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BUY ALERT

UniQure: A Dark Horse in the Gene Therapy Field

By Zack Fink

- **Look to buy uniQure (QURE) at ~$20 ahead of 2015 events, including phase I/II hemophilia B data expected mid-2015 and Glybera EU commercial launch. UniQure is differentiated from other gene therapy companies because of commercial launch revenue and manufacturing capabilities, on the order of a few million Euros in year one.**
- **UniQure provides for a trade into AMT-060 Hemophilia B data, OR long-term opportunity. We view QURE as a gene therapy leader (partnership with 4D molecular therapeutics and scalable, in-house manufacturing).**
- **Spark Therapeutics' (ONCE) IPO on January 30 was HOT. $50 share price at Friday's close values the company at $1.2 billion. uniQure is a $375 million company, and these two companies' commercial-stage and development programs are QUITE similar. We suspect the valuation disparity will begin to close this year into hemophilia data for QURE.**
- **Understand that QURE is high-risk into hemophilia B data (we outline our bullish outlook here), but QURE could have Options listed in the next 6 months to allow for a hedge. In the interim, equity is our only vehicle.**

[Gene therapies will be a key theme in 2015 for healthcare investors, thus it's worth knowing the field. We suggest revisiting our prior resarch on bluebird bio (BLUE) **for additional background.]**

UniQure NV (QURE) is a Dutch **commercial-stage biotechnology** company pioneering therapeutics in the gene therapy field, also the developer of **Glybera**, the first and only gene therapy product to receive regulatory approval in the European Union. Despite this, **uniQure carries a comparatively low valuation next to clinical-stage gene therapy peers,** many of which have gone public only in the last two years. These include **bluebird bio (BLUE), Avalanche (AAVL),** and most recently **Spark Therapeutics (ONCE)** Spark priced its initial public offering at $23 on Thursday and traded as high as $51.9 in the Friday

session, valuing this latest gene therapy entrant at ~$1.2B (closing price of $50).
We see uniQure as a dark horse in the field, in-part because of numerous catalysts in 2015 that will put fresh eyes on this European company. UniQure IPO'd in early 2014 and only began to capture attention in the second half of the year.

Our investment thesis centers around the fact that uniQure is a **commercial-stage, fully integrated (manufacturing) gene therapy company** with two value-driving events this year: Glybera's European commercial launch in the 1st quarter of 2015 and phase I/II data for uniQure's hemophilia B product candidate around mid-2015.

UniQure's hemophilia B program is marginally lagging a similar therapeutic at **Baxter International (BAX),** and Baxter could have data on its own program sometime this year. "When" is a complete unknown. Meanwhile, Spark will also bring its hemophilia B candidate into the clinic this year. Spark has captured the attention of Wall St, in-part, because the hemophilia program is partnered with Pfizer (PFE). That's certainly compelling, but we outline in this report why uniQure may have a leg up on the competition. Finally, we point to the valuation disparity between QURE and SPARK - $375 million vs $1.2 billion. We suspect this gap will continue to close in 2015.

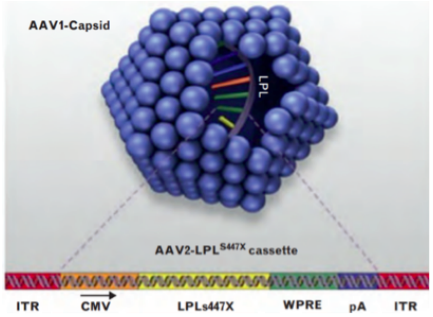
Glybera: The first gene therapy approved in the EU for the treatment of severe LPLD

Lipoprotein lipase deficiency (LPLD) is a rare autosomal recessive genetic disease caused by diminished or absent LPL enzyme protein expression - a result of a mutated LPL gene. The LPL enzyme is required by tissues in the body to process chylomicrons, also called triglyceride-carrying (fat) particles. Without adequate LPL enzyme activity, chylomicrons will build up in the blood potentially leading to severe hyper-chylomicronemia and chronic pancreatitis. Relatively large chylomicrons clog pancreatic ducts leading to painful and potentially life-threatening pancreatic inflammation. Individuals diagnosed with LPLD are required to adhere to an extremely low-fat diet and abstain from alcohol to ameliorate the chances of severe chronic pancreatitis.

The therapeutic goal of treating LPLD is to lower chylomicron blood plasma concentrations, after which pancreatic ducts have a lower chance of becoming clogged, thus reducing the risk of potentially life-threating pancreatitis and LPLD-related complications. In theory, LPLD could be treated with LPL-enzyme replacement therapies; however, this has thus far not been possible due to the short half-life of the enzyme.

Prior to Glybera's EU approval, there was no approved therapy for the treatment of LPLD.

What is Glybera?



Glybera (Alipogene tiparvovec) is designed to restore LPL enzyme activity **by delivering the functional human LPL gene variant LPLS447X in a replication-deficient recombinant adeno-associated virus serotype 1 (rAAV1) vector (shown above)**. The Glybera drug product is a sterile solution for injection presented in single-use vials containing 3E12 genomic copies (gc) of alipogene tiparvovec. Glybera is administered once at multiple intramuscular injection sites at a dose of 1E12 [gc/kg].

