Dravet syndrome pipeline and opportunities review | 2022

Dravet syndrome is a genetic 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. There are three symptomatic treatments approved by both the FDA and the EMA for the treatment of seizures in Dravet syndrome: Diacomit (stiripentol), Epidiolex/Epidyolex (cannabidiol oral formulation) and Fintepla (fenfluramine). The latter two led to multi-billion acquisitions of GW Pharma by Jazz Pharma, and of Zogenix by UCB Pharma. Takeda has taken sole ownership of soticlestat, currently in Phase 3 trials, after co-development with Ovid Therapeutics. There is already preliminary efficacy data for the first treatment specifically designed to increase SCN1A levels (STK-001 from Stoke Therapeutics), and there are additional genetic and potentially disease-modifying treatments in early and late preclinical development. Overall the Dravet syndrome pipeline comprises 3 approved drugs and 16 additional treatments in development from late preclinical to Phase 3. This report reviews the state of the Dravet syndrome drug development pipeline as of December of 2022 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, often denominated as developmental and epileptic encephalopathies or DEEs. 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 include those programs in development for the symptomatic treatment of Dravet syndrome or for the disease-modifying treatment of SCN1A-related epilepsies, and not programs specifically designed to correct other genes (e.g. GABRG2, SCN1B).

The pharmacological management of Dravet syndrome focuses largely on the use antiepileptic 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 antiepileptic drugs, most commonly including the drugs valproate, clobazam, stiripentol, cannabidiol and fenfluramine. Only a minority of about 10% of patients are seizure-free (Aras et al., 2015, Lagae et al., 2018), although these statistics need to be reviewed after broadspread market uptake of fenfluramine.

The first generation of therapies developed for Dravet syndrome 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 an emergent class of second-generation drugs pursuing the de-risked mechanism of action of approved treatments, notably follow-ons to fenfluramine (Fintepla). Most of these compounds would have the potential to treat other forms of epilepsy.

A third generation of treatments, which address the cause of the disease by seeking to restore the abnormal Nav1.1 channel function or expression levels, is also under development and the most advanced program (STK-001 from Stoke Therapeutics) is already in Phase 2 trials. As the Dravet syndrome pipeline becomes more mature and competition increases, the pipeline is shifting towards less symptomatic treatments and more disease-targeting approaches. This shift in treatment modality is also leading to a shift in trial design.

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; Bayat et al., 2015; Wu et al., 2015; Rosander and Hallböök 2015). Recent incidence studies of children with epilepsy increase the incidence of epilepsy caused by 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 diagnosed prevalence of Dravet syndrome in Europe as about 11,000 cases (Auvin et al., 2018). Taking all these factors into account, the Dravet syndrome prevalence in the major markets is estimated to be about 30,000 patients (28,000 estimate from Ovid Therapeutics for US + EU5; 35,000 estimate from Stoke Therapeutics for US, Canada, Japan, Germany, France and UK).

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 developing treatments for Dravet syndrome are also eligible for the Rare Pediatric Disease Designation by the FDA that might result in a Priority Review Voucher after drug approval. Priority Review Vouchers are a tradeable

commodity and help maximize the return on investment in therapeutics targeting rare pediatric diseases.

Epidiolex/Epidyolex (cannabidiol oral solution) by GW Pharmaceuticals launched in the US in 2018 and is on track to launch in the 5 major European / UK countries by end of 2022 following approval in late 2019. It is currently approved for Dravet syndrome, Lennox-Gastaut syndrome (LGS) and Tuberous Sclerosis Complex. The US list price for Epidiolex is an average of $32,500 per patient per year depending on patient's weight, and has been projected to reach peak sales of $2,5B by 2027 combining these three indications plus off-label use (*Bank of America projections from 2020*). GW Pharma was subsequently acquired by Jazz Pharma in 2021 for $7.2B because of the blockbuster potential of Epidiolex/Epidyolex.

Fintepla (fenfluramine) by Zogenix launched in the US in June 2020, with an average list price of about $96,000 per patient per year, or about three times the cost of Epidiolex, and is also projected to grow into blockbuster sales with the combined sales from Dravet syndrome, LGS and potential following indications *(Pharmaceutical Technology 2020 article).* UCB Pharma acquired Zogenix for $1.9B in March 2022.

