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Clinical Pharmacologic Characteristics of Taletrectinib

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Background

- Taletrectinib is an oral, potent, CNS-active, selective, next-generation ROS1 inhibitor[1,2]
- Across two Phase 2 studies, TRUST-I and TRUST-II, taletrectinib showed robust, durable efficacy and favorable safety in patients with ROS1+ NSCLC[3]
- Taletrectinib (600 mg QD) is currently approved in China and the United States for the treatment of adult patients with locally advanced or metastatic ROS1+ NSCLC[4,5]
- Here, we report the key findings from pharmacologic studies of taletrectinib

Abbreviations

AUC, area under the curve; AUC_{inf}, area under the concentration-time curve from zero hours to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to time of the last quantifiable concentration; BCRP, breast cancer resistance protein; CI, confidence interval; C_{max}, maximum plasma concentration; CNS, central nervous system; CYP, cytochrome P450; DDI, drug–drug interaction; GMR, geometric mean ratio; IQR, interquartile range; MATE, multidrug and toxin extrusion protein; NSCLC, non-small cell lung cancer; P-gp, p-glycoprotein; PK, pharmacokinetics; Q, quartile; QD, once daily; ROS1, ROS proto-oncogene 1; $t_{1/2}$, terminal half-life; t_{max}, time of maximum concentration

References

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4. Nuvation Bio Press Release. Accessed July 09, 2025. https://investors.nuvationbio.com/news/news-details/2025/Nuvation-Bio-Receives-Approval-from-Chinas-National-Medical-Products-Administration-for-Taletrectinib-for-Patients-with-Advanced-ROS1-positive-Non-Small-Cell-Lung-Cancer
5. IBTROZI™ (taletrectinib) Prescribing Information 2025

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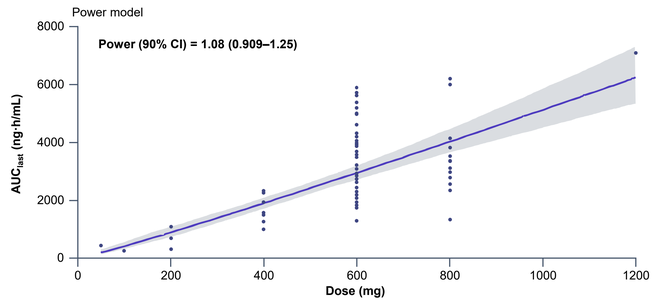
Methods

- The clinical pharmacologic characteristics of taletrectinib were evaluated in 10 Phase 1 or 2 clinical studies:
  - Five Phase 1 studies in healthy participants:
    - To evaluate DDIs, absorption, metabolism, and elimination of taletrectinib
  - Five Phase 1 or 2 studies in patients with cancer:
    - To evaluate repeat-dose PK (50–1200 mg QD taletrectinib), including PK across subgroups

Results: Clinical PK

- Multiple-dose studies evaluating taletrectinib at 50–1200 mg QD were conducted in patients with cancer
- Taletrectinib AUC exposures increased in a dose-proportional manner for 50–1200 mg QD doses (*Figure 1*)
- Taletrectinib was absorbed quickly after oral administration, with a median t_{max} between 2–6 hours
- Steady state was reached by Day 8 after 7 days of QD dosing, with an accumulation ratio of 3.3–4.5 at 600 mg QD
- The mean $t_{1/2}$ was approximately 80–100 hours in healthy participants ($t_{1/2}$ could not be calculated in patients with cancer); effective $t_{1/2}$ was approximately 66 hours, supporting QD dosing
- Plasma protein binding was concentration-dependent, with lower binding rates observed at higher concentrations, ranging from 96.5% with 100 ng/mL to 92.6% with 10,000 ng/mL
- The apparent steady state volume of distribution in patients with cancer was estimated to be 9820 L, indicating wide tissue distribution
- PK parameters were similar between healthy participants and patients with cancer

Figure 1. PK Parameter Dose Linearity: AUC_{last} vs Dose Over the 50–1200 mg Repeated Oral Dose Range (Steady State)

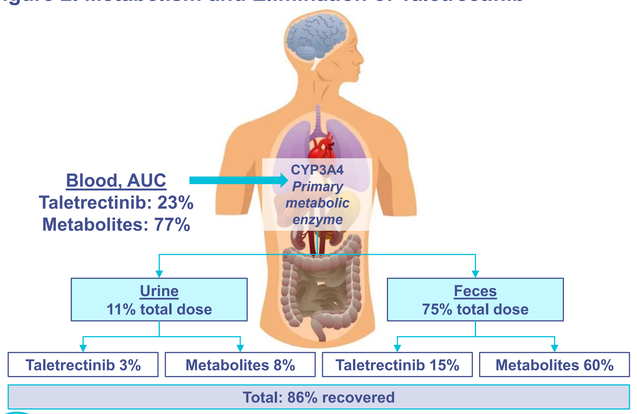


Pooled data from Phase 1 and 2 studies; data for the 600 mg QD dose are exclusively from Phase 2.

