COWEN
AND COMPANY

Biotechnology

Ultragenyx

Equity Research

Initiating Coverage

February 25, 2014

Price: $58.01 (02/24/2014)
Price Target: NA

OUTPERFORM (1)

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Key Data

Symbol	NASDAQ: RARE
52-Week Range:	$62.48 - 35.15
Market Cap (MM):	$1,736.0
Net Debt (MM):	$(86.2)
Cash/Share:	$24.92
Dil. Shares Out (MM):	25.0
Enterprise Value (MM):	$1,790.4
ROIC:	NA
ROE (LTM):	NA
BV/Share:	$(15.35)
Dividend:	NA

FY (Dec)	2013E	2014E	2015E
Revenue (MM)			
Q1	$0.0A	$0.0	-
Q2	$0.0A	$0.0	-
Q3	$0.0A	$0.0	-
Q4	$0.0	$0.0	-
Year	$0.0	$0.0	$0.0
Earnings Per Share			
Q1	$(0.37)A	$(0.40)	-
Q2	$(0.45)A	$(0.44)	-
Q3	$(0.44)A	$(0.45)	-
Q4	$(0.34)	$(0.50)	-
Year	$(1.60)	$(1.80)	$(1.90)

Initiating: In Rare Company

The Cowen Insight

We are initiating coverage of Ultragenyx with an Outperform rating. We believe that management's experience and strategy will allow Ultragenyx to become a leading provider of therapeutics for rare, severe metabolic disorders. The company features four clinical stage candidates with aggregate commercial potential of >$2B. We expect RARE shares to outperform as these drugs progress in development.

Taking Orphans To A New Place.

Members of Ultragenyx's management team were amongst the first to realize the promise of drugs for severe, rare diseases. Management has applied its experience to the pursuit of a new in-licensing based business model that prioritizes flexible solutions to novel diseases, drugs with clear mechanisms, a risk-managed development strategy, and capital efficient execution. The company's pipeline includes candidates sourced mainly from academia, and mainly drugs that Ultragenyx intends to commercialize on a worldwide basis.

Clinical Pipeline Features Two Biologics ...

KRN23 is an antibody in Phase II development for X-linked hypophosphatemia (XLH). XLH patients cannot retain phosphate and suffer from a form of rickets that is refractory to Vitamin D. KRN23 is an antibody being developed by Ultragenyx and partner Kyowa Hakko Kirin that reduces levels of FGF23, a protein that has recently been identified as the central mediator of this disease. Animal model and early human (Phase I) data are compelling, and we view KRN23 as a relatively low-risk development and commercial candidate with >$1B in worldwide potential. Ultragenyx is expected to share in roughly a third of the drug's economics. rhGUS represents another low-risk development candidate. This enzyme replacement therapy is in a Phase I/II trial for MPS7, a potential $100MM worldwide opportunity

...And Two Small Molecule Substrate Replacement Therapies.

Triheptanoin, a seven carbon chain fatty acid is being developed in Phase II trials as an alternative source of fuel in patients with fatty acid oxidation disorders (FAOD) and Glut1 deficiency syndrome (Glut1 DS). The drug's metabolic profile should prove superior to existing dietary alternatives, and early clinical data support this view. FAOD and Glut1 DS could each represent $400MM+ markets for triheptanoin. SA-ER, and extended release form of sialic acid, is in a randomized Phase II trial for HIBM, a rare muscle disease. Initial data from the study have produced intriguing signs of activity.

RARE Likely To Join An Elite Breed Of Biotechs.

Ultragenyx raised $126MM in a January IPO and is financed into 2016 and through potential value creating milestones on all of its programs. Assuming 2027 sales of $1.5B, and a revenue multiple in line with that being accorded to Alexion and BioMarin, RARE might be worth $80/share.

At A Glance

Our Investment Thesis

KRN23's animal model and early human (Phase I) data are compelling, and we view it as a relatively low-risk candidate with >$1B in worldwide potential. Triheptanoin's metabolic profile should prove superior to existing dietary alternatives, and early clinical data support this view. FAOD and Glut1 DS could each represent $400MM + markets for triheptanoin. SA-ER, and extended release form of sialic acid, is in a randomized Phase II trial for HIBM, a rare muscle disease. Initial data from the study have produced intriguing signs of activity. Ultragenyx is financed into 2016 and through potential value creating milestones on all of its programs. We expect the stock to outperform as milestones on these and other programs are achieved.

Forthcoming Catalysts

- Phase I/II repeat dosing data for KRN23 in adult XLH patients
- Phase I/II data for rhGUS in MPS7
- Data from Phase II trial extension of SA-ER in HIBM in late 2014

Base Case Assumptions

- KRN23 is launched in 2018; achieves sales of over $1B in XLH
- Triheptanoin is launched for Glut1 DS in 2018 and LC-FAOD in 2019; achieves nearly $1B in sales by 2027
- rhGUS is launched in 2017 for MPS7; achieves $100MM in sales by 2027

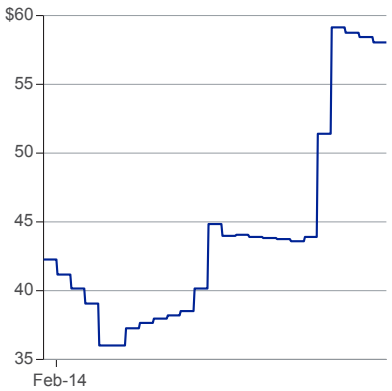
Upside Scenario

- SA-ER demonstrates clear efficacy in HIBM; achieves commercial success
- Triheptanoin demonstrates a cognitive benefit for Glut1 DS patients
- Increased screening expands the diagnosed ex-U.S. LC-FAOD patient population

Downside Scenario

- Repeat dosing of KRN23 generates anti-KRN23 antibodies
- Triheptanoin fails to demonstrate a benefit in Glut1 DS patients
- Orphan drug pricing comes under pressure

Price Performance



Source: Bloomberg

Company Description

Ultragenyx is focused on developing novel therapeutics for rare, serious metabolic disorders. Ultragenyx has built a multi-faceted pipeline via business development that contains four clinical candidates for five indications. KRN23 is a monoclonal antibody specific for FGF23 being developed for X-linked hypophosphatemia (XLH) under a collaboration with Kirin. KRN23 is currently in Phase I/II trials expected to readout in 2014. Triheptanoin is a wholly owned 7-chain carbon alternative source of energy in Phase II trials for long-chain fatty acid oxidation disorders (LC-FAOD) and glucose transporter 1 deficiency (Glut1 DS). Data for both indications is anticipated for 2015. rhGUS is an enzyme replacement therapy in Phase I for the lysosomal storage disease MPS7. Data is expected in H2:14, and could propel rhGUS straight into Phase III. Finally, sialic acid extended release (SA-ER) is in Phase II trials for HIBM which is proposed to be driven by a lack of sialic acid.

Analyst Top Picks

	Ticker	Price (02/24/2014)	Price Target	Rating
Ultragenyx	RARE	$58.01	$NA	Outperform
Sunesis Pharmaceuticals	SNSS	$5.27	$NA	Outperform
Exelixis	EXEL	$6.93	$NA	Outperform

A Rare Investment Opportunity

Ultragenyx is focused on developing novel therapeutics for rare, serious metabolic disorders. Following the success of others in this space (Genzyme, Alexion, BioMarin, Synageva) investors have come to appreciate that the orphan disease business model features many favorable attributes, including the potential for lesser R&D investment, shorter clinical trial timelines, reduced regulatory risk, premium pricing, and a worldwide commercial infrastructure that can be leveraged to support multiple products. Given past successes and estimates that over 4,000 human genetic disorders are caused by a single gene defect, many investors are seeking out additional opportunities in this arena, which remains one of the hottest subsectors within biotech.

While access to capital may be plentiful, the challenges to creating a leading orphan disease company are not trivial. They include identifying good drug candidates, partnering with patient and physician communities to advance their development, and collaborating with regulators to get them approved. The team at Ultragenyx is highly advantaged in this regard. CEO Emil Kakkis, who previously led BioMarin's efforts in rare diseases (as CMO) may have more experience developing drugs for orphan diseases than anyone on the planet. Dr. Kakkis also serves as President and Founder of a non-profit organization (EveryLife Foundation for Rare Diseases) that seeks to accelerate innovation in rare diseases. His work in this capacity has brought him into contact with academic groups and regulators interested in advancing novel therapies. Dr. Kakkis and a team that includes others with prior experience at BioMarin, Genzyme, Intermune, and Enobia know that development for rare diseases is different, and are pursuing an innovative strategy for finding and developing rare disease therapeutics. The team at Ultragenyx believes in:

1. *Open mindedness* – working within rare diseases requires the ability to learn about new indications, and the flexibility to embrace new solutions.

2. *Drugs with clear mechanisms* – genetic diseases are often caused by single gene defects and can often be treated with enzyme replacement therapies or substrate replacement therapies.

3. *A risk-managed development strategy* – in rare diseases it is likely that something that is "known" about a disorder will prove to be wrong. As such situations are encountered, risk needs to be managed.

4. *Creative solutions* – clinical trials in rare diseases are limited to a small number of patients, and need to be designed creatively in order to derive the maximum information from a modest sample size.

5. *Rapid, capital efficient execution* – the company intends to put money into clinical/regulatory development (as opposed to say manufacturing) in an effort to de-risk programs as soon as possible.

Multi-Faceted Pipeline Built Via Business Development

Ultragenyx is pursuing an in-licensing-based business model. The company's pipeline has been sourced entirely within the last 4 years, and mostly from academia. Certain candidates appear simply to have been overlooked. Others may not have been selected due to IP considerations (something Ultragenyx places less weight on given

its view that patents are often obtainable later in the development process). In at least one instance (KRN23), Ultragenyx was chosen as a development partner because of its expertise in the field of rare disorders. We don't expect that every candidate within Ultragenyx's pipeline will succeed, but some likely will, and as others fail, replenishment via additional product in-licensings will follow.

Four Clinical Candidates For Five Indications

Ultragenxy's pipeline includes four clinical candidates, and one preclinical candidate. Three of the therapeutics are biologic in nature (KRN23, rhGUS, and rhPPCA), and the company owns worldwide rights to four of the five candidates. Ultragenyx is advancing triheptanoin in development for two separate disorders, long-chain fatty acid oxidation disorders (LC-FAOD) and Glut1 deficiency syndrome (Glut1 DS).

Ultragenyx Pipeline

Candidate	Description	Indication	Pre-clinical	Phase 1	Phase 1/2 or Phase 2	Phase 3 or Pivotal	Ultragenyx Commercial Rights
KRN23 (UX023)	Anti-FGF23 monoclonal antibody	XLH					■ U.S. and Canada: Joint with KHK* (profit share) ■ Mexico, Central & South America
rhGUS (UX003)	Enzyme replacement	MPS 7					■ Worldwide
rhPPCA (UX004)	Enzyme replacement	Galactosialidosis					■ Worldwide
Triheptanoin (UX007)	Substrate replacement	LC-FAOD					■ Worldwide
Triheptanoin (UX007)	Substrate replacement	Glut1 DS					■ Worldwide
SA-ER (UX001)	Substrate replacement	HIBM					■ Worldwide (excluding Japan and certain other Asian territories)

Source: Ultragenyx

Our thoughts on Ultragenyx's clinical programs are summarized below.

A. ***KRN23*** *(anti-FGF23 mAb) for X-linked hypophosphatemia*. Ultragenyx and partner Kyowa Hakko Kirin are taking advantage of new biological insights that identify FGF23 as the key mediator of this form of vitamin D-resistant rickets. Antibodies to FGF23 have been shown to normalize levels of phosphate in animal models and humans, opening up a low-risk development path to market. Ultragenyx is entitled to roughly one-third of a worldwide economics in a drug with sales potential in excess of $1B.

B. ***Triheptanioin*** *(UX007)*. Triheptanoin is a seven-chain carbon source of energy in development for two metabolic disorders.

1. *Long-chain fatty acid oxidation disorders (LC- FAOD)*. Patients with LC-FAOD can't break down certain fats, and rely on carbohydrates or medium chain oils for fuel. In theory, triheptanoin represents a vastly superior energy source capable of feeding multiple substrates into the Krebs cycle for glucose production. Data from patients treated within academic cohorts support our optimism that UX007 might achieve U.S. sales of $200MM+ in this opportunity, and similar sales ex-U.S.

2. *Glut deficiency syndrome (Glut1 DS).* Glut1 DS is characterized by the inability to transport glucose across the blood-brain barrier. Triheptanoin could be a good alternative source of fuel for the brain given it is metabolized to compounds that can be converted into glucose. Proof-of-concept is still mostly lacking, but Glut1 DS could represent another sizeable ($250MM+) U.S. market for the drug.

C. ***rhGUS*** *(UX003) for MPS7*. Recombinant human beta-glucuronidase (rhGUS) is an enzyme replacement therapy (ERT) for MPS7, one of the less common lysosomal storage disorders (LSDs). A single case report suggests the drug is active, and the track record of ERTs in LSDs make us highly optimistic for ultimate success. We estimate rhGUS's worldwide market at ~$100MM.

D. ***SA-ER*** *(UX001) for hereditary inclusion body myopathy.* Sialic acid extended release (SA-ER) replenishes a substrate known to be deficient in this rare, severe progressive muscle disorder. A randomized Phase II trial indicated SA-ER safely improved muscle strength in a time and dose dependent manner as assessed by one functional scale. We have not modeled sales of SA-ER pending additional data on the drug's activity.

Ultragenyx In Rare Company

Ultragenyx completed an IPO in January raising net proceeds of approximately $126MM. Inclusive of ~$64MM in cash prior to the offering, the company is financed well into 2016 and through several important milestones.

Ultragenyx - Upcoming Milestones/Events

Indication/Milestone	Timing
Phase I/II repeat dosing data for KRN23 in adult XLH	2014
Phase I/II data for UX003 (rhGUS) in MPS7	2014
Initiate KRN23 Phase II trial in pediatric XLH	H2:14
Discussions with the FDA regarding uGAG as a Phase III endpoint for MPS7	H2:14
Data from the Phase II extension study of UX001 (SA-ER) in HIBM	Late 2014
24-week data from UX007 (triheptanoin) trial in LC-FAOD	2015
Phase II data for KRN23 in pediatric XLH	2015
Phase III data for UX003 (rhGUS) in MPS7	2015
8-week data from UX007 (triheptanoin) trial in Glut1 DS	2015

Source: Cowen and Company

Shares of RARE have been well received by the public markets, and have appreciated 176% from the IPO offering price. The company now sports a market cap of approximately $1.8B. While Ultragenyx's valuation has become more substantial, we believe there is much room for upside should the company progress toward becoming a leader in the orphan disease marketplace.

