Dravet syndrome pipeline and opportunities review | 2020

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Dravet syndrome is a genetic neurological rare disease characterized by refractory epilepsy, intellectual disability, behavioral and movement disorders, and a high mortality rate. In recent years Dravet syndrome has received significant attention from the pharmaceutical industry, and the pipeline has matured to include not only symptomatic, but also disease-modifying treatments. Following the approvals of Diacomit (stiripentol) from Biocodex and Epidiolex / Epidyolex (cannabidiol oral formulation) from GW Pharmaceuticals, Fintepla (fenfluramine) by Zogenix has recently become the third drug approved by both the FDA and the EMA for the treatment of seizures in Dravet syndrome. Soticlestat, in co-development by Ovid Therapeutics and Takeda, is being evaluated for a potential registrational program after positive Phase 2 data, and there are additional programs in the pipeline exploring second-generation therapies to fenfluramine. Importantly, 2020 saw a key transition in clinical trials for Dravet syndrome, with the initiation of the first clinical trial with a therapy specifically designed to increase SCN1A levels: STK-001 from Stoke Therapeutics. There are additional genetic and potentially disease-modifying treatments in early and late preclinical development, including an AAV-based gene therapy. Overall the Dravet syndrome pipeline comprises 3 approved drugs and 12 additional treatments in development from late preclinical to Phase 3 trials. This report reviews the state of the Dravet syndrome drug development pipeline as of end 2020 and discusses current and future opportunities.

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1. Dravet syndrome - Overview

Dravet syndrome is one of the better-known rare diseases where epilepsy is one of the main symptoms. Previously known as severe myoclonic epilepsy of infancy, Dravet syndrome is a neurological rare disease caused in the majority of cases by loss-of-function mutations in one copy of the SCN1A gene (Claes et al., 2001). As a result of these mutations, patients with Dravet syndrome fail to produce sufficient levels of functional Nav1.1 sodium channel, preventing inhibitory neurons from firing properly. The consequence is an imbalance between brain excitation and inhibition that results in refractory epilepsy, intellectual disability, behavioral and movement disorders (Dravet 2011).

The mortality rate is high, with 15% of patients dying by adolescence and 20% by early adulthood (Genton et al., 2011).

For the purpose of this pipeline review we will only cover those products in development for the symptomatic treatment of Dravet syndrome or for the disease-modifying treatment of SCN1A-related epilepsies, but not those specifically designed to correct other gene dysfunctions that give raise to syndromes similar to Dravet (e.g. GABRG2, SCN1B).

The main pharmacological management of Dravet syndrome focuses largely on the use anti-epileptic medications (Chiron 2011). Importantly, sodium channel blockers, which are often a first-line

medication for the treatment of epilepsy, are contraindicated in Dravet syndrome and can aggravate the disease severity (Ceulemans et al., 2011; Guerrini et al., 2012; de Lange et al., 2018). Most patients with Dravet syndrome are taking combinations of 3 or more anti-epileptic drugs, most commonly valproate, clobazam, stiripentol, topiramate and levetiracetam. None of these drugs alone achieves complete seizure suppression in these patients and only a minority (about 10%) of the patients are seizure-free (Aras et al., 2015, Lagae et al., 2018).

The first generation of therapies in development for the treatment of Dravet syndrome also focuses on achieving improved seizure control. This includes compounds against traditional epilepsy targets, such as GABA receptors, as well as novel first-in-class therapeutics that target new pathways not previously used in epilepsy. There is also an emergent class of second-generation therapeutics that follow the step of the most advanced cannabidiol formulation (Epidiolex) and the most advanced serotonergic drug (Fintepla). Most of these compounds would have the potential to treat other forms of epilepsy.

A third generation of treatments that aim to restore the abnormal Nav1.1 channel function or expression levels includes multiple programs in development, with the most advanced program initiating clinical trials in patients in 2020. As the Dravet syndrome pipeline becomes more mature and competition increases, the pipeline is shifting towards less symptomatic treatments and more disease-targeting therapeutics.

2. Demographic and commercial considerations

The incidence of Dravet syndrome caused by SCN1A mutations is reported to be around 1 in 20,000 live births (Brunklaus et al., 2012; Wu et al., 2015; Bayat et al., 2015; Rosander and Hallböök 2015). Recent incidence studies of children with epilepsy, not necessarily diagnosed with Dravet syndrome, increase this number (incidence of SCN1A mutations) to 1 out of every 12,200 live births (Symonds et al., 2019).

Underdiagnosis is a common problem in rare diseases, which reduces actual market size. A study estimated the diagnostic awareness-adjusted prevalence of Dravet syndrome in Europe (i.e. the number of patients that have received the diagnosis) as of about 11,000 cases (Auvin et al., 2018). Using these estimates, the number of patients with a diagnosis of Dravet syndrome in the US and the EU5 alone would be about 14,000 patients. Therefore, the treatable population in the two large markets would be at least 14,000 patients provided that approval labels do not restrict any age or disease severity, although this number is likely to grow with improved diagnostic rates.

Dravet syndrome meets the criteria to be considered an orphan indication by both the FDA and the EMA (ceiling of less than 200,000 people in the US or less than 5 in 10,000 people in Europe). This means that products in development for Dravet syndrome can obtain an orphan drug designation and benefit from incentives such as reduced fees, tax credits, and 7 (FDA) or 10 years (EMA) of market exclusivity once approved.

Companies with a treatment approved for Dravet syndrome are also eligible for a Rare Pediatric Disease Priority Review Voucher by the FDA. Priority Review Vouchers are a tradeable commodity and can be used to maximize the return on investment in therapeutics targeting rare pediatric diseases.

The year 2018 saw the approval and market launch in the US of two drugs for treating Dravet syndrome: Diacomit (stiripentol) by Biocodex, and Epidiolex (cannabidiol oral solution) by GW Pharmaceuticals. In June 2020, FDA also approved Fintepla (fenfluramine). These approvals provide a reference for the price for the disorder in the US.

FDA approved Diacomit (stiripentol) in the US on 20 August 2018 for patients 2 years of age and older with Dravet syndrome. The drug had been available in Europe since 2007 and in Canada and Japan since 2012. Financial information about Diacomit US pricing and market is not readily available. Diacomit annual cost for an average patient of 30 kg was reported to be of about $14,000 per patient per year according to Health Canada (2014), or €3,000 to €14,000 per patient per year according to the National Center for Pharmacoeconomics of Ireland (2019). Epidiolex launched in the US on November 1, 2018. The list price for Epidiolex is an average of $32,500 per patient per year depending on patient's weight. In its first 9 months of 2020, Epidiolex made $378.6 million in global sales (prior to EU launch), including not only Dravet syndrome but also Lennox-Gastaut and Tuberous Sclerosis Complex prescriptions, and is on track to becoming a blockbuster following commercial launches in more European countries and potential addition of a European approval for Tuberous Sclerosis Complex (*GW, investor presentation December 2020*).

Fintepla launched in the US in July 2020, with a list price of about $96,000 per patient per year, or about three times the cost of Epidiolex.

3. Therapeutics development: clinical and preclinical protocols

The current clinical trial design for Dravet syndrome follows the usual standards for anti-epileptic medications. Fourteen double-blind placebo-controlled trial protocols for Dravet syndrome have been listed by a total of 10 companies, not including open-label trials or basket trials including patients with Dravet syndrome (Table 1). Two of these clinical trials, cannabidiol (INSYS Therapeutics) and clobazam (Lundbeck) were withdrawn. The remaining trials listed are the ones for Diacomit, Epidiolex, Fintepla, Belviq, EPX-100, Translarna, and Soliclestat, and STK-001. All of the clinical trials except for STK-001 followed the same trial design (see also Table 1), namely 12 to 14 weeks of treatment duration as an add-on to baseline medication in children and adolescents ages 2 to 18 years old, measuring as the primary endpoint the percentage change from baseline in frequency of convulsive seizures per 28 days as compared to placebo. Trials often include the percentage of responder patients, defined as those experiencing a reduction in seizures of 50% of more, as an additional endpoint, as this is often requested by the EMA.

