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Acceleration of rare disease therapeutic development: a case study of AGIL-AADC

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Rare-disease drug development is both scientifically and commercially challenging. This case study highlights Agilis Biotherapeutics (Agilis), a small private biotechnology company that has developed the most clinically advanced adeno-associated virus (AAV) gene therapy for the brain. In an international collaboration led by Agilis with National Taiwan University (NTU) Hospital and the Therapeutics for Rare and Neglected Diseases (TRND) program of the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health, Agilis' gene therapy for aromatic L-amino acid decarboxylase deficiency (AADC), AGIL-AADC, was granted biologics license application (BLA)-ready status by the FDA in 2018, only 18 months after being licensed from NTU by Agilis. Here, we highlight the factors that enabled this remarkable pace of successful drug development for an ultra-rare disease.

Introduction

Drug development for rare and orphan diseases is one of the most challenging spaces in the biopharmaceutical industry. Defined in the USA as a condition affecting 200 000 patients or fewer, orphan diseases present obstacles for both industry and academic researchers [1]. Small patient pools, and often, a lack of understanding of the mechanisms and epidemiology of such diseases, make it difficult to design and conduct clinical trials to produce viable efficacy data to gain US Food and Drug Administration (FDA) marketing approval. In addition, there is a considerable funding gap between preclinical and clinical research, sometimes dubbed the 'Valley of Death', which causes many promising therapies to fall through the cracks [2]. The burden falls on the private

sector to bridge this gap, which continues to widen. To help the 30 million patients in the USA and the 350 million patients globally who have a rare disease [3], we need to reconfigure our traditional ideas about clinical research, funding, and public–private partnerships.

The Valley of Death between basic and clinical research is indisputably a roadblock to efficient drug development for rare diseases. In part, this is because the interests of the different parties in medical discovery are misaligned. On the one hand, academic researchers are motivated by the hope of understanding the biology behind a disease, but often lack the funding or expertise to translate their findings to drug development. Their objective is scientific discovery, funded by government grants supporting basic research with no expectation of a financial return on

investment (ROI). On the other hand, industry focuses on clinical research [4], that is, projects funded by private capital with a shorter investment horizon and a nontrivial possibility of achieving a positive ROI. Investors are hesitant to bridge the gap between these two ends of the spectrum because of the longevity of the investment and the high probability of failure.

This funding gap is particularly problematic for rare diseases, where low disease prevalence makes both patient accrual and the economics of the drug challenging. However, regulators, academics, and industry members can collaborate to make progress. Here, we highlight one such collaboration, exploring crucial factors that enabled the successful progress of Agilis Biotherapeutics' AGIL-AADC product candidate, a BLA-ready gene therapy for the treatment of

AADC deficiency. AGIL-AADC is currently the most clinically advanced central nervous system (CNS) gene therapy under development.

Background

AADC deficiency is an ultra-rare autosomal recessive disease caused by a nonfunctional AADC enzyme, which normally synthesizes serotonin and dopamine, among other important compounds. As a result, patients with AADC deficiency lack crucial neurotransmitters, including serotonin, dopamine, norepinephrine, epinephrine, and melatonin, and have severe developmental and motor deficiencies. Historically, only a few patients have been diagnosed with AADC deficiency [5]. The life expectancy of patients with severe AADC deficiency has been reported to be under a decade. Over their entire lifespan, patients with severe AADC deficiency achieve few or no motor development milestones, such as head control, sitting, or standing, and consequently are fully dependent. In 2012, Hwu et al. described 20 patients with AADC deficiency, all of whom failed to achieve any milestones by a mean age of 4.75 years [6]. Other symptoms include dystonia, seizures, hypokinesia, and ptosis. There is currently no FDA-approved disease-modifying therapy for AADC deficiency, and Agilis' gene therapy candidate is the sole approach in clinical development.