Leading Rare Disease Companies

Company	Stage of Development	Market Cap	2014 Revenue Multiple
Alexion	Profitable	$36.9B	14.5X
BioMarin	Several marketed products	$11.6B	17.2X
Synageva	In Phase III	$3.4B	NA
Ultragenyx	In Phase II	$1.8B	NA

Source: Cowen and Company

We find it difficult to assign a discreet value to the company's assets. This reflects Ultragenyx's multi-faceted pipeline, uncertain estimates for the quality and timing of data, and the difficulties inherent in estimating rare disease patient populations. Nonetheless, we view Ultragenyx's product portfolio as highly compelling, and capable of supporting ~$1.6B in revenue attributable to RARE shareholders by 2027.

Ultragenyx Pipeline: Peak Sales Potential

Candidate	Est. 2027 WW Sales	% Ownership	RARE's Ownership of Sales
KRN23	$1.47B	33%	$486MM
Triheptanoin for FAOD	$405MM	100%	$405MM
Triheptanoin for Glut1 DS	$572MM	100%	$572MM
rhGUS	$106MM	100%	$106MM
SA-ER	--	100%	--
Total	**$2.56B**		**$1.57B**

Source: Cowen and Company

Other commercial stage rare disease companies (Alexion, BioMarin) are trading at 14-17X 2014 sales. The table below depicts what Ultragenyx's stock might be worth assuming the company is capable of generating 2027 sales of $500M to $2.5B and achieving a similar revenue multiple. We would expect RARE shares to outperform the market as the company provides investors with additional evidence of value generation over time.

Scenario Analysis: Estimating RARE's Per Share Valuation

	2027 Sales To RARE				
Sales Multiple	**$500MM**	**$1.0B**	**$1.5B**	**$2.0B**	**$2.5B**
5x	$8.87	$17.74	$26.62	$35.49	$44.37
7.5X	$13.31	$26.62	$39.30	$53.24	$66.54
10X	$17.75	$34.49	$53.23	$70.98	$88.73
12.5X	$22.18	$44.36	$66.55	$88.73	$110.91
15X	$26.62	$53.24	$79.86	$106.48	$133.10
17.5X	$31.06	$62.11	$93.17	$124.22	$155.28
20X	$35.49	$70.98	$106.48	141.97	$177.63
22.5X	$39.93	$79.86	$119.79	159.72	$199.65

Note: Assumes 20% discount rate. Source: Cowen and Company

Ultragenyx Quarterly P&L

	2012A	Q1:13A	Q2:13A	Q3:13A	Q4:13E	2013E	Q1:14E	Q2:14E	Q3:14E	Q4:14E	2014E
KRN23 Revenue											
Triheptanoin Revenue											
rhGUS Revenue											
Collaborative/Grant/Other Revenue											
Total Revenue	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Y/Y growth											
COGS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
GMs											
R&D	12.6	5.7	7.2	6.8	7.0	26.6	9.0	10.5	11.0	12.0	42.5
SG&A	3.3	1.1	1.0	1.0	1.0	4.1	2.5	3.0	3.0	3.5	12.0
Total Expenses	**16.0**	**6.7**	**8.2**	**7.8**	**8.0**	**30.8**	**11.5**	**13.5**	**14.0**	**15.5**	**54.5**
Operating Income/Loss	**(16.0)**	**(6.7)**	**(8.2)**	**(7.8)**	**(8.0)**	**(30.8)**	**(11.5)**	**(13.5)**	**(14.0)**	**(15.5)**	**(54.5)**
Interest Income/Expense	0.0	0.0	0.1	0.1	0.0	0.2	0.0	0.0	0.0	0.0	0.0
Other Income/Expense	(0.4)	(0.0)	(0.4)	(0.7)	(0.5)	(1.7)	(0.5)	(0.5)	(0.5)	(0.5)	(2.0)
Pre-tax Income/Loss	(16.3)	(6.7)	(8.6)	(8.4)	(8.5)	(32.3)	(12.0)	(14.0)	(14.5)	(16.0)	(56.5)
Tax rate (%)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Provision for income taxes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net Income (Loss)	**(16.3)**	**(6.7)**	**(8.6)**	**(8.4)**	**(8.5)**	**(32.3)**	**(12.0)**	**(14.0)**	**(14.5)**	**(16.0)**	**(56.5)**
Accretion and dividends on convertible preferred stock	(3.2)	(2.6)	(2.6)	(2.6)	0.0	(7.9)	0.0	0.0	0.0	0.0	0.0
Net Income (Loss) attributable to common stockholders	**(19.6)**	**(9.4)**	**(11.2)**	**(11.1)**	**(8.5)**	**(40.1)**	**(12.0)**	**(14.0)**	**(14.5)**	**(16.0)**	**(56.5)**
GAAP EPS	**($1.81)**	**($0.37)**	**($0.45)**	**($0.44)**	**($0.34)**	**($1.60)**	**($0.40)**	**($0.44)**	**($0.45)**	**($0.50)**	**($1.80)**
Diluted Shares	10.8	25.0	25.0	25.0	25.0	25.0	30.0	31.8	31.9	32.1	31.5

Source: Cowen and Company

Ultragenyx Annual P&L

	2012A	2013E	2014E	2015E	2016E	2017E	2018E
KRN23 Revenue	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Triheptanoin Revenue	0.0	0.0	0.0	0.0	0.0	0.0	20.0
rhGUS Revenue	0.0	0.0	0.0	0.0	0.0	11.0	29.0
Collaborative/Grant/Other Revenue	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Revenue	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**11.0**	**49.0**
COGS	0.0	0.0	0.0	0.0	0.0	2.0	7.6
GMs						*0.8*	*0.8*
R&D	12.6	26.6	42.5	50.0	65.0	70.0	73.0
Total Expenses	**16.0**	**30.8**	**54.5**	**65.5**	**83.0**	**112.0**	**140.6**
	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Operating Income/Loss	**(16.0)**	**(30.8)**	**(54.5)**	**(65.5)**	**(83.0)**	**(101.0)**	**(91.6)**
Interest Income/Expense	0.0	0.2	0.0	0.0	0.0	0.0	0.0
Other Income/Expense	(0.4)	(1.7)	(2.0)	(1.0)	(0.3)	(0.3)	(0.3)
Pre-tax Income/Loss	(16.3)	(32.3)	(56.5)	(66.5)	(83.3)	(101.3)	(91.9)
Provision for income taxes	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net Income (Loss)	**(16.3)**	**(32.3)**	**(56.5)**	**(66.5)**	**(83.3)**	**(101.3)**	**(91.9)**
Accretion and dividends on convertible preferred stock	(3.2)	(7.9)	0.0	0.0	0.0	0.0	0.0
Net Income (Loss) attributable to common stockholders	**(19.6)**	**(40.1)**	**(56.5)**	**(66.5)**	**(83.3)**	**(101.3)**	**(91.9)**
GAAP EPS	**($1.81)**	**($1.60)**	**($1.80)**	**($1.90)**	**($2.25)**	**($2.60)**	**($2.30)**
Diluted Shares	10.8	25.0	31.5	35.0	37.0	39.0	40.0

Source: Cowen and Company

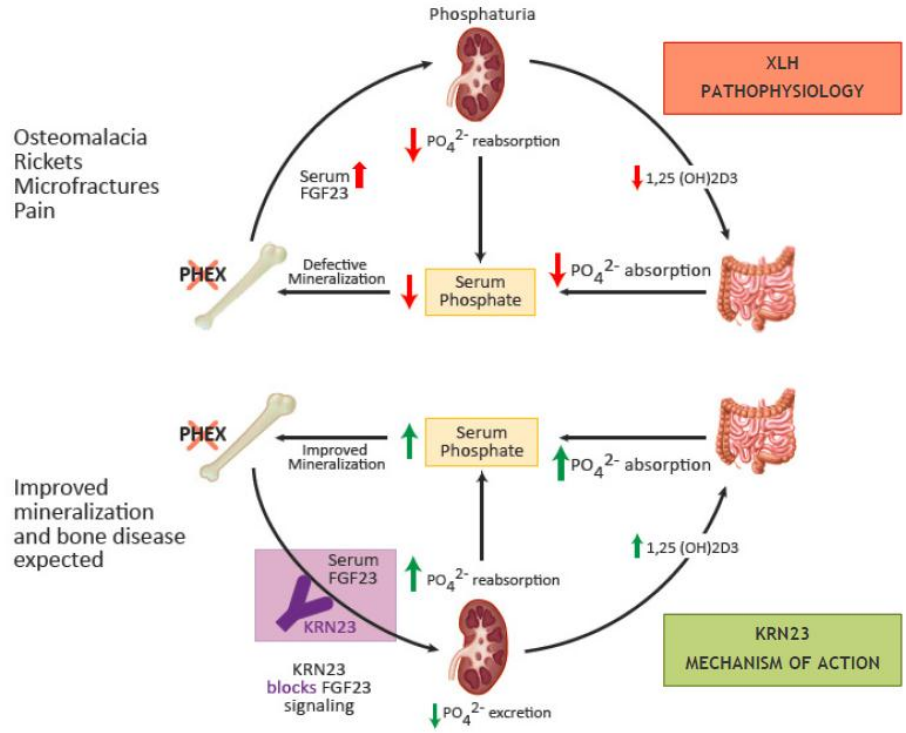
KRN23: Plugging The Hole In The Phosphate Bucket

KRN23 is a fully human monoclonal antibody directed against FGF23 being developed for the treatment of X-linked hypophosphatemia (XLH). Kyowa Hakko Kirin Pharma (KHK) generated this antibody and performed initial development work. In September 2013, Kirin partnered KRN23 with Ultragenyx whereby the two companies would split development costs, Ultragenyx would lead all development activities, and commercialization activities would be split. XLH (a form of vitamin D resistant rickets) is caused by mutations in the PHEX gene (located on the X chromosome) that generate aberrant production of FGF23 and subsequent failure in renal phosphate reabsorption. This leads to defective bone mineralization, and ultimately bowed legs, bone fractures, and other morbidities. Kirin has performed a single dose Phase I study of KRN23 in adults with XLH. This trial generated promising changes in serum phosphate without the appearance of SAEs. Repeat dosing data is expected in 2014, followed by Phase II and III trials in pediatric XLH. FDA approval is possible as soon as 2018. With an estimated 3,000 pediatric and 9,000 adult patients in the US alone, we believe KRN23 has worldwide sales potential of $1.5B. Ultragenyx is estimated to receive approximately a third of the worldwide value of KRN23.

X-Linked Hypophosphatemia

First described by Greek physicians in the first century AD, rickets is a disease that presents clinically as softened bones leading to fractures and the characteristic bowing of long, load bearing bones such as the femur. Rickets is caused by a breakdown in calcium and/or phosphorus regulation. In the 1920's, cod liver oil and ultimately Vitamin D were found to cure most cases of rickets. However, a subset of the disease remained resistant to typical vitamin D supplementation. Within, this subset of patients a smaller cohort of patients were identified for which vitamin-D resistant rickets was associated with aberrant phosphate regulation and inherited via a dominant X-linked fashion. This disease was given the name X-linked hypophosphatemia (XLH). Ultimately, the genetic basis of XLH was determined to be any number of mutations causing the absence of functional Phosphate-regulating neutral endopeptidase (PHEX). The PHEX protein is primarily expressed in osteoblasts and osteocytes where it regulates the production and/or destruction of another protein, FGF23. When PHEX mediated regulation is absent, concentrations of FGF23 throughout the body increase dramatically. While the disease phenotype manifests in the bones, it is in fact mediated distally by the effects of FGF23 on the kidneys. Elevated FGF23 concentrations are detected by the kidney and the activity of the renal sodium phosphate cotransporter is inhibited. This causes phosphate reabsorption to be reduced and phosphate wasting to occur via urinary excretion. In addition, renal production of the active Vitamin D metabolite $1,25(OH)_2$Vitamin D_3 (calcitriol) is suppressed by excess FGF23.

XLH Pathophysiology and KRN23's Mechanism of Action



Source: Ultragenyx

The resulting hypophosphatemia leads to rachitic bones (rickets), short stature, dentin malformation, and weakened ligaments. XLH causing mutations are estimated to occur in 1:20,000 live US births. While analyses of subpopulations have not been published, our consultants believe XLH is primarily a disease of Caucasian ancestry. Consultants also note that different mutations result in a range of hypophosphatemia and clinical symptoms. Approximately two-thirds of pediatric patients have a familial history of XLH and are identified by blood and urine phosphate analysis at birth. The remaining third of patients are identified when they begin to walk and their legs start to bow.

Current therapy seeks to refill the body's phosphate as quickly as the excess FGF23 drains it. In order to accomplish this, physicians prescribe large doses of phosphate to replace the leaking phosphate, and Vitamin D, in the form of calcitriol, to promote its incorporation into bones. In order to maintain phosphate levels, this regimen is generally prescribed for administration 4 times per day. However, our consultants indicate patient compliance usually limits its use to just 2 doses per day. If patients manage to adhere to therapy, they will witness bone improvements as increased serum phosphate is mineralized. Unfortunately, Vitamin D supplementation also causes serum calcium to increase. Over the long-term, elevated serum calcium generates calcifications including in the tendons and kidneys. The calcifications in turn cause decreased joint and/or organ function. A secondary effect of exposure to high levels of Vitamin D is an elevation of parathyroid hormone production, which can ultimately lead to hyperparathyroidism, which counteracts traditional phosphate supplementation by increasing bone resorption.

