**Tables**

**Table 1** – Patient demographics and baseline characteristics.

|  |  |
| --- | --- |
| **Demographic** | **Value** |
| Patients – N | 21 |
| Female – N (%) | 11 (52) |
| Age (years) – median (range) | 12 (6-17) |
| Weight (kg) – median (range) | 43.5 (23.6-69.8) |
| Height (cm) – median (range) | 153 (122-191) |
| Mutation homozygous F508del – N (%)  Mutation heterozygous F508del – N (%)   * Other mutations – N (%)   + 3849+10kbC→T   + A455E | 16 (76)  5 (24)  1 (5)  4 (19) |
| Children per age/dosing group – N (%)   * 6-11 y <30 kg * 6-11 y ≥30 kg * 12-17 y | 3 (14)  7 (33)  11 (52) |
| Co-morbidities – N (%)   * CF-related diabetes * Distal intestinal obstruction syndrome * Exocrine pancreatic insufficiency | 0 (0)  4 (19)  20 (95) |
| Laboratory parameters – median (range)   * ALAT (U/L) * ASAT (U/L) * Bilirubin (µmol/L) | 22 (13-39)  27 (18-50)  3 (1-12) |
| Samples for PK analysis – N (%)   * Plasma samples * DBS samples | 97  13 (13)  84 (87) |
| Samples per patient – median (range) | 5 (2-7) |

*Variables are presented as numbers (%) or median (range min – max).*

*Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; PK, pharmacokinetic; DBS, dried blood spot.*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Parameters | Tezacaftor | | | Tezacaftor-M1 | | | Ivacaftor | | | Ivacaftor-M1 | | Ivacaftor-M6 | |
| **Estimates**  Value  (RSE) [Shr] | **Bootstrap**  Median  (95% CI) | **Prior type$** | **Estimates**  Value  (RSE) [Shr] | **Bootstrap**  Median  (95% CI) | **Prior type$** | **Estimates**  Value  (RSE) [Shr] | **Bootstrap**  Median  (95% CI) | **Prior type$** | **Estimates**  Value  (RSE) [Shr] | **Bootstrap**  Median  (95% CI) | **Estimates**  Value  (RSE) [Shr] | **Bootstrap**  Median  (95% CI) |
| CL#  (L/h/70kg) | 1.95  (6) | 1.93  (1.71-2.24) | - | 1.01  (6) | 1.00  (0.905-1.13) | - | 15.9  (9) | 15.8  (13.3-19.1) | - | 2.10  (10) | 2.10  (1.74-2.61) | 12.2  (16) | 12.2  (8.81-17.3) |
| Vc#  (L/70kg) | 38.4  (7) | 38.5  (33.6-45.6) | V | 4.86  (28) | 4.89  (4.53-5.50) | I | 178  (20) | 176  (111-342) | V | 0.1 \* Viva | 0.1 \* Viva | 0.1 \* Viva | 0.1 \* Viva |
| Q#  (L/h/70kg) | 0.19  (29) | 0.190  (0.181-0.203) | M | 3.70  (19) | 3.67  (2.83-4.25) | M | 13.2  (25) | 13.0  (11.5-15.4) | M | - | - | - | - |
| Vp#  (L/70kg) | 36.4  (29) | 36.4  (36.4-36.4) | M | 37.5  (10) | 37.5  (37.0-38.5) | I | 106  (26) | 104.5  (97.7-119) | M | - | - | - | - |
| Ka  (h-1) | 2.95  (10) | 2.94  (2.88-3.00) | I | - | - | - | 0.506  (10) | 0.505  (0.482-0.523) | I | - | - | - | - |
| D1  (h) | 1.06  (28) | 1.08  (0.885-1.34) | M | - | - | - | 2.59  (10) | 2.59  (2.41-2.77) | I | - | - | - | - |
| Inter-individual variability | | | | | | | | | | | | | |
| CL | 0.064  (19) [6] | 0.057  (0.0062-0.14) | - | 0.054  (19) [5] | 0.048  (0.012-0.11) | - | 0.15  (37) [5] | 0.13  (0.018-0.28) | - | 0.18  (38) [3] | 0.17  (0.028-0.33) | 0.46  (37) [3] | 0.42  (0.17-0.83) |
| Residual variability | | | | | | | | | | | | | |
| Prop. Error | 0.26  (9) | 0.26  (0.21-0.30) | - | 0.20  (9) | 0.20  (0.16-0.24) | - | 0.34  (10) | 0.33  (0.26-0.41) | - | - | - | - | - |
| Prop. Error  Plasma | - | - | - | - | - | - | - | - | - | 0.37  (24) | 0.36  (0.18-0.52) | 0.98  (25) | 0.94  (0.56-1.38) |
| Prop. Error  DBS | - | - | - | - | - | - | - | - | - | 0.36  (10) | 0.35  (0.29-0.42) | 0.50  (10) | 0.50  (0.36-0.62) |

**Table 2** – PK parameter estimates of tezacaftor, tezacaftor-M1, ivacaftor, ivacaftor-M1 and ivacaftor-M6 of the final population PK models.

