SUPPLEMENTARY DATA

Title: Evaluation of Absorption and Metabolism-based DDI Potential of Pexidartinib in Healthy Subjects

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### SUPPLEMENTARY TABLES

**Supplementary Table 1** Input parameters for the pexidartinib model

| Parameter          | Pexidartinib |
|--------------------|--------------|
| MW                 | 418          |
| log P              | 335          |
| Compound type      | Monoprotic Base |
| pKa                | 5.2          |
| B:P                | 0.56         |
| fu                 | 0.002        |
| Vss (L/kg)<sup>a</sup> | 0.24        |
| V<sub>sac</sub> (L/kg)<sup>a</sup> | 0.11        |
| k<sub>in</sub> (h<sup>-1</sup>)<sup>a</sup> | 0.48        |
| k<sub>out</sub> (h<sup>-1</sup>)<sup>a</sup> | 0.05        |
| fa                 | 0.60         |
| ka (h<sup>-1</sup>) | 0.5          |
| fu<sub>gut</sub>  | 0.0038       |
| CL<sub>int, CYP3A4</sub> (µl/min/pmol)<sup>c</sup> | 2.07        |
| CL<sub>int, UGT1A4</sub> (µl/min/mg)<sup>c</sup> | 307.5       |
| CLR (L/h)          | 0            |
| Ki (µM) – CYP3A4   | 4.01         |
| fu<sub>mic</sub>   | 0.83         |
| k<sub>inact</sub> (h<sup>-1</sup>) – CYP3A4 | 1.356       |
| Ind<sub>max</sub> (fold) – CYP3A4 | 16          |
| IndC<sub>50</sub> (µM) – CYP3A4 | 0.16        |

<sup>a</sup>Optimised from in vivo data for 1200 mg dose.

<sup>b</sup>Set to a predicted value to improve the recovery of predicted C<sub>max</sub> and AUC.

<sup>c</sup>Retrograde calculation from CL<sub>po</sub> (8.54 L/h) using fm<sub>CYP</sub> of 0.45 and fm<sub>UGT</sub> of 0.55.

B:P, blood to plasma ratio; CL<sub>int</sub>, intrinsic clearance; CL<sub>R</sub>, renal clearance; CYP, Cytochrome P450; fa, fraction absorbed; fu, fraction unbound in plasma; fu<sub>gut</sub>, fraction of drug unbound in the gut; fu<sub>mic</sub>, free fraction of drug in an in vitro microsomal preparation; IndC<sub>50</sub>, half-maximal induction; Ind<sub>max</sub>, maximum fold induction; k, constant; ka, absorption rate constant; K<sub>i</sub>, inhibitory constant; k<sub>inact</sub>, maximum potential rate of inactivation; MW, molecular weight; V<sub>sac</sub>, volume of single adjustable compartment; V<sub>SS</sub>, volume of distribution at steady state.
Supplementary Table 2 Mean predicted and observed (mean±SD) Day 1 and Day 15 exposure of pexidartinib in patients receiving multiple oral dose (400 mg QD) for 15 days

| Parameter | Day 1 | | Day 15 | |
|---|---|---|---|---|
| | $C_{\text{max}}$ | $\text{AUC}_{(0-24\text{h})}$ | $C_{\text{max}}$ | $\text{AUC}_{(0-24\text{h})}$ |
| Mean | 4320 | 37664 | 4823.76 | 50758.43 |
| Trial 1 | 3865 | 32597 | 4153.41 | 41008.67 |
| Trial 2 | 4544 | 38264 | 5204.50 | 54377.83 |
| Trial 3 | 6123 | 48600 | 6380.03 | 57122.61 |
| Trial 4 | 4573 | 30266 | 4584.13 | 34637.55 |
| Trial 5 | 3967 | 40125 | 5001.78 | 63753.90 |
| Trial 6 | 4335 | 42855 | 5364.82 | 67134.50 |
| Trial 7 | 2448 | 25215 | 3093.85 | 38913.60 |
| Trial 8 | 5190 | 45636 | 5388.26 | 53151.45 |
| Trial 9 | 3333 | 30451 | 4006.80 | 45522.40 |
| Trial 10 | 4819 | 42633 | 5060.01 | 51961.83 |
| Observed | 3290 | 38055 | 3480 | 41900 |
| | (1610) | (5055) | (1130) | (11400) |
| Predicted/Observed | 1.31 | 0.90 | 1.39 | 1.21 |