Compound	Sponsor	Trial Identifier	Number of patients	Age (years)	Treatment phase	Primary endpoint	Status
Diacomit (stiripentol)	Biocodex	STICLO-FR# STICLO-IT#	41 and 24	3-18	2 months	50% seizure reduction	FDA and EMA approved
Epidiolex (cannabidiol)	GW Pharma	NCT02091375 NCT02224703	120 and 186	2-18	14 weeks	% change in convulsive seizures	FDA and EMA approved
Fintepla (fenfluramine)	Zogenix	NCT02682927* NCT02826863* NCT02926898	*combined; 119 and 115	2-18	14 weeks	% change in convulsive seizures	FDA and EMA approved
Belviq (lorcaserin)	Eisai	NCT04572243	58	2+	14 weeks	% change in convulsive seizures	Phase 3, recruiting
EPX-100 (clemizole)	Epygenix	NCT04462770	24	2-17	12 weeks	% change in convulsive seizures	Phase 2, recruiting
Translarna (ataluren)	NYU/PTC	NCT02758626	8	2-12	12 weeks	Safety (secondary: % change in seizures)	Completed Ph2
Soticlestat (OV935)	Ovid / Takeda	NCT03650452	60	2-17	12 weeks	% change in convulsive seizures	Completed Ph2
STK-001	Stoke	NCT04442295	48	2-18	7 months	Safety (secondary: % change in seizures)	Phase 1/2 recruiting
Cannabidiol	INSYS	NCT02318563	86	1-30	12 weeks	% change in convulsive seizures	Withdrawn
Clobazam	Lundbeck	NCT02174094	0	1-16	16 weeks	% change in convulsive seizures	Withdrawn prior to enrollment

Table 1 | **List of corporate double-blind placebo-controlled clinical trials in Dravet syndrome ordered by the stage of each program.** Except for the SAD study from Stoke Therapeutics, open-label trials, open-label extension trials, or basket trials including patients with Dravet syndrome are not included.

The first study in patients with STK-001 is a Single Ascending Dose study, administering one dose of the antisense oligonucleotide (ASO) with a 6-month follow up. Although the primary endpoint is safety, the main efficacy (secondary) outcome of the study is also reduction in seizure frequency.

In the preclinical space, the main endpoints analyzed during mouse proof of concept studies are changes in the hyperthermia seizure threshold, changes in spontaneous seizure frequency, and changes in mortality rate.

4. Dravet syndrome pipeline review – individual programs

The following sections review the state of the Dravet syndrome drug development pipeline as of end of 2020 (Table 2), focusing on the developments during the last 18 months since the publication of the 2019 report.

Compound names, mechanism of action if known, available clinical data (or mouse data if no clinical data is available), stage of development, date of orphan drug designation, and planned

trial initiation or IND / NDA filing, are reported for each compound in development.

All information used in this publication has been compiled from publicly available sources including clinical trial databases, publications, conference presentations, press releases, company websites, and sponsor SEC filings.

4.1. Symptomatic and improved-symptomatic treatments

4.1.1. Diacomit (stiripentol) - Biocodex

The first drug to be approved for the treatment of Dravet syndrome is Diacomit (stiripentol), marketed by Biocodex. Diacomit first obtained a conditional marketing authorization in Europe in 2007, and later a full

Company	Drug name(s)	Stage Dec 2020	ODD FDA/EMA
Biocodex	Diacomit (stiripentol)	Market	2008/2001[1]
Encoded Therapeutics	ETX101 (Gene Therapy)	Preclinical	2020 / -
Epygenix Therapeutics	EPX-100 (clemizole)	Phase 2 (placebo)	2017 / -
	EPX-200 (lorcaserin)	Phase 2 (open label)	2017 / -
	EPX-300 (trazodone)	Phase 2 (open label)	2017 / -
Eisai	Lorcaserin	Phase 3	2020 / -
GW Pharmaceuticals	Epidiolex / Epidyolex (cannabidiol oral solution)	Market	2013 / 2014
NeuroCycle	NCT10015	Preclinical	- / -
Ovid Therapeutics / Takeda	Soticlestat (OV935)	Phase 2 (placebo)	2017 / -
PTC Therapeutics	Translarna (ataluren)	Phase 2 (placebo)[2]	- / -
Sarepta / StrideBio	Gene Therapy	Preclinical	- / -
Stoke Therapeutics	STK-001 (ASO)	Phase 1/2 (SAD)	2019 / -
Supernus Pharmaceuticals	SPN-817 (huperzine A)	Phase 1	2017 / -
Tevard Biosciences / Zogenix	Gene Therapy / tRNA	Preclinical	- / -
Xeris Pharmaceutical	Diazepam	Phase 1	2018 / -
Zogenix	Fintepla (fenfluramine)	Market	2013 / 2014

Table 2 | **List of companies with active programs in development for Dravet syndrome**

Notes: [1]After 10 years in the market, stiripentol no longer has the orphan drug status in Europe; [2]Trial failed to demonstrate seizure reduction, development for Dravet syndrome presumably discontinued. ODD: Orphan Drug Designation year.

marketing authorization in 2014 to be used in combination with valproate and clobazam for the treatment of seizures in Dravet syndrome (EMA/476469/2014).

Diacomit acts by enhancing GABAergic transmission and it is a potent inhibitor of several cytochrome P450 isoenzymes, leading to an increase in the active metabolite of clobazam that is thought to be partly responsible for the efficacy observed.

Diacomit received the FDA orphan drug designation for treating seizures in Dravet syndrome in 2008, and the marketing authorization on 20 August 2018 (*FDA drug approval package, NDA 206709 and 207223*). Diacomit is indicated in the US for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.

After a 10-year period of market exclusivity following its initial approval by the EMA, Diacomit is no longer an orphan medicine in Europe, but it still enjoys 7 years of market exclusivity for the treatment of the Dravet syndrome in the US following the 2018 marketing authorization.

4.1.2. Epidiolex (cannabidiol) – GW Pharmaceuticals

Epidiolex (brand name Epidyolex in Europe) is a liquid formulation of plant-derived cannabidiol, a non-psychoactive component of the cannabis plant, developed and marketed by GW Pharmaceuticals. In the US, Epidiolex is marketed through GW's subsidiary Greenwich Biosciences. Epidiolex obtained orphan drug designations for the treatment of Dravet syndrome in 2013 (FDA) and 2014 (EMA). It received the FDA marketing authorization for the adjunctive treatment of seizures associated with Dravet and Lennox-Gastaut syndrome on June 2018, and the European approval on September 2019. Compared to the US approval, the European label is more restrictive as it specifies the indication as "adjunctive therapy of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam, for patients 2 years of age and older". As of December 2020, Epidyolex has launched in Germany and UK and is nearing commercial launches in France, Spain and Italy (*GW investor presentation December 2020*). In the mean time, it has also received an approval by FDA for the use in Tuberous Sclerosis Complex (August 2020; EMA submission under review) and it has been descheduled by DEA (April 2020) and reclassified by the UK Home Office as schedule 5 drug (May 2020), making it easier for patients to access Epidiolex.

The NDA and MAA package for Epidiolex included results from three Phase 3 studies and an open label extension study with a total of over 1,400 subjects treated. The Phase 3 trial in Dravet syndrome included data from 120 patients and was published in the New England Journal of Medicine (NCT02091375, Devinsky et al., 2017). The average reduction of seizure frequency while taking Epidiolex was 39% (primary endpoint), the percentage of patients who had at least a 50% reduction in convulsive seizure frequency was 43% (secondary endpoint), and the percentage of patients who had their overall condition improved according to their caregiver in the caregiver global impression of change scale was 62%

(CGIC, secondary endpoint). The difference between Epidiolex-treatment group and placebo in all of these endpoints was significant. In November of 2018, GW Pharma announced the results of a second Phase 3 clinical trial in Dravet syndrome (NCT 02224703), later published in JAMA Neurology (Miller et al., 2020). The trial included 199 patients divided into three arms including two doses of Epidiolex. Both trial doses met the primary and all key secondary endpoints and were consistent with a safe and tolerable profile, leading to FDA and EMA approvals.

4.1.3. Fintepla (fenfluramine) – Zogenix

Fenfluramine is a serotonin receptor agonist in development by Zogenix for the treatment of Dravet syndrome. It obtained orphan drug designations for the treatment of Dravet syndrome in 2013 (FDA) and 2014 (EMA). In 2020, Fintepla was approved by both FDA (June 2020, NDA 212102) and EMA (December 2020, EMA/CHMP/510338/2020), making it the third treatment indicated in both markets for the treatment of Dravet syndrome.