Although the prevalence of the disease in the USA and globally is unknown, a recent study screened 127 987 newborns in Taiwan from September 2013 to December 2015 and found an AADC deficiency incidence of 1 out of 32 000 live births, which translates to a prevalence of <1000 in Taiwan [7]. The prevalence in Asia might be somewhat higher than in the West because of a founder mutation, although this has not been empirically demonstrated to date. However, an epidemiological retrospective study, led by Keith Hyland of MNG laboratories, revealed an estimated birth prevalence of 1:68,000 in non high-risk populations. Given this result, it is likely there are misdiagnoses of AADC deficiency as cerebral palsy, epilepsy, or other movement disorders in the USA [8].

AAV gene therapy

Gene therapy has the potential to provide durable efficacy or even a cure for diseases that have been difficult to treat in the past, but the method has been technologically challenging and biologically uncertain. Several high-profile failures in the clinic in the 30 years since its origins have set the field back [9], including a death in a clinical trial for ornithine transcarbamylase (OTC) deficiency and cases of leukemia in a human study for severe combined immunodeficiency (SCID) [10,11].

However, advances in technology and extensive clinical trials in gene therapy (with 2000 clinical trials ongoing or completed to date) have yielded breakthroughs over the past decade [12]. Since 2012, when Glybera, the first gene therapy approved worldwide, was granted marketing authorization by the European Medicines Agency (EMA), four more gene therapies have been brought to market: Strimvelis for SCID by GSK in May 2016 [13], Kymriah for relapsed/refractory B cell acute lymphoblastic leukemia by Novartis in September 2017 [14], Yescarta for relapsed/refractory large B cell lymphoma by Kite/Gilead in October 2017 [15], and Luxturna for Leber congenital amaurosis by Spark Therapeutics in December 2017 [16].

In particular, AAV-based strategies have an abundance of promising therapeutics with potentially curative clinical data. On December 19, 2017, Luxturna was the first in vivo AAV gene therapy to receive FDA approval. AveXis published Phase I data for its AAV gene therapy in 15 patients with spinal muscular atrophy type 1, which showed 100% event-free survival versus the 8% observed in historical controls at 20 months of age [17]. Additionally, Biomarin, Spark Therapeutics, and UniQure have all released promising data from their AAV gene therapy programs in patients with hemophilia [18–21].

AAV gene therapy is particularly well suited for CNS diseases because neurons are typically post mitotic (i.e., no longer capable of cell division), which increases the likelihood of long-term gene expression. Past efforts have focused on lysosomal storage diseases arising from single gene mutations, such as Batten's disease, Gaucher disease, Pompe disease, metachromatic leukodystrophy, and various mucopolysaccharidoses [22]. The pathology of these neurodegenerative diseases is based on a missing recycling enzyme, leading to protein substrate accumulation and progressive cell death.

Gene therapies for these diseases face unique challenges, including delivery and cerebral atrophy. The blood–brain barrier (BBB) prevents intravenous administration, thus requiring intracranial injections, which can inhibit the widespread dispersion of viral vectors throughout the brain [22]. As a result, many regions of the brain that are not reached by the therapy will continue to atrophy. In diseases characterized by rapid neurodegeneration, identifying and treating patients before debilitating degenerative damage occurs is an additional challenge.

AADC deficiency is also a CNS disease and is particularly amenable to treatment with AAV gene therapy. AADC deficiency differs fundamentally from lysosomal storage diseases because its pathology is not neurodegenerative. As a neurotransmitter disorder, its pathology stems from a missing enzyme for a localized subset of neurons in the substantia nigra and ventral tegmental area (VTA) of the midbrain that produce dopamine and serotonin [5]. Therefore, the widespread distribution of vectors throughout the brain is not necessary, and intracranial administration localized to the putamen alone can yield substantial therapeutic benefits.

Agilis Biotherapeutics

Agilis is a clinical-stage gene therapy company founded in 2013 and headquartered in Cambridge, MA, USA. The company specializes in the development of DNA therapeutics for patients with rare genetic diseases of the CNS. In addition to AGIL-AADC, Agilis has a deep pipeline, including AGIL-FA for the treatment of Friedreich ataxia (FA), AGIL-AS for the treatment of Angelman syndrome (AS), and other undisclosed programs targeting neurodevelopmental and neurodegenerative disorders [23]. Given the scope of the mission of the company and the other projects under development, AGIL-AADC was a logical addition to the Agilis pipeline.