Results: Metabolism and Elimination

- From a clinical mass balance study in eight healthy adult males, of a single oral dose of 200 mg taletrectinib, with a radioactive tracer to follow the elimination path (5 µCi [^{14}C]-taletrectinib), at least 80% of the dose was absorbed
  - The liver is the major route of elimination, with 75% of the dose recovered in feces; renal elimination plays a minor role, with only 11% of the dose recovered in urine (*Figure 2*)

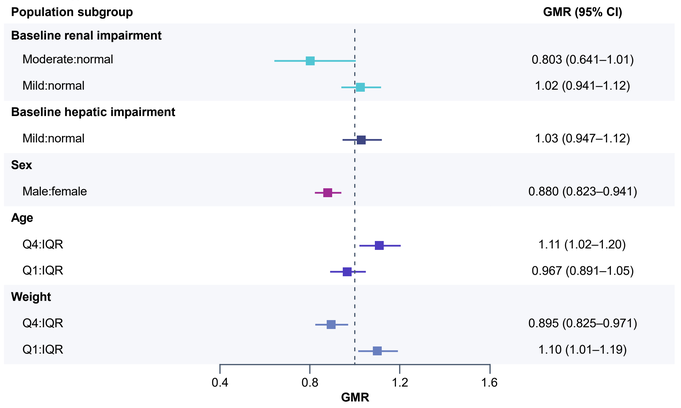
Figure 2. Metabolism and Elimination of Taletrectinib



Results: Population PK

- At 600 mg QD, no clinically significant PK differences in steady state average concentration were observed based on age, sex, weight, mild hepatic impairment, or mild-to-moderate renal impairment (*Figure 3*)

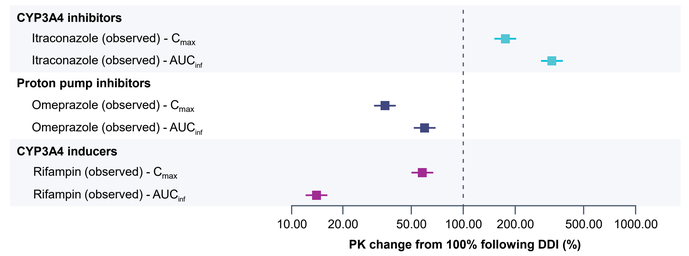
Figure 3. Population PK Analysis of Steady State Average Concentration



Results: Drug–Drug Interactions

- *In vitro* results indicated that CYP3A4 is the primary enzyme for metabolizing taletrectinib and that taletrectinib may:
  - Inhibit CYP3A4, CYP2D6, CYP2C8, P-gp, BCRP, MATE1, MATE2-K
  - Induce CYP1A2, CYP3A
- Taletrectinib has pH-dependent solubility and may be affected by changes in pH, such as when using proton pump inhibitors
- Clinical DDI studies were therefore conducted in healthy participants to evaluate the effect of coadministering strong CYP3A4 modulators, proton pump inhibitors, and P-gp substrates on taletrectinib PK or vice versa
- Itraconazole (strong CYP3A4 inhibitor) increased plasma C_{max} and AUC_{inf} of taletrectinib, while rifampin (strong CYP3A4 inducer) decreased C_{max} and AUC_{inf} (*Figure 4*)
- Omeprazole (proton pump inhibitor) decreased C_{max} and AUC_{inf} of taletrectinib (*Figure 4*)
- Taletrectinib had no clinically significant effect on digoxin (P-gp substrate) PK exposure (data not shown)

Figure 4. Impact of Coadministration With Other Drugs on Taletrectinib Exposure



Conclusions

- Taletrectinib shows dose-proportional PK with a long $t_{1/2}$, enabling QD dosing
- At the approved taletrectinib dose of 600 mg QD, PK parameters were consistent across demographic subgroups and were not significantly affected by mild hepatic impairment or mild-to-moderate renal impairment
- Since metabolism of taletrectinib primarily occurs via the CYP3A4 enzyme, CYP3A4 modulators may have an effect on taletrectinib exposure and this should be considered in clinical practice
- Additionally, proton pump inhibitors appear to impact taletrectinib exposure and this should be factored into prescribing practices

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