Unlike Diacomit and Epidyolex, the label for Fintepla in Europe does not require concomitant treatment with clobazm. In the US, both Epidiolex and Fintepla are indicated for the treatment of patients with Dravet syndrome without requiring concomitant treatment with clobazam.

Fintepla's approval is based on two positive pivotal trials which included a total of 232 patients with Dravet syndrome as well as data from an interim analysis of a long-term, open-label extension study in 330 Dravet syndrome patients treated up to 3 years. A first Phase 3 clinical trial resulted from a combination of two studies with identical trial protocol (NCT02682927 and NCT02826863), and was published in December 2019 (Lagae et al, 2019). The results were highly significant, with the dose of 0.8 mg/kg/day resulting in a 64% reduction in mean monthly convulsive seizures when compared to placebo (primary endpoint). Twenty-five percent of the patients treated with this dose of Fintepla experienced 0 or 1 seizures during the duration of the clinical trial. Both caregiver and investigator Global Impression of Change as well as pediatric Quality of Life were also highly significantly improved in the treated patients, and the drug had good tolerability. Cardiotoxicity was not observed in the study. On the basis of these results, Fintepla obtained the FDA Breakthrough Therapy Designation in Q1 2018, although following the approvals of Diacomit and Epidiolex in the US later that year, the FDA rescinded the designation (*Zogenix press release, May 2019*).

A second pivotal Phase 3 clinical trial (NCT02926898) followed the European standard of care in which the experimental drug is evaluated as an add on to stiripentol and used the same primary endpoint as the first study (reduction in mean monthly convulsive seizures when compared to placebo). The study was published in JAMA Neurology (Nabbout et al., 2020). When added to stiripentol and additional baseline medication, Fintepla led to a median reduction in monthly seizure frequency of 62.5%, versus 1.2% reduction in the placebo-treated group. As in the first study, no patient exhibited cardiac valvulopathy or pulmonary hypertension at any time in the study.

As of December 2020, Zogenix prepares for the first EU commercial launch in Germany in Q1 2021 after launching in the US in late July 2020. Zogenix also recently reported positive results of a third Phase 3 study of Fintepla in Dravet syndrome to support registration in Japan and is exploring potential uses for the treatment of seizures associated with other rare epilepsies (*Zogenix press release December 2020*).

4.1.4. Soticlestat (OV935 / TAK-935) – Ovid Therapeutics, Takeda

Soticlestat (also OV935 or TAK-935) is a first-in-class, highly selective inhibitor of the enzyme cholesterol 24 hydroxylase co-developed by Takeda and Ovid Therapeutics for the treatment of rare developmental and epileptic syndromes including Dravet syndrome. It obtained the orphan drug designation for the treatment of Dravet syndrome in 2017 (FDA).

OV935 is an indirect negative modulator of the NMDA receptor and has shown anti-epileptic activity in preclinical epilepsy and seizure models, including reducing seizure frequency and severity and preventing premature mortality in a mouse model of Dravet syndrome (*American Epilepsy Society meeting, December 2018*).

Ovid and Takeda completed a randomized, placebo-controlled, Phase 1b/2a basket trial with OV935 in adults with rare developmental and epileptic encephalopathies (NCT03166215). The primary objective of the trial was to assess safety and tolerability, and it enrolled 18 adults with developmental and epileptic encephalopathies (*Ovid press release, December 2018*). OV935 achieved the primary endpoint of safety and tolerability, also observing a potential drug-drug interaction with perampanel. During the latest period of seizure counting of the open-label phase (from day 65 of treatment to day 92), patients not taking perampanel had a median seizure frequency reduction of 61% and a 54.5% responder rate (*Ovid press release, December 2018*).

Ovid and Takeda also run two pediatric clinical trials with OV935: the ELEKTRA study (double-blind, placebo-controlled Proof-of-Concept) in patients with Dravet syndrome and Lennox-Gastaut syndrome, and the ARCADE (open-label) study in patients with CDKL5 deficiency disorder (CDD) and Duplication 15q (Dup15q) syndrome (*Ovid press release, September 2018*). The ELEKTRA Phase 2 trial (NCT03650452) met the primary endpoint of reducing seizure frequency in children with Dravet syndrome and Lennox-Gastaut syndrome (*Takeda press release, August 2020*). Specifically, the Dravet syndrome cohort of 51 patients demonstrated a 33.8% median reduction in convulsive seizure frequency compared to a 7.0% median increase in patients taking placebo during the full 20-week treatment period of the study (median placebo-adjusted reduction in seizure frequency wass 46.0%; p=0.0007). Based on these data, the companies announced plans to meet with regulatory authorities to discuss initiation of a Phase 3 registrational program for soticlestat in patients with Dravet syndrome (*Takeda press release, August 2020; Ovid press release, November 2020*).

4.1.5. SPN-817 (Huperzine A) – Supernus Pharmaceuticals

In September 2018, Supernus Pharmaceuticals announced tit had acquired Biscayne Neurotherapeutics, a company developing a proprietary formulation of huperzine A, previously known as BIS-001, for the treatment of epilepsy (*Supernus Pharma press release, September 2018*). Huperzine A is a brain-penetrant acetylcholinesterase inhibitor, originally extracted from a traditional Chinese medicine, with preclinical efficacy in multiple epilepsy models that has the potential to be a first-in-class treatment for epilepsy indications (Wong et al., 2016). SPN-817 received an orphan drug designation for the treatment of Dravet syndrome in 2017 (FDA).

The press release reporting the acquisition explained that "Supernus plans on studying SPN-817 initially in catastrophic pediatric epilepsy disorders such as Dravet Syndrome." A Phase I trial in in adult patients with refractory complex partial seizures was listed as ongoing in early 2019 (*Supernus SEC files, March 2019*) and is still listed as the current stage for the project (Supernus pipeline in company website, December 2020).

4.1.6. XP-0863 – Diazepam – Xeris Pharmaceutical

In 2018, Xeris Pharma obtained an orphan drug designation for the treatment of Dravet syndrome with a novel formulation of diazepam (FDA). The company describes the new formulation as an injectable alternative to rectal diazepam administration for the treatment of acute repetitive seizures and Dravet syndrome (*Xeris Pharma website*). In May of 2019, the company announced positive results from a Phase 1 study in healthy volunteers. Based on these results, Xeris anticipated initiating a Phase 2 open-label study with intramuscular administration of diazepam in patients with seizure disorders in 2H2019 (*Xeris Pharma press release, May 2019*). As of December 2020, the company indicates that it has received Fast Track designation by the FDA for the treatment of acute repetitive seizures and that is looking for a development and commercialization partner to advance the program (*Xerix press release, November 2020*). It is not clear if that will include further development of XP-0863 for Dravet syndrome or only for the treatment of acute repetitive seizures.

4.1.7. Second-generation serotonergic treatments – Eisai and Epygenix Therapeutics

Lorcaserin was approved under the commercial name Belviq for the treatment of obesity and marketed by Eisai. It has a similar mechanism of action to Fintepla (fenfluramine), but has no activity on 5HT2B, the serotonin receptor that appeared to drive the safety concerns that led to fenfluramine original withdrawal from the market. Therefore, lorcaserin was seen as a more promising therapeutic for obesity, targeting primarily 5HT2C receptors. However it followed fenfluramine's fate and was withdrawn from the market in February 2020 due to different safety concerns. In the meantime, lorcaserin had begun to be prescribed off-label to patients with Dravet syndrome, and Eisai agreed to keep those patients under an ongoing Expanded Access Program

(NCT04457687) following the voluntary withdrawal of Belviq from the market. In September 2020, Eisai announced the initiation of a Phase 3 trial with lorcaserin in Dravet syndrome (NCT04572243), enrolling 58 patients and with a target completion in late 2021 (protocol NCT04572243 and Eisai press release September 2020). Eisai received an orphan drug designation for the treatment of Dravet syndrome with lorcaserin in August 2020.

Epygenix Therapeutics is developing three drug candidates previously approved for other indications that also act via modulation of the serotonin signalling pathway for the treatment of Dravet syndrome and other genetic epilepsies: clemizole (EPX-100), lorcaserin (EPX-200) and trazodone (EPX-300). The three drug candidates obtained the orphan drug designation for the treatment of Dravet syndrome in 2017 (FDA). In September 2020, Epygenix initiated a 24-patient Phase 2 study with clemizole/EPX-100 in Dravet syndrome (NCT04462770).