Once the Agilis team established the license agreement for AGIL-AADC with NTU in January 2016, it was clear that a considerable amount of time and resources would need to be invested to gain FDA approval. The clinical data, although promising, had been collected open-label in Taiwan at a single center, which raised the question of whether clinical research needed to be conducted again with a US-based treatment center and patient pool. If the FDA decided that Agilis was required to repeat the clinical trials in the USA, it would take several additional years and cost the company tens of millions of dollars before a BLA package for marketing approval could be generated and presented to the FDA.

Moreover, generating the preclinical data package required by the FDA, including animal safety testing and biodistribution analyses, as well as a full manufacturing package, would require substantial capital that Agilis might not have been able to raise because of the orphan-category commercial market. AGIL-AADC could have entered its own unique 'Valley of Death' in early 2016.

By July 2017, after a year of intensive work requiring sourcing data to the case records,

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database auditing, and further statistical analysis, a comprehensive data package was presented to an FDA review panel, which judged AGIL-AADC to be BLA ready. The FDA provided significant guidance in chemistry, manufacturing and control (CMC), nonclinical safety, and expectations for the clinical data presentation [24]. Contingent on the commercial manufacturing package, Agilis expects to submit a BLA in 2019 and to begin its commercial launch upon approval. This expedited timeline (Fig. 1), from in-licensing in 2016 to anticipated BLA submission in 2019, will save the company millions of dollars in expenses for clinical research, but, more importantly, it will cut crucial years from the development and approval process, through which current patients with AADC deficiency cannot afford to wait.

Three key factors enabled the verdict of the FDA, each of which we consider in turn below: (i) the rigorously collected clinical data from Taiwan; (ii) an effective public–private partnership between Agilis Biotherapeutics and NCATS; and (iii) the ability of the team to highlight the data and clinical benefits in patients treated with the gene therapy and present a persuasive package to the FDA.

Foreign clinical data and collaboration with NTU

Taking advantage of the localized pathology of AADC deficiency, Paul Hwu, professor of pediatrics at NTU Hospital, collaborated with the University of Florida Powell Gene Therapy Center to manufacture an AAV gene therapy to deliver a functional DOPA decarboxylase (DDC) gene, which encodes the AADC enzyme and corrects the AADC deficiency phenotype. Hwu based his delivery and dosing rationale on that used for many years in treatment for Parkinson's disease

(PD). A similar AAV construct is being tested in patients with PD in Phase II clinical trials [25].

The first proof of concept, a compassionate use study using AGIL-AADC to treat patients with severe AADC deficiency, was carried out by Hwu from February 2010 to December 2011 in eight patients ranging from 2 to 8 years of age. These patients were followed up to 5 years after treatment and evaluated based on their improvement in three metrics: the Alberta Infant Motors Scale (AIMS); the Peabody Developmental Motor Scales (PDMS-2); and the Comprehensive Development Inventory for Infants and Toddlers (CDIIT). The results of the gene therapy were promising because patients demonstrated improvements in all three scores [6]. These same patients were later entered into a long-term follow-up study.

Dr Hwu presented these clinical trial results at the American Society of Gene and Cell Therapy (ASGCT) Annual Meeting in May 2015, including videos of patient improvement several years after gene therapy. Impressed by these patient outcomes, Mark Pykett, the CEO of Agilis, approached Dr Hwu to discuss the potential for global development and commercialization of the gene therapy (Mark Pykett and Jodi Cook, pers. Commun, 2017). In September 2015, Agilis entered into a sponsored research agreement with Dr Hwu and NTU. In January 2016, Agilis and NTU announced an exclusive worldwide license agreement for the treatment of AADC deficiency using the gene therapy under development by Dr Hwu. This gene therapy would be developed under the name AGIL-AADC (Mark Pykett and Jodi Cook, pers. Commun, 2017).