Glybera Clinical Trial and Regulatory Overview

Glybera was tested in 3 early clinical trials. These three trials formed the basis for uniQure's (then known as Amsterdam Therapeutics) marketing authorization application in the EU for Glybera in December of 2009. The EMA rejected the application, and it was not until October 2012 – after lengthy back in forth between uniQure and regulatory agencies – that Glybera received marketing authorization from the EMA for use in individuals diagnosed with severe LPLD. The EMA initially rejected Glybera due to insufficient evidence of a clinical benefit. It was not until the data matured (longer-follow-up), and combined data from all three trials were available, that there was sufficient evidence of Glybera's long-term clinical benefit to warrant an approval. These three trials are summarized in the table below:

Glybera Early Clinical Summary			
	AMT-10-01 [1]	**AMT-11-01** [2]	**AMT-11-02** [3]
Product	AAV1-LPL^{S447X} (mammalian mfg.)	Glybera (baculovirus mfg.)	Glybera (baculovirus mfg.)
Trial Design	Phase I open-label dose escalation	Phase II open-label dose escalation	Phase II/III open-label + immunosuppressive regimen
Efficacy Endpoint	>40% Reduction in fasting plasma triglycerides	>40% reduction in fasting plasma triglycerides 3-12 weeks after therapy	>40% reduction in fasting plasma triglycerides 12 weeks after therapy Achieve improved clearance of

			post-prandial chylomicrons
Dose	1E11 [gc/kg] (n=4) 3E11 [gc/kg] (n=4)	3E11 [gc/kg] (n=2) 3E11 [gc/kg] + immunosuppressive regimen (n=4) 1E12 [gc/kg] + immunosuppressive regimen (n=8)	1E12 [gc/kg] (n=5)
Results	All subject demonstrated a reduction in fasting plasma triglycerides (3/8 subjects had >40% reduction)	7/14 subjects achieved the primary endpoint of >40% reduction in fasting plasma triglycerides	3/5 patients demonstrated reduction in post-prandial chylomicrons at week 12 and week 52
Safety	Well tolerated with No SAEs	Well tolerated, 1 SAE related to drug product: Fever after drug administration (resolved within 12h)	1 SAE (high prob. of pulmonary embolism) potentially related to drug product
Other	Dose-dependent AAV1 capsid T-cell response	9/14 subjects experienced moderate and non-persistent AAV1 capsid T-cell response	

The EMA has required that uniQure complete a post-approval clinical trial and establish a patient registry to continue assessing the long-term clinical benefit of Glybera. Despite having not initiated this trial yet, uniQure has continued to demonstrate and assess the long-term benefit of Glybera in a fourth clinical trial, AMT-011-03. This is a long-term follow-up study that enrolled 19 individuals previously treated with Glybera. In June of 2014, uniQure released a retrospective analysis of these individuals that compares an equal time period of up to six years before and after Glybera treatment. The compares documented pancreatitis and abdominal pain events and resulting hospital stay (in days):

n =19	Pre-treatment (up to 6 years)			Post-treatment (up to 6 years)		
	Events	Rate (events/year)	Total hosp. days	Events	Rate (events/year)	Total hosp. days
Documented pancreatitis	19	0.21	143	10	0.11	75
Abdominal pain consistent with pancreatitis	18	0.20	116	11	0.12	107

In summary, this long-term follow up data demonstrated that [4]:

- Glybera led to an approximate 40-50% reduction in post-treatment pancreatitis events and abdominal pain events consistent with pancreatitis.
- **No severe pancreatitis up to six years after Glybera treatments**
- An approximate 50% decrease in hospitalization rate and number of days spent in hospital following Glybera treatment, including only one ICU stay.
- **Glybera was generally well-tolerated with no identifiable long-term safety concerns.**

We believe this data further validates the clinical benefit, clinical efficacy, and quality of life improvement experienced by individuals following Glybera treatment. We believe this data should assist in facilitating adoption of Glybera as a treatment for patients diagnosed with severe LPLD.

UniQure has entered into a commercialization agreement with Chiesi for Glybera (and for hemophilia B, discussed below) in the European Union (EU). Of note, uniQure receives 20-30% royalties on EU Glybera net sales. UniQure retains full product rights to Glybera in the US, Canada, and Japan.
We view Glybera as a revenue-generating asset that will bring in a few million euros in its first year on the market to support operating expenses - we do not view Glybera as a major top- or bottom-line driver in 2015. With a total population of 500 million in the EU and an LPLD incidence of 4.6 patients per million (estimates from uniQure), there may be as many as 2300 LPLD patients in the EU. We assume approximately 50% of diagnosed individuals have severe pancreatitis/LPLD, for about 1150 severe LPLD patients in the region. Approximating 50% of individuals seek treatment and are amenable to Glybera, and modeling 2% market penetration in year one with a price of $1.0m and 30% royalties from Chiesi, this comes out to ~$3.45m in royalties in the first year. We have low expectations for the Glybera launch given this is the first commercial gene therapy product, but would be pleased to see even a handful of patients having undergone therapy by the end of the year. Again, we view the program as offering non-dilutive support to uniQure's R&D efforts.

