Ultragenyx Case Studies:

Rare Pediatric Disease Priority Review Voucher (PRV)

Mepsevii® PRV	Crysvita® PRV
Date issued: November 2017	**Date issued:** April 2018
Disease state: mucopolysaccharidosis type VII (MPS VII)	**Disease state:** X-linked hypophosphatemia (XLH)
First-in-class therapy: • Mepsevii is the only approved therapy for MPS VII; standard of care prior to Mepsevii approval was supportive only • MPS VII affects ~200 people in commercially accessible geographies	**First-in-class therapy:** • Crysvita is the only approved therapy for XLH and the first disease-specific treatment that targets the underlying cause of XLH; standard of care for XLH prior to Crysvita approval was oral phosphate replacement and vitamin D (both addressed symptoms only) • XLH affects ~50,000 people in commercially accessible geographies
About MPS VII • Most patients with MPS VII die between their teenage years and thirties • MPS VII is an ultrarare disease that would normally never get a treatment developed despite the science that exists	**About XLH** • Key symptoms of XLH include — for children — slowed growth, short stature, skeletal deformities, rickets, bowed legs, knock knees, dental abscesses and impaired physical function and — for adults — spontaneous fractures, early degenerative joint disease, dental abscesses, hearing loss, fatigue, muscle stiffness and impaired mobility
Date sold / recipient: January 2018 / Novartis	**Date sold / recipient:** June 2018 / Gilead
Proceeds from sale: $130 million	**Proceeds from sale:** $40 million (PRV was sold for $80 million and proceeds were shared equally between Ultragenyx and our development partner, Kyowa Kirin)

"It is difficult to rely on the potential receipt and subsequent use or sale of a rare pediatric disease priority review voucher (PRV) in making decisions about our portfolio when it is not clear that the voucher program will continue to exist as we develop our programs. The real value of the voucher program is the ability to sell a PRV to recoup costs of development of a program and apply those proceeds to invest in additional potential therapies for rare and ultrarare diseases."

Emil D. Kakkis, M.D., Ph.D.

Founder, CEO, and President

Sale of the PRVs allowed Ultragenyx to use the proceeds to:

Defray the costs of development of triheptanoin for the treatment of long chain fatty acid oxidation disorders (LC-FAOD)

- Dojolvi® was subsequently approved by the FDA in June 2020
- Dojolvi is the only approved therapy for LC-FAOD; standard of care for LC-FAOD prior to Dojolvi approval was avoidance of fasting, MCT oil and a low fat/high carb diet
- LC-FAOD affects ~8,000-14,000 people in commercially accessible geographies
- Key symptoms of LC-FAOD include hypoglycemia, muscle rupture, muscle pain and weakness, fatigue, heart failure and decreased muscle tone
- Patients with LC-FAOD can appear "normal" and then suddenly develop severe symptoms or life-threatening complications

Defray the costs of development of Crysvita for tumor-induced osteomalacia (TIO)

- Crysvita was subsequently approved to treat TIO in June 2020
- Crysvita is the only approved therapy for TIO; standard of care for TIO prior to Crysvita approval was surgery, oral phosphate replacement and vitamin D (all addressed symptoms only, not underlying disease)
- TIO affects ~2,000-4,000 patients in commercially accessible geographies
- TIO is an ultrarare disease that most companies would have never studied

Advance research and development of our gene therapy programs

DTX301 for OTC deficiency

- Phase 3 trial ongoing
- Standard of care currently is low protein diet and ammonia scavengers; only curative approach is liver transplant
- OTC deficiency affects ~10,000 patients in commercially accessible geographies
- OTC deficiency involves accumulating and irreversible neurocognitive damage
- OTC deficiency is an episodic devastating disease that is exacerbated by infectious illnesses and leads to serious hospitalization; death from an ordinary cold is possible

DTX401 for GSDIa

- Phase 3 trial is fully enrolled and data is anticipated 1H24
- Standard of care is limited (diet and cornstarch only); only curative approach is liver transplant
- GSDIa affects ~6,000 patients in commercially accessible geographies
- All children and 90% of adults with GSDIa need to be awakened at night for cornstarch dosing; oversleeping can result in severe hypoglycemia, seizures and death if even one cornstarch dose is missed

Enter into a new partnership with GeneTx Biotherapeutics LLC regarding the development of GTX-102 for the treatment of Angelman syndrome

- We subsequently acquired GeneTx in July 2022
- Expecting Phase 1/2 expansion data in 1H24 and End of Phase 2 discussions with FDA in mid-2024
- Standard of care currently is anti-seizure medication and supportive care to attempt to manage symptoms; no specific treatment currently exists to treat underlying disease
- Angelman syndrome affects ~60,000 patients in commercially accessible geographies
- Individuals with Angelman syndrome have developmental delay, balance issues, motor impairment, and debilitating seizures. Some individuals with Angelman syndrome are unable to walk and most do not speak. Anxiety and disturbed sleep can also be serious challenges. While individuals with Angelman syndrome have a normal lifespan, they require continuous care and are unable to live independently.

Other programs in our portfolio have received rare pediatric disease designation

Three of our programs in development (UX111 for the treatment of Sanfilippo syndrome; UX143 for the treatment of osteogenesis imperfecta; and GTX-102 for the treatment of Angelman syndrome) have received rare pediatric disease designation and, if approved by the FDA, may potentially receive a PRV.