The Taiwanese investigators subsequently initiated a Phase I/II trial enrolling an additional ten patients under a protocol approved by an institutional review board and the Taiwan Food

and Drug Administration. Its primary efficacy outcomes were an increase in the PDMS-2 score of greater than ten points and an increase in homovanillic acid (HVA) or 5-hydroxyindoleacetic acid (5-HIAA) concentrations (metabolites of dopamine and serotonin, respectively) in the cerebrospinal fluid 12 months after treatment. Secondary efficacy outcomes included: body-weight gain; an increase in FDOPA, a tracer for AADC; and improved scores on the AIMS and the Bayley-III Scales for Infant and Toddler Development. All ten patients met and surpassed the primary endpoint of a ten-point PDMS-2 score increase. In fact, PDMS-2 scores increased by a median 62 points ($P = 0.005$), representing a life-changing improvement in motor milestones for patients who would otherwise fail to develop [7,26]. Patient monitoring and data collection are still ongoing and are now supported by Agilis' sponsored research agreement.

Certain prior groundwork by other parties helped to provide a foundation for Agilis to build on to meet their development and regulatory milestones efficiently. Earlier work in PD gene therapy using AAV2 set an excellent precedent for an optimal AAV serotype and was leveraged by Dr Hwu to establish the dose rationale and intraputamenal delivery strategy in AADC deficiency. Crucially, this lowered the cost and increased the speed of early clinical development because it negated the need for significant preclinical experimentation and optimization, which might have been required otherwise (e.g., the development of AADC-deficiency animal models). Additionally, the higher visibility of AADC deficiency in Taiwan sped up the patient-finding process and the characterization of the disease. Using the extensive work by the Taiwanese researchers, Agilis was able to structure and quantify the natural history of the

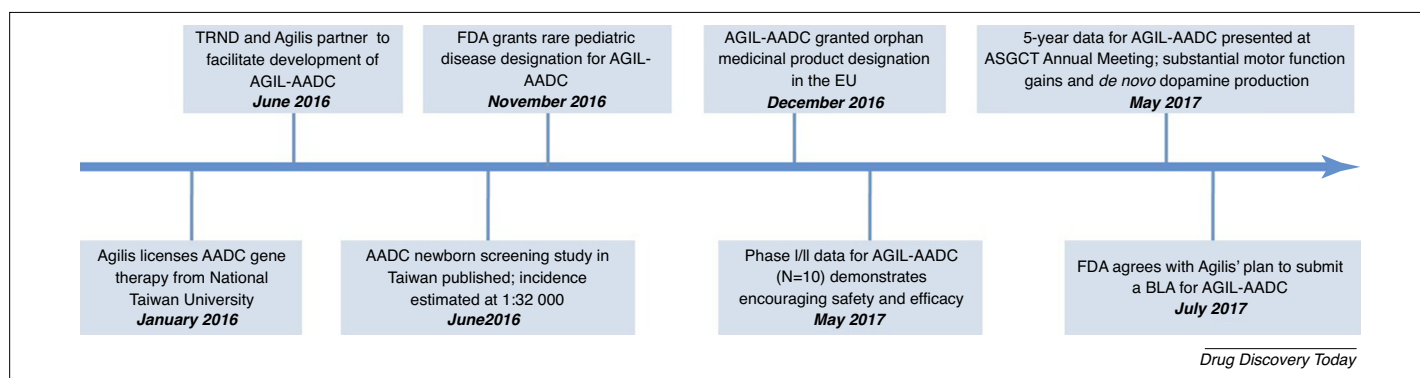|			
TRND and Agilis partner to facilitate development of AGIL-AADC **June 2016**	FDA grants rare pediatric disease designation for AGIL-AADC **November 2016**	AGIL-AADC granted orphan medicinal product designation in the EU **December 2016**	5-year data for AGIL-AADC presented at ASGCT Annual Meeting; substantial motor function gains and de novo dopamine production **May 2017**
Agilis licenses AADC gene therapy from National Taiwan University **January 2016**	AADC newborn screening study in Taiwan published; incidence estimated at 1:32 000 **June2016**	Phase I/II data for AGIL-AADC (N=10) demonstrates encouraging safety and efficacy **May 2017**	FDA agrees with Agilis' plan to submit a BLA for AGIL-AADC **July 2017**

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FIGURE 1

Timeline of Agilis Biotherapeutics-aromatic L-amino acid decarboxylase deficiency (AGIL-AADC) development. Abbreviations: ASGCT, American Society of Gene and Cell Therapy; BLA, biologics license application; EU, European Union; FDA, US Food and Drug Administration; TRND, Therapeutics for Rare and Neglected Diseases.

disease to put AGIL-AADC into its correct context for regulators.

