Co-Crystal Case Study

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The Challenge

Free base drugs in development may have low solubility which makes them unsuitable for clinical use without an enabled formulation. To address this challenge, comprehensive evaluations of salt, spray-dried-dispersions, and co-crystal formulations often take place in early development that would improve solubility and enable oral administration of new drugs.

- Use of “Agent X” as a co-crystal helps achieve optimal solubility and absorption characteristics of an investigational new drug.
- Nonclinical toxicology studies* had been conducted with a drug substance as a sprayed-dried-dispersion (SDD) form and not the co-crystal form.
- Therefore, only literature sources existed for “Agent X” prior to heading into the clinic.

*1-month rat and dog w/ recovery, in-vitro hERG, Ames, in-vitro MN, & phototoxicity studies conducted with the SDD form.

Available Background Information

"Agent X":

- Has active properties. Purported antioxidant, anti-inflammatory, and antimicrobial properties.
- Has not been used in FDA-approved medicines.
- Is ubiquitously found in food and naturally consumed as part of the human diet. Examples: nuts, berries, fruits (e.g. pomegranates).
- Was evaluated in subchronic repeat dose studies in rodent (4 to 13-week duration) with NOAELs being achieved, and no notable safety concerns identified in rodents.
  - Human equivalent doses of "Agent X" at the NOAELs in rat and mouse study would be 1.2g/day and 4.9g/day, respectively.
  - Dose multiple of >3X the max anticipated "Agent X" level that would be achieved in the clinic.
  - These nonclinical studies were limited and did lack safety pharmacology endpoints.
- Was well tolerated in several human clinical trials.
  - Although there are limited human trials evaluating "Agent X" alone, multiple human trials have been conducted with the class or products containing "Agent X", including trials with approximate "Agent X" levels ≤800 mg/day, and have revealed no reported adverse effects.
  - The maximum possible dose of "Agent X" as part of the co-crystal form of our drug substance would be ≤ 340 mg/day.

Available genetic toxicology data from published literature:

- NIOSH data indicates that "Agent X" and its esters may have protective properties as assessed in an Ames test.
- A micronucleus test in bone marrow of mice (2,000 mg/kg/day) was performed up to limit dose, and no micronucleus induction.
- A reverse mutation test in bacteria (TA98, TA100, TA1535, TA1537, and TA1538) was performed up to 10 mg/plate. Results were negative with and without metabolic activation.

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Questions to the Panel

- Should we conduct further genetox work (or any further GLP toxicology studies) with “Agent X” before proceeding with our IND submission and moving into the clinic?

- What would the panel recommend as a path forward for “Agent X”?

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Actual Outcome

pIND meeting requested with the FDA:

- Briefing document presented the background literature. The briefing document included published data with “Agent X” and did not contain any LOXO drug substance nonclinical data.
- Since timing was not optimal from when we would receive our feedback to first-human-dose, we opted to proactively proceed with a battery of toxicology studies with “Agent X” alone:
  - 28-day rat study
  - In-vitro hERG
  - Ames
  - In-vitro MN
- These studies with “Agent X”-alone were ongoing at the time, so were not included in the IND submission.

- Reasons why we proactively conducted repeat dose and genetic tox studies:
  - Risk mitigation – we did not want to delay bringing our drug to patients.
  - Plans to publish the data for future reference.
  - If future programs were to use this co-crystal form, we would have strong support for it’s use in the future

- Feedback received by FDA was optimal:

  Question: Does the FDA agree with the Sponsor’s position that the published toxicological data for “Agent X” supports its use as a co-crystal for a first-in-human phase 1 study in cancer patients?

  FDA Response: Yes. The published toxicology data appear adequate to support the use of “Agent X” in the proposed phase 1 clinical trial.

- Only LOXO drug substance nonclinical data was submitted as part of the IND. We did not include any LOXO-generated “Agent X” nonclinical data. The only data with “Agent X” that was submitted was a bridging PK study showing that the two forms (SDD vs. co-crystal) were comparable.