4.1.8. Second-generation GABAergic treatments – NeuroCycle Therapeutics

In February 2019, NeuroCycle Therapeutics announced the award of a $0.5M Small Business Innovation Research grant from the NINDS to evaluate its advanced α2/α3 selective GABAA PAMs in models of Dravet Syndrome (*NeuroCycle press release*). The lead compound, named NCT10004 (previously alsoNCT10015), is currently undergoing IND-enabling studies, intended for the treatment of Dravet syndrome (*NeuroCycle website*). There have been no news on this program since 2019.

The benzodiazepine clobazam is not specifically approved for the treatment of Dravet syndrome but it is one of the most commonly used drugs in the disorder (Aras et al., 2015). Both Diacomit (stiripentol) and Epidiolex/ Epidyolex (cannabidiol) include in their approval label the indication to be “used in combination with clobazam”. Stiripentol, approved for the treatment of epilepsy in Dravet syndrome, is also increases GABAergic activity. NCT10015 therefore has the potential to be a next-generation GABAergic treatment for Dravet syndrome.

4.2. Disease-targeting treatments

4.2.1. Read-through therapies: Translarna (ataluren) – PTC Therapeutics, and Tevard Biosciences

Nonsense mutations are those that introduce a premature stop codon into a gene sequence, preventing the cell from producing a complete protein. So called “read-through therapies” enable the ribosome to move past this defect and complete a functional protein. In many genetic diseases a percentage of the patients carry nonsense mutations and are candidates for treatment with Translarna. 15-20% of patients with Dravet syndrome are estimated to carry nonsense mutations.

Ataluren is a read-through medication developed by PTC Therapeutics that is approved in Europe for the treatment of Duchenne muscular dystrophy patients

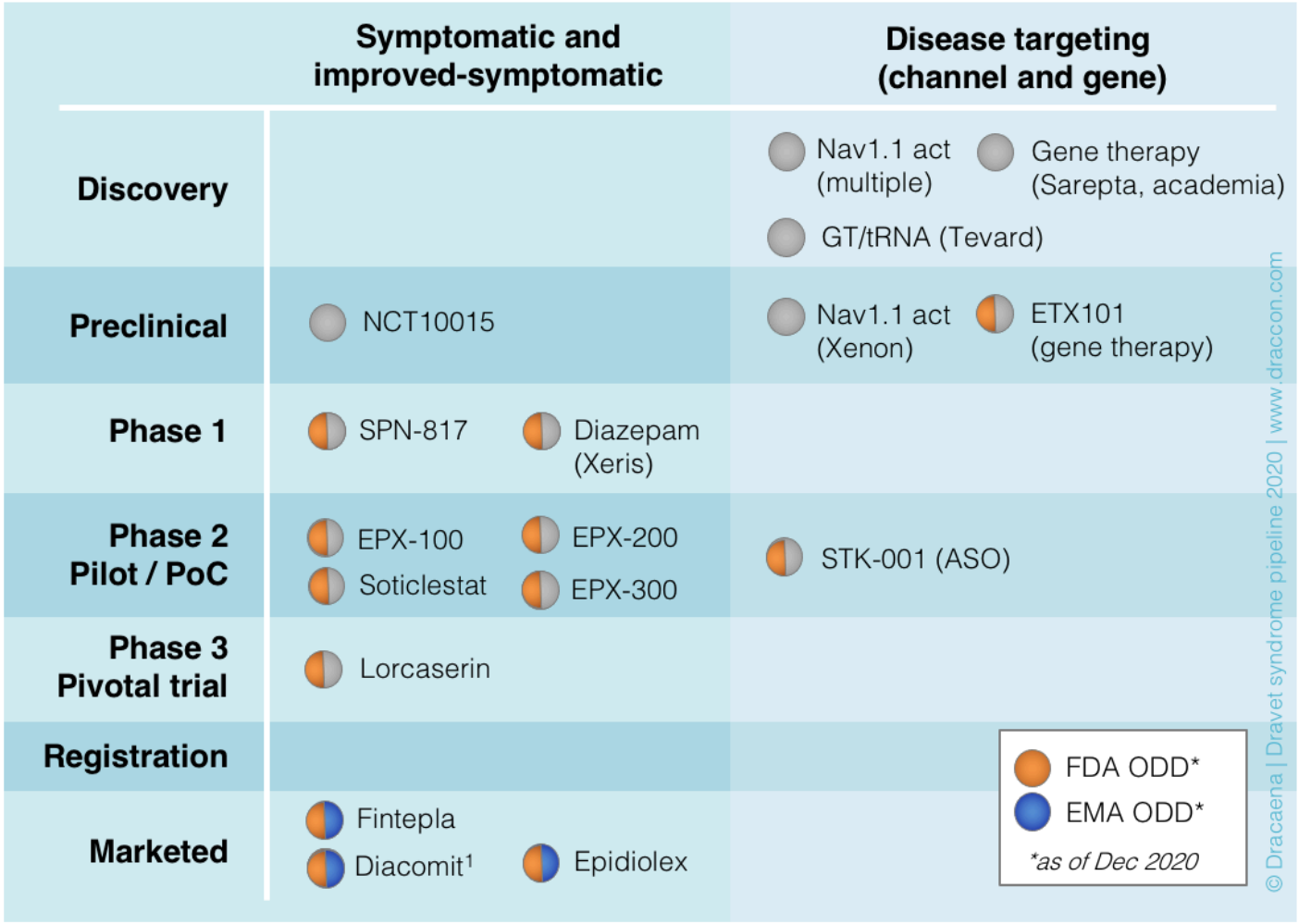

Figure 1 | **Dravet syndrome pipeline overview and maturity state**

Therapeutics that could be developed for Dravet syndrome but for which the developer has not indicated specific plans or intention to develop for Dravet syndrome are not included. [1]After 10 years in the market, stiripentol no longer has the orphan drug status in Europe

with nonsense mutations who are able to walk, under the brand name of Translarna (EMA provisional approval 2014, renewed in 2016).

An investigator-initiated study evaluated the safety and efficacy of ataluren for treating Dravet syndrome caused by nonsense mutations and the related CDKL5 deficiency syndrome caused by nonsense mutations (NCT02758626). The study failed to show efficacy in Dravet syndrome (*Devinsky, CDKL5 Forum 2020*) and is presumably discontinued for this indication. We have removed this program from the Dravet syndrome pipeline figure and table of companies with active programs (Figure 1 and Table 1).

In 2020, Tevard Biosciences announced that it is developing and applying two novel tRNA-based gene therapy platforms for the treatment of Dravet syndrome and other rare diseases caused by haploinsufficiency and/or nonsense mutations that are not amenable to traditional approaches to gene therapy (*company website*). In December 2020 it announced a

partnership with Zogenix to discover and advance novel drug candidates for the treatment of Dravet syndrome and other genetic epilepsies. Specifically, Tevard will utilize its two discovery platforms focused on mRNA stabilization and nonsense codon suppression (or read-though) as part of the collaboration (*Tevard Biosciences press release*).

4.2.2. ASO treatments: STK-001 – Stoke Therapeutics

Stoke Therapeutics is developing the first disease-modifying treatment for Dravet syndrome, an antisense oligonucleotide (ASO) therapy targeting SCN1A pre-mRNA maturation that upregulates Nav1.1 protein expression in rodents, human cell lines and non-human primates. The lead candidate uses Stoke's TANGO technology (Targeted Augmentation of Nuclear Gene Output) to target RNA splicing and increase protein expression in diseases caused by haploinsufficiency. The program, named STK-001, follows a similar approach to Spinraza and will be administered via intrathecal injection into the spinal fluid.

In June 2019, Stoke raised $142 million in an IPO, with STK-001 as the most advanced program in the company pipeline (*Stoke Therapeutics, Press release June 2019*). Details on the TANGO technology and the preclinical proof-of-concept for STK-001 in Dravet syndrome models have been published (Lim et al., 2020; Han et al., 2020). In mice with SCN1A haploinsufficiency, a single intracerebroventricular dose of a lead ASO increased production of Nav1.1 and met the two main preclinical endpoints in Dravet syndrome mouse models which are seizure reduction and animal survival (Han et al., 2020). Stoke has also shown biodistribution and target engagement of STK-001 in non-human primates (*AES 2019 meeting*) and dosed the first patient in a Phase 1a/2b study in August 2020 (*Stoke Therapeutics press release*).