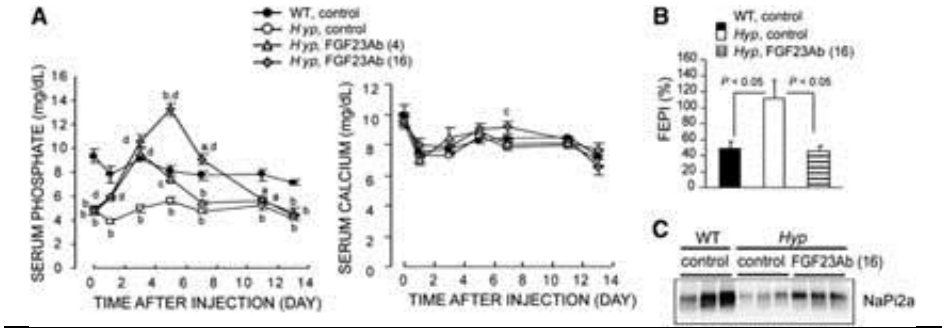
Rachitic Bones as a Result of XLH

Source: Kirin Presentation at ASBMR 2013

KRN23 Compensates For Mutant PHEX In Mice

KRN23 is a fully human monoclonal antibody specific for FGF23 that was developed by Kirin and out-licensed to Ultragenyx in 2013. KRN23 seeks to treat XLH by going to the root of the problem; binding excess serum FGF23 and blocking it from triggering phosphate wasting in the kidney. Kirin used the Hyp mouse (a model for XLH with a deleted PHEX gene) for pre-clinical studies of the KRN23 antibody. In these studies, a single dose of either 4 or 16mg/kg of FGF23 specific antibody generated serum phosphate equal to or greater than wild-type (panel A left) while calcium levels were unaltered (panel A right). In addition, at the higher dose phosphate excretion was reduced to wild type levels (panel B), and expression of the renal cotransporter was restored (panel C).

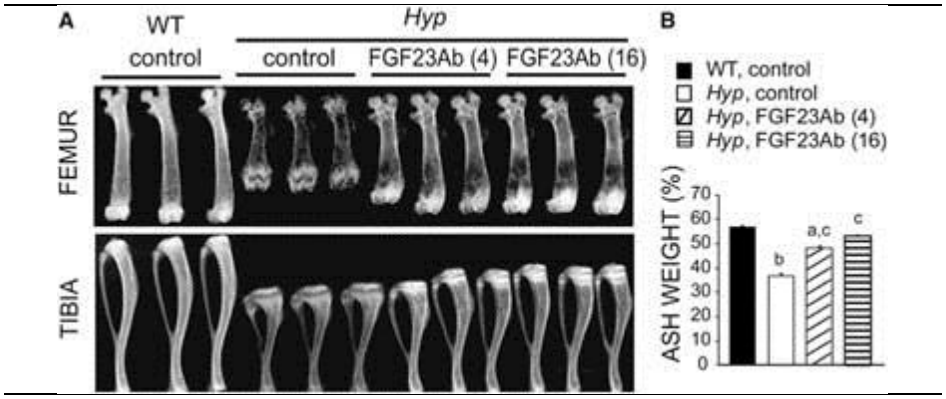
Single Dose of Anti-FGF23 Antibody Reverses Hypophosphatemia and Hyperphosphuria In Hyp Mice



Source: Aono Y, et al. J. of Bone and Mineral Research 2009

Having demonstrated that an anti-FGF23 antibody could reverse the urine, renal, and serum phenotypes of XLH in the mouse model, Kirin went on to examine if prolonged exposure would improve bone morphology. At 4wks of age Hyp mice were given 4 weekly injections of the anti-FGF23 antibody at either 4 or 16mg/kg. Relative to untreated Hyp mice, tail-length (a characteristic defect of Hyp mice) steadily increased throughout the 28 days of treatment, although neither treatment group reached WT levels within this short timeframe. In addition, femur and tibia lengths (panel A) and bone density (panel B) were increased following 28 days of treatment.

28 days of Anti-FGF23 Antibody Improved Hyp Mice Bone Morphology



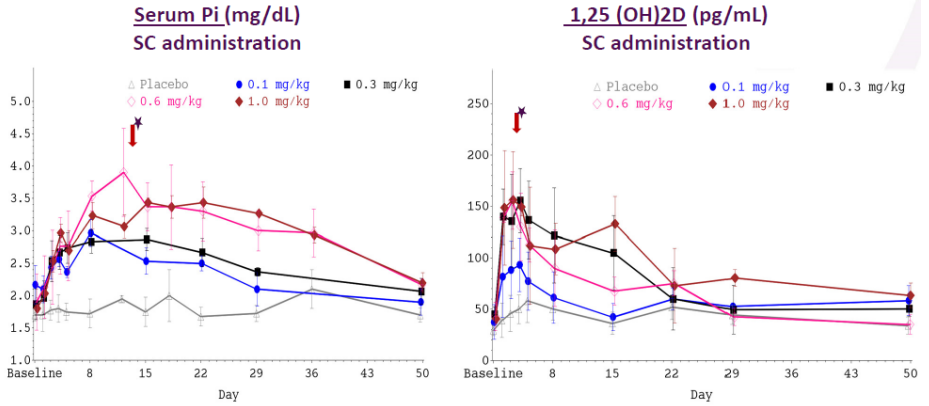
Source: Aono Y, et al. J. of Bone and Mineral Research 2009

Proof-of-Concept Demonstrated In Humans

Following the successful animal model experiments, Kirin initiated Phase I trials of the anti-FGF23 antibody (KRN23). The initial Phase I trial consisted of a randomized, double-blind, placebo controlled, single study of KRN23 in 38 adults with XLH. Patients were randomized to receive placebo, 0.003-0.3mg/kg of intravenous KRN23, or 0.1 to 1.0mg/kg of sub-cutaneous KRN23. Both I.V. and S.C. administration produced dose-related increases in serum phosphate. The S.C. route produced stronger and more durable serum phosphate responses that at the higher doses lasted beyond 29 days post-injection. Healthy individuals can display a wide range of serum phosphate, although ~3.5mg/dL is considered "normal". A 0.6 and 1.0 mg/kg

single dose of KRN23 allowed XLH patients to maintain normal serum phosphate for greater than a month. While serum 1,25(OH)$_2$Vitamin D$_3$ levels also increased, this effect was not quite as durable, and generally receded within 15 days post-injection.

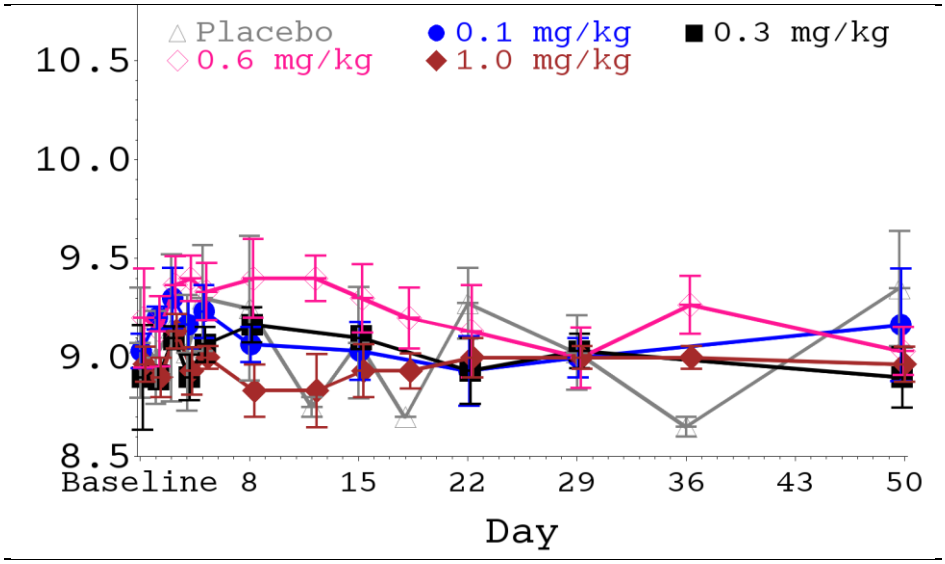
A Single Dose of KRN23 Increases Serum Phosphate and Vitamin D



Source: Ultragenyx

Importantly, no durable changes in serum calcium, serum parathyroid hormone, or urinary calcium were observed. Therefore, one would expect long term exposure to KRN23 might lack the calcification side-effects associated with the current therapy. 24/29 (83%) KRN23 patients experienced an AE compared to 4/9 (44%) in the placebo group. The most common AEs were elevated serum amylase (17%) and back pain (17%). It is unclear why serum amylase could be increased by an FGF23 specific antibody. However, bone and muscle pain are known symptoms of XLH and hypercalcemia as well as a side-effect of treating rickets with calcitriol. Therefore, the incidence of back pain may be an on-target effect of KRN23. No SAEs were observed. Since KRN23 is designed to be taken chronically, it is important to note that no anti-KRN23 antibodies were detected.

No Changes in Serum Ca (mg/dL) Were Observed Following S.C. Administration of KRN23



Source: Kirin presentation at ASBMR 2013

Multi-Dose Trial Underway

KHK has initiated a Phase I/II repeat-dosing extension study. For this trial, 23 patients from the Phase I trial will be given FGF23 every 28 days for up to an additional 4 doses. Patients will be followed for up to 13.5 months and evaluated for both safety and efficacy. The primary efficacy endpoint will continue to be serum phosphate. Additional efficacy endpoints include bone biomarkers, density and quality, as well as assessments of overall quality of life. Data from this trial is expected in 2014. Assuming a positive result, Ultragenyx intends to initially focus on developing KRN23 for the pediatric setting with a Phase IIb trial followed by a pivotal Phase III trial to support a product launch in 2018. An adult Phase IIb trial is expected to run concurrently to the pediatric Phase III trial. If all goes well on the pediatric track, the adult Phase IIb may be sufficient for label expansion beyond the pediatric setting.

KRN23's Long-Term Development

There is little doubt that KRN23 is capable of restoring serum phosphate in the chronic setting, however serum phosphate has not been accepted by the FDA as an approvable endpoint. Consequently, management expects to use one or more of the repeat-dosing study's bone assessments as a primary endpoint in future pivotal trials. Importantly, current therapy generates improvements in bone within 6 months. Therefore, bone based endpoints should not generate lengthy pivotal trials.

Ultragenyx's plan to focus on the pediatric setting should help prevent a lengthy trial and decrease the risk associated with a bone endpoint as well. Pediatric XLH patients tend to have the highest morbidity and therefore potential for benefit. Additionally, pediatric bones turnover more rapidly than adult bones, allowing for a shorter timeframe required to observe a similar improvement in bone morphology. Consequently, we do not view the FDA's likely requirement of a bone based endpoint as a significant risk to KRN23's development.

In theory, one safety consideration for chronically administered KRN23 is the potential for hypercalcemia. Single doses of KRN23 generated spikes in serum $1,25(OH)_2$Vitamin D_3 that did not translate into an increase in serum calcium. Still, it is possible that over time the spikes in $1,25(OH)_2$Vitamin D_3 could generate serum calcium elevations. It is important to note that the current standard of care generates significant calcium disregulation. Therefore, while neither ideal nor expected, some alteration to serum calcium levels can be tolerated given KRN23's likely significant improvements in phosphate regulation.

Consultants also note that if FGF23 is eliminated serum phosphate might "go through the roof". Therefore, if KRN23 lowers FGF23 concentrations too much serum phosphate could become elevated beyond the normal range, allowing for precipitates to form in organs such as the kidney. The formation of phosphate precipitates requires sustained serum phosphate levels of 7-8 mg/dL. In Phase I, KRN23 generated peak phosphate concentrations of just 4 mg/dL.

KRN23 Addresses A >$1B WW Opportunity

In September 2013, KHK and Ultragenyx signed a collaboration to further develop KRN23. KHK's unfamiliarity with orphan drug development led them to Ultragenyx's management team, which has significant experience in this area. Under the terms of this relationship, Ultragenyx will direct and fund 50% of development efforts in return for varying commercial rights around the world. For the first 5 years post-launch in the U.S., KHK is entitled to a supply price for manufacturing KRN23. Ultragenyx will initially control all U.S. commercialization activities but KHK will gradually takeover nearly all commercialization responsibilities over the course of the initial 5-year period. After the subtraction of KHK's supply price, all profits are split 50:50 during the 5-year period. Following this period, the profit share is converted into a royalty system. Under the royalty arrangement, Ultragenyx is entitled to a mid-high 20% royalty on KRN23's U.S. sales. This royalty is intended to mimic Ultragenyx's 50:50 profit share. In Europe, KHK is responsible for all commercialization activities and will pay Ultragenyx a 10% royalty. In Latin America, Ultragenyx is responsible for commercialization and owes KHK a low single-digit royalty in addition to the payment of a supply price to KHK for producing KRN23. In both the US and Latin America, the supply price is a fixed percentage of net sales. Therefore, while the supply price may provide KHK an additional profit margin, it insulates Ultragenyx from cost manipulations meant to shift the burden of other KHK programs onto Ultragenyx. In total, Ultragenyx will receive approximately one-third of KRN23's economic value.

XLH is believed to affect approximately 3,000 pediatric patients and 9,000 adult patients in the United States. Given XLH's significant effect on quality of life and the unpalatable nature of the standard of care, we anticipate any new therapy will be rapidly adopted and command pricing of ~$50,000/year. As a result we model the U.S. pediatric and adult settings as totaling a $600MM market opportunity by 2027. Under the terms of KHK and Ultragenyx's partnership, this would translate into $160MM in U.S. derived profits to Ultragenyx. In the EU, we model an equivalently sized market with an approximate 6-12 month lag due to management's projected filing timelines. This would produce $59MM in 2027 Ultragenyx revenue. A further 6-12 month lag in approvals is anticipated for Latin America, we model the Latin American market to be 50% of the US market. Given Ultragenyx's ownership of the majority of these rights, Latin America is modeled to generate $255MM in Ultragenyx revenue in 2027. In total, we model 2027 worldwide KRN23 sales of $1.474B with Ultragenyx booking just under a 3rd of these for a total of $474MM.

