Supplementary Information

Insights into the patient variability during ivacaftor-lumacaftor therapy in cystic fibrosis

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**Supplementary Table 1.** Parameters from 125 mg ivacaftor + 200 mg lumacaftor combination label information

|                  | Ivacaftor  | Lumacaftor |
|------------------|------------|------------|
| **Initial Parameters** |            |            |
| T<sub>max</sub>  | 4h         | 4h         |
| CL/F             | 25.1 L/h   | 2.38 L/h   |
| V/F              | 86L        |            |
| Half-life        | 9h         | 26h        |
| Dose             | 250 mg     | 400 mg     |
| AUC              | 3.66 ug/mL*h | 198 ug/mL*h |
| C<sub>max</sub>  | 0.602 ug/mL | 25 ug/mL   |

|                  |            |            |
| **Calculated Parameters** |            |            |
| k<sub>el</sub>     | 0.077 1/hr | 0.0277 1/hr |
| k<sub>a</sub>      | 0.583 1/hr | 0.897 1/hr  |

T<sub>max</sub> = amount of time that a drug is present at the maximum concentration; CL/F = oral clearance; V/F = Drug volume of distribution; AUC = Area under the curve; C<sub>max</sub> = amount of drug is present at the maximum concentration; k<sub>el</sub> = elimination rate constant; k<sub>a</sub> = absorption rate constant
Supplementary Table 2. Demographics of CF patients

|          | Age (y) | Weight (kg) | Height (cm) |
|----------|---------|-------------|-------------|
| Max      | 52      | 77.2        | 189.3       |
| 3rd Quartile | 25      | 61.1        | 171.0       |
| Median   | 19      | 53          | 164.0       |
| Mean     | 21.8    | 54.5        | 164.8       |
| 1st Quartile | 16      | 48          | 158.8       |
| Min      | 13      | 37.3        | 144.5       |
| Missing  | 1       | 1           | 1           |
| STD      | 8.17    | 9.08        | 9.65        |

Footnote: The total number of patients N = 60 (Site: Melbourne: 1, Berlin: 8, Innsbruck: 9, Munich: 17, Paris: 25) including 35 female and 25 male patients.
Supplementary Table 3. Pharmacokinetic Analysis - $T_{\text{max}}$ and $C_{\text{max}}$

|               | Ivacaftor | Ivacaftor-M1 | Ivacaftor-M6 | Lumacaftor |
|---------------|-----------|--------------|--------------|------------|
| $T_{\text{max}}$ (hours) |           |              |              |            |
| Max           | 14.5      | 10           | 10           | 14.5       |
| 3rd Quartile  | 4         | 4.5          | 4.5          | 4          |
| Median        | 4         | 4            | 4            | 4          |
| Mean          | 3.58      | 3.88         | 3.486        | 3.39       |
| 1st Quartile  | 2.5       | 2.5          | 2.5          | 2.5        |
| Min           | 0         | 0            | 0            | 0          |
| STD           | 9.36      | 10.5         | 11.3         | 9.63       |
| Missing       | 1         | 2            | 3            | 1          |

|               |          |              |              |            |
|---------------|----------|--------------|--------------|------------|
| $C_{\text{max}}$ (mg/L) |      |              |              |            |
| Max           | 0.952    | 8.42         | 4.56         | 4.42       |
| 3rd Quartile  | 0.100    | 1.35         | 0.61         | 1.70       |
| Median        | 0.059    | 0.044        | 0.206        | 0.503      |
| Mean          | 0.107    | 1.27         | 0.627        | 1.06       |
| 1st Quartile  | 0.024    | 0.020        | 0.085        | 0.415      |
| Min           | 0        | 0            | 0            | 0.030      |
| STD           | 0.160    | 2.14         | 0.988        | 0.899      |
Supplementary Figure 1. Overview of genetic, inter-individual and other factors contributing to poor responses for CF modulator therapy