Collaboration with NCATS TRND

Situated at the nexus between academia, industry, and nonprofit organizations, NCATS at the National Institutes of Health (NIH) is uniquely positioned to address the rare diseases that few other drug developers will consider because of its mission and portfolio approach to therapeutic development. By collaborating with academic and organizational thought leaders and industry experts, its Therapeutics of Rare and Neglected Diseases (TRND) program works to bring new therapeutics to milestone validation stages, acting as a catalyst to the efforts of the private sector. By disassembling the development pipeline, smaller and nimbler organizations can focus on segments of the development process with adequate funding and appropriate expertise, turning the preclinical development process from a marathon with a single runner to a team-oriented relay race.

The initial TRND portfolio quickly established a successful track record [27]. Given that 80% of the >7000 rare diseases have a monogenic pathology, protein replacement therapy and gene therapy are the most logical treatment modalities to correct these diseases at their root causes. In 2015, TRND created a pilot gene therapy platform and began to source its inaugural projects.

This expansion was timely for Agilis because it sought all means possible to fund its expanding pipeline of gene therapy candidates, including a nondilutive development partnership to conduct the supplementary studies required to achieve FDA approval for AGIL-AADC (Mark Pykett and Jodi Cook, pers. Commun, 2017). TRND was seeking projects designed to address specific translational pain points for gene therapy development so that the program could use its resources and expertise to help develop new technologies and models broadly applicable to all gene therapy development work (Nora Yang, pers. Commun, 2017). Dr Jodi Cook, the Chief Operating Officer of Agilis, approached Dr Nora Yang at TRND in July 2015 to discuss the possibility of collaboration between TRND and Agilis, after seeing Dr Yang's presentation of the NCATS TRND program at the 2014 National Organization for Rare Disorders (NORD) Summit (Mark Pykett and Jodi Cook, pers. Commun, 2017).

Agilis' AGIL-AADC has the hallmark features sought in TRND's public call for pilot gene therapy projects. For instance, TRND stated on its public website that the program sought collaborations with researchers in academia and the biotech industry on nascent gene therapy projects that address major challenges for this new modality of treatment, such as tissue-specific delivery, improving manufacturing processes, and innovative regulatory pathways to harmonize clinical data generated outside of the USA [28]. The focus of the company on CNS had the potential for a larger impact in other disease areas, and its patient-centric mindset and commitment to the eradication of ultra-rare diseases aligned with the stated values of NCATS (Nora Yang, pers. Commun, 2017). Furthermore, key circumstances of AGIL-AADC were unprecedented for TRND. First, it would be one of the first gene therapies in the TRND portfolio. Second, the regulatory considerations of single-arm, open-label, foreign clinical data in the context of compelling clinical findings, although challenging, provided an opportunity to approach this issue with the FDA. Finally, the ultra-rare status of AADC deficiency was a good fit with a TRND effort to develop a standard protocol for patient finding to locate patients with potentially underdiagnosed and/or misdiagnosed ultra-rare diseases.

TRND uses a well-publicized in-depth review process to select proposed collaborations [29]. Each proposal is reviewed by TRND staff, external drug development experts, and NIH staff in relevant institutes and centers for the proposed science, competitiveness within the disease research area, and feasibility of drug development. Proposals are evaluated against five dimensions: target and therapeutic validation; strength of current data package; feasibility to reach first-in-human clinical trials; medical impact relative to current standard of care; and likelihood of external adoption.