KRN23 Revenue Model

U.S.	2018 Year 1	2019 Year 2	2020 Year 3	2021 Year 4	2022 Year 5	2023 Year 6	2024 Year 7	2025 Year 8	2026 Year 9	2027 Year 10
# of Pediatric Patients with XLH in US	3,000	3,030	3,060	3,091	3,122	3,153	3,185	3,216	3,249	3,281
% on Therapy	*55%*	*65%*	*70%*	*75%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*
# on Pediatric Patients on Therapy	1,650	1,970	2,142	2,306	2,497	2,522	2,548	2,573	2,599	2,625
% on KRN23	*7%*	*25%*	*40%*	*55%*	*68%*	*78%*	*82%*	*84%*	*84%*	*85%*
# of Pediatric Patients on KRN23	116	497	861	1,268	1,698	1,967	2,095	2,159	2,173	2,241
# of Adult Patients with XLH in US	9,000	9,090	9,181	9,273	9,365	9,459	9,554	9,649	9,746	9,843
% on Therapy	*44%*	*55%*	*60%*	*65%*	*70%*	*75%*	*75%*	*75%*	*75%*	*75%*
# on Adult Patients on Therapy	3,944	5,000	5,474	5,993	6,514	7,074	7,178	7,257	7,345	7,390
% on KRN23	*7%*	*25%*	*40%*	*55%*	*68%*	*75%*	*75%*	*75%*	*75%*	*75%*
# of Adult Patients on KRN23	273	1,270	2,190	3,292	4,436	5,277	5,383	5,443	5,501	5,557
Total # of Patients on KRN23	388	1,768	3,050	4,560	6,134	7,245	7,478	7,602	7,675	7,798
Price per patient (000)	$50	$53	$55	$58	$61	$64	$67	$70	$74	$78
Total KRN23 US Revenue (MM)	**$19.4**	**$92.8**	**$168.2**	**$263.9**	**$372.8**	**$462.3**	**$501.1**	**$534.8**	**$566.9**	**$604.8**
Supply Price as % of Revenue	*7%*	*7%*	*7%*	*7%*	*7%*					
Supply Cost of KRN23 (MM)	$1	$6	$12	$18	$26					
Costs Attributable to KRN23 (MM)	$55	$75	$95	$110	$125					
Total KRN23 Profit (MM)	($37)	$11	$61	$135	$222					
RARE's share of profit (MM)	($18)	$6	$31	$68	$111					
RARE's Royalty as % of revenue						27%	27%	27%	27%	27%
Royalty Paid to RARE (MM)						$123	$133	$142	$150	$160
RARE's U.S. KRN23 Revenue (MM)	**($18.5)**	**$5.7**	**$30.7**	**$67.7**	**$110.9**	**$122.5**	**$132.8**	**$141.7**	**$150.2**	**$160.3**
ROW										
EU Total Sales (MM)	$10	$56	$130	$216	$318	$418	$482	$518	$551	$586
RARE's Royalty as % of revenue	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Royalty Paid to RARE on EU Sales (MM)	**$1.0**	**$5.6**	**$13.0**	**$21.6**	**$31.8**	**$41.8**	**$48.2**	**$51.8**	**$55.1**	**$58.6**
Latin American Total Sales (MM)	$0	$10	$46	$84	$132	$186	$231	$251	$267	$283
Supply Price as % of Revenue	*7%*	*7%*	*7%*	*7%*	*7%*	*7%*	*7%*	*7%*	*7%*	*7%*
Supply Price of KRN23 (MM)	$0	$1	$3	$6	$9	$13	$16	$18	$19	$20
Royalty due to KRN as % of revenue	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
RARE's Revenue on Latin American Sales (MM)	**$0.0**	**$8.7**	**$41.8**	**$75.7**	**$118.8**	**$167.8**	**$208.0**	**$225.5**	**$240.7**	**$255.1**
RARE's WW Revenue From KRN23 in XLH (MM)	**($17.5)**	**$20.0**	**$85.5**	**$165.0**	**$261.5**	**$332.0**	**$389.0**	**$419.0**	**$446.0**	**$474.0**

Source: Cowen and Company

Triheptanoin: One Molecule For Multiple Energy Disorders

Triheptanoin is being developed as an alternative fatty acid which the body can metabolize and utilize as an energy source. Ultragenyx owns the worldwide rights to Triheptanoin, which was originally developed at the Baylor Research Institute. Academic researchers have successfully used triheptanoin for over a decade to bypass a constellation of long-chain fatty acid oxidation disorders (LC-FAOD) in compassionate use and investigator sponsored trials. Left untreated, LC-FAODs can lead to energy starvation in muscle cells, rhabdomyolysis, kidney failure and death. Ultragenyx intends to validate the data from the academic setting with a recently initiated Phase II trial. Following a subsequent Phase III trial, FDA approval and a commercial launch are anticipated for 2019. With 2,000-3,500 patients in the U.S., we model the FAOD market as a $405MM WW opportunity.

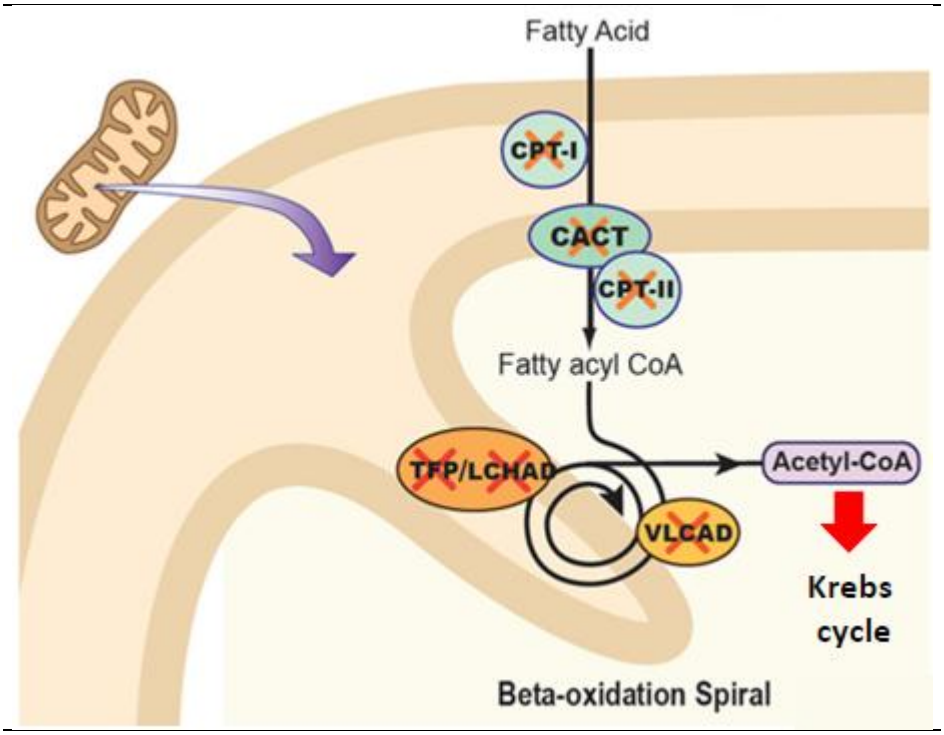
Triheptanoin's metabolites may also be able to cross the blood brain barrier. Once across the blood:brain barrier, the metabolites can be converted to glucose and used for energy. Therefore, Ultragenyx believes triheptanoin can be used to treat glucose transporter type-1 deficiency syndrome (Glut1 DS). Glut1 DS is characterized by the inability to transport glucose (the primary source of energy in the brain) across the blood:brain barrier. Left untreated, this leads to seizures, movement disorders, and development delays. Ultragenyx plans to develop triheptanoin for the treatment of Glut1 DS simultaneously to its work on FAOD. An adaptive Phase II trial in Glut1 DS began in early 2014 with data expected in 2015. Following a Phase III trial, FDA approval might occur in 2018. Glut1 DS is a fairly large indication with 3,000-7,000 patients in the U.S. We model peak sales in the WW Glut1 DS market at $572MM. Therefore in total triheptanoin could support nearly $977MM in WW sales across the FAOD and Glut1 DS indications.

LC-FAOD Starves The Krebs Cycle

Long-chain fatty acid oxidation disorders (LC-FAOD) are a group of genetic diseases where patient's mitochondria are unable to metabolize long chain fatty acids (the body's stored energy) into acetyl-coenzyme A (AC-CoA), which can then be fed into the Krebs cycle (the energy producing engine of a cell) to generate energy for cellular processes. Without the ability to utilize fatty acids, patients are dependent upon glucose for energy. When LC-FAOD patients exercise, suffer from an illness, or fast overnight the available glucose is quickly depleted. Without a method for breaking down fat stores, hypoglycemia, acute muscle rupture (rhabdomyolysis), and heart failure can occur. In addition to these acute problems, LC-FAOD patients also suffer from persistent energy imbalances which lead to low muscle tone and chronic muscle pain/fatigue.

The metabolism of fatty acids into acetyl-CoA requires a number of steps each involving one or more enzymes. A mutation in any of these genes, can cause LC-FAOD. The severity of LC-FAOD depends upon the nature of the mutation and the gene it affects. 20 year mortality rates in these diseases are as high as 90%, and LC-FAODs may be responsible for up to 50% of sudden infant deaths (SIDS). Over the past decade, LC-FAODs have become part of standard newborn screening protocols in the U.S.. Our consultants believe this will result in decreased mortality and the ability to proactively treat these patients. Outside of the U.S., newborn screening is not yet standard, although it is increasing in prevalence. In the absence of proactive newborn detection, LC-FAOD patients are identified following hospitalization as a result of a hypoglycemic event. In this scenario, an LC-FAOD is suspected when hypoglycemia is observed in the absence of ketones. The absence of ketones indicates a blockage upstream of acetyl-CoA production rather than within the Kreb's cycle which would cause a buildup of acetyl-CoA and ultimately ketone bodies. Ultragenyx believes there are between 2,000 and 3,500 LC-FAOD patients in the U.S.

LC-FAOD Associated Mutations Block Acetyl-CoA Production



Source: Ultragenyx

Standard Of Care Results In Significant Morbidity And Mortality

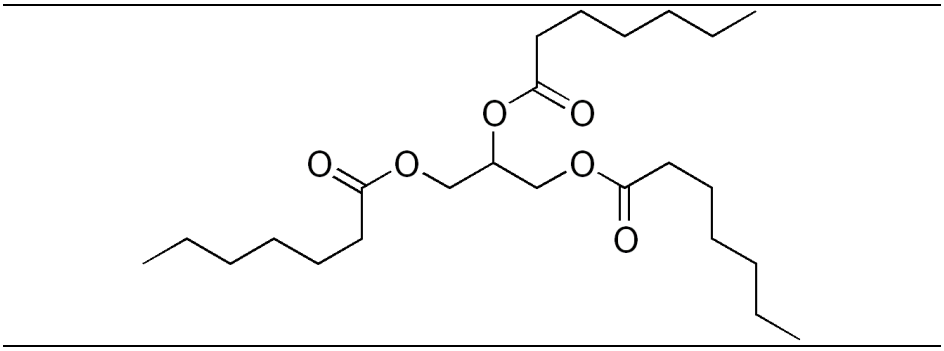
The current treatment paradigm is focused on developing a specialized diet for each patient. Patients are instructed to consume a high-carb low-fat diet while diligently avoiding fasting. Medium-chain fatty acids are capable of crossing the mitochondrial membrane in the absence of the long-chain fatty acid machinery. Once in the mitochondria, medium-chain fatty acids can be metabolized into substrates of the Krebs cycle by medium chain fatty acid oxidation enzymes. Therefore, many patients survive on non-FDA-approved medium-chain triglyceride oil (MCT-oil) preparations derived from plant extracts such as palm or coconut oil. Compliance with MCT-oil based diets is difficult due to impurities in the oil preparation which give it an unpleasant smell and taste. MCT-oil based diets cost patients about $10K/year and reduce but do not eliminate hypoglycemic events and LC-FAOD morbidity/mortality. In fact, a study of 180 French patients diagnosed from 1977-2009 found that just 56% survived despite receiving the standard of care. This survival rate differed greatly by mutation. For example, patients with CPT-I mutations exhibited a 75% survival rate while just 8% of patients with CACT mutations were alive at the time of analysis.

Triheptanoin Looks To Improve Upon MCT-oils

Triheptanoin is a pure medium-length odd-chain fatty acid. It is converted into ketone bodies and heptanoate (a C7 fatty acid). The ketone bodies can either be converted into glucose or be utilized directly as an alternative energy source. Heptanoate is able to gain access to the mitochondria where it is processed by the medium chain fatty acid oxidation machinery. MCT-oils are processed by this machinery to generate Acetyl-CoA molecules (#1 in the below mechanism of action diagram). These

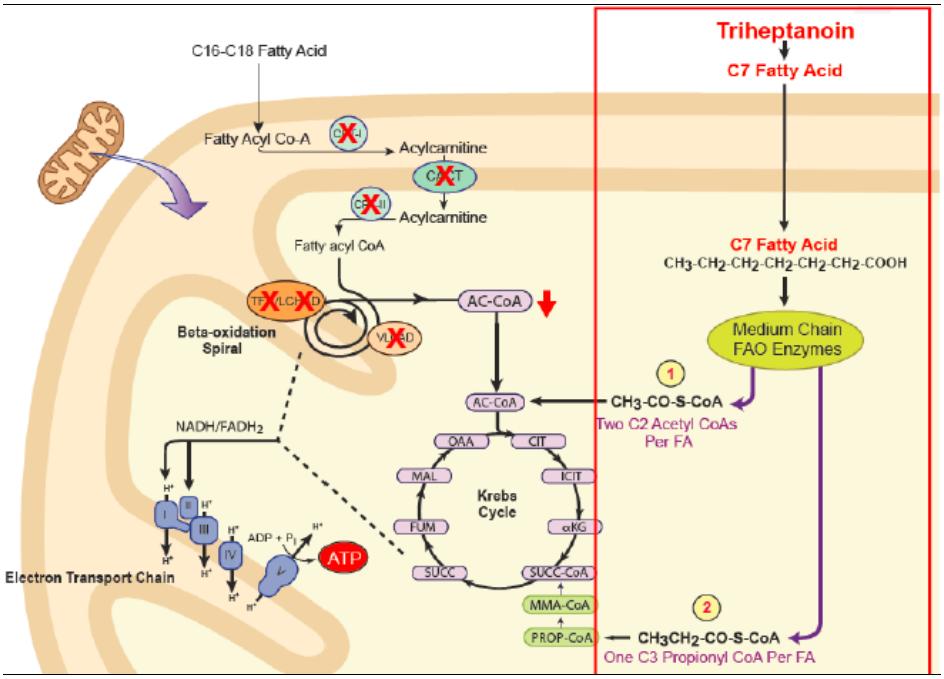
molecules restock the krebs cycle's need for acetyl-CoA (AC-CoA), and allow it to begin running again. Unlike MCT-oil, triheptanoin/heptanoate contains an odd number of carbons. This allows heptanoate to also be metabolized into an important secondary metabolite, Propionyl-CoA (#2 in the below mechanism of action diagram). Propionyl-CoA can be processed into MMA-CoA to restock succinate-CoA for the Krebs cycle. Roe, *et al.* report that cellular leakage of succinate may be the cause of MCT-oil's incomplete Krebs cycle restoration in LC-FAOD patients. As a result, Ultragenyx believes triheptanoin provides a superior source of cellular energy by 1) providing a source of ketone bodies/glucose and 2) providing improved restoration of Krebs cycle function.