Following the steps of GW Pharma and Zogenix, Takeda is also developing a small molecule called soticlestat for the treatment of Dravet syndrome and LGS. The program was initially brought into the clinic as a co-development together with Ovid Therapeutics, but in 2021 after positive data form Phase 2 studies Takeda secured the global rights for soticlestat back from Ovid, with Ovid eligible to receive up to $856M in payments, including $196M upfront *(company press release)*.

These three programs validate a commercial model that we can call the "Dravet syndrome plus" model, where anti-seizure drugs are developed for 2 or 3 rare epilepsy syndromes with Dravet syndrome as the first indication, seeking a potential combined blockbuster market and leading to successful exits as trade sale or through product license to larger companies.

3. Therapeutics development: clinical and preclinical protocols

The current clinical trial design for Dravet syndrome follows the usual standards for antiepileptic medications, with the exception of two new disease-targeting treatments from Stoke Therapeutics and Encoded Therapeutics.

Sixteen double-blind placebo-controlled trial protocols for Dravet syndrome have been listed by a total of 10 companies, not including open-label trials or academic trials (Table 1). The ten products are stiripentol (Biocodex), cannabidiol (GW Pharma/Jazz), fenfluramine (Zogenix/UCB Pharma), lorcaserin (Eisai), soticlestat (Takeda), ataluren (PTC Therapeutics), EPX-100 (Epygenix), LP352 (Longboard Pharma), STK-001 (Stoke Therapeutics) and ETX101 (Encoded Therapeutics).

Except for the last two products, which are an antisense oligonucleotide (ASO) and a gene therapy, all other programs are for anticonvulsant small molecules and followed the same trial design template. The main protocol elements

Compound	Sponsor	Trial Identifier	Number of patients	Age (years)	Treatment phase	Efficacy endpoint	Status (Dec 2022)
Diacomit (stiripentol)	Biocodex	STICLO-FR STICLO-IT	41 and 24	3-18	2 months	50% seizure reduction (responder rate)	FDA and EMA approved
Epidiolex (cannabidiol)	GW Pharma (now Jazz Pharma)	NCT02091375 NCT02224703	120 and 186	2-18	14 weeks	% change in convulsive seizures	FDA and EMA approved
Fintepla (fenfluramine)	Zogenix (now UCB)	NCT02682927* NCT02826863* NCT02926898	*combined; 119 and 115	2-18	14 weeks	% change in convulsive seizures	FDA and EMA approved
Belviq (lorcaserin)	Eisai	NCT04572243 (MOMENTUM1)	58	2+	14 weeks	% change in convulsive seizures	Phase 3, recruiting
Soticlestat (TAK-935)	Takeda	NCT03650452 (ELEKTRA) NCT04940624 (SKYLINE)	60 142	2-17 2-21	12 weeks 16 weeks	% change in convulsive seizures	Completed Phase 2 Phase 3 recruiting
Translarna (ataluren)	NYU/PTC	NCT02758626	8	2-12	12 weeks	Safety (secondary: % change in seizures)	Completed Phase 2
EPX-100 (clemizole)	Epygenix	NCT04462770 (ARGUS)	100	2-17	20 weeks	% change in convulsive seizures	Phase 2, recruiting
LP352	Longboard Pharma	NCT05364021 (PACIFIC)	50	12-65	75 days (15+60d)	Safety (secondary: % change in seizures)	Phase 2 recruiting
STK-001	Stoke Therapeutics	NCT04442295 (MONARCH) ISRCTN99651026 (ADMIRAL)	up to 134 up to 60	2-18	24 weeks	Safety (secondary: % change in seizures)	Phase 1/2 recruiting Phase 1/2 recruiting
ETX101	Encoded Therapeutics	NCT05419492 (ENDEAVOR)	22	6-36 months	52 weeks (seizure at week 16)	Safety (secondary: % change in seizures)	Not yet recruiting

Table 1 | **List of corporate double-blind placebo-controlled clinical trials in Dravet syndrome ordered by the stage of each program.** Open-label extension trials, withdrawn trials or academic trials not included.

are 12 to 14 weeks of treatment duration as an add-on to baseline medication, patients ages 2 to 18 years old, and percentage change from baseline in frequency of convulsive seizures per 28 days (as compared to placebo) primary endpoint. Clinical trials often include the percentage of responder patients, defined as patients experiencing a reduction in seizures of 50% of more, as an additional endpoint, as this is often requested by the EMA. Two additional trials with cannabidiol (INSYS) and with clobazam (Lundbeck) were listed in the past and later withdrawn and also followed this standard trial design.