After TRND's in-depth review of a proposal by Agilis submitted in January 2016, the company was selected by TRND for collaboration under a Cooperative Research and Development Agreement (CRADA) with the NIH in June 2016, enabling it to receive in-kind resources, access to government contracts, a scientific development team, and project management support via the TRND program. Drs Yang and Cook co-led and managed a multidisciplinary project team comprising Agilis and TRND development scientists for all aspects of the strategic planning and operational execution.

A typical TRND project team comprises members of NCATS scientific staff and scientists from the collaborating organization, with membership determined by the need of the project. TRND houses a group of academic and industry professionals across an array of fields, including pharmacology, toxicology, molecular biology, chemical genomics, medicinal and process chemistry, project and portfolio management, and intellectual property protection. At the time that Agilis was awarded its CRADA, it had four employees dedicated to executing its mission. During the TRND collaboration, the team was expanded to over 40 diverse experts, including TRND scientific and management staff and development scientists working in contract research organizations (CROs) under NCATS-managed government contracts.

The first order of business of the team was to delineate the gaps between where the program stood and a successful product marketing approval by the FDA. The development activities needed to bridge these gaps were then put into a sequence, according to time and resource constraints [30]. This gap analysis identified several requirements for filing with the FDA: animal safety, toxicity, and biodistribution testing; CMC; and biostatistical analyses of clinical data. The team also identified that a US epidemiology study would be crucial to defining the true prevalence of this disease, while helping to locate patients with AADC deficiency who could benefit from this therapy. Within the Agilis-TRND project team, roles were assigned based on the expertise of each stakeholder.

TRND had the experience and in-house resources to direct CMC research at a government-owned, contractor-operated biologics manufacturing facility. The CMC team comprised several contractors and employees focused on CMC planning, process and assay development, and large-scale manufacturing of a clinical grade AGIL-AADC product to support clinical trials (Nora Yang, pers. Commun, 2017). Similar to many current gene therapies, AGIL-AADC was initially developed by academic researchers, and the manufacturing process has been conducted at academic centers and small contract manufacturing companies. Thus, Agilis' further development of AGIL-AADC needed to implement a robust manufacturing process suitable for later-stage clinical trials, approval, and commercialization, which the CMC team needed to address, starting with manufacturing plasmids, testing different HEK293 master cell banks, optimizing upstream and downstream manufacturing processes, and developing comparability and potency bioassays, among others.

Safety, toxicology, and biodistribution studies are other crucial components for FDA regulatory approval. The Agilis–TRND toxicology team designed a comprehensive nonclinical safety study in rodents and achieved FDA agreement

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that the protocol could support its regulatory filing. A good laboratory practice (GLP) non-clinical safety study has been conducted at a well-established global CRO under NCATS contract and the results will be used to support the registration of AGIL-AADC.

The Agilis–TRND collaboration proved to be mutually beneficial. Agilis gained access to a nondilutive development partnership, a workforce, and a network of diverse stakeholders. TRND has developed gene vector manufacturing capability via a government contractor. Together, both organizations gained patient-finding experience for an ultra-rare disease, established a precedent for regulatory registration with open-label, single-arm clinical data conducted outside of the USA, and contributed to the potential approval of a life-altering therapy for patients with AADC deficiency.

Expedited approval strategy

Following Agilis' end-of-phase 2 (EOP2) type B meeting with the FDA in July 2017, AGIL-AADC was deemed ready for a BLA from a clinical perspective. This decision, just 18 months after in-licensing the program, was helped by open communication between the joint Agilis–TRND team and the FDA, and by a strong presentation of existing clinical data in a format consistent with the guidance and regulations.

Consistent with the mission of expediting the availability of the gene therapy for patients in need, the regulatory strategy of the Agilis–TRND project team evolved as the team compiled and analyzed the data, seeing a significant magnitude of effect that was unprecedented in the natural history cases. At the EOP2 meeting with the FDA, the manufacturing, preclinical and clinical data package was presented, and the agency provided guidance on Agilis' plan to submit a BLA [31]. To prepare for the EOP2 meeting, the Agilis–TRND team needed to carefully examine the existing clinical data and apply sophisticated statistical analyses and modeling from which FDA registration strategies and clinical trial protocols were formulated. To conduct such analyses, a group of experienced biostatisticians was needed, with appropriate funding required to complete the analyses in a timely fashion. Agilis and TRND teams conducted a search for qualified biostatistics assistance and TRND quickly executed a contract with a biostatistical contracting organization, StatKing, which had a demonstrated capability and a successful track record to provide the project team with statistical analysis plans, interim analyses, and efficacy and safety

data analyses of the NTU studies, including integrated clinical study reports.