AUC$_{(0-24\text{h})}$, area under the plasma concentration-time curve from time 0 to 24 hours, $C_{\text{max}}$, maximum plasma concentration, QD, once daily, SD, standard deviation.
Supplementary Table 3  Mean predicted and observed (mean±SD) Day 1 and Day 15 exposure of pexidartinib in patients receiving multiple oral dose (600 mg QD) for 15 days

| Parameter | Day 1 | | Day 15 | |
|-----------|-------|---|-------|---|
|           | $C_{\text{max}}$ | AUC$_{(0-24h)}$ | $C_{\text{max}}$ | AUC$_{(0-24h)}$ |
| Mean      | 6458  | 55658 | 6910  | 70723 |
| Trial 1   | 5775  | 48031 | 6035  | 58568 |
| Trial 2   | 6795  | 56539 | 7342  | 73332 |
| Trial 3   | 9162  | 71868 | 9090  | 77948 |
| Trial 4   | 6829  | 44552 | 6590  | 48157 |
| Trial 5   | 5936  | 59571 | 7347  | 93733 |
| Trial 6   | 6468  | 63110 | 7403  | 88853 |
| Trial 7   | 3665  | 37517 | 4429  | 54375 |
| Trial 8   | 7769  | 67677 | 7907  | 76471 |
| Trial 9   | 4993  | 45390 | 5867  | 65667 |
| Trial 10  | 7185  | 62322 | 7094  | 70126 |
| Observed  | 5250  | 56181 | 8160  | 107000 |
|           | (1740)| (13840)| (4070)| (45500)|
| Predicted/Observed | 1.23 | 0.99 | 0.85 | 0.66 |

$\text{AUC}_{0-24h}$, area under the plasma concentration-time curve from time 0 to 24 hours,
$C_{\text{max}}$, maximum plasma concentration, QD, once daily, SD, standard deviation
**Supplementary Table 4** Mean predicted and observed (mean±SD) Day 1 and Day 15 exposure of pexidartinib in patients receiving multiple oral dose (500 mg BID) for 15 days

| Parameter | Day 1 | Day 15 |
|-----------|-------|--------|
|           | \(C_{\text{max}}\) (ng/mL) | \(\text{AUC}_{(0-6\text{h})}\) (ng/mL.h) | \(C_{\text{max}}\) (ng/mL) | \(\text{AUC}_{(0-6\text{h})}\) (ng/mL.h) |
| Mean      | 5399  | 24781  | 7218  | 36204 |
| Trial 1   | 4887  | 21140  | 6035  | 28573 |
| Trial 2   | 5843  | 27733  | 8092  | 41662 |
| Trial 3   | 4457  | 21049  | 6535  | 33944 |
| Trial 4   | 4410  | 20909  | 6174  | 31789 |
| Trial 5   | 6407  | 29926  | 9085  | 46644 |
| Trial 6   | 5449  | 25195  | 6654  | 32837 |
| Trial 7   | 5144  | 22426  | 6310  | 30031 |
| Trial 8   | 7705  | 34081  | 8354  | 38770 |
| Trial 9   | 4945  | 23130  | 8124  | 42759 |
| Trial 10  | 4742  | 22217  | 6813  | 35033 |
| Observed* | 1900  | 6280   | 8820  | 42800 |
|           | (449) | (4370) | (3170) | (14300) |
| Predicted/Observed | 2.84  | 3.95   | 0.82  | 0.85  |

*Observed data are for the combined 1000 mg/day dataset (500 mg BID and 400 /600 mg split dose). AUC\(_{0-6\text{h}}\), area under the plasma concentration-time curve from time 0 to 6 hours, BID, twice daily, \(C_{\text{max}}\), maximum plasma concentration, SD, standard deviation.
Supplementary Table 5 Mean predicted and observed (mean±SD) Day 1 and Day 15 exposure of pexidartinib in patients receiving multiple oral dose (1000 mg given as split doses of 400 mg and 600 mg) for 15 days