Structure of Triheptanoin



Source: Wikimedia Commons

Triheptanoin's Mechanism of Action



Source: Ultragenyx

Triheptanoin Has A History Of Use In Academia

Triheptanoin was originally developed at Baylor Research Institute, where it was used for over a decade in multiple investigator-sponsored open-label studies. In total 130 patients were treated with triheptanoin, 65 of whom suffered from a LC-FAOD. Six of the 65 LC-FAOD patients died, although none of the deaths were considered related to triheptanoin therapy. Three SAEs (muscle cell rupture, elevated CK, and myoglobinuria) were considered possibly related to treatment, although each are also typical symptoms of LC-FAOD. In 2006, a cumulative summary of 48 patients with a variety of mutations (CPT-I, CPT-II, CACT, VLCAD, LCHAD, TFP, and SCAD) resulting in an LC-FAOD was published. This study examined changes in reported symptoms on standard of care and triheptanoin therapy. Improvements were seen across multiple organ systems, including cardiac symptoms, muscle rupture events, feelings of fatigue, hypoglycemia, liver size, and retinopathy.

Patients Suffering LC-FAOD Symptoms Before and After Triheptanoin

	# Symptomatic Patients*	
Symptoms	Before triheptanoin**	After triheptanoin
Cardiac	10	1
Muscle rupture	36	15
Weakness/fatigue	44	10
Low blood sugar	24	1
Liver enlargement	26	2
Retinopathy	3	3

Source: Ultragenyx; Roe and Mochel 2006

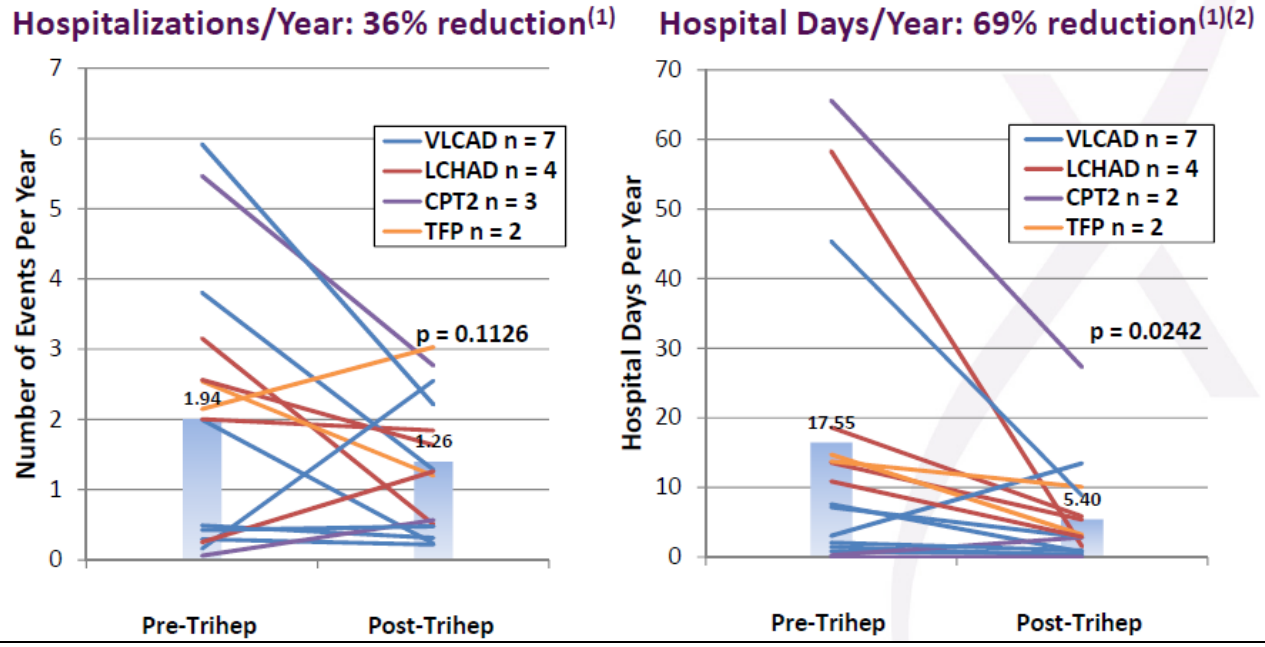
Ultragenyx has also performed a retrospective analysis of 20 LC-FAOD patients' medical charts before and after initiation of triheptanoin therapy. Patients in this analysis were treated with triheptanoin for as long as 13 years. Following the initiation of triheptanoin therapy patients spent 69% (p=0.0242) fewer days/year in the hospital and suffered from 96% (p=0.0091) fewer hypoglycemic events/year. While not significant there was also a strong trend towards a reduction in the number of hospitalizations (36%) Management believes the difference between reductions in hospitalizations and days spent in the hospital is best explained by the fragility of patients on the standard of care. Management reports that physicians routinely admit LC-FAOD patients for monitoring whenever they show up in the ER no matter how minimal their LC-FAOD symptoms. This is because small changes in patient routines/diets can result in a rapid spiraling of a patient's well-being. Therefore, physicians exercise caution and keep the patient in hospital. Management hypothesizes that given this operating procedure, triheptanoin was able to largely prevent extended stays due to severe LC-FAOD symptoms, but had lesser impact on the number of hospitalizations. There was also a trend towards a reduction in peak

creatine kinase (CK) during rhabdomyolysis events (68%). Peak CK is an important measure of the extent to which muscle destruction is occurring during an episode of rhabdomyolysis.

The above findings, reveal improvements in not only patient symptoms but also use of health care resources. The former will be important for gaining FDA approval, while the latter will provide a strong economic argument to payers in support of reimbursing triheptanoin's likely pricing premium versus existing dietary options.

Retrospective Analysis of Triheptanoin versus Standard of Care in LC-FAOD

Description	Pre-treatment	Post-treatment	% Decrease	n	p value
Mean total hospital days/year[1,2]	17.55	5.40	69%	15	**0.0242**
Mean total hospitalizations/year[1]	1.94	1.26	36%	16	0.1126
Mean infant total hospitalizations/year[3]	13.01	1.37	89%	4	0.0892
Mean hypoglycemia total hospital days/year[1,2,4]	8.42	0.18	98%	9	**0.0257**
Mean hypoglycemia events/year[1,4]	0.92	0.04	96%	9	**0.0091**
Mean rhabdomyolysis total hospital days/year[1,5]	5.94	2.16	64%	9	0.1224
Mean rhabdomyolysis events/year[1,5]	1.05	0.68	35%	11	0.4604
Mean peak creatine kinase (units) for rhabdomyolysis events[1,5]	85,855	25,797	68%	7	0.1279



Source: Ultragenyx

Ultragenyx Moves Triheptanoin Into Phase II

Building upon the academic use of triheptanoin and retrospective analyses, Ultragenyx initiated an open-label Phase II trial in February 2014. This study will enroll 30 severely affected LC-FAOD patients aged 6 months to 35 years. Inclusion criteria include:

1) Genetically confirmed LC-FAOD (CPTII, VLCAD, or LCHAD) deficiency

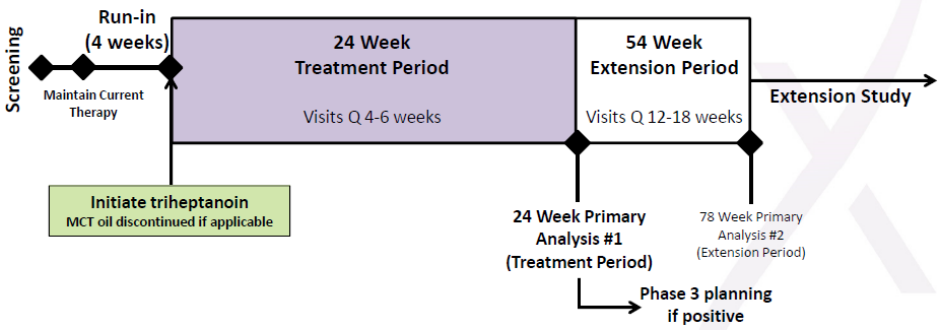
2) Currently managed on a stable treatment regimen which may include high carb diet, avoidance of fasting, carnitine and/or MCT oil

3) Chronically elevated CK with major associated clinical events; episodic CK elevations with associated muscle dysfunction; at least 3 ER visits/hospitalizations in the past year (or 5 in the past 2 years) as a result of hypoglycemia, rhabdomyolysis, or exacerbation of cardiomyopathy; or functional cardiomyopathy requiring medical management

As a result, enrolled patients will be patients who are being actively treated with the existing standard of care yet are still suffering from significant effects of their LC-FAOD. This will provide Ultragenyx with ample opportunity to demonstrate improvements in clinical outcomes.

Once enrolled, patients will be maintained on standard of care for 4 weeks in order to establish baseline characteristics for each patient, and allow them to serve as their own control. After this 4 week run-in patients' existing regimen will be replaced with triheptanoin for 24 weeks at a dose representing 25-35% of daily caloric intake spread across at least 4 administrations/day. Patients will be evaluated every 4-6 weeks for exercise tolerance (12 minute walk test, cycle ergometry, muscle strength and CK levels), hypoglycemia, liver size, and cardiac disease. Additional data collection will include the frequency of hospitalizations and ER visits. The primary analysis will be run at the end of this 24 week treatment period, although patients will continue to be dosed for an additional 54-week extension period. During the extension period patient visits will occur every 12-18 weeks. Initial 24 week data are expected to be available in 2015.

LC-FAOD Phase II Trial Design



Source: Ultragenyx

Triheptanoin's Path To Approval

Given the benefits observed in retrospective analyses, we anticipate detection of positive signals at 24 and 78 weeks. Particularly likely, is a positive effect on hypoglycemic events. While hypoglycemia may cause long-term cardiac/muscle dysfunction, it is unlikely the FDA is willing to accept this as a surrogate endpoint. However, CK levels are considered a predictor of rhabdomyolysis and could function as an approvable endpoint. In fact, management believes a significant CK effect could be grounds for an approval. Ultragenyx will likely utilize the Phase II data to also identify a valid Phase III clinical endpoint among exercise tolerance, liver size, and cardiac function. Management expects a Phase III trial to include an MCT oil control arm. This would help Ultragenyx drive home the potential clinical and possibly pharmacoeconomic advantages of triheptanoin.

LC-FAOD Might Be A $400MM WW Opportunity

We model an NDA being filed in late 2017 following a Phase III trial and FDA approval occurring in late 2018. Composition of matter patents expire in 2020. Ultragenyx is pursuing a number of additional patents surrounding the purity of triheptanoin and its use in additional indications. Triheptanoin purity is important for 1) proper dosing and 2) fatty acid impurities that are known to give the preparation a bad taste. In addition, triheptanoin would be a new chemical entity. Therefore, Ultragenyx would be entitled to market exclusivity of 5 years in the U.S. and 10 years in the EU. Ultragenyx is also pursuing an orphan disease certification for LC-FAOD which would grant triheptanoin an 7 years of exclusivity in the U.S. and 10 years in the E.U. Consequently, we believe triheptanoin is protected well into the next decade.

Using the midpoint of LC-FAOD patient estimates we model 2,750 treatable patients in the U.S. Disease severity is variable within this population, with some patients being relatively easily managed using existing dietary and/or MCT-oil methods while others suffer severe consequences despite pursuing therapy. As a result, we model an initial penetration of 50% for all therapeutic options, with 10% of treated patients opting for triheptanoin in the first year on the market. Over time we believe triheptanoin's significant clinical benefit will convince increasing numbers of LC-FAOD patients to transition from MCT oil or begin pharmacologic therapy. In fact, our consultant believes triheptanoin will ultimately push MTC-oil off the market. Therefore, our model projects the penetration of all therapeutic options increasing to 75%, with 80% of treated patients opting for triheptanoin over the first 10 years on the market. While triheptanoin should command a premium over existing options, management believes the relatively large patient population, presence of dietary therapies, and small molecule nature of the product will prevent ultra-premium pricing. Thus, we model Ultragenyx charging approximately $80K/yr. This leads our model to project initial U.S. sales of $11MM in 2018 growing to $208MM in 2027. Ex-U.S. sales are expected to lag by approximately one year due to filing timelines. Given the larger population base but lower pricing in these markets we expect over time they will grow to a nearly equal size as the U.S. market. This translates into 2027 worldwide sales of $405MM.