One of the key challenges with Dr Hwu's NTU data was the lack of a concurrent control group. AADC deficiency is a relatively unknown disease and there is little existing research on which to map disease progression. The clinical data collected by the two studies documented the progression of each patient with two scoring metrics, both of which are validated scales of childhood motor development, but not validated in patients with AADC deficiency: the PDMS-2 and the AIMS. In 2017, Wassenberg et al. published a comprehensive literature review of AADC deficiency and reported on observed motor milestones [5]. In lieu of a concurrent control, the Agilis team extracted motor milestone achievements from the clinical data and used this published review study to help compile a valid historical control to illustrate the lack of motor score progression in untreated patients. This medically meaningful comparison illustrated how the treated children gained crucial developmental motor milestones and the natural history controls did not. The team believed that the magnitude of effect was substantial enough to warrant a BLA.

In April 2017, Agilis submitted a request for an EOP2 type B meeting with the agency. The FDA granted a face-to-face meeting on July 7, 2017. To help present the clinical effects of AGIL-AADC, Agilis invited one of the patients enrolled in the clinical trial, an American citizen, and her family to attend the FDA meeting. After hearing of the success of the first compassionate-use trial, the patient and her family moved from their home in Pennsylvania to receive the therapy in Taiwan, where she ultimately began her journey to a miraculous recovery. The patient and the testimony of her family helped to demonstrate a need for AGIL-AADC within the USA and showcased the benefits of the therapy in a more personal manner. Agilis also invited Dr Hwu to participate in the meeting, which focused on the clinical trials conducted in Taiwan and the historical control developed from the natural history, a crucial component for FDA approval. Paired with five years of data, the assembled package made a compelling case for proceeding directly to a BLA, an approach that stepped over the conventional 'starting from the IND application', affirming that the clinical data package was complete, in full compliance with FDA regulation, and ready for BLA filing. Although there was some risk in asking the FDA to consider this regulatory approach, the Agilis–TRND team agreed it was more valuable to accelerate access to this promising therapy for

patients with no other options, and in doing so also save millions in development dollars.

Discussion

The creation of innovative therapeutics for ultra-rare diseases requires overcoming unique challenges. On the development front, drug developers must spend significant resources finding patients for clinical trials, characterizing understudied diseases, and developing a historical control data set, all in addition to creating a drug that works. On the commercial front, companies must face the uncertainty of poorly quantified patient populations, lack of disease awareness by physicians, and potential under-diagnosis of the disease. A misstep in the patient-finding process can completely undermine the commercial prospects of a novel ultra-rare therapy.

Given the potential cost benefits and strong patient pools that can be attained with an international data set, it appears that rare disease initiatives would benefit from foreign-based clinical trials. However, the percentage of NDA applications submitted to the FDA with solely foreign data has been estimated at 8%, suggesting a perceived need for US data [32]. The number of drugs and biologics that have been approved with foreign data are few and far between. Successes include: Sirturo, for multidrug-resistant pulmonary TB, which received orphan designation and accelerated approval in December 2012 with data from a randomized, double-blind, placebo-controlled trial as well as a single-arm and open-label trial conducted in sites across South Africa, South America, Asia, and Eastern Europe [33]; Rixubis, for Hemophilia B, which received FDA approval in June 2013 with data from a Phase I/III trial conducted in South America, Europe, and Asia [34]; and Vermox Chewable, for roundworm and ringworm infections, which received FDA approval in October 2016 with data solely from a randomized, double-blind, placebo-controlled Phase III trial with three sites in Ethiopia and Rwanda [35]. It is possible that broader use of foreign data, where appropriate, would provide opportunities to accelerate the development and approval of needed drugs, as the Agilis case highlights, with the compelling benefits of a thoughtfully presented international data set.