AMT-060: uniQure's Hemophilia B Program

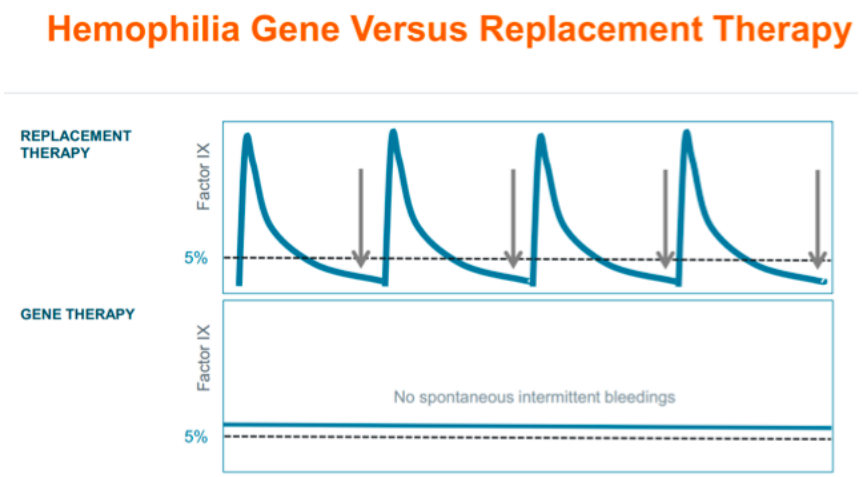
UniQure – in collaboration with Chiesi – is developing an AAV gene therapeutic to treat hemophilia B. UniQure has entered into a co-development and commercialization agreement in the EU with Chiesi for this program (UniQure retains full product rights worldwide non-EU). UniQure and Chiesi share equally in development costs associated with the program, and uniQure will receive between 25 and 35% royalties on future sales. We view this program as meaningful because of the market opportunity and the (very modest) validation it could have for a gene therapy in hemophilia A, a larger market opportunity for uniQure (discussed further below). Hemophilia B affects around 28 thousand individuals globally. Approximately 19.6 thousand of these individuals, those with mild or severe hemophilia (70% total), could be eligible for gene therapy. Adjusting 50% for eligibility criteria, uniQure's target population could be 9,800 individuals worldwide. With a gene therapy priced at a modest $500,000, single-administration "cures" for hemophilia could generate on the order of $5 billion worldwide

What is Hemophilia B?

Hemophilia B is a genetic disorder affecting the gene encoding human coagulation factor IX (FIX). FIX is a critical protein for proper blood clotting. Defects in the FIX gene results in severe Hemophilia B patients producing <1% of normal FIX concentration. This low concentration results in frequent spontaneous bleeding episodes which are associated with significant disease burden, poor quality of life, and early death [5]. Current standard of care treatment for Hemophilia B involves prophylactic FIX protein concentrate injections in order to prevent bleeding episodes. FIX protein therapy only offers a *degree* of protection and certainly does not provide the opportunity for a cure. In addition, prophylactic FIX concentrate therapy is extremely expensive; is associated with its own side effects such as FIX inhibitor formation; reduces quality of life because of treatment burden; and still lacks adequate protection from bleeding episodes:

The graph on the left is FIX concentration (y-axis) vs. time (x-axis) for typical prophylactic FIX concentrate therapy. This graph shows how prophylactic FIX concentrate therapy results in high FIX concentration for a short amount of time, however, this high FIX concentrate dissipates in an exponential fashion. This produces prolonged periods of time **where individuals on prophylactic FIX concentrate therapy have a concentration of FIX that is <1% of normal FIX levels.** As shown in the above right graph, the longer individuals with hemophilia B have FIX levels below 1% of normal per week, the greater the number of predicted bleeding episodes per year [6].

UniQure, with its academic partner St. Jude Children's Research Hospital, have pioneered a gene therapy for hemophilia B that could act as a 'one time treatment.' Hemophilia B is an ideal target for gene therapy because it is molecularly well understood. It is the result of a single gene defect, and **very moderate increases in FIX concentration (increase in >1% of normal) can result in significant decrease in disease burden. The goal of gene therapy for hemophilia B is for the patient to produce constant endogenous FIX protein in host cells, preventing FIX concentration from dropping below 5% of normal** – below 5% and a diagnosed individual is at risk for spontaneous bleeding episodes. The graphic below compares prophylactic FIX concentrate replacement therapy to theoretical gene therapy outcomes [6]:

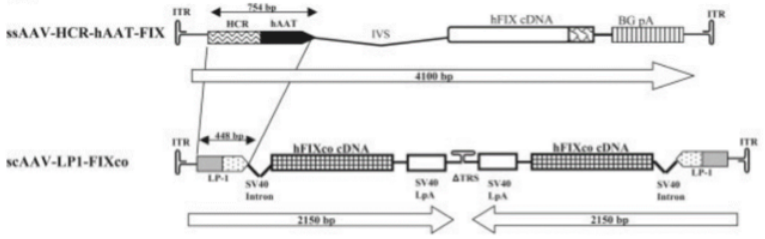


In 2008, UniQure entered into a license agreement with St. Jude which granted UniQure an exclusive license to patent rights relating to expression of human FIX in gene therapy vectors. In addition, this license agreement granted UniQure exclusive rights to make, import, distribute, use, and commercialize products containing human FIX covered by the patent claim in the field of gene therapy for hemophilia B. St. Jude's initiated a phase I/II trial of scAAV2/8-LP1-hFIXco in hemophilia B patients in 2010, pioneering the use of self-complementary AAV vectors (scAAV). scAAV2/8-LP1-hFIXco is a self-complementary serotype 2/8 AAV vector carrying a transgene that includes a codon-optimized human FIX gene. The scAAV2/8-LP1-hFIXco transgene also contains the liver specific promoter LP1, **which limits the FIX gene expression to only hepatocytes.** scAAV2/8-LP1-hFIXco has been robustly characterized and validated in multiple preclinical models [7-9].