The Phase 1a/2b study, known as the MONARCH trial (NCT04442295), is enrolling 48 participants, ages 2 to 18, in an open-label Single Ascending Dose study consisting of a single intrathecal ASO administration and a 7-month follow up. According to clinicaltrials.gov, the primary outcomes are safety and pharmacokinetics, and the secondary outcome measures include change in seizure frequency over 12 weeks, caregiver and clinical Global Impression of Change, and Quality of Life. With these secondary outcome measures, the Single Ascending Dose study is likely to already provide early efficacy data. Preliminary safety and pharmacokinetic data are anticipated in 2021 (*Stoke press release October 2020*). The FDA temporarily place a partial trial hold on the highest proposed dose, which was later cleared, and the company is preparing to add a Multiple Ascending Dose portion to the MONARCH study (*Stoke press release October 2020*).

In preparation for later-stage clinical trials, Stoke has started an observational study in Dravet syndrome patients ages 2 to 18, called the BUTTERFLY study, anticipated to last two years and to include a collection of clinical outcome measures with potential utility for future trials. At the American Epilepsy Society meeting in December 2020, Stoke

presented some early conclusions from the baseline assessment of the patients in the observational study establishing the feasibility of some neurocognitive assessments in this population. This study is likely to help guide clinical trial design in Dravet syndrome not only for STK-001 but also to all other programs targeting the disease biology.

4.2.3. Gene therapy: ETX101 – Encoded Therapeutics

Encoded Therapeutics is developing an AAV-based gene therapy approach to increasing SCN1A gene transcription and rescuing haploinsufficiency in patients with Dravet syndrome. The therapy, named ETX101, has the potential to become the second disease-modifying therapy to reach clinical trials for the treatment of Dravet syndrome after Stoke Therapeutics' ASO lead program.

ETX101, was granted Orphan Drug Designation and Rare Pediatric Disease Designation by the FDA for the treatment of SCN1A+ Dravet Syndrome (*Encoded Therapeutics, press release July 2020*).

The SCN1A gene had so far been deemed not amenable for AAV-based gene therapy due to its large size. Encoded was able to overcome the limitations of AAV viral gene therapy by expressing an engineered transcription factor to upregulate SCN1A expression in these cells, and presented preclinical date from their program in 2019 showing GABAergic cell-specific expression of SCN1A mRNA and Nav1.1 channel in a mouse model of Dravet syndrome, leading to a reduction in seizures and morality (*ASGCT and AES 2019*). In December 2020, the company also presented data on biodistribution of ETX101 in non-human primates, and prepares to start the first clinical trial in the second half of 2021 (*company website*). In preparation for interventional trials, Encoded has also initiated an observational study in patients with Dravet syndrome ages 6 to 60 months called ENVISION (NCT04537832) to explore the feasibility of cognitive, motor and behavioral assessments in addition to seizure-related aspects in this population and to help inform their clinical trials (*company website*).

4.2.4. Gene therapy: Sarepta and StradeBio

In November 2019, Sarepta announced a partnership with StrideBio to secure the rights to a collection of AAV-based gene therapies that includes a program for Dravet syndrome (*Sarepta press release November 2019*). There are no news on this program after the initial announcement. Sarepta currently has more than 40 programs in development (*company website*) and it is unclear how many of these are actively progressing. It is also unclear what approach the companies are using to target Dravet syndrome using AAV given the gene size limitations.

4.2.5. Nav1.1 activators: Xenon Pharma

Xenon Pharma, a Canadian company specialized in ion channel modulators, has identified selective small molecule potentiators of Nav1.1 activity and

presented early proof-of-principle in mice with SCN1A haploinsufficiency at the American Epilepsy Society meeting in December 2020 (*AES 2020 and Xenon press release December 2020*). Because patients with Dravet syndrome have 50% of the normal Nav1.1 channel levels, small molecule activators might be able to compensate for the reduced active protein levels, and represent a fourth and novel approach to treating haploinsufficiency in Dravet syndrome, complementing read-tough approaches, ASOs and gene therapies.

4.3. Other possible therapies for Dravet syndrome

The following programs have either been in development for Dravet syndrome previously and it is not clear if they are any longer active, or could potentially be developed for Dravet syndrome based on the drugs mechanism of action, or are still at early preclinical stages. These are therefore potential therapeutics that might join the Dravet syndrome pipeline.

4.3.1. Second-generation cannabidiol-based treatments

INSYS Therapeutics was developing a liquid formulation of cannabidiol for the treatment of epilepsy and had announced a Phase 3 trial in children and young adults with Dravet syndrome that was later withdrawn (NCT02318563). INSYS obtained an orphan drug designation for the treatment of Dravet syndrome with its synthetic cannabidiol oral solution in 2014 (FDA). The company filed for bankruptcy in June 2019 and Chilion Group Holdings US Inc acquired the rights for the program (*press release August 2019)*, which is currently development by Benuvia Therapeutics for Infantile Spasms and no longer being developed for Dravet syndrome (*company website*).

Zynerba Pharmaceuticals is developing a transdermal gel-formulation of synthetic cannabidiol for a number of indications including developmental and epileptic encephalopathies (ZYN002). The product also appears to be in development for other disorders and the company has not announced specific clinical trials plans in Dravet syndrome (company website).

It seems likely that Epidiolex will remain the only cannabidiol formulation to be specifically developed and approved for the treatment of Dravet syndrome, as follow up formulations explore different markets. We have therefore removed these programs from the Dravet syndrome pipeline figure and table of companies with active programs (Figure 1 and Table 1).

4.3.2. OPK88001 (CUR-1916) – OPKO Health

OPK88001 is an antisense oligonucleotide in development by OPKO Health that displaces an endogenous repressor of SCN1A transcription. Through this activity, OPK88001 increases expression of SCN1A and partly restores the level of Nav1.1 channel in affected tissues. It obtained the orphan drug designation for the treatment of Dravet syndrome from both the FDA (2017) and the EMA (2017).

In a mouse model of Dravet syndrome, the murine version of OPK88001 was

shown to increase expression of Nav1.1 by 30% and to significantly reduce seizures (Hsiao et al., 2016). The human-specific version of the oligonucleotide was also shown to successfully elevate gene transcription in the brain of a non-human primate (Hsiao et al., 2016).

Following the 2016 publication, OPKO communicated the expected initiation of clinical trials with OPK88001 in patients with Dravet syndrome (Phase 2a) within 2018. Details about the clinical trial protocol or timelines have not yet been made public. The program is listed as preclinical in the company website, but it is no longer listed in the corporate presentations since 2019 (*company website*). It is unclear if the program is delayed or if it has been discontinued. We have removed this program from the Dravet syndrome pipeline figure and table of companies with active programs (Figure 1 and Table 1).

4.3.3. Academic gene therapy and gene editing

There are several academic programs in early discovery stages that aim to develop gene therapy and gene editing approaches for patients with Dravet syndrome due to SCN1A mutations. Because of the early stage of these programs, they may or may not ultimately progress into the clinical phase.

In January 2020, a group from the San Raffaele Scientific Institute in Italy published early proof-of-concept with an approach to increase the activity of the endogenous SCN1A promoter by inserting enhancing elements with CRISPR/Cas9 (Colasante et al., 2020). There are also efforts ongoing to use lentiviral vectors or two AAVs to increase the levels of SCN1A in Dravet syndrome at UCL in the UK, and a European consortium is exploring the use of two additional large-capacity virus vectors, human and canine adenovirus, to deliver SCN1A to neurons in Dravet syndrome. None of these programs has been published. An Italian group from the Scuola Internazionale Superiore di Studi Avanzati (SISSA) is at early stages of exploring the use of RNA-based therapeutics to overexpress SCN1A expression from the good copy of the gene (*SISSA announcement*).

4.3.4. Sodium channel modulators: Lundbeck, The Gladstone Institute, Florey Institute

In addition to the program from Xenon, there are multiple efforts to develop small molecules or peptides able to selectively activate or open Nav1.1.