The clinical program for the ASO STK-001 includes a Single Ascending Dose Phase 1 followed by a Multiple Ascending Dose Phase 2 directly in patients with endpoints measured after 6 months. Although the primary outcomes are safety- and PK-related, the main efficacy (secondary) outcome of the study is also reduction in seizure frequency. Encoded Therapeutics has already listed their first trial in patients with the gene therapy ETX101 although as of December of 2022 the trial is not yet recruiting and is awaiting for an IND. The single-administration gene therapy will also follow a 2-part Phase 1/2 trial, starting with open-label dose escalation and moving into a randomized, double-blind, sham delayed-treatment control, dose-selection study. They primary outcomes are safety related and the main efficacy (secondary) outcome of the study is also reduction in seizure frequency measured at week 16.

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

Importantly, there is a mouse model of Dravet syndrome available for preclinical drug testing through the Epilepsy Therapy Screening Program of the NINDS (http://www.nind.nih.gov/ETSP).

4. Dravet syndrome pipeline review – individual programs

The following sections review the state of the Dravet syndrome drug development pipeline as of December of 2022 (Table 2), focusing on the developments since the publication of the December 2020 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

Company	Product name(s)	Stage Dec 2022	ODD / OMPD
Biocodex	Diacomit (stiripentol)	Market	2008/2001[1]
Bright Minds Biosciences	BMB-101 (5HT agonist)	Phase 1	- / -
CAMP4 (OPKO program)	CMP-SCN (ASO)	Preclinical	2017 / 2017
Encoded Therapeutics	ETX101 (Gene Therapy)	Preclinical	2020 / -
Epygenix Therapeutics	EPX-100 (clemizole)	Phase 2 (placebo)	2017 / -
	EPX-200 (lorcaserin)	Phase 2 (open label)	2017 / 2021
	EPX-300 (trazodone)	Phase 2 (open label)	2017 / -
Eisai	Lorcaserin	Phase 3	2020 / -
Jazz (former GW Pharma)	Epidiolex / Epidyolex (cannabidiol)	Market	2013 / 2014
Longboard Pharma	LP352 (5HT agonist)	Phase 1/2	- / -
Lundbeck	Nav1.1 activators	Preclinical	- / -
Neuroene Therapeutics	NT102 (vitK analogue)	Preclinical	2021 / -
PTC Therapeutics	Translarna (ataluren)	Phase 2 (placebo)[2]	- / -
reMYND	ReS3-T (Pde6δ)	Preclinical	- / -
Sarepta / StrideBio	Gene Therapy	Preclinical	- / -
Stoke Therapeutics	STK-001 (ASO)	Phase 1/2	2019 / 2022
Sumitomo Pharmaceuticals	DSP-0378 (GABA PAM)	Phase 1	- / -
Supernus Pharmaceuticals	SPN-817 (huperzine A)	Phase 2 (open label)	2017 / -
Takeda	Soticlestat (OV935)	Phase 2 (placebo)	2017 / -
Tevard Bio	Gene Therapy / tRNA	Preclinical	- / -
UCB (former Zogenix)	Fintepla (fenfluramine)	Market	2013 / 2014
Xenon Pharma	5HT agonist	Preclinical	2022 / -
	Nav1.1 activators	Preclinical	- / -
Xeris Pharmaceutical	Diazepam	Phase 1	2018 / -

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

ODD: Orphan Drug Designation (FDA); OMPD: Orphan Medicinal Product Designation (EMA). 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.

Designation, and planned trial initiation or IND/NDA filing, are also reported for each compound or genetic therapy 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 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 marketing authorization in 2014 to be used in combination with valproate and clobazam for the treatment of seizures in Dravet syndrome (EMA/476469/2014).