scAAV2/8-LP1-hFIXco Pre-clinical data package

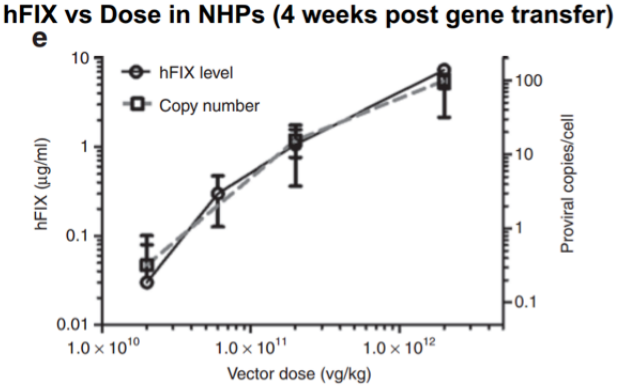
In the first preclinical study of the original therapeutic, *Nathwani et al* demonstrated the benefits of utilizing scAAV vectors over rAAV vectors. More specifically, the authors also demonstrated in the non-human primate model the robust improvement of scAAV2/8-LP1-hFIXco over previous rAAV gene therapeutics

for hemophilia B. The key reason for utilizing scAAV vectors lies in working around the rate limiting step of traditional rAAV vectors - transcription of the ssDNA transgene into dsDNA. A graphical depiction of the ssDNA transgene used in the rAAV hemophilia B trial (above) and of the self-complementary transgene used in the scAAV2/8-LP1-hFIXco construct is below [7].



Of note, these first two studies were the first proof of concept studies of scAAV in hemophilia B that demonstrated a dose-dependent, therapeutic expression in the NHP model using both scAAV2/8 and scAAV2/5 constructs [7-8].

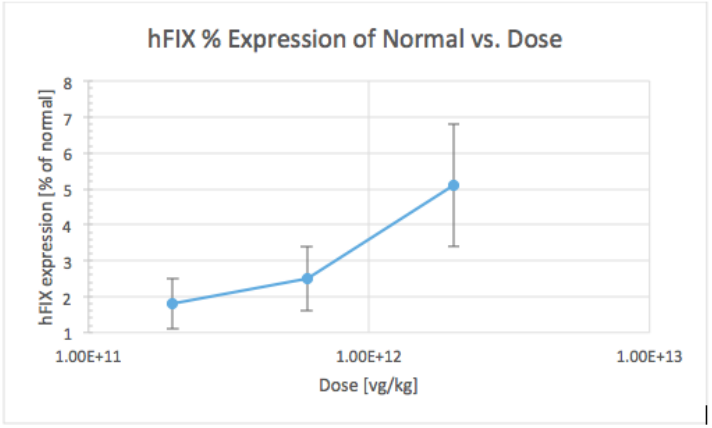
Nathwani et al expanded on this promising preclinical data by administering scAAV2/8-LP1-hFIXco to a larger cohort of NHPs (n=24), confirming the dose-dependent hFIX expression (shown below). In addition, scAAV2/8-LP1-hFIXco was well-tolerated at all doses, with expression measured out at least 5 years [9].

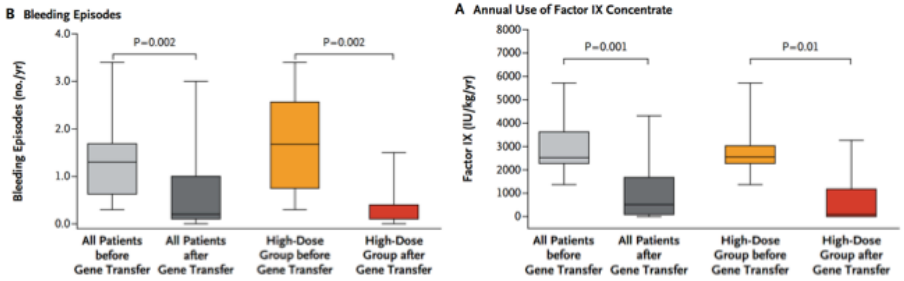


Following these impressive pre-clinical results, **St. Jude Children's Research Hospital began enrolling severe Hemophilia B patients in a phase I/II clinical trial in 2010**.

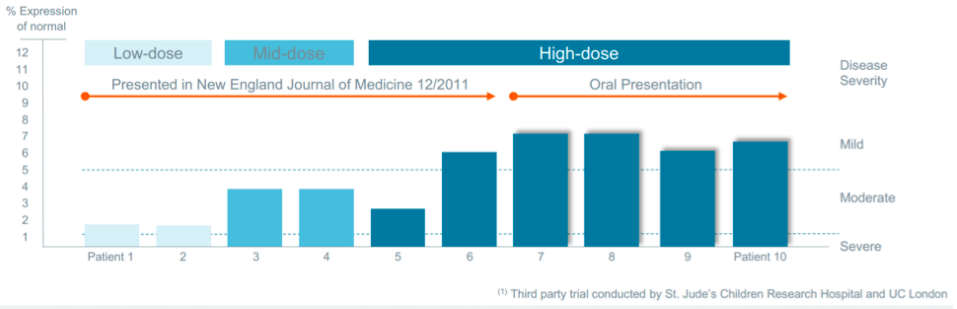
St. Jude's Phase I/II scAAV2/8-LP1-hFIXco

Initial data from this phase I/II study were published in the New England Journal of Medicine (NEJM) in 2011, with long-term follow up data published in NEJM in 2014 [10-11]. **This first-in-human clinical trial confirmed that the dose-dependent hFIX production in NHPs translated into a dose-dependent hFIX production and clinical efficacy in humans (total n=10)**:





As a reminder, **hemophilia B complications can be significantly ameliorated (along with a significant decrease in hFIX usage) with only a very modest (>1%) increase in hFIX expression**. **As shown below, increasing long-term hFIX expression by just 1% of normal transitions a severe hemophilia B patient into the moderate hemophilia B phenotype, a highly clinically relevant improvement.**



Notably, **the high dose cohort (n=6) had a steady-state plasma level of hFIX equal to 5.1% of normal. This translated into statistically significant reductions in annual hFIX concentrate usage and the annual number of bleeding episodes, 96% (p=0.03) and 94% (p=0.03) respectively**. This high-dose cohort also showed a capsid-specific T-cell response to the AAV2/8 vector. Minor complications

related to immune responses to the AAV vector weeks after administration were handled with steroid treatment. **FIX activity has been detected for as long as four years post-treatment (follow-up still ongoing), and across all dose cohorts 4/7 FIX concentrate transfusion-dependent subjects became prophylactic transfusion independent**. Peripheral administration of scAAV2/8-LP1-hFIXco was well tolerated with minimal side effects.

