**Supplemental Material**

**Article Title:** Absorption, Metabolism, and Excretion, In Vitro Pharmacology, and Clinical Pharmacokinetics of Ozanimod, a Novel Sphingosine 1-Phosphate Receptor Agonist

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**Supplemental Figure 1.** Mass Spectral Fragmentation of Ozanimod









**Supplemental Figure 2.** Mass Spectral Fragmentation of RP101075



**Supplemental Figure 3.** Mass Spectral Fragmentation of RP101075



**Supplemental Figure 4.** Mass Spectral Fragmentation of CC112273



**Supplemental Figure 5.** Mass Spectral Fragmentation of CC1084037 (aka RP100798)



**Supplemental Figure 6.** Formation of Metabolite RP101075 by Recombinant Enzymes (A) and Inhibition by CYP Selective Inhibitors (B)



**Supplemental Table 1.** Exposure Coverage and Multiples in Nonclinical Safety Studies

|  |  |  |  |
| --- | --- | --- | --- |
| **Study Description****(Study No.)****Day** | **Species** | **Dose****(mg/kg/day)** | **Mean Exposure Multiplesa** |
| **Ozanimod** | **RP101124** | **CC112273b** | **CC1084037b** | **Total Active Drug (Ozanimod, CC112273 and CC1084037)c** |
| **Combined Sexd** | **Combined Sex** | **Combined Sex** | **Combined Sex** | **Sum Totals** |
| 26-week RepeatedDose Day 178 | Rat | 0.2 (NOAEL) | 10.4 | 17.7 | 0.0446 | 0.00360 | 0.620 |
| 2 | 143 | 220 | 0.623 | 0.176 | 8.54 |
| 30 | 2550 | 4180 | 14.7 | 3.08 | 155 |
| 39-week RepeatedDose Day 274 | Monkey | 0.1 (NOAEL) | 3.73 | 0.445 | 0.316 | 0.363 | 0.515 |
| 1 | 41.2 | 15.4 | 3.03 | 3.23 | 5.20 |
| 15 | 683 | 209 | 61.1 | 71.2 | 97.6 |
| 6-month Carcinogenicity Week 26 | Mouse | 8 | 1680 | 106 | 2.95 | 1.40 | 96.6 |
| 25 | 5200 | 296 | 12.0 | 4.85 | 302 |
| 80 | 16300 | 902 | 37.1 | 15.5 | 943 |
| 2-year CarcinogenicityDay 185 | Rat | 0.2 | 8.65 | 29.3 | 0.0446 | 0.00360 | 0.521 |
| 0.7 | 36.9 | 94.3 | -- | -- | 2.07 |
| 2 (NOAEL) | 126 | 212 | 0.623 | 0.176 | 7.58 |

a Calculation = ratio of Animal Species Exposure (ng∙hr/mL)/Human Exposure (ng∙hr/mL).

b Nonclinical species exposure based on the analyte exposure concentration from 14-day bridging GLP-compliant PK Studies (rat, mouse, rabbit, and monkey).

c Total active drug multiple is cumulative exposure of ozanimod+CC112273+CC1084037 divided by total human ozanimod+CC112273+CC1084037. These 3 contribute to 94% of total active exposure of the drug in humans.