Lundbeck has a discovery program looking for Nav1.1 activators to treat a number of neurological conditions including epilepsy (Jensen et al., 2014; Frederiksen et al., 2017). Lundbeck has shown efficacy of the Nav1.1 activator AA43279 in a mouse model of induced seizures but has not yet published results in a mouse model of Dravet syndrome (Frederiksen et al., 2017). A recent publication reports efficacy of AA43279 in a zebrafish model of Dravet syndrome (Weuring et al., 2020). The Gladstone Institute of Neurological Disease also has an active program for discovering selective Nav1.1 activators, and Florey Institute of Neuroscience and Mental Health and the University of Melbourne has published a mouse study using intracerebroventricular infusion of the spider venom peptide and Nav1.1

activator Hm1a in mice with Dravet syndrome (Richards et al., 2018).

5. Dravet syndrome pipeline review – pipeline overview and maturity state

5.1. Moving towards disease-modification

Figure 1 summarizes the current state of the Dravet syndrome drug development pipeline as of December 2020. There are in total 11 individual programs ranging from preclinical to Phase 3 clinical trial stages, and three approved medications (Fintepla, Epidiolex, and Diacomit). Two of these programs are for the same molecule (lorcaserin, by Epygenix and Eisai). Additional, earlier discovery programs, searching for Nav1.1 channel activators and gene-replacement approaches, have also been highlighted.

With the recent European approval of Fintepla, there are now three approved medications for the treatment of Dravet syndrome in both the US and Europe. Some of these are also pursuing approvals in other territories but for the scope of this pipeline we have focused on these two territories. The approvals are not identical, with Diacomit label being restricted to patients already taking clobazam, and Epidyolex having the same limitation in the European label but not in the US.

Behind these frontrunners there are multiple compounds in the Dravet syndrome pipeline with a variety of mechanism of action.

From a high-level perspective, a partition of the Dravet syndrome pipeline into three larger categories becomes apparent:

(1) First generation of symptomatic therapeutics. These are first-in-class drugs that have either already demonstrated clinical efficacy for treating Dravet syndrome, or have a compelling preclinical data package that supports the use of the mechanism for Dravet syndrome. Although some of these mechanisms might have efficacy in multiple disease domains beyond improving seizure control, for the purpose of this review we will refer to therapies that do not target SCN1A or Nav1.1 as symptomatic. In addition to the already-approved Diacomit (GABA modulator), Epidiolex (cannabidiol) and Fintepla (fenfluramine), the first-generation approaches for the symptomatic treatment of Dravet syndrome include an indirect negative modulator of NMDA receptors (Soticlestat) and an acetylcholinesterase inhibitor (SPN-817).

(2) The proof of clinical efficacy obtained by Diacomit, Epidiolex and Fintepla for the GABAergic, cannabidiol and serotonergic classes opened the door to a second generation of aspiring best-in-class symptomatic treatments. This class includes fenfluramine follow-ups lorcaserin by Eisai and Epygenix and two additional repurposed candidates with serotonergic activity by Epygenix. NeuroCycle is also developing a next-generation GABAergic lead for the treatment of Dravet syndrome. Two cannabidiol formulations were also previously in development for Dravet syndrome.

(3) There is a growing class of therapeutic approaches from multiple modalities in development with the potential ability to directly treat the genetic defects that cause Dravet

syndrome, either by facilitating read-through in the case of nonsense mutations, by increasing expression of the functional SCN1A copy that all patients have, or by increasing activity of the ion channel. The most advanced programs are by Stoke Therapeutics and Encoded Therapeutics. These disease-targeting approaches represent a third generation of treatments, which are potentially disease-modifying, and where improvements across multiple disease symptoms are expected.

Overall the Dravet syndrome pipeline is currently very diversified and highly competitive, with best-in-class follow-up strategies already in place. It is also a relatively mature pipeline, with a number of disease-targeting and potentially disease-modifying programs already in development.

5.2. Moving towards SCN1A

Dravet syndrome is not a mono-genetic disorder. The diagnosis is based on clinical criteria, and for a large majority of patients (estimated around 80% of the cases) the Dravet syndrome clinical presentation results from mutations in the SCN1A gene. The remaining cases present Dravet syndrome due to different (likely genetic) factors.

The pipeline transition from symptomatic treatments to gene or protein-targeting treatments also means a transition from therapies that treat all patients with Dravet syndrome to therapies that are only indicated for those carrying SCN1A mutations.

On the one hand, this will impose restrictions in the drug label as the indication will be limited to a subset (albeit the majority) of cases with Dravet syndrome. On the other hand, these therapy modalities also have the potential to expand beyond Dravet syndrome, and will be able to target additional therapeutic indications, such as Alzheimer's disease or schizophrenia, which have been shown to be associated with reduced Nav1.1 protein levels or activity (Jensen et al., 2014).

Expansion of indication beyond Dravet syndrome is more likely for small molecules, such as the one from Xenon Pharma, than for the more invasive programs such as the antisense oligonucleotide from Stoke Therapeutics or the gene therapy from Encoded Therapeutics, which are likely better targeted to Dravet syndrome and other severe epilepsy presentations also caused by SCN1A mutations. In these additional severe clinical presentations, ASOs and gene therapy have the potential to impact multiple disease domains or comorbidities, and dramatically change the course of the neurodevelopmental disability. The progression and increasing number of these programs in the Dravet syndrome pipeline is a sign of pipeline maturity.

5.3. A necessary evolution in clinical trial design for Dravet syndrome

The transition from first-generation symptomatic treatments to disease-targeting and potentially disease-modifying treatments for Dravet syndrome requires a change in clinical trial design. With the exception of the Phase1b/2a study with the ASO STK-001, the current trial design, summarized in Table 1, is restricted to 12 to 14-week long trials measuring reduction in seizure frequency as the

primary endpoint, and, as a result, Diacomit, Epidiolex and Fintepla are all indicated "for the treatment of seizures associated with Dravet syndrome". It is likely the future approvals relying on seizure frequency as the primary endpoint will also be indicated for the treatment of seizures in the disorder, and not for the treatment of the disorder.

New clinical trials with antisense oligonucleotides and gene therapies will require a different trial design, including significantly longer trials with different clinical outcome measures. Section 6 reviews the challenges that the Dravet syndrome field faces, including trial readiness for these new treatment modalities, as well as the opportunities that it continues to offer to drug developers.

6. Challenges and opportunities

6.1. Challenge: Increasing competition

At the current stage of pipeline development, it is possible that Dravet syndrome will lose the initial appeal that drove many of the current programs in development to pursue this indication.

Several of the companies that are currently pursuing Dravet syndrome are developing drugs with anticonvulsant activity that are not new chemical entities. To offset their weaker intellectual property position, these companies target orphan forms of epilepsy in order to secure market protection through orphan drug market exclusivity. As a relatively common rare disease that is largely monogenic and that had, until recently, no FDA-approved drug, Dravet syndrome is an ideal target. However, one of the requirements by the EMA to secure orphan drug status after approval is to demonstrate significant benefit over existing approved medications. After Epidyolex and Fintepla it might be significantly harder to secure the orphan drug status for Dravet syndrome in Europe based only on seizure activity.

Given than most compounds with anticonvulsant activity could pursue many epilepsy indications, the increased competition around Dravet syndrome might drive sponsors away from the syndrome and towards other orphan disorders with epilepsy that have no approved medications yet, including CDKL5 Deficiency Disorder, PCDH19 encephalopathy or SCN2A-related disorders. As more patients get diagnosed with other rare epilepsy syndromes, these are poised to gain popularity as attractive target indications for drugs with anticonvulsant activity that want to be first or second to market and enjoy market exclusivity.

6.2. Challenge: Trial feasibility and trial design

For companies developing symptomatic drugs for the *treatment of seizures* in Dravet syndrome, the main current challenge is patient recruitment. The clinical trial protocol for this indication has been de-risked, regulators agree on endpoints, trial duration is clear, and there are plenty of well-established medical centers able to carry out these trials. The main challenge, therefore, is to reach sufficient patients who are not currently

taking one of the additional experimental medications, either as part of a clinical trial, or an open-label extension, or under compassionate use. The recent approvals of Epidiolex and Fintepla in both the US and Europe will ease this burden, making all of the patients currently taking these medications eligible to enroll in additional trials provided that they meet the enrollment criteria. Opening eligibility to patients over 18 years of age will also make recruitment easier, since previous clinical trials have capped enrollment age to 18 years old or younger. Last, increased disease awareness following three drug approvals is likely to lead to increased diagnosis and a larger patient community that might become available for clinical trials.