U.S. LC-FAOD Revenue Model

	2019	2020	2021	2022	2023	2024	2025	2026	2027
# of LC-FAOD cases	2,750	2,778	2,805	2,833	2,862	2,890	2,919	2,948	2,978
% on Triglyceride Therapy	*50%*	*55%*	*60%*	*65%*	*70%*	*75%*	*75%*	*75%*	*75%*
# on Therapy	1,375	1,528	1,683	1,842	2,003	2,168	2,189	2,211	2,233
UX007 Mkt Share	*10%*	*20%*	*35%*	*50%*	*60%*	*70%*	*75%*	*80%*	*80%*
# on UX007	140	302	587	921	1,202	1,512	1,639	1,760	1,788
Price per patient per year (000)	$79	$83	$87	$91	$96	$101	$106	$111	$116
U.S. LC-FAOD UX007 Revenue (MM)	**$11.0**	**$25.0**	**$51.0**	**$84.0**	**$115.0**	**$152.0**	**$173.0**	**$195.0**	**$208.0**

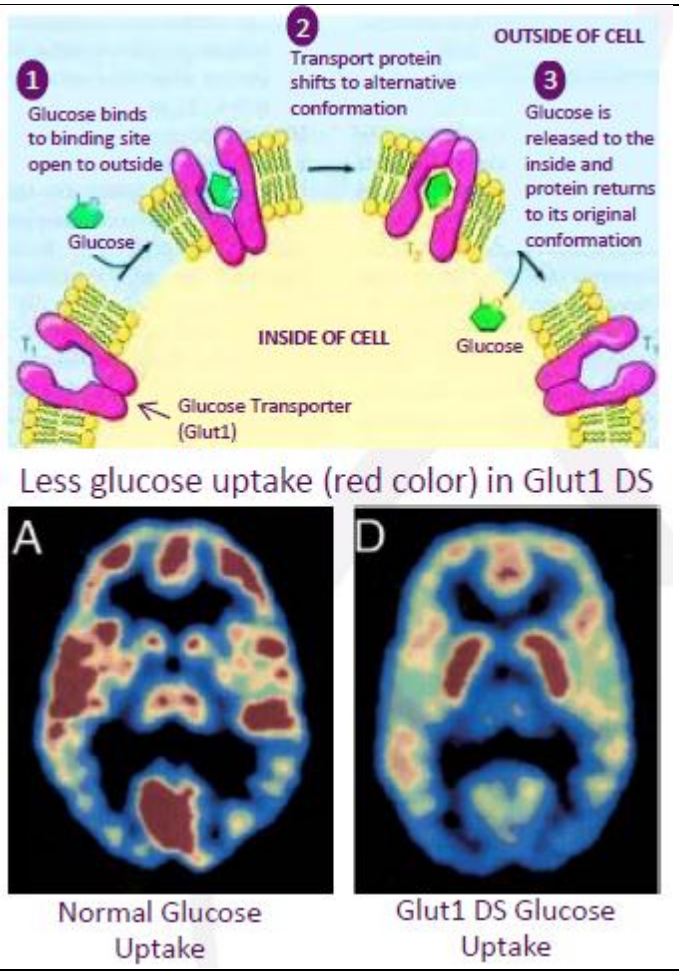
Source: Cowen and Company

GLUT1 Deficiency

Cells in the brain are largely reliant upon circulating glucose for their energy needs. In order to obtain glucose from the circulation, it must be actively transported across the blood-brain barrier using a glucose transporter (Glut1). Mutations (generally in SLC2A1) cause Glut1 expression to be reduced and/or transport efficiency to be compromised, starving the brain of energy. Energy starvation in the brain can result in seizures, movement disorders, and developmental delays. This is termed Glut1 deficiency syndrome (Glut1 DS). A Glut1 DS diagnosis is made by analyzing the glucose concentration in cerebrospinal fluid, testing red blood cells for glucose uptake (Glut1 is also expressed on red blood cells), and/or genetic tests. The U.S. Glut1 DS patient population is believed to be between 3,000 and 7,000, although this number has been rising as an increasing proportion of seizure patients are found to harbor a Glut1 mutation. Severity of symptoms is dependent upon the exact mutation and how significantly it decreases glucose transport across the blood-brain barrier. Symptom severity can range from limited abnormal movements to severe cognitive/developmental defects.

Glut1 DS patients are managed using a ketogenic diet (70-80% of calories from fat; <10% from carbs) and in some patients anti-epileptic drugs. As the name implies a ketogenic diet causes the body to generate ketone bodies. The massive overload of fat causes metabolic pathways to become overwhelmed, and ketone bodies to build up in the bloodstream. Circulating ketone bodies are capable of crossing the blood brain barrier where they are utilized as a glucose alternative. This partially restores the brain's energy supply. Consultants report that a ketogenic diet and/or anti-epileptics suppress approximately 80% of epileptic events and 33% of movement disorders, but generally do not help with cognitive symptoms. Our consultant describes the work of ingesting ~80% of calories from fat as "eating butter all day". This is a difficult task to achieve, and if maintained can lead to pancreatic and hepatic problems from the excessive intake of lipids. Our consultant reports that compliance is difficult and most patients eventually give up. It is unclear if the lack of cognitive performance on ketogenic diets is because of incomplete energy restoration on a ketogenic diet, poor diet compliance, or damage occurring prior to the initiation of therapy.

Glut1 DS Mechanism and Effect

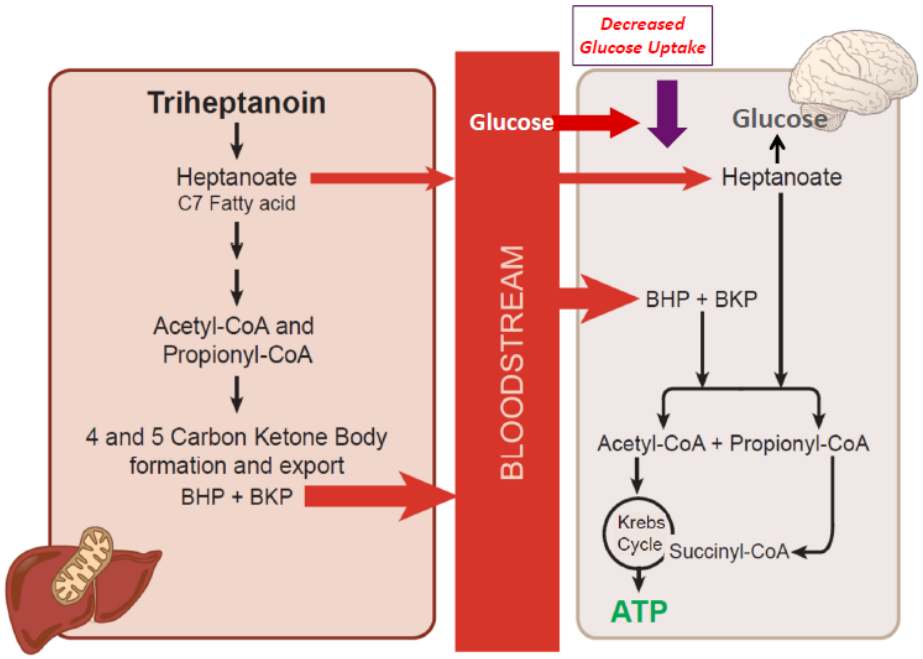


Source: Ultragenyx

Triheptanoin Gets Energy Across the Blood-Brain Barrier

Triheptanoin is metabolized into heptanoate and ultimately ketone bodies. Just as in a ketogenic diet, the ketone bodies are capable of crossing the blood brain barrier where they are utilized as a glucose alternative. Unlike the fats contained in a ketogenic diet, heptanoate is capable of crossing the blood brain barrier. Once in the brain, heptanoate can either be converted into 2 molecules of glucose (the default energy molecule of the brain) or fed into the Kreb's cycle. Importantly, this could provide a more efficient method for getting calories to the brain as compared to a ketogenic diet. As a result of the increased efficiency of energy transfer and the lowered compliance burden, our consultants hope that triheptanoin can not only prevent seizures but also improve movement disorders and possibly even cognitive development.

Triheptanoin's Metabolites Cross the Blood-Brain Barrier

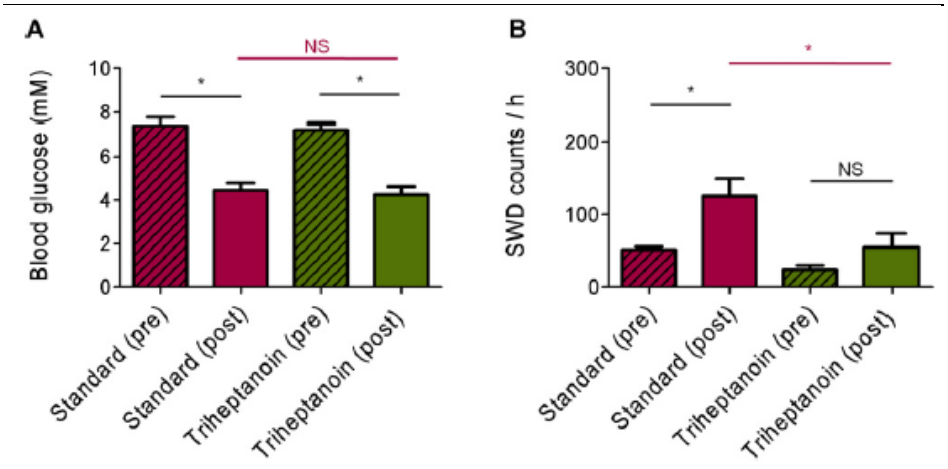


Source: Ultragenyx

Triheptanoin Prevents Seizures In A Mouse Model

Researchers are able to induce seizures in mice by injecting mice with large doses of insulin. This insulin injection causes blood glucose levels to fall precipitously. Low blood glucose translates into glucose starvation in the brain and the onset of seizures. Using this model, Kim *et al.* examined the ability of triheptanoin to supplement the brain's energy needs. Mice were injected with insulin and then fed a standard diet or a triheptanoin containing diet. The insulin injection generated a decrease in blood glucose under both dietary conditions (left panel). When mice were fed a standard diet, the reduced blood glucose corresponded with a significant increase in seizures. However, when mice were fed triheptanoin a significant protection from seizures was observed (right panel).

Triheptanoin Protects Mice From Glucose Deprivation Associated Seizures



Source: Kim TH, et al.

Clinical Experience Indicates Triheptanoin May Work In Humans Too

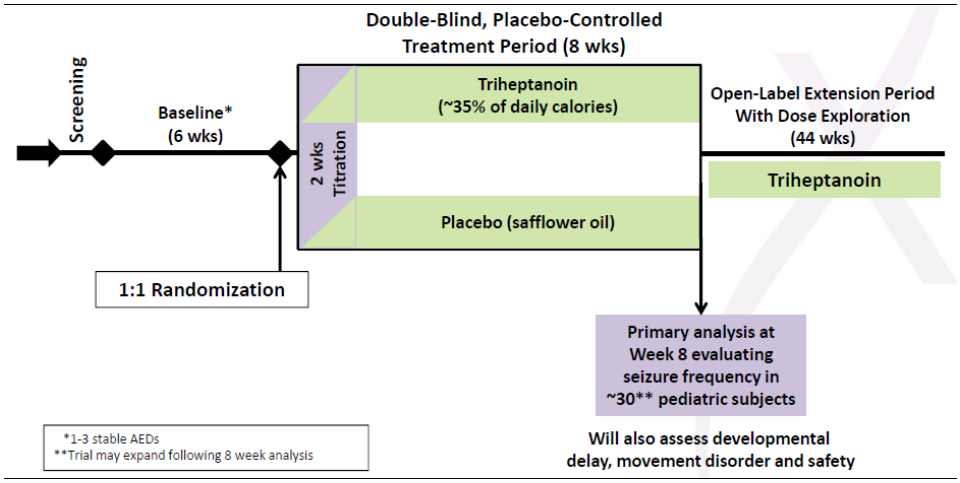
In order for a Glut1 DS therapy to make a meaningful impact on a patient's development it must be safe in the pediatric setting. In the previously described investigator-initiated LC-FAOD studies 51 neonate/pediatric patients have been treated. 23 of these patients have been treated for greater than 5 years. Within this patient population no safety issues have been detected. Dr. Juan Pascual at UT-Southwestern has treated Glut1 DS patients with triheptanoin under an investigator initiated trial. At the Curing The Epilepsies 2013 conference, Dr. Pascual indicated that triheptanoin therapy resulted in an increased oxygen cerebral metabolic rate as observed by MRI, decreased seizures, and improved neuropsychological performance.

Ultragenyx Plans A Phase II Trial in Glut1 DS

In December 2013, the FDA approved Ultragenyx's IND application for triheptanoin for the treatment of Glut1 DS. As of February 2014, clinicaltrials.gov indicates that Ultragenyx has begun enrollment in a Phase II study. The study will enroll 30 Glut1 DS patients aged 3-17 who are either not on or not fully compliant with a ketogenic diet. Management expects these patients to be on 1-3 antiepileptic drugs. Patients will also need to have experienced an average of five observable seizures per month over the past six months. Enrolled patients will be followed for six weeks to establish a baseline. During this period patients must experience at least four observable seizures per month with no 3-week seizure-free period. Patients eligible for the treatment phase will be randomized to receive triheptanoin at a dose of ~35% of caloric intake or placebo (sunflower oil) for a 2-week titration period, and then eight weeks of full treatment. Efficacy will be assessed by monitoring seizure frequency at week 8. Secondary analyses will also be performed using assessments of developmental delays and movement disorders. Data read-out is expected to occur in 2015.

At the 8-week analysis an independent data monitoring committee will review the data and consider expanding the patient enrollment. In fact, the clinicaltrials.gov listing of the trial allows for up to 50 patients. In addition, patients completing this trial will be offered enrollment in an open-label extension study lasting 44 weeks. The extension study is planned to include dose explorations.

Glut1 DS Phase II Trial Design



Source: Ultragenyx

Glut1 DS Market Opportunity Is Substantial

No comprehensive analysis of the incidence of SLC2A1 mutations has been performed. However, published literature suggests there are 3,000-7,000 Glut1 DS patients in the U.S. based upon evaluations of the frequency of seizure disorders and the rate at which Glut1 associated mutations are discovered in these patients. Increasing awareness of alternative/motor forms of Glut1 DS could lead this number to increase over time. We model 5,000 people afflicted with Glut1 DS in the U.S. Given the extreme burden of maintaining a ketogenic diet we estimate just 50% of these patients currently pursue therapy. We project FDA approval and a commercial launch of triheptanoin for Glut1 DS in 2018. Ex-U.S. launches are expected to lag approximately one year behind the U.S. market. Ultragenyx hopes to show an efficacy benefit versus ketogenic diet, but our consultants believe greater convenience combined with non-inferiority will allow triheptanoin to become the dominant therapy in the space. As a result, we project triheptanoin will ultimately achieve a 60% share of the Glut1 DS therapy market. In addition, we model triheptanoin's ease of use expanding the treated population. As in LC-FAOD, we believe the size of the patient population, small molecule nature of triheptanoin, and competitive pressure of dietary options will generate an initial price of $75K/yr for triheptanoin. We model Glut1 DS derived triheptanoin sales in the U.S. of $20MM in 2018 growing to $286MM in 2027. When combined with ROW sales we project a 2027 WW sales opportunity of $572MM. In conjunction with the LC-FAOD indication UX007 has the potential to generate $977MM in revenue for Ultragenyx.