| Parameter | Day 1 | Day 15 |
|-----------|-------|--------|
|           | \(C_{\text{max}}\) | \(\text{AUC}_{(0-6h)}\) | \(C_{\text{max}}\) | \(\text{AUC}_{(0-6h)}\) |
| Mean      | 4326   | 19886  | 6414   | 32687  |
| Trial 1   | 3915   | 16972  | 5277   | 25442  |
| Trial 2   | 4680   | 22236  | 7247   | 37814  |
| Trial 3   | 3570   | 16886  | 5894   | 31064  |
| Trial 4   | 3533   | 16771  | 5532   | 28884  |
| Trial 5   | 5133   | 24007  | 8141   | 42443  |
| Trial 6   | 4367   | 20219  | 5856   | 29323  |
| Trial 7   | 4122   | 18012  | 5512   | 26745  |
| Trial 8   | 6175   | 27372  | 7179   | 33793  |
| Trial 9   | 3961   | 18553  | 7397   | 39525  |
| Trial 10  | 3799   | 17828  | 6101   | 31835  |
| Observed *| 1900   | 6280   | 8820   | 42800  |
|           | (449)  | (4370) | (3170) | (14300) |

Predicted/Observed 2.28 3.17 0.73 0.76

*Observed data are for the combined 1000 mg/day dataset (500 mg BID and 600/400 mg split dose).

\(\text{AUC}_{0-6h}\), area under the plasma concentration-time curve from time 0 to 6 hours, \(C_{\text{max}}\), maximum plasma concentration, SD, standard deviation.
**Supplementary Table 6** Mean predicted and observed exposure of pexidartinib in healthy subjects receiving a single oral dose of 600 mg pexidartinib in the presence and absence of itraconazole treatment

| Parameter     | Control | +Itraconazole | Ratio |
|---------------|---------|---------------|-------|
|               | $C_{\text{max}}$ | $AUC_{\infty}$ | $C_{\text{max}}$ | $C_{\text{max}}$ | $AUC_{\infty}$ | $C_{\text{max}}$ |
|               | (ng/mL) | (ng/mL.h)    | (ng/mL) | (ng/mL) | (ng/mL.h) | (ng/mL) |
| Predicted     | 3218    | 70146         | 4164    | 126155  | 1.29      | 1.80     |
| (95% CI)      | (20.1)  | (24.3)        | (35.3)  | (27.0)  | (1.27-1.32)| (1.75-1.84)|
| Observed      | 4137    | 74115         | 6308    | 135354  | 1.48      | 1.73     |
| (95% CI)      | (20.1)  | (24.3)        | (35.3)  | (27.0)  | (1.24-1.78)| (1.58-1.89)|

$AUC_{\infty}$, area under the curve from time 0 to infinity, CI, confidence interval, $C_{\text{max}}$, maximum plasma concentration.
**Supplementary Table 7** Mean predicted exposure of pexidartinib in cancer subjects receiving a single dose of 400 mg pexidartinib in the presence and absence of rifampicin treatment. The refined pexidartinib model was used.

| Induction model | Parameter       | Pexidartinib | Pexidartinib + rifampicin | Ratio     |
|-----------------|-----------------|--------------|---------------------------|-----------|
|                 |                 | C<sub>max</sub> | AUC<sub>∞</sub> | C<sub>max</sub> | AUC<sub>∞</sub> | C<sub>max</sub> | AUC<sub>∞</sub> |
|                 |                 | (ng/mL)       | (ng.h /mL)              | (ng/mL)   | (ng.h /mL)     |             |               |
| Default         | Geo Mean (90%CI) | 7827          | 42164                    | 4429      | 18946          | 0.57        | 0.45          |
|                 |                 | (90%CI)       |                          | (0.53-0.60) | (0.42-0.49)    |             |               |
| Additive        | Geo Mean (90%CI) | 7827          | 42164                    | 4137      | 17117          | 0.53        | 0.41          |
|                 |                 | (90%CI)       |                          | (0.5-0.56) | (0.38-0.44)    |             |               |
| Multi           | Geo Mean (90%CI) | 7827          | 42164                    | 3097      | 11393          | 0.40        | 0.27          |
|                 |                 | (90%CI)       |                          | (0.25-0.29) | (0.38-0.42)    |             |               |
| Observed (HV)   | Geo Mean (90%CI) |              |                          |           |               | 0.67        | 0.37          |
|                 |                 | (90%CI)       |                          | (0.51-0.89) | (0.29-0.47)    |             |               |

*Dose is different from 600 mg daily dose in the current analysis.