Stiripentol acts by enhancing GABAergic transmission and 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. At the American Epilepsy Society meeting in 2022 Biocodex reported additional mechanisms as potentially related to stiripentol anti-seizure activity.

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 initial approval in the US was for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. This approval has been expanded in 2022 to include patients 6 months of age and older, weighing 15 pounds or more and 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 by GW Pharmaceuticals and initially marketed in the US through its subsidiary Greenwich Biosciences. The company was acquired in 2021 by Jazz Pharma for $7.2B *(company press release).*

Epidiolex/Epidyolex obtained Orphan Drug Designations for the treatment of Dravet syndrome in 2013 (FDA) and 2014 (EMA). It first received the FDA marketing authorization for the adjunctive treatment of seizures associated with Dravet syndrome and LGS on June 2018, followed by 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 LGS or Dravet syndrome, in conjunction with clobazam, for patients 2 years of age and older". It is currently approved for treatment of patients with Dravet syndrome, LGS and Tuberous Sclerosis Complex, with FDA approval for patients 1 year of age and older and EMA approval for patients 2 years of age and older.

As of December of 2022 it is also in Phase 3 trials for Doose syndrome. In addition to being in the market in the US, Jazz expected Epidyolex to be launched in all five key European markets by year end (*Jazz Pharma 3Q 2022 update*). The drug has been descheduled by the DEA (2020) and reclassified by the UK Home Office as Schedule 5 drug (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 initially developed by Zogenix for the treatment of Dravet syndrome. It obtained Orphan Drug and Orphan Medicine Product Designations for the treatment of seizures in Dravet syndrome in 2013 (FDA) and 2014 (EMA).

In 2020, it was approved under the brand name of Fintepla by both FDA (June 2020, NDA 212102) and EMA (December, EMA/CHMP/510338/2020), making it the third treatment indicated in both markets for the treatment of Dravet syndrome, and it is approved for patients ages 2 and over. Unlike Diacomit and Epidyolex, the label for Fintepla in Europe does not require concomitant treatment with clobazam. In the US, both Epidiolex and Fintepla are indicated for the treatment of patients with Dravet syndrome without requiring concomitant treatment with clobazam.

Zogenix was acquired by UCB Pharma in 2022 for $1.9B. Shortly after, fenfluramine was also approved for LGS (FDA, March 2022), and is currently in Phase 3 clinical trials for CDKL5 Deficiency Disorder.

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. 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 2018, although following the approvals of Diacomit and Epidiolex in the US later in that same year the FDA rescinded the designation (*Zogenix press release, May 2019*).

A second pivotal Phase 3 clinical trial (NCT02926898) followed the standard of care in Europe and was evaluated as an add-on to stiripentol. The trial 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.

4.1.4. Soticlestat (TAK-935) – Takeda

Soticlestat (TAK-935) is a first-in-class, highly selective inhibitor of the enzyme cholesterol 24 hydroxylase that was initially discovered by Takeda and then co-developed by Takeda and Ovid Therapeutics for the treatment of rare developmental and epileptic syndromes including Dravet syndrome. It is currently solely developed by Takeda for Dravet syndrome and LGS. Soticlestat obtained the Orphan Drug Designation for the treatment of Dravet syndrome in 2017 by the FDA and appears to not yet have a designation by the EMA for Dravet syndrome (it did obtain the Orphan Medicinal Product Designation by EMA for Lennox-Gastaut syndrome in 2021).

As a result of the inhibition of the enzyme cholesterol 24 hydroxylase, soticlestat reduces 24S-hydroxycholesterol (24HC) in the brain. Reduction of 24HC has been shown to reduce glutamatergic signaling and neuroinflammation, which may have downstream effects on seizure susceptibility. It has shown antiepileptic activity in multiple preclinical epilepsy and seizure models, including reducing seizure frequency and severity and preventing premature mortality in a mouse model of Dravet syndrome (*Hawkins et al., 2021*).