U.S. Glut1 DS Revenue Model

	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
U.S.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
# of Glut1 DS cases (000)	5,000	5,050	5,101	5,152	5,203	5,255	5,308	5,361	5,414	5,468
% on Therapy	*50%*	*55%*	*60%*	*65%*	*70%*	*75%*	*75%*	*75%*	*75%*	*75%*
# on Therapy	2,500	2,778	3,060	3,348	3,642	3,941	3,981	4,021	4,061	4,101
UX007 Mkt Share	*11%*	*20%*	*30%*	*38%*	*45%*	*55%*	*60%*	*60%*	*60%*	*60%*
# on UX007	267	559	919	1,278	1,645	2,173	2,388	2,416	2,436	2,458
Price per patient per year (000)	$75	$79	$83	$87	$91	$96	$101	$106	$111	$116
U.S. Glut1 DS UX007 Revenue (MM)	**$20.0**	**$44.0**	**$76.0**	**$111.0**	**$150.0**	**$208.0**	**$240.0**	**$255.0**	**$270.0**	**$286.0**

Source: Cowen and Company

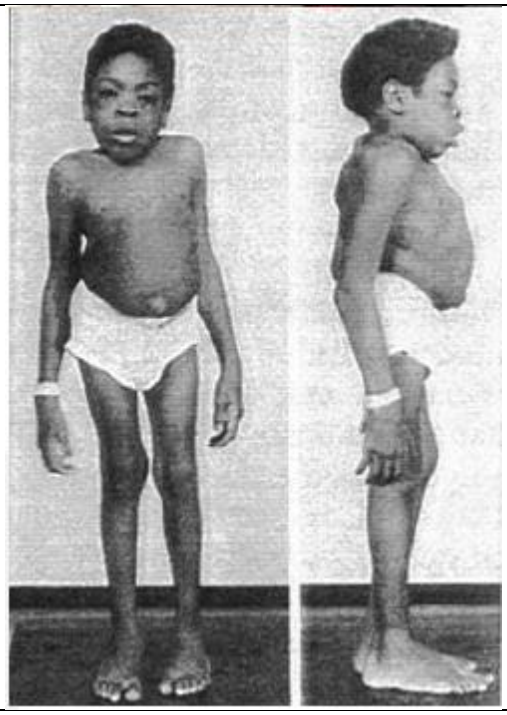
rhGUS: Enzyme Replacement for MPS7

MPS7 is an ultra-rare lysosomal storage disorder characterized by a deficieny in β-glucuronidase activity. In children with the disorder, glycosaminoglycans accumulate in multiple organs. These accumulations lead to numerous progressively worsening symptoms throughout the body, and ultimately an early death ranging from a few weeks after birth up 30 years of age. Ultragenyx is developing UX003, a recombinant human β-glucuronidase for use as an enzyme replacement therapy in these patients. A Phase I/II trial of rhGUS is underway, and an impressive case study has been reported from a treated patient. Interim Phase I/II efficacy data is expected in 2014, with approval occurring as soon as 2017. We model rhGUS as having the potential to generate just over $100MM in WW sales.

MPS7: A Lysosomal Storage Disease That Has Been Left Behind

Mucopolysaccharidosis Type VII (MPS7 or Sly Syndrome) is one of at least 11 mucopolysaccharidosis disorders, a class of multi-system lysosomal storage diseases. These disorders are all characterized by single gene mutations that either eliminate or reduce the functional ability of an enzyme involved in breaking down mucopolysaccharides (a.k.a. glycosaminoglycans or GAGs). In MPS patients, GAGs accumulate inside cells and overtime impair organ function. Approximately 200 patients in the developed world suffer from MPS7, which is characterized by an autosomal recessive inheritance of β-glucuronidase (GUS) deficiency leading to the accumulation of heparin sulfate, dermatan sulfate, and/or chondroitin 4,6-sulfate in multiple organs. Symptoms include an enlarged liver, enlarged spleen, chest deformities, short stature and other skeletal deformities, joint pain, heart disease, corneal clouding, hernias, hearing loss and developmental delay. In addition, the enlarged liver and spleen can combine with an abnormal ribcage to cause lung failure. The progressive lung disease often results in pulmonary insufficiency requiring a tracheostomy. Overtime GAG accumulation in joints causes an evolution in symptoms from tolerable joint pain to severe pain and ultimately the inability to walk. Different GUS mutations are associated with varying severity of the disease. The most severe form, is discovered at birth when the neonate presents with non-immune hydrops fetalis. This is a condition where a massive amount of fluid is retained throughout the body. Non-immune hydrops fetalis is usually fatal with infants rarely surviving beyond a few months of age.

MPS7 Morphological Symptoms



Source: Ultragenyx

rhGUS Following A Well Worn Path

In recent years effective therapies have been developed for four MPS disorders. An additional three (including rhGUS) MPS diseases have therapies in development. All of these therapies are enzyme replacements where a recombinant version of the mutated enzyme is administered via IV. Prior MPS therapies (Aldurazyme, Elaprase, Vimizim, Naglazyme) have logically dealt with the most common of MPS disorders with incidences in the thousands of patients worldwide. With a patient population of approximately 200, MPS7 is an ultraorphan disease and one of the rarest MPS disorders. As such, it has previously been ignored. Ultragenyx is now seeking to replicate the proven MPS enzyme replacement approach by manufacturing recombinant human β-glucuronidase and delivering it to MPS 7 patients via IV.

MPS Diseases

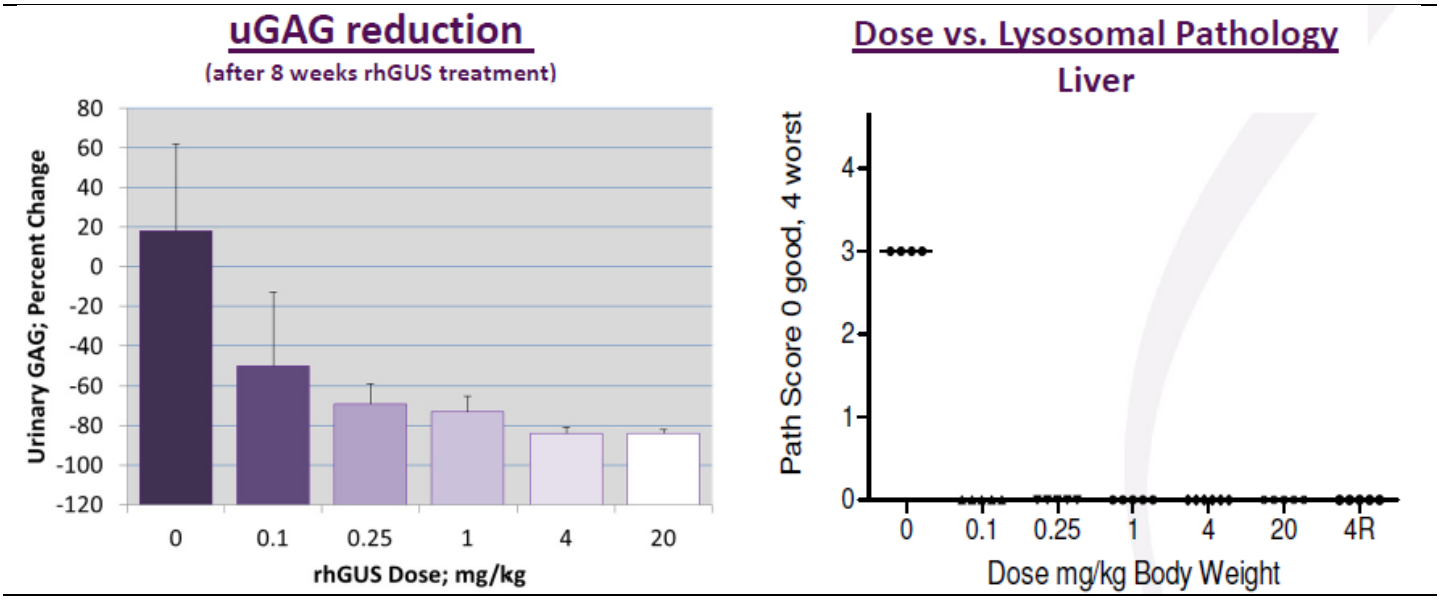
Disease	Incidence/Prevalence	Enzyme Deficiency	Therapy	Company	Stage	2013 Sales (MM)
MPS I	1700 WW	α-L-iduronidase	Aldurazyme (laronidase)	BioMarin	Approved	$162.6
MPS II	2000 WW	iduronate-2-sulfatase	Elaprase (rhI2S)	Shire	Approved	$545.6
MPS IIIA	1:70000 live births	heparan-N-sulfatase	HGT-1410 (rhHNS)	Shire	Phase IIb	N/A
MPS IIIB	1:140000 live births	α-N-acetylglucosaminidase	SBC-103 (rNAGLU)	Synageva	Preclinical	N/A
MPS IIIC	1:1000000 live births	acetyl-CoA-glucosaminide acetyltransferase				
MPS IIID	1:1000000 live births	N-acetylglucosamine 6-sulfatase				
MPS IVA	3000 WW	N-acetylgalactosamine 6-sulfatase	Vimizim (rhGALNS)	BioMarin	Approved	N/A
MPS IVB	1:75000 live births	β-galactosidase				
MPS VI	1250 WW	arylsulfatase B	Naglazyme (rhARSB)	BioMarin	Approved	$271.2
MPS VII	200 WW	β-glucuronidase	UX003 (rhGUS)	Ultragenyx	Phase I/II	N/A
MPS IX	1 WW	hyaluronidase				

Source: Cowen and Company

rhGUS Is Active In A Mouse Model Of MPS7

Enzyme replacement therapies are simple in theory. However, when generating a recombinant gene construct that effectively produces the enzyme *in vitro*, developing a purification protocol that maintains enzyme activity, and achieving enzyme uptake within the target tissue(s), significant issues can arise. Using a mouse model of MPS7, Ultragenyx has demonstrated that it has overcome these hurdles with UX003. MPS7 mice were treated with 0-20mg/kg of IV rhGUS every week for 8 weeks. Following treatment with rhGUS, the recombinant enzyme was found in numerous tissues including the brain, bone, heart, kidney, liver, lung, muscle and spleen. In addition, GAG accumulation in the urine (uGAG) was reduced >80% at some doses. Finally, lysosomal liver pathology was eliminated.

MPS Diseases



Source: Ultragenyx

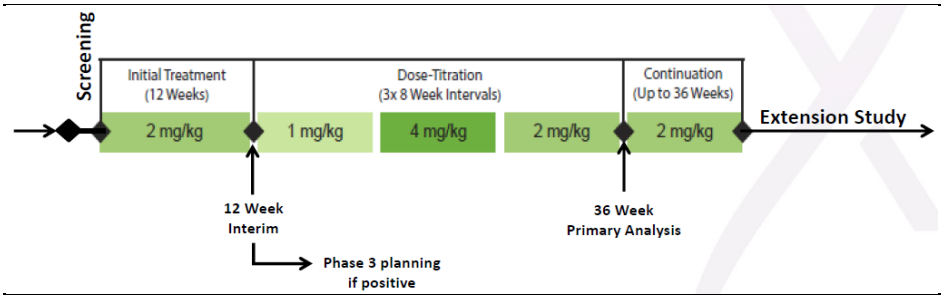
Phase I/II Trial Of rhGUS Underway

In December 2013, Ultragenyx initiated a Phase I/II trial of rhGUS in 4-5 MPS7 patients aged 5-30 years of age with at least two of these patients aged 20-30. Patients will be treated with 2mg/kg of UX003 for an initial treatment period of 12 weeks. An interim efficacy assessment will be performed following this 12 week period. Data from this stage is expected in 2014. The initial treatment period will then be followed by a dose titration phase which consists of a series of three 8-week treatment intervals at 1mg/kg, 4mg/kg, and finally 2mg/kg. After a total of 36 weeks of treatment the primary efficacy analysis will be performed (a continuation phase will treat patients for up to an additional 36 weeks). In addition to a safety analysis, the primary efficacy endpoint is uGAG excretion at 36 weeks. Secondary endpoints, include a 6 minute walk test, 3 minute stair climb, pulmonary function (FVC, FEV1, and MVV1), height/weight growth, and shoulder range of motion. Given the complete lack of approved therapies, management believes "success" is any statistically significant change in uGAG. Nonetheless, management is looking for a dose which achieves >50% reduction in uGAG. Importantly, the EMA has already agreed to uGAG as a valid

Phase III primary endpoint. Management reports that FDA discussions on this topic will occur after the accumulation of at least the interim 12 week treatment data. Management expects to move directly to a Phase III trial if activity is observed in the Phase I/II trial. Ultragenyx anticipates that a Phase III trial might enroll ~12 patients for a total data package of <20 patients.

At the World Lysosomal Disease Network Symposium in February 2014, Ultragenyx presented a case study of a 12-year old patient with advanced MPS7 who was treated with rhGUS under an emergency IND. At baseline, this patient presented with respiratory insufficiency. Following 14 weeks of treatment, the patient showed a reduction in uGAG, liver size, spleen size, improvement in pulmonary function. Caregivers reported improved stamina and an increase in time spent at school. No infusion-associated reactions were reported.

rhGUS Phase I/II Trial Design



Source: Ultragenyx

MPS7 Might Be A ~$100MM Opportunity

Given the small patient numbers required and the relatively short timelines for a pivotal trial, we anticipate rhGUS being approved by the FDA in late 2017, with ROW approvals following shortly thereafter. Due to the severity of disease and the complete lack of alternative treatment options, we anticipate rhGUS rapidly achieving near universal use among MPS7 patients. As an enzyme replacement therapy for an ultra-orphan disease rhGUS should garner ultra-premium pricing. We model initial pricing of approximately $500K/yr in the U.S. We anticipate rhGUS will produce $29MM in revenue during 2018 (its first full year on the market) and increase to greater than $100MM by 2025.