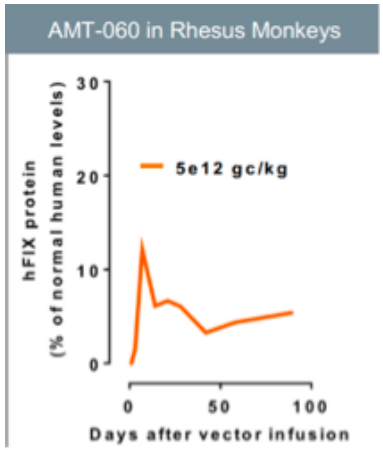
A concern going forward with AAV gene therapies is the unwanted immune response to the AAV vector, like that demonstrated in this clinical trial. This immune response has been a contributing factor to *why* previous trials using rAAV2 vectors have failed to demonstrate adequate safety and efficacy in the clinic. In this phase I/II trial, the utilization of a self-complementary cross-serotyped AAV2/8 vector facilitated the circumvention of this immune response, to a degree**. This engineered scAAV2/8 vector facilitates greater efficacy at significantly smaller doses (less potentially immunogenic AAV2/8 vector needed).**

The phase I/II data are impressive; however, there may be room for safety and efficacy improvements via manufacturing modifications. **The AAV2/8 formulation administered in this clinical trial is believed to have approximately 80% of AAV2/8 vectors empty (not containing therapeutic self-complementary LP1-hFIXco transgene encapsulated). By decreasing the percentage of empty vectors, lower doses might be used that would provide similar or greater safety and efficacy** – we will discuss this below in the "Manufacturing" section.

AMT-060-01: scAAV2/5-LP1-hFIXco UniQure Phase I/II Clinical Trial
UniQure owns the IP covering the sc-LP1-hFIXco transgene; however, the AAV2/8 vector IP belongs to **Baxter (BAX).** Therefore, **uniQure used a *similar* AAV2/5 vector that carries the same exact sc-LP1-hFIXco transgene in their current Hemophilia B product - AMT-060.** *Nathwani et al* originally characterized scAAV2/5-LP1-hFIXco in a NHP model (non-baculovirus manufacturing) [7]. The current scAAV2/5-LP1-hFIXco vector system is produced using uniQure's proprietary baculovirus insect-based manufacturing platform. This manufacturing process differentiates uniQure's AAV platform and hemophilia B programs from all other companies. Importantly, uniQure's baculovirus manufacturing platform **enables a low portion of empty AAV2/5 capsids to be incorporated into the main gene therapy product.** As we discussed in the previous section, this low number of empty AAV2/5 capsids – which we will discuss in more detail below – could prove to be critical in facilitating a more robust safety profile and efficacy in humans.

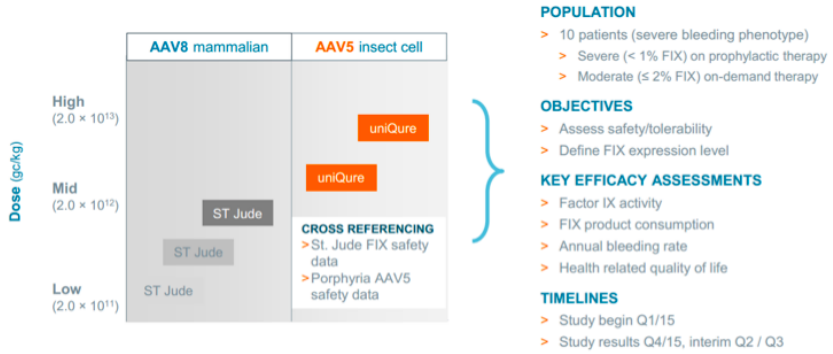
AMT-060 Pre-clinical Data Package
As mentioned previously, *Nathwani et al* characterized the scAAV2/5-LP1-hFIXco construct – using mammalian manufacturing – in the NHP model [7-9]. UniQure expanded on this preclinical data package with a presentation at the American Association of Hematology's (ASH) 2014 Annual Meeting

demonstrating scAAV2/5-LP1-hFIXco safety and efficacy – using proprietary baculovirus manufacturing – in a preclinical NHP model (n = 12). In this experiment, *Nijmeijer et al* infused groups of 3 NHPs at doses ranging from 5E11 to 0.93E14 [gc/kg]. As shown below, administration of scAAV2/5-LP1-hFIXco construct at a dose of 5E12 [gc/kg] results in similar hFIX production compared to NHPs who have previously received the scAAV2/8-LP1-hFIXco construct.



AMT-060 Clinical Overview and scAAV2/5 Review

The clinical development plan and timeline for this first-in-human phase I/II dose-escalation clinical trial of peripheral vein administration of the scAAV2/5-LP1-hFIXco construct is shown below [6].



The graphic above illustrates the higher doses of AAV gene therapy product that uniQure's proprietary baculovirus manufacturing can facilitate. **UniQure will initiate this phase I/II clinical trial in the 1st quarter of 2015, with interim safe/efficacy data as early as mid-2015.** As with any first-in-human clinical trial – particularly in the gene therapy field – there is significant risk associated with the safe administration of a new vector and transgene construct. However in this case, the scAAV2/5-LP1-hFIXco construct has been clinically derisked to a degree because of St. Jude's clinical experience with the scAAV2/5-LP-1hFIXco construct, and because of the clinical use of the AAV2/5 construct discussed below.