Of course, quality is a crucial factor when considering the use of foreign trial data. Regulatory governance can dictate the requirements within control and experimental arms, the level of evidence required, and review and approval timelines, and is a key consideration when

evaluating foreign data [36]. Another key question is whether the patient population is generalizable to the USA; patient-finding studies such as that by Wassenburg et al. helped to resolve this issue in the case of AGIL-AADC [5].

The clear vote of confidence from the FDA in the AGIL-AADC clinical data brings hope to the ultra-rare disease space by setting a precedent for drugs or biologics with exceptionally compelling foreign clinical data in cases of crucial unmet medical need. The supplementary preclinical studies conducted by the Agilis–TRND team have also enabled TRND to develop crucial in-house capabilities and protocols to efficiently satisfy the CMC, biodistribution, and epidemiology needs of future gene therapy projects in their portfolio.

Agilis is now laying the groundwork to tackle the AGIL-AADC commercial opportunity. In addition to the process of scaling up the manufacture of AGIL-AADC, Agilis is starting numerous patient-finding initiatives, including an epidemiology study in the USA, as well as initiatives in educating physicians to incorporate AADC deficiency diagnostic tests into their workflow, and the development of a predictive model based on diagnostic patterns to identify physicians who might have a misdiagnosed patient with the disease. These initiatives are meant to ensure that no potential patient with AADC deficiency is overlooked.

Another vote of confidence in Agilis' efforts and results in just 4.5 years comes in the form of a corporate acquisition. Dr Cook was approached in early summer 2018 by representatives from PTC Therapeutics (PTC) and led negotiations that resulted in a public announcement on July 19, 2018, that Agilis was to be acquired by PTC for US$200 million upfront (US$50 million in cash, US$150 million in common stock). Potential future payments to Agilis include US$745 million in development and commercial milestones. US$60 million of these milestones are contingent on near-term events, including the acceptance of a BLA for AGIL-AADC. The transaction also includes 2–6% royalties on net sales for two of Agilis' preclinical-stage programs.

PTC is a commercial-stage biotech company focused on orphan diseases that conducts internal drug discovery in addition to acquiring external programs. The transaction marks PTC's first foray into AAV gene therapy and the decision to build a gene therapy franchise. Accordingly, Mark Pykett will join PTC as the Chief Innovation Officer and Jodi Cook will join as the Head of Gene Therapy Strategy, with others from the Agilis team also staying on.

Although AGIL-AADC has not yet received FDA approval, this potential US$1 billion transaction highlights the value that Agilis has created with a patient-centric collaborative approach and in leveraging all types of funding source, including private investment and a public–private partnership with TRND. Looking ahead, the merger will also accelerate and derisk the delivery of AGIL-AADC to children with AADC deficiency. PTC has a global commercial platform, an existing regulatory infrastructure across the world that can accelerate the filing for approval in multiple territories beyond the USA, and significant resources to support AGIL-AADC in case unexpected issues were to arise.

In merely 18 months, AGIL-AADC has been accelerated through a translational 'Valley of Death' and is now positioned for FDA submission and review and potential US approval. The acquisition by PTC of Agilis provides market validation of Agilis' approach and, together, the two teams will rapidly advance AGIL-AADC to patients globally. This case study of Agilis demonstrates the power of public–private partnerships and international collaboration orchestrated by a committed and focused small private biotech. With the proper alignment of stakeholders, the challenges of rare disease drug development can be addressed more successfully, and life-saving therapies need not fall through the cracks.

Conflict of interest statement
S.D. reports no conflicts; S.H. is an associate at a biotech-focused investment fund; A.L. reports personal investments in private biotech companies, is an advisor to BridgeBio Pharma, a director of Roivant Sciences and the MIT Whitehead Institute for Biomedical Research, and an Overseer of Beth Israel Deaconess Medical Center. Agilis is not in the portfolio of any of the investment funds, and is not in any way associated with the companies that the authors are affiliated with.

Acknowledgments

Appendix A. Supplementary data
Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drudis.2018.12.006.

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