*# Apparent CL (CL/F), Q (Q/F) and Vc/p (V**c/p/F) were described for the parent compounds, and apparent CL (CL/F \* fm), Q (Q/F \* fm) and Vc/p (Vc/p/F \* fm) for the metabolites. In the final models CL, Q and Vc/p were allometrically scaled to weight (kg): CL = θCL \* (weight/70)0.75, Q = θQ \* (weight/70)0.75 and Vc/p = θV \* (weight/70)1 for both the parent compounds and the metabolites if applicable.*

*$ Prior types: V, vague (105); M, moderately informative (RSE 30%); I, informative (RSE 10%).*

*Abbreviations: RSE, relative standard error in %; Shr., shrinkage in %; CI, confidence interval; CL, clearance; Q, intercompartmental clearance; Vc, central volume of distribution; Vp, peripheral volume of distribution; fm, fraction metabolized into metabolite; Ka, absorption rate constant; D1, zero-order absorption into the depot compartment; prop. Error, proportional error; DBS, dried blood spot.*

**Table 3** – AUC estimates by the final pharmacokinetic models versus reported AUC in product information.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | Dose\* (mg/day) | AUC# (mg\*h/L)  Mean (SD) | Reported AUC$ (mg\*h/L) (3)  Mean (SD) |
| Tezacaftor | 6-11y < 30 kg | 50 | 53.2 (12.9) | 58.9 (17.5) |
| 6-11y ≥ 30 kg | 100 | 91.7 (25.5) | 107 (30.1) |
| 12-17y | 100 | 66.2 (11.4) | 97.1 (35.8) |
| Adult | 100 |  | 85.9 (28.0) |
| Tezacaftor-M1 | 6-11y < 30 kg | (50) | 107 (30.4) | 126 (30.0) |
| 6-11y ≥ 30 kg | (100) | 192 (47.3) | 193 (45.8) |
| 12-17y | (100) | 124 (21.8) | 146 (35.7) |
| Adult | (100) |  | 126 (34.9) |
| Ivacaftor | 6-11y < 30 kg | 150 in 2 doses | 7.51 (2.34) | 7.1 (1.95) |
| 6-11y ≥ 30 kg | 300 in 2 doses | 17.5 (7.29) | 11.8 (3.89) |
| 12-17y | 300 in 2 doses | 13.3 (3.39) | 11.4 (5.5) |
| Adult | 300 in 2 doses |  | 11.4 (4.14) |
| Ivacaftor-M1 | 6-11y < 30 kg | (150 in 2 doses) | 14.9 (9.32) |  |
| 6-11y ≥ 30 kg | (300 in 2 doses) | 34.2 (16.8) |  |
| 12-17y | (300 in 2 doses) | 21.1 (3.46) |  |
| Adult | (300 in 2 doses) |  |  |
| Ivacaftor-M6 | 6-11y < 30 kg | (150 in 2 doses) | 4.78 (2.20) |  |
| 6-11y ≥ 30 kg | (300 in 2 doses) | 15.8 (13.9) |  |
| 12-17y | (300 in 2 doses) | 7.97 (4.81) |  |
| Adult | (300 in 2 doses) |  |  |

*\* Tezacaftor daily dose is administered in one dose, ivacaftor daily dose is given in two equal doses.*

*# AUC0-24h ss for elexacaftor, elexacaftor-M23, tezacaftor, and tezacaftor-M1. AUC0-12h ss for ivacaftor, ivacaftor-M1 and ivacaftor-M6.*

*$ For ivacaftor-M1 and ivacaftor-M6 no AUC are reported in the product information of Symkevi®. Exposures in ≥ 30 kg to < 40 kg weight range are predictions derived from the population PK model. (3)*

*Abbrevations: AUC, area under the curve; SD, standard deviation.*

**Table 4** - Cmax and half-lives estimates by the final pharmacokinetic models versus reported in the product information.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | Dose\* (mg/day) | Cmax (mg/L)  Mean (SD) | Reported  Cmax# (mg/L) (3)  Mean (SD) | T½ (h)  Mean (SD) | Reported  T½# (h) (3)  Mean (SD) |
| Tezacaftor | 6-11y < 30 kg | 50 | 4.01 (0.660) | 6.52 (1.83) | 116 (1.10) | 156 (52.7) |
| 6-11y ≥ 30 kg | 100 | 6.61 (0.910) | 124 (9.79) |
| 12-17y | 100 | 4.39 (1.12) | 136 (7.14) |
| Pooled |  | 4.84 (1.40) | 132 (9.87) |
| Ivacaftor | 6-11y < 30 kg | 150 in 2 doses | 0.840 (0.208) | 1.28 (0.440) | 9.78 (1.88) | 9.3 (1.7) |
| 6-11y ≥ 30 kg | 300 in 2 doses | 1.80 (0.600) | 14.0 (6.18) |
| 12-17y | 300 in 2 doses | 1.34 (0.308) | 14.9 (2.71) |
| Pooled |  | 1.40 (0.449) | 14.4 (3.85) |

***#*** *Cmax and half-lifes mean (SD) reported values as described in the product information (3) are PK parameters of tezacaftor and ivacaftor at steady-state in pooled data from adolescent(>12 years)/adult patients with CF receiving 100-300 mg tezacaftor-ivcaftor daily.*

*Abbrevations: Cmax, maximum concentration; T½, half-life; SD, standard deviation.*