AMT-021: AAV2/5 gene therapy product for Acute Intermittent Porphyria

UniQure has an ongoing phase I program – AMT-021 – that utilizes the same AAV2/5 construct with a different transgene engineered to treat Acute Intermittent Porphyria (AIP). AMT-021 consists of an AAV2/5 construct carrying the PBGD gene to liver cells (hepatocytes). In May 2014, uniQure released interim results from this clinical trial, revealing that a total of 8 patients received a single dose of up to 2E13 [gc/kg] of AMT-021. There were no safety concerns as a result of AMT-021 administration, and biopsies around 45 weeks post-infusion revealed detectable PBGD DNA genetic material inside hepatocytes (shown below):

Vector		Documented AAV transfection		S-ALT levels		
Serotype	*Dose (gc/kg)*	*Liver biopsy*	*Detectable PBGD DNA*	*Peak (IU/L)*	*Time*	*Immune Suppression*
AAV5	5×10^{11}	Yes	+	WNL	6 months	No
AAV5	5×10^{11}	Yes	++	WNL	6 months	No
AAV5	2×10^{12}	Yes	+	WNL	6 months	No
AAV5	2×10^{12}	Yes	++	WNL	6 months	No
AAV5	6×10^{12}	No	N/A	WNL	6 months	No
AAV5	6×10^{12}	Yes	+++	WNL	6 months	No
AAV5	2×10^{13}	Yes	++	WNL	6 months	No
AAV5	2×10^{13}	No	N/A	WNL	6 months	No
Abbreviations: WNL, within normal limits; AAV, adeno-associated virus; ALT, alanine aminotransferase						

In October 2014, UniQure announced 1 year top-line data from this trial showcasing AMT-021's safety and hepatocyte transfection in human subjects.

The clinical experience of both AMT-021 and scAAV2/8-LP1-hFIXco in combination supports our theory that AMT-060 will potentially be safe and demonstrate clinically beneficial efficacy in the clinic. In addition, an interviewed patient talks about potentially having signs of efficacy from AMT-021 treatment HERE.

UniQure's two specified goals with AMT-060:

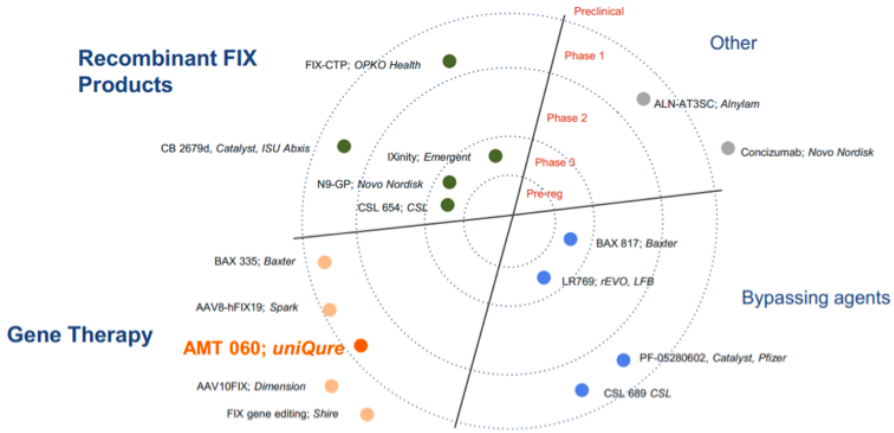
- **>5% hFIX concentration**
- **a 90% reduction in FIX concentration infusion and bleeding rate**

Hemophilia B Competition and Spark Therapeutics IPO

There is significant competition emerging in hemophilia B, spanning across numerous therapeutic modalities [6]:

Future Competitive Environment

Product Pipeline



Because of its potential for a one-shot or multi-year “cure”, if successful, gene therapy will set the bar for other therapeutic modalities. Emerging gene therapies will garner a significant portion of the future hemophilia B market, if not the entirety with time.

Sparing the details, Baxter’s BAX335 is currently the biggest threat to uniQure’s hemophilia B program for a number of reasons. First, it is the most advanced in the clinic. Baxter has already dosed patients, with data at any time in 2015. Second, the AAV2/8 vector has robust validation from the St Jude’s trial. Baxter is a large company, however, and a successful hemophilia b product won’t move the needle in the same way that it will for a smaller company. This is why we like uniQure as a pure-play gene therapy and hemophilia B investment vehicle. We believe there is more than enough room for **multiple winners in the Hemophilia B space**: some patient populations will be amenable to only certain AAV therapeutic vectors because of the presence of serotype-specific neutralizing antibodies – a key exclusion criteria in St. Jude’s and many other AAV clinical trials.

Spark Therapeutics (ONCE) – another AAV gene therapy company – IPO’d on the morning of January 30. Spark is nearing approval for its lead product, SPK-RPE65 in genetic blindness settings, pending data from a pivotal phase III study later this year. **Spark also has a hemophilia B program** – partnered with Pfizer (PFE) – that will enter the clinic in the 1st half of 2015. This program is potentially *behind* uniQure.