AUC<sub>∞</sub>, area under the curve from time 0 to infinity, CI, confidence interval, C<sub>max</sub>, maximum plasma concentration, HV, healthy volunteers.
**Supplementary Fig. 1** Simulated (lines; 10 x 5 virtual individuals) and observed (individual data points; from Study 108-01) plasma concentration-time profiles of pexidartinib after multiple oral dose (400 mg daily) for 15 days. The grey lines represent the outcomes of simulated individual trials (10 x 5), and the black line is the mean data for the simulated population (n = 50). The grey dashed line represents the 95th and 5th percentile of the simulated data.
Supplementary Fig. 2 Simulated (lines; 10 x 6 virtual individuals) and observed (individual data points; from Study 108-01) plasma concentration-time profiles of pexidartinib after multiple oral dose (600 mg daily) for 15 days. The grey lines represent the outcomes of simulated individual trials (10 x 6), and the black line is the mean data for the simulated population (n = 60). The grey dashed line represents the 95th and 5th percentile of the simulated data.
Supplementary Fig. 3 Simulated (lines; 10 x 13 virtual individuals) and observed (individual data points; from Study 108-01, n=5 for day 1 and n=13 for day 15) plasma concentration-time profiles of pexidartinib after multiple oral dose (500 mg twice daily) for 15 days (a) and during the last dosing interval (b). The respective observed mean data are shown in Fig. c and d. The grey lines represent the outcomes of simulated individual trials (10 x 13), and the black line is the mean data for the simulated population (n = 130). The grey dashed line represents the 95th and 5th percentile of the simulated data.
Supplementary Fig. 4 Simulated (lines; 10 x 19 virtual individuals) and observed (data points; from Study 108-01) plasma concentration-time profiles of pexidartinib after multiple oral dose of 1000 mg per day (split doses of 400 mg and 600 mg) for 15 days (a and c) and during the last dosing interval (b and d). The observed individual data (a-b) or mean data (c-d) are over-laid. The grey lines represent the outcomes of simulated individual trials (10 x 19), and the black line is the mean data for the simulated population (n = 190). The grey dashed line represents the 95th and 5th percentile of the simulated data.

(a)
Supplementary Fig. 5 Simulated (lines; 10 x 16 virtual individuals) and observed (data points; from Study PL3397-A-U118) mean plasma concentration-time profiles of pexidartinib after a single oral dose (600 mg) in the presence (dashed line, filled circles) and absence (solid line, open circles) of multiple daily doses of itraconazole (200 mg twice daily on day 1 followed by 200 mg once daily on days 2-18) plotted on a linear (a) and logarithmic (b) scale. The grey lines represent the outcomes of simulated individual trials (10 x 16) and the solid/dashed black line is the mean data for the simulated population (n = 160).
Supplementary Fig. 6 Simulated mean plasma concentration-time profiles of pexidartinib following a single oral dose of pexidartinib (400 mg) in the absence of rifampicin (solid black line) and on the 11th day of 20 days of dosing of rifampicin (600 mg daily) (dashed black line) in cancer subjects. The grey lines represent the mean values for each of the 10 trials. The refined model was used. The default option for CYP enzyme induction was applied.
Supplementary Fig. 7 Simulated mean plasma concentration-time profiles of pexidartinib following multiple oral doses of pexidartinib (400 mg twice daily) in the absence (solid black line) and presence (dashed black line) of rifampicin 600 mg daily in cancer subjects. The refined model was used. The default option for CYP enzyme induction was applied.
**Supplementary Fig. 8** Simulated CYP3A4 activity profile in the (a) liver and (b) small intestine following a single oral dose of pexidartinib (400 mg) in the absence (solid black line) and presence (dashed black line) of rifampicin 600 mg daily in cancer subjects. The refined model was used. The default option for CYP enzyme induction was applied.

SI: small intestine.

(a)
Amount of active CYP3A4 (SI)

Active Enzyme (%) vs Time (h)
**Supplementary Fig. 9** Simulated CYP3A4 activity profile in the (a) liver and (b) small intestine following multiple oral doses of pexidartinib (400 mg twice daily) in the absence (solid black line) and presence (dashed black line) of rifampicin 600 mg daily in cancer subjects. The refined model was used. The default option for CYP enzyme induction was applied.
SI: small intestine