As discussed before, companies might want to include endpoints beyond seizure frequency in their clinical trials in order to demonstrate broader efficacy and obtain a label not restricted to the treatment of epilepsy (seizures) in Dravet syndrome. This differentiation will be important to demonstrate significant benefit in Europe, maintaining orphan status, and to secure a better pricing position. Some of the first-generation drugs in the Dravet syndrome pipeline, like Soticlestat from Takeda and Ovid and SPN-817 from Supernus, are expected to provide a broad therapeutic benefit to patients with Dravet syndrome based on their mechanism of action and would be excellent candidates to go after the broader label. Disease-modifying therapeutics that act by increasing gene and protein expression, and that are also more invasive treatments than current oral small molecule approaches, will also need to show broader efficacy beyond seizures in order to provide a better benefit-risk ratio.

Two important developments that will be needed are the development and validation of non-seizure-related endpoints suitable for documenting improvements in other disease domains, as well as most likely extending the duration of the clinical trial treatment phase beyond the current 3-month period to enable the capture of these new clinical outcomes.

The current observational studies by Stoke Therapeutics and Encoded Therapeutics have been specifically designed to inform companies and regulators about outcome measures and potential endpoints for the upcoming "beyond seizures" clinical trials, and Stoke already presented some baseline data from their study indicating feasibility for some neurocognitive assessments in this population (*AES 2020*). The way these studies are being designed and implemented makes them exceptionally valuable not only for the respective companies but for the entire Dravet syndrome field, helping it transition from a "Dravet syndrome as an epilepsy" stage into a "Dravet syndrome as an neurodevelopmental disorder" new drug development and trial design stage.

These studies are different from classical Natural History Studies which are often broader in scope (for example Encoded Therapeutic's observational study is focused on kids younger than 5), use assessments that are of clinical utility but might not be of regulatory utility, and are often not run using the same methodology as interventional studies. These design and methodological differences limit the usefulness of many

Natural History Studies for informing interventional trial design, when compared to these trial-enabling observational studies. Additionally, some of these trial-enabling observational studies, which follow interventional study design and methodology and might include capture of safety-like events, might potentially be used to replace or contribute to comparator arms in trials, which is particularly valuable for gene therapies.

It is likely that additional companies developing advanced therapeutics for Dravet syndrome will not need to sun similar studies of their own and instead will follow the clinical trial designed agreed by regulators and Stoke, and potentially Encoded, in particular if these trial designs prove successful in the initial studies.

6.3. Challenge: Biodistribution

Companies developing advanced therapeutics for Dravet syndrome face an important additional challenge which is the one of reaching the target cells in the target brain regions. Some of this challenge is technological (for example limited biodistribution of some viral vectors) and some is scientific (for example knowing which cells require Nav1.1 or how much they need). This does not apply to small molecules that act on other pathways, such as the ones reviewed in section 4.1. For a more complete list and discussion of these challenges we refer the reader to the Pipeline 2019 review.

On the scientific front, it appears clear that overexpression of SCN1A beyond wild-type levels is not toxic, based on Stoke Therapeutics data in wild-type mice and non-human primates, the existence of a BAC mouse overexpressing SCN1A, and the absence of a "SCN1A duplication syndrome" in the medical literature. But it is not yet clear if restoring wild-type expression is necessary in order to see disease improvement, or if partial rescue of expression will be sufficient (or which symptoms will improve with partial rescue, versus which ones require full rescue). It is also still unclear if restoring SCN1A expression only in GABAergic neurons has different outcomes to general SCN1A increase in different cell populations, or how broad expression throughout the brain is needed.

Technologically, the main challenge with advanced therapeutics is to achieve sufficient distribution throughout the brain, given that Dravet syndrome is neurological and requires gene rescue across the brain, as opposed to very localized gene delivery. This is determined both by the modality chosen (ASO vs virus, and AAV vs other virus types) and by the route of administration, and is currently a major challenge for CNS treatments. For therapies that require repeated brain administration such as ASOs, developing the best reagent that minimizes the frequency of administration required will also limit the burden to patients, improving trial recruitment and retention and quality of life.

6.4. Challenge: Biomarkers

There is no measurable peripheral expression of SCN1A, and advanced treatments are likely to use central administration. This creates the challenge of being able to measure Nav1.1 expression in the brain to

confirm target exposure and desired expression levels. Because of the need for interim results assessment, measuring an increase in Nav1.1 levels or GABAergic network activity might also help confirm proof-of-mechanism and appropriate target engagement. It will also add supporting information that any perceived improvement is due to normalization of GABAergic network activity, and the measurements might also be needed for marketing authorization.

Therapies requiring multiple brain administrations such as ASOs might be able to measure SCN1A or Nav1.1 in the CSF, but "once only" viral-based approaches still need to identify alternative ways to confirm target engagement (i.e. Nav1.1 increase). Short of a direct measurement of Nav1.1 protein level, some of the network image signatures such as gamma-wave oscillations might be used a surrogate or network normalization (presumably due to rescue of protein levels). It would be recommendable to include these potential biomarkers in the trial design.

6.5. Challenge: Change in the Standard of Care

The arrival of Fintepla to the US and EU markets will lead to a change in the Standard of Care and reduce the fraction of patients with Dravet syndrome that currently quality for clinical trials. Before Epidiolex and Fintepla, about half of the patients with Dravet syndrome in Europe did not meet the usual criteria for inclusion of 4 convulsive seizures a month (Aras et al., 2015). With the arrival an adoption of these two medications, in particular Fintepla, this fraction is likely to be reduced substantially, making it not only harder to recruit patients into studies (if enrollment criteria remain as it is) but also questioning how representative that fraction of the population would be.

It is likely that seizure reduction will remain as a primary endpoint in clinical trials for Dravet syndrome, even with advanced therapeutics that are likely to also improve multiple comorbidities. However, because clinical trials for these therapeutics are likely to be longer than 12 weeks, it might be possible to include patients with less seizure frequency and still collect enough seizures over time to be able to determine efficacy in this outcome. The main challenge of a post-Fintepla Standard of Care will be for other anticonvulsant medications in development, as these are likely to be still assessed using the current short trial design. Fintepla is still not widely available, but trials starting in 2022 or later will face a challenge to find sufficient number of patients who have had access to the Standard of Care yet remains with high enough seizure frequency to make 12-week trials feasible.

6.6. Opportunity: Why Dravet syndrome is an excellent indication for these new approaches

Despite this list of challenges, Dravet syndrome remains an excellent indication for many new approaches able to address neurological rare diseases. Because the disease is a haploinsufficiency, it enables the development of therapeutics that target the non-mutated gene copy, to boost expression, or that target the existing ion channels to increase their activity. We have a good understanding of the

disease epidemiology, and the patient population is large for a rare disease. This makes the disorder rare enough to qualify as an orphan indication, and common enough to make clinical trials feasible and provide an attractive market. There are also established networks of clinical centers with experience running clinical trials, and it is easy to identify KOLs and suitable trial sites. The convenience of seizures as a suitable endpoint makes the disease much less risky than other rare neurological diseases, such as those in the autism spectrum, where an effective treatment might fail a trial due to a poor choice of clinical outcome measures. Seizures might also provide an earlier readout of efficacy, and with the outcome measure research currently being done by Stoke and Encoded, new clinical trial design will also soon be de-risked for future advanced therapeutics. Dravet syndrome also has excellent preclinical models with translational outcomes, making the preclinical development and the research of target protein levels, cell populations or brain regions much easier than diseases where preclinical models fail to recapitulate patient phenotypes. Last, the patient community in Dravet syndrome is well-organized and very mature, offering the possibility to collaborate with drug developers and be not just the potential customer or a source of trial volunteers, but also key partners in the process of developing a new therapy.

Therefore, the growing competition around developing anticonvulsant medications with efficacy in Dravet syndrome does not mean that there is no unmet medical need or that there is no space for new therapeutics. On the contrary, the burden of Dravet syndrome is significant, and the unmet medical need still includes (1) poor seizure control for 90% of the patients, (2) early mortality in 15 to 20% of the patients, (3) no medications to treat the non-seizure aspects of the syndrome, and (4) a large number of patients not receiving the standard of care because of not having a correct diagnosis.

For companies developing medications able to treat the non-seizure aspects of the disease, and in particular for companies able to develop therapeutics that will rescue the gene or the protein defects, Dravet syndrome remains an excellent therapeutic indication with many advantages for drug development over other rare diseases.