This is critical. The high-profile nature of Spark’s IPO – demonstrated by the IPO being upsized to $23/share– should lead investors to seek out other hemophilia B gene therapy plays, such as uniQure. The similarities between the two are stark: both commercial-stage (or nearly commercial in the case of SPK-RPE65) have small addressable populations, and the hemophila B programs are at a similar stage of development. At $50 per share, Spark is a $1.2 billion company. **We view uniQure – with present**

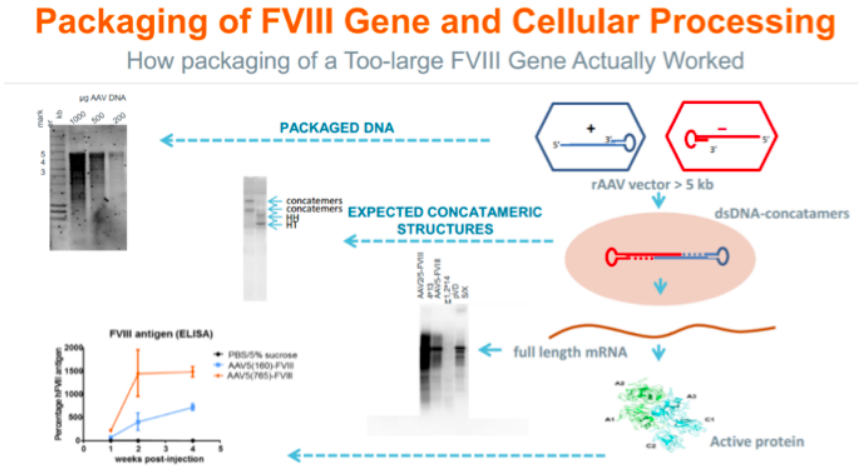
available data – as having a more validated, liver-targeted gene therapy program and a more attractive valuation.

uniQure has differentiated themselves in a number of ways, but of most importance to market opportunity is that they have strong IP backing the AAV2/5 vector. Serotype AAV5 has a low capsid homology **and the lowest seroprevalance compared to other serotypes** [12-13]. Essentially, uniQure's AAV2/5 vector platform could have significant advantages because more patients will be amenable to treatment.

uniQure's Hemophilia A Program

UniQure also has a hemophilia A program – a program they retain full commercial rights to – in the pre-clinic. Where Hemophilia B is characterized by a mutation(s) that results in insufficient functional **FIX** production, hemophilia A is characterized by insufficient functional **FVIII** production. The similarities between Hemophilia A and B make hemophilia A a logical target for gene therapy; however, the FVIII gene is much larger than the FIX gene. It is significantly more difficult to deliver to host cells and packaging a functional FVII gene in a single scAAV or rAAV vector is nearly impossible.
UniQure has developed unique rAAV transgenes that are able to circumvent the oversized transgene and the rate-limiting step in AAV gene therapy: the conversion of traditional rAAV ssDNA transgene into dsDNA.

In a pilot experiment, **uniQure delivered 2 partial dsDNA transgenes encoding complementary strands of the dsDNA FVIII gene.** The complementary dsDNA transgenes packaged in rAAV2/5 are co-transfected into target cells, each delivering their complementary strand of the full dsDNA transgene. See below [6].



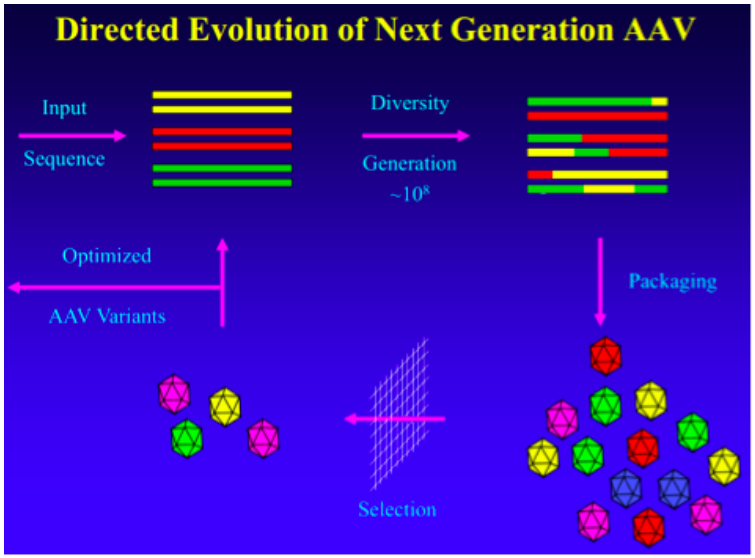
Once transfected into target cells, the complementary partial dsDNA transgene combine into full dsDNA-

concatamers encoding the FVIII protein. These dsDNA-concatamers (each >5kb!) are then used to transcribe the FVIII mRNA, leading to the production of functional FVIII. UniQure is currently testing an improved, proprietary variant of the two complementary partial dsDNA transgenes in preparation for NHP studies being initiated in 1Q 2015.

Of note, uniQure is working to decrease the size of the complementary partial dsDNA transgenes to improve the QUALITY of the product. The QUALITY (not potency) of the product is a function of the transgene size – the smaller the transgene, the higher the quality of product.
Hemophilia A is an important tack-on for uniQure's liver-targeted AAV program because of its similarity to Hemophilia B with a larger disease indication (shown below) [6]:

FEATURES	HEMOPHILIA A	HEMOPHILIA B
PREVALENCE	1 : 5,000 males	1: 30,000 males
COMMON CLINICAL SYMPTOMS	Haemarthroses, muscle haematoma	Haemarthroses, muscle haematoma
BLEEDING FREQUENCY/YEAR	12 – 30	12 – 30 (?)
FVIII/FIX HALF-LIFE (H)	12	18

