}$ = maximum observed concentration; CV = coefficient of variation; N = number of subjects; N/A = not applicable; NC = not calculated; $t_{1/2}$ = apparent terminal elimination half-life; $t_{last}$ = time of last observed concentration; $t_{max}$ = time of maximum observed concentration; $V_z$/F = apparent volume of distribution based on the terminal phase after oral administration.

### Metabolite Profile in Plasma

- Pooled $AUC_{0-312}$ represents >90% of $AUC_{0-\infty}$ (**Table 1**)
- Based on profiling, etrasimod accounted for 49.3% of the total plasma exposure (AUC) of total radioactivity, with the remainder divided among multiple minor circulating metabolites (**Table 2**)
- The most abundant circulating minor metabolites were M3 (hydroxyl; 8.3%) and M6 (ketone; 8.5%) as determined by AMS
- Direct injection of diluted pooled plasma resulted in a similar percentage of circulating components as the extracted pooled sample (results not shown)

**Table 2. Percent of total radioactivity and corresponding estimated $AUC_{0-312}$ of etrasimod and metabolites in plasma**

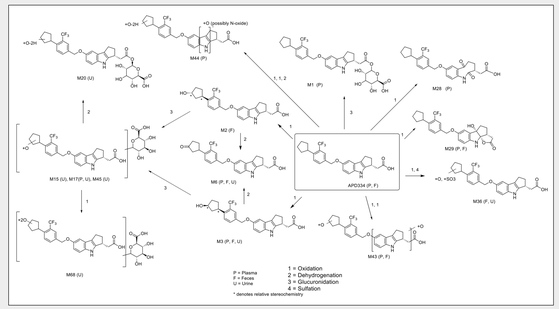
| Compound/Metabolite | Percent (%) of Total Radioactivity | $AUC_{0-312}$ (ng-eq·h/g)[a] |
|---|---|---|
| Etrasimod | 49.3 | 2074.7 |
| M3 | 8.3 | 348.2 |
| M6 | 8.5 | 359.5 |
| Region 1 (Unknown) | 1.3 | 53.5 |
| Region 2 (Unknown) | 0.8 | 32.4 |
| M17+M43 | 4.6 | 192.8 |
| M28 | 6.1 | 258.5 |
| M29 | 2.3 | 95.6 |
| Sum of unknown trace metabolites | 18.9 | 794.8 |
| Total [$^{14}$C] | 100 | 4210 |

Pooled plasma $AUC_{0-312}$ extraction efficiency was 76.3%. The same pooled plasma sample was diluted and directly injected, resulting (not shown) in similar percentages of total radioactivity (based on % region of interest for AMS).
[a]Calculated using the following equation: $AUC_{0-312}$= Percent of Total Radioactivity x total plasma $AUC_{0-312}$ pooled radioactivity (4210 ng-eq·h/g) / 100.

### Metabolite Profile in Excreta

- The predominant drug-related moieties found in the feces were M3, M36 (oxidation followed by sulfation), and etrasimod, reflecting 22.1%, 18.9%, and 11.2%, respectively, of the total administered dose; the remainder was spread across multiple other oxidative and glucuronidation metabolites (**Figure 4**)
- The small amount of the total administered dose excreted in urine was divided among multiple metabolites, with no intact drug (etrasimod) detected

**Figure 4. Biotransformation scheme of etrasimod in humans**




## CONCLUSIONS

- The results from this study suggest that etrasimod is both extensively absorbed and metabolized, given the relatively low proportion of intact drug found in the excreta
- Etrasimod exhibited slow clearance but undergoes extensive metabolism via oxidation, dehydrogenation, sulfation, glucuronidation, and combinations of these reactions
- Etrasimod is the only single major drug-related entity present in the systemic circulation (i.e., >10% of total radioactivity exposure) and is thus expected to be the primary contributor of pharmacologic activity in the clinic
- Hepato-biliary excretion is the predominant elimination route of etrasimod and its associated metabolites
- The multiple biotransformation pathways of etrasimod are likely to decrease the risk of PK drug-drug interactions resulting from effects of any coadministered perpetrator drugs

### References

1. Peyrin-Biroulet L, et al. *Automimmun Rev*. 2017;16(5):495–503.
2. Al-Shamma H, et al. *J Pharmacol Exp Ther*. 2019;369:311–317.
3. Sandborn WJ, et al. *Am J Gastroenterol*. 2018;113(Suppl):S327–S328.
4. Hop CE et al. *J Pharm Sci*. 1998;87: 901–903.

### Disclosures

All authors are employees of Arena Pharmaceuticals, Inc.

### Acknowledgements

This study was funded by Arena Pharmaceuticals, Inc., San Diego, CA. Covance (Madison, WI) conducted the study and assessments, and Pharmaron (Gaithersburg, MD) carried out AMS. Jennifer Giel, PhD, on behalf of inScience Communications, Springer Healthcare (Philadelphia, PA) provided medical writing support, which was funded by Arena Pharmaceuticals, Inc.

ARENA PHARMACEUTICALS