7. Summary

Dravet syndrome is an orphan epilepsy disorder with multiple non-seizure comorbidities and high unmet medical need. In the last 7 years, Dravet syndrome has gained significant attention from the pharmaceutical industry, and the pipeline has grown from only one drug approved (stiripentol, ex-US) to a dozen of development programs and three approved drugs. Some of this popularity is due to an industry-wide move away from highly competitive large indications (such as non-orphan epilepsy) and towards orphan indications.

The Dravet syndrome pipeline shows signs of maturity, with a third generation of disease-targeting treatments, including small molecules, ASOs and viral-based gene therapies, differentiating themselves from the first and second generation of symptomatic treatments. 2020 marked a transition of the Dravet syndrome pipeline with the first trial of an ASO therapy that increases SCN1A mRNA levels.

As the Dravet syndrome pipeline evolves from symptomatic treatments to disease-targeting therapeutics, new challenges emerge. The success of the disease-targeting programs that are reaching and initiating clinical trials will depend on the quality of natural history studies, the development and validation of non-seizure outcome measures, and the identification of suitable biomarkers. Changes in the Standard of Care after Fintepla will also impact future clinical trials design and feasibility.

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Among the featured companies, Ana Mingorance PhD has acted as a consultant for GW Pharmaceuticals, Ovid Therapeutics, and Encoded Therapeutics. None of the featured companies was involved or provided any funding for this report. All information about drug development programs used for the pipeline review has been collected from publicly available sources including clinical trial databases, publications, conference presentations, press releases, company websites, and SEC filings. Opinions expressed on the clinical and drug development perspective section are those of the author alone.

REFERENCES

Aras LM, Isla J, Mingorance-Le Meur A. The European patient with Dravet syndrome: results from a parent-reported survey on antiepileptic drug use in the European population with Dravet syndrome. Epilepsy Behav. 2015 Mar;44:104-9.

Auvin S, Irwin J, Abi-Aad P, Battersby A. The Problem of Rarity: Estimation of Prevalence in Rare Disease. Value Health. 2018 May;21(5):501-507.

Bayat A, Hjalgrim H, Møller RS. The incidence of SCN1A-related Dravet syndrome in Denmark is 1:22,000: a population-based study from 2004 to 2009. Epilepsia. 2015 Apr;56(4):e36-9.

Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain. 2012 Aug; 135(Pt 8):2329-36.

Ceulemans B. Overall management of patients with Dravet syndrome. Dev Med Child Neurol. 2011 Apr;53 Suppl 2:19-23.

Chiron C. Current therapeutic procedures in Dravet syndrome. Dev Med Child Neurol. 2011 Apr;53 Suppl 2:16-8.

Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet. 2001 Jun;68(6): 1327-32.

Colasante G, Lignani G, Brusco S, Di Berardino C, Carpenter J, Giannelli S, Valassina N, Bido S, Ricci R, Castoldi V, Marenna S, Church T, Massimino L, Morabito G, Benfenati F, Schorge S, Leocani L, Kullmann DM, Broccoli V. dCas9-Based Scn1a Gene Activation Restores Inhibitory Interneuron Excitability and Attenuates Seizures in Dravet Syndrome Mice. Mol Ther. 2020 Jan 8;28(1): 235-253.

Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S; Cannabidiol in Dravet Syndrome Study Group. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017 May 25;376(21):2011-2020.

de Lange IM, Gunning B, Sonsma ACM, van Gemert L, van Kempen M, Verbeek NE, Nicolai J, Knoers NVAM, Koeleman BPC, Brilstra EH. Influence of contraindicated medication use on cognitive outcome in Dravet syndrome and age at first afebrile seizure as a clinical predictor in SCN1A-related seizure phenotypes. Epilepsia. 2018 Jun; 59(6):1154-1165

Dravet, C. (2011), The core Dravet syndrome phenotype. Epilepsia, 52: 3-9

Frederiksen K, Lu D, Yang J, Jensen HS, Bastlund JF, Larsen PH, Liu H, Dekermendjian K, Badolo L, Laursen M, Hougaard C, Yang C, Svenstrup N, Grunnet M. A small molecule activator of Nav1.1 channels increases fast-spiking interneuron excitability and GABAergic transmission in vitro and has anti-convulsive effects in vivo. Eur J Neurosci. 2017 In Press

Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome. Epilepsia. 2011 Apr;52 Suppl 2:44-9.

Guerrini R. Dravet syndrome: the main issues. Eur J Paediatr Neurol. 2012 Sep;16 Suppl 1:S1-4.

Hsiao J, Yuan TY, Tsai MS, Lu CY, Lin YC, Lee ML, Lin SW, Chang FC, Liu, Pimentel H, Olive C, Coito C, Shen G, Young M, Thorne T, Lawrence M, Magistri M, Faghihi MA, Khorkova O, Wahlestedt C. Upregulation of Haploinsufficient Gene
Expression in the Brain by Targeting a Long Non-coding RNA Improves Seizure Phenotype in a Model of Dravet Syndrome. EBioMedicine. 2016 Jul;9:257-277

Han Z, Chen C, Christiansen A, Ji S, Lin Q, Anumonwo C, Liu C, Leiser SC, Meena, Aznarez I, Liau G, Isom LL. Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. Sci Transl Med. 2020 Aug 26;12(558):eaaz6100

Jensen HS, Grunnet M, Bastlund JF. Therapeutic potential of Na(V)1.1 activators. Trends Pharmacol Sci. 2014 Mar; 35(3):113-8. doi: 10.1016/j.tips.2013.12.007.

Lagae L, Brambilla I, Mingorance A, Gibson E, Battersby A. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol. 2018 Jan;60(1):63-72.

Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, Devinsky O, Cross JH, Guerrini R, Talwar D, Miller I, Farfel G, Galer BS, Gammaitoni A, Mistry A, Morrison G, Lock M, Agarwal A, Lai WW, Ceulemans B; FAiRE DS Study Group. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2019 Dec 21;394(10216):2243-2254

Lim KH, Han Z, Jeon HY, Kach J, Jing E, Weyn-Vanhentenryck S, Downs M, Corrionero A, Oh R, Scharner J, Venkatesh A, Ji S, Liau G, Ticho B, Nash H, Aznarez I. Antisense oligonucleotide modulation of non-productive alternative splicing upregulates gene expression. Nat Commun. 2020 Jul 9;11(1):3501

Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, Saneto RP, Checketts D, Dunayevich E, Knappertz V; GWPCARE2 Study Group. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. JAMA Neurol. 2020 May 1;77(5): 613-621

Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, Stephani U, Laux L, Wirrell E, Knupp K, Chiron C, Farfel G, Galer BS, Morrison G, Lock M, Agarwal A, Auvin S; FAiRE, DS Study Group. Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA Neurol. 2020 Mar 1;77(3): 300-308

Richards KL, Milligan CJ, Richardson RJ, Jancovski N, Grunnet M, Jacobson LH, Undheim EAB, Mobli M, Chow CY, Herzig V, Csoti A, Panyi G, Reid CA, King GF, Petrou S. Selective Na(V)1.1 activation rescues Dravet syndrome mice from seizures and premature death. Proc Natl Acad Sci U S A. 2018 Aug 21;115(34):E8077-E8085

Rosander C, Hallböök T. Dravet syndrome in Sweden: a population-based study. Dev Med Child Neurol. 2015 Mar 13;57(7):628-633

Symonds JD, Zuberi SM, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort, Brain, Volume 142, Issue 8, August 2019, Pages 2303–2318

Weuring WJ, Singh S, Volkers L, Rook MB, van 't Slot RH, Bosma M, Inserra M, Vetter I, Verhoeven-Duif NM, Braun KPJ, Rivara M, Koeleman BPC. NaV1.1 and NaV1.6 selective compounds reduce the behavior phenotype and epileptiform activity in a novel zebrafish model for Dravet Syndrome. PLoS One. 2020 Mar 5;15(3):e0219106

Wong JC, Dutton SB, Collins SD, Schachter S, Escayg A. Huperzine A Provides Robust and Sustained Protection against Induced Seizures in Scn1a Mutant Mice. Front Pharmacol. 2016 Oct 17;7:357.

Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, Kuzniewicz MW. Incidence of Dravet Syndrome in a US Population. Pediatrics. 2015 Nov;136(5):e1310-5.