4D Molecular Therapeutics Partnership
In January 2014, UniQure and 4D Molecular Therapeutics announced a broad collaboration to generate next-generation AAV gene therapy vectors targeting the liver and central nervous system (CNS). UniQure is guiding to have novel next-generation liver-targeted and CNS-targeted AAV variants generated in 2016 and entering the clinic in 2016/2017. 4D Molecular Therapeutics is a company spun out by University of California-Berkley researchers to develop their "directed evolution" technology. Directed evolution is a type of vector engineering, along with rational design, that harnesses the natural genetic diversification and selection process to progressively engineer an improved AAV vector. A summary of the directed evolution process is shown below [6]:



Improvements through the directed evolution approach relate to, circumventing the following conventional AAV hurdles:

- Neutralization by pre-existing antibodies
- Inefficient delivery to target tissues in vivo
- Inefficient spread within the target tissue
- Inability to target specific cells
- Inefficient update into target cells
- Intellectual property limited or non-existent

UniQure is guiding for pipeline candidates using these next-generation AAV vectors to enter the clinic in 2016/2017. Nevertheless, we view this collaboration as an incremental positive as validation of this management team's savviness in the gene therapy field. Direct evolution platforms are poised to play a critical role in facilitating the next generation of AAV gene therapy vectors, with 4D Molecular Therapeutics possessing one of the most advanced platforms.

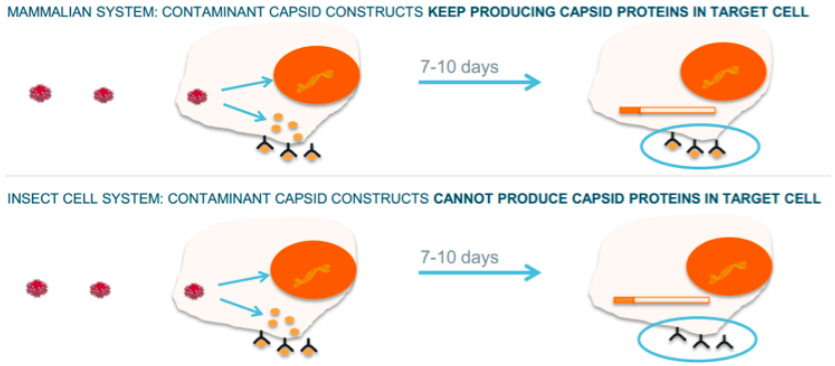
Manufacturing

UniQure has developed their own manufacturing process using the baculovirus insect cell-based platform. This insect-based platform has numerous benefits over traditional AAV manufacturing techniques like HSV-, adenovirus-, and plasmid-based, including

- Superior safety, immunogenicity, and quality
- Scalable and cost efficient

- Validated clinically and by regulatory authorities

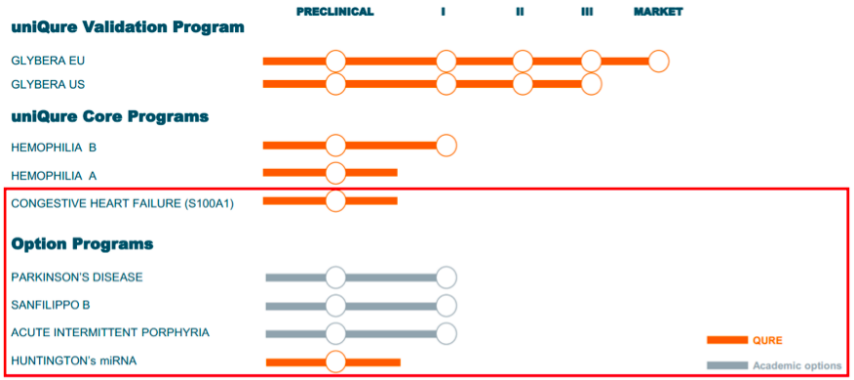
AAV manufacturing is a rather complex topic, but we offer one example – superior safety – that showcases the baculovirus platform's benefits over traditional techniques. Sparing the technical details, the platform leads to the production of significantly less immunogenic AAV vectors (bottom panel) [6]:



Contamination of non-therapeutic AAV vectors during manufacturing is an important detail to consider because it can lead to a significantly narrower therapeutic window and worse safety profile. This allows uniQure to use higher doses in the clinic than conventionally manufactured AAV vectors, illustrated by uniQure's AAV2/5 AIP program and AMT-030 entering the clinic this quarter. It is also important to note that UniQure's in-house, regulatory-body-validated baculovirus platform enables the rapid development of AAV-based therapeutics.

Other UniQure and Partnered Programs

UniQure has 1 in-house program for heart failure and 4 academic option programs that are not discussed in detail in this report:



We do not include a deep-dive into these programs because they are not key components of our investment thesis; however, these programs demonstrate UniQure's broad "net" across the AAV field. In fact, uniQure leveraging its AAV platform to expand its broad reach via partnership/licensing agreements

was demonstrated in January when the company granted IP related to AAV5 and GDNF to Treeway, to develop a gene therapy for ALS.

With a catalyst-filled 2015 and the realization of revenue from Glybera, UniQure as a company could be approaching a significant inflection point – an inflection that could lead to an increase in valuation.

Upcoming Catalysts:

- 1Q 2015:
  - Glybera commercial launch
  - Hemophilia B phase I/II trial initiation/dosing (**towards March**)
- Mid-2015:
  - Hemophilia B phase I/II interim data readout of lowest dose cohort [n=5] (end 2Q-beginning 3Q)
- Mid-2016:
  - Hemophilia B phase I/II clinical trial completion

Risks

- **Gene therapy sentiment shift.**
- **Safety/efficacy issues with previously treated Glybera, scAAV2/8-LP1-hFIXco, or any other related uniQure program.**
- **Slow rollout of Glybera (though expectations are not high).**
- **Binary risk event with hemophilia B data.**

References

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