Protagonist Therapeutics

Rusfertide: Removal of FDA Clinical Hold

Conference Call

October 11, 2021

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Removal of FDA Clinical Hold on Rusfertide Clinical Development Program

- **We have received written notification from the FDA indicating the removal of the full clinical hold**
  - Protagonist is now permitted to resume dosing in all clinical trials of rusfertide
- **Protagonist's clinical team will coordinate with investigators to**
  - Submit amended documents to the Ethics Review Board
  - Reconsent patients.
- **Changes to Phase 2 study include**
  - Cancer surveillance rules
  - Augmented, regular dermatological examinations
  - Stopping rules
- **Plans for the Phase 3 registrational trial of rusfertide in polycythemia vera are on track**
  - Trial initiation in Q1 2022

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26-Week GLP RasH2 Mouse Carcinogenicity Study Summary

Benign (Non-malignant) and Malignant Skin/Subcutis Tumor Findings

- Rusfertide-related effects on skin but no dose response and not in other tumor types associated with model
- No effects on mortality with no other rusfertide-related macroscopic observations
- Non-statistically significant incidence of malignant squamous cell carcinoma in one male and one female mouse
  - Were considered rusfertide-related because of the morphogenetic relationship with benign squamous cell papilloma and the statistical significance for this combined finding

	Rusfertide							
Sex	Male				Female			
Dose Level (mg/kg/dose)	0	6.25	12.5	25	0	6.25	12.5	25
Number of Animals	25	25	25	25	25	25	25	25
Skin/Subcutis								
B-Papilloma, squamous cell	0	2	2	2	0	0	3*	3*
M-Carcinoma, squamous cell	0	1	0	0	0	0	1	0
B-Papilloma, squamous cell or M-Carcinoma, squamous cell	0	3*	2	2	0	0	4*	3*

B = Benign; M = Malignant

* = $p<0.05$

- No rusfertide-related neoplastic lesion findings were noted in any preclinical toxicity studies including 6-month rat and 9-month cynomolgus monkey chronic toxicity studies
- Complementary to planned 2-yr rat carcinogenicity GLP study

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Reported Cases of Cancer from Rusfertide Safety Database

	Subject	Condition/Trial	Prior medical condition/treatment Rx	Event	Rusfertide Exposure @ Event	Report date	Subject Disposition	Relationship to Rusfertide by PTGX (Initial*/Post-rasH2 Findings)
1	54 y.o. female	β-thalassemia PTG-300-03	Liver iron overload Non-alcoholic fatty liver disease. Nodular, scarred liver suggesting cirrhosis	Routine MRI: liver mass Bx:cholangiocarcinoma	9 mos	Q2 2020	Discontinued (DC)	Not related/Not related
2	71 y.o. male	Hereditary Hemochromatosis PTG-300-06	Pancreatic mass (detected pre-dose)	Bx:Pancreatic adenocarcinoma	13 days	Q3 2021	DC	Not related/Not related
3	73 y.o. female	Polycythemia Vera PTG-300-04	Basal cell carcinomas Melanoma Squamous cell carcinomas (SCC)-14 in 2yrs prior to enrollment.	3 SCC in situ; rx: curettage 3 SCC in situ; rx: Moh's	49 days 85 days	Q3 2021	Continued through 10/21	Not related/Possibly related
4	65 y.o. male	Polycythemia Vera PTG-300-04	Hydroxyurea (6 years) Thyroid cancer treated with iodine 131	Acute myeloid leukemia (AML)	9 mos	Q3 2021	DC	Not related/Possibly related

*Investigator viewed as not related

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Clinical Hold Response Elements

- **Inform investigators and patients of rasH2 mouse model findings and 4 cases of cancer reported in rusfertide clinical program (2 in PV (squamous cell skin and AML), 1 in HH (pancreatic cancer), and 1 in Beta-Thal (cholangiocarcinoma)**
  - Update the Investigator's Brochure with pre-clinical and clinical cancer findings
  - Revise the Informed Consent
- **Review of safety database for other carcinogenic events and other safety signals**
  - No additional cancer events
  - No new safety signals
- **Revise ongoing and planned Phase 2 and 3 protocols to enhance the safety of patients**
  - Subject and study stopping rules based on development of human cancer
  - Cancer surveillance rules incorporated
    - Augmented dermatologic examinations
    - Age, gender, and disease specific cancer surveillance as per standard guidelines
    - Phase 3 study to exclude patients with invasive cancer within 5 years; no other required changes to Phase 3 inclusion/exclusion criteria
- **No additional pre-clinical or clinical studies required to remove the clinical hold**

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Concluding Remarks

FDA removal of clinical hold in just three weeks

Patient safety remains our top priority

Efficiency in Resolution

Rusfertide holds potential for a favorable clinical benefit-risk profile in disease areas of unmet need

Favorable Benefit vs. Risk

Presentations of new data on rusfertide at select medical conferences by EOY 2021

- **Oral presentation at AASLD in Nov 2021**
- **Other presentation at a medical conference by year end**

New Data Presentations

Plan to initiate the Phase 3 study of rusfertide in polycythemia vera in Q1 2022

- **No major changes expected to inclusion/exclusion criteria except 5-year cancer free requirement prior to enrollment**
- **We anticipate no substantive effect on enrollment**

Phase 3 Initiation

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Thank you