MPS7 Revenue Model

	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
U.S.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11
# of MPS 7 cases	85	86	87	88	88	89	90	91	92	93	94
UX007 Mkt Share	*26%*	*45%*	*64%*	*75%*	*79%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*
# on UX007	22	38	55	66	70	76	77	77	78	79	79
Price per patient per year (000)	$500	$520	$541	$562	$585	$608	$633	$658	$684	$712	$740
U.S. Glut1 DS UX007 Revenue ($MM)	**$11.0**	**$20.0**	**$30.0**	**$37.0**	**$41.0**	**$46.0**	**$48.5**	**$51.0**	**$53.5**	**$56.0**	**$58.8**
R.O.W.											
# of MPS 7 cases	115	116	117	118	120	121	122	123	125	126	127
UX007 Mkt Share	*0%*	*15%*	*36%*	*56%*	*65%*	*71%*	*75%*	*75%*	*75%*	*75%*	*75%*
# on UX007	0	18	42	66	78	86	91	92	93	94	95
Price per patient per year (000)	$500	$500	$500	$500	$500	$500	$500	$500	$500	$500	$500
R.O.W. Glut1 DS UX007 Revenue (MM)	**$0.0**	**$9.0**	**$21.0**	**$33.0**	**$39.0**	**$43.0**	**$45.5**	**$46.0**	**$46.5**	**$47.0**	**$47.5**
Total WW UX007 Revenue (MM)	**$11.0**	**$29.0**	**$51.0**	**$70.0**	**$80.0**	**$89.0**	**$94.0**	**$97.0**	**$100.0**	**$103.0**	**$106.3**
% growth Y/Y		*164%*	*76%*	*37%*	*14%*	*11%*	*6%*	*3%*	*3%*	*3%*	*3%*

Source: Cowen and Company

SA-ER: Pumping Up Muscle Strength By Restoring Sialic Acid

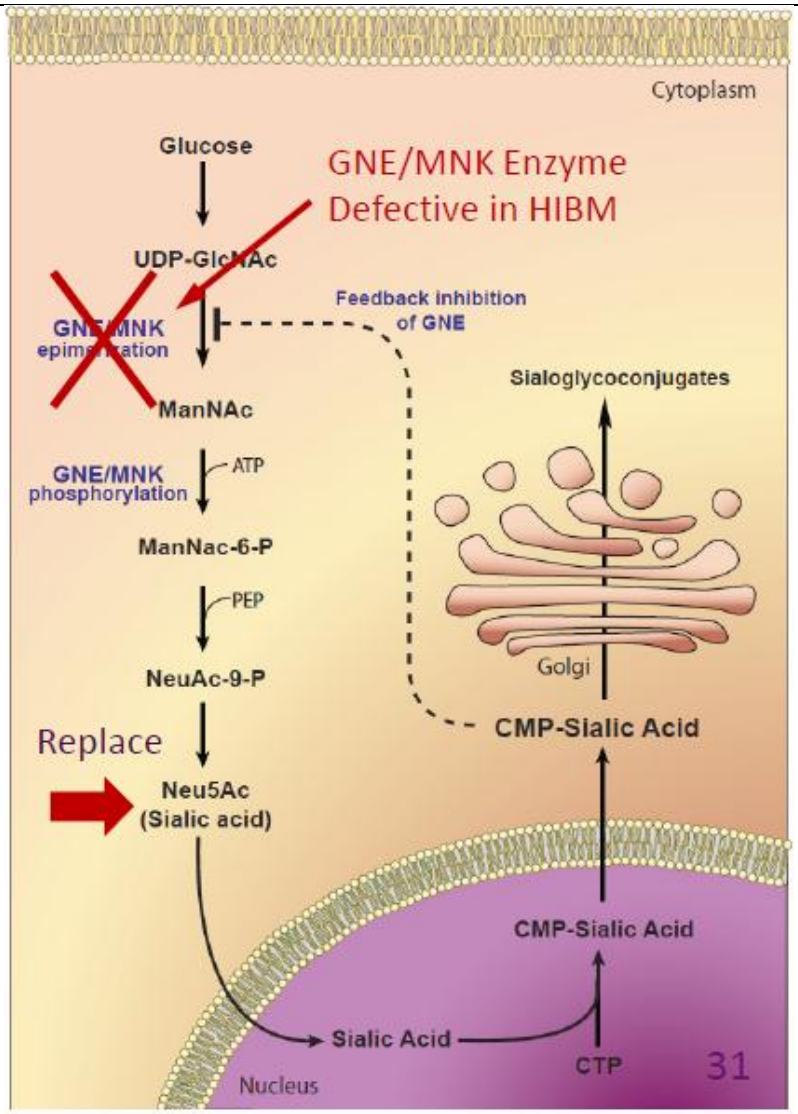
Hereditary Inclusion Body Myopathy (HIBM) is a rare progressive muscle disease that presents in the late teens or twenties and ultimately leads to the loss of major muscle function. HIBM is caused by mutations that reduce/eliminate GNE/MNK epimerase or kinase activity. The defect in GNE/MNK activity blocks sialic acid biosynthesis, which is believed to lead to the generation of the hallmark inclusion bodies. Ultragenyx is developing UX001, an extended-release formulation of sialic acid, for HIBM. SA-ER is designed to bypass the GNE/MNK blockade of sialic acid biosynthesis, thereby restoring normal muscle function. SA-ER has produced intriguing albeit inconclusive Phase II results. In December 2013, Ultragenyx extended the Phase II trial to include a higher total sialic acid dosage. This higher dosage will be achieved by combining immediate release sialic acid with UX001's extended release formulation. Data from this expansion is expected in late 2014.

HIBM: A Progressive Muscular Myopathy

Hereditary Inclusion Body Myopathy (HIBM) is a disease of the muscle fibers that leads to progressive muscle atrophy. While HIBM is inherited, it generally does not generate symptoms until the late teens or twenties. HIBM patients have a mutation that eliminates or reduces the activity of GNE/MNK and causes characteristic inclusion bodies in muscle cells and the progressive break down of muscle fibers, leading to muscle atrophy and ultimately disability from a lack of motor function. Different mutations cause variations on this disease, with particular muscles affected and/or spared although generally muscle atrophy starts in the legs and progresses to other muscles. The mechanism by which GNE/MNK mutations lead to inclusion bodies and HIBM symptoms is not fully understood. However, GNE/MNK is known to play a vital role in sialic acid biosynthesis and HIBM patients are known to be deficient in this sugar that is often attached onto proteins to create functionality. Mouse models of HIBM show improvements in phenotype following sialic acid supplementation. Consequently, Ultragenyx is developing an extended release oral formulation of sialic acid, UX001 or SA-ER.

HIBM's prevalence in the general population is not well defined. Some ethnic groups are known to have a high prevalence of HIBM. For example, within the Persian Jewish population it is estimated that 1:1600 people have or will develop HIBM. Ultragenyx has performed surveys of U.S. myopathy clinics to gain a better understanding of HIBM's prevalence. Management reports that these surveys suggest 300-400 HIBM patients reside in the U.S. corresponding to a total of 1200-2000 worldwide.

GNE/MNK and Sialic Acid Biosynthesis



Source: Ultragenyx

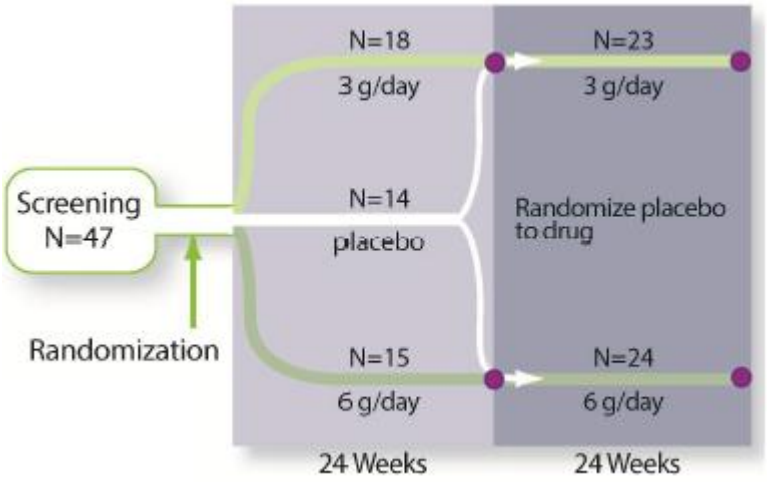
SA-ER Phase II Data Show Modest Benefits

Ultragenyx is in the midst of a Phase II double-blind trial for UX001 in HIBM. For this trial 46 HIBM patients were initially randomized to placebo, 3g/day of SA-ER, or 6g/day of SA-ER for 24 weeks. After 24 weeks, placebo patients were randomized to begin receiving SA-ER at either 3g/day or 6g/day. In addition to testing safety, the trial includes assesments of muscle strength, mobility, function, self-reported levels of

disability, and changes in quality of life. At 24 weeks, a modest dose-dependent positive effect on muscle strength (particularly at the upper extremities) was observed. As expected the placebo group's muscle strength declined over this period. The treatment effect was most pronounced in patients with greater walking ability (>200m in the 6 minute walk test) at baseline. Creatine kinase (a marker of muscle cell lysis) levels also trended towards improvement in the 6g/day group compared to placebo. Muscle biopsies designed to evaluate the effect of SA-ER on protein sialylation were inconclusive. No SAEs were observed during the first 24 weeks of treatment.

In December 2013, Ultragenyx released results of the full 48 week analysis. At this time point, improved trends were observed relative to the 24 week check. The 6g/day group experienced an increase in upper extremity muscle strength, while the 3g/day group experienced a decline in muscle strength. The difference between groups in the change in muscle strength from baseline was statistically significant. Management reports that the treatment effect was also greater in patients with less advanced disease. When lower extremity muscle strength was tested, no statistically significant treatment effect was observed. The patient reported GNE Myopathy Functional Activity Scale, generated a trend towards improvement in the 6g/day group versus the 3g/day group although statistical significance was not reached. No significant changes in the 6 minute walk test were observed. Finally, no SAEs were observed in either dose group. The most common AE was gastrointestinal upset. Full data is expected to be presented at a medical conference in 2014.

UX001 Phase II Trial Design



Source: Ultragenyx

Given the more encouraging results at 48 weeks, Ultragenyx has extended the trial with all patients being dosed with 6g of UX001 plus 6g of immediate release sialic acid per day. All 46 patients from the original Phase II trial have elected to continue and Ultragenyx has added 10 additional previously treatment-naïve patients. Data from the extension study is expected in late 2014.

SA-ER's Future Still Coming Into Focus

While laboratory studies provide a strong logic behind the sialic acid biosynthesis hypothesis, it is not a certainty that repairing/bypassing the sialic acid biosynthesis

pathway will benefit HIBM patients. SA-ER has generated some positive signals, but nothing dramatic enough to support a model build-up. SA-ER's future development will hinge on the results of the higher doses and longer treatment durations of the Phase II extension trial.

NIH Working on Its Own Sialic Acid Therapy

NIH and its partner New Zealand Pharma are also developing a potential HIBM therapy based upon the sialic acid hypothesis. The synthesis of sialic acid from glucose is a multistep process. Several of these steps occur beyond the GNE/MNK mutation generated biosynthetic blockade. While Ultragenyx seeks to replenish sialic acid directly, NIH and New Zealand Pharma seek to deliver N-acetyl mannosamine (ManNAc) the immediate byproduct of GNE/MNK's normal function in sialic acid biosynthesis. Since the remainder of the sialic acid biosynthesis pathway is intact in HIBM patients, pharmacologically supplied ManNAc should be converted to sialic acid within the cell. A Phase I trial for ManNAc was completed in July 2013. Ultragenyx anticipates a Phase II trial being initiated although NIH has not announced its plans.

Valuation Methodology And Risks

Valuation Methodology

Biotechnology:
In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

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Investment Risks

Biotechnology:
There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Risks To The Price Target

Investing in development stage biotechnology companies is risky, and many things could prevent Ultragenyx from achieving the success we model.

Addendum

Stocks Mentioned In Important Disclosures

Ticker	Company Name
EXEL	Exelixis
SNSS	Sunesis Pharmaceuticals
RARE	Ultragenyx

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Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

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Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

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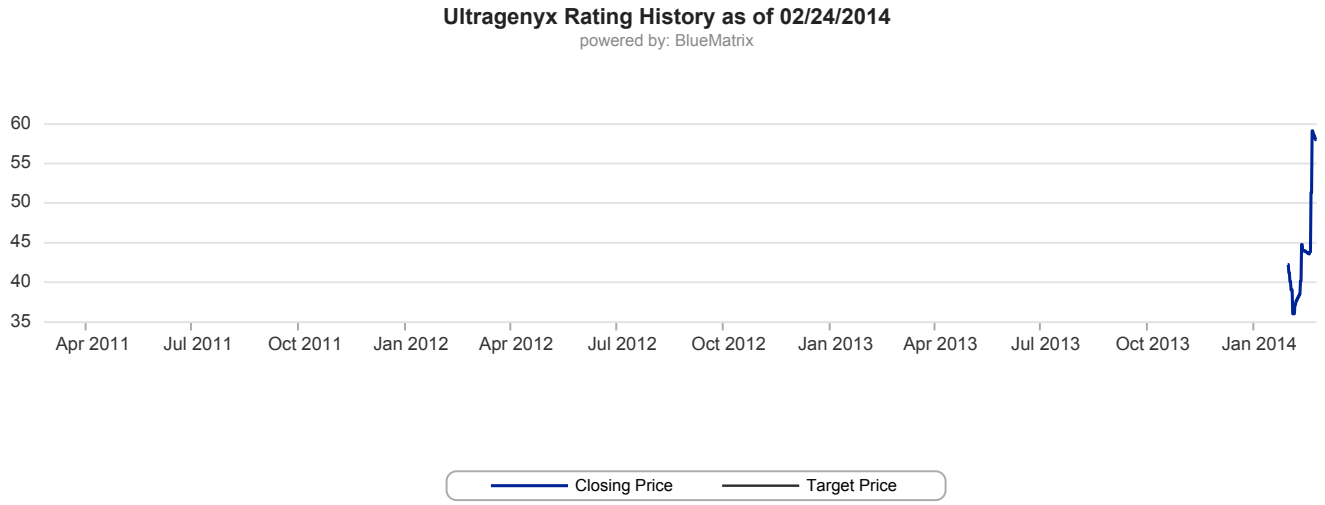

Exelixis Rating History as of 02/24/2014
powered by: BlueMatrix

Rating Change - 2/21/2006 - Rating Outperform

Sunesis Pharmaceuticals Rating History as of 02/24/2014
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Rating Change - 2/21/2006 - Outperform Rating

Legend for Price Chart:

I = Initation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | UR = Price Target Under Review | T = Terminated Coverage | $xx = Price Target | NA = Not Available

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