The first evaluation of soticlestat for epilepsy by Ovid and Takeda was a randomized, placebo-controlled, Phase 1b/2a basket trial in adults with DEEs (NCT03166215). Afterwards, Ovid and Takeda run two pediatric clinical trials

with soticlestat: the ELEKTRA study (NCT03650452, double-blind, placebo-controlled Proof-of-Concept) in patients with Dravet syndrome and LGS, and the ARCADE (open-label) study in patients with CDKL5 deficiency disorder (CDD) and Duplication 15q syndrome. The ELEKTRA Phase 2 trial met the primary endpoint of reducing seizure frequency in children with Dravet syndrome and LGS *(Han et al., 2022)* 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 was 46.0%; p=0.0007).

In March of 2021 Takeda secured global rights from Ovid to develop and commercialize soticlestat for Dravet syndrome and LGS, with Ovid eligible to receive up to $856M in payments. As of December of 2022, soticlestat is in Phase 3 clinical trials for Dravet syndrome and LGS.

The ongoing Phase 3 trial for Dravet syndrome (SKYLINE, NCT04940624) is aiming to enroll 142 patients ages 2 to 21 and follows the standard Dravet syndrome anticonvulsant trial design described in section 3 of this report. The drug requires a 4-week titration period, followed by a 12-week maintenance period, and primary outcome measures are percent change from baseline in convulsive seizure frequency per 28 days for the entire treatment duration (16 weeks) and for the maintenance period (last 12 weeks). The second outcome measure was requested by the EMA according to the trial protocol. The trial is expected to last until March 2023 *(Takeda clinical trial website)*. Soticlestat will potentially be the fourth drug approved for the treatment of seizures in Dravet syndrome.

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

Huperzine A is a brain-penetrant acetylcholinesterase inhibitor, originally extracted from a plant used in 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)*. In September 2018, Supernus announced the acquisition of Biscayne Neurotherapeutics, the company that originally developed a proprietary formulation of huperzine A (BIS-001/ SPN-817) for the treatment of epilepsy. SPN-817 received an o Orphan Drug Designation for the treatment of Dravet syndrome in 2017 (FDA).

Although in the acquisition press release Supernus mentioned pans to develop SPN-817 for the treatment of Dravet syndrome *(September 2018 press release),* Supernus has not yet issued any guidance about future orphan indications for this program. After completing Phase 1 trials for the new formulation, Supernus is initiating an open-label Phase 2 trial in adult patients with treatment-resistant seizures (NCT05518578).

4.1.6. NT102 – Neuroene Tx

NT102 is a novel experimental drug with anticonvulsant potential in multiple epilepsy model that acts by targeting mitochondria dysfunction (*Neuroene website*). In 2021, NT102 received the Orphan Drug Designation by the FDA for the treatment of seizures in Dravet

syndrome. There is limited information about the compound, which is currently listed in the company website as in preclinical stage for the treatment for Dravet syndrome.

4.1.7. ReS3-T – reMYND

In November 2021, reMYND announced that it had initiated a collaboration with the US NINDS Epilepsy Therapy Screening Program to test the drug candidate ReS3-T, which acts via Pde6δ (*reMYND press release*). The same press release indicated that ReS3-T had efficacy in multiple pre-clinical models of epilepsy, including Dravet Syndrome. There is also limited information about the reMYND compound. The program is preclinical and listed as in development for Alzheimer's disease and epilepsy.

4.2. Second-generation (improved-symptomatic) treatments

4.2.1. Second-generation serotonergic programs

Following the approval of Fintepla (fenfluramine), up to six small molecule drugs targeting serotonin receptors are at different stages of clinical trials for Dravet syndrome (see Figure 1).

The most advanced fenfluramine follow-on program is lorcaserin from Eisai, currently in Phase 3 clinical trials for Dravet syndrome. Lorcaserin was initially approved for the treatment of obesity under the commercial name Belviq and marketed by Eisai. It has a similar mechanism of action to fenfluramine, but has no activity on 5-HT2b, the serotonin receptor that appeared to drive the cardiac and pulmonary safety concerns that led to the withdrawal of fenfluramine from the market for obesity. Therefore, lorcaserin was seen as a more promising drug for obesity, targeting primarily 5-HT2c receptors. However it ended up following fenfluramine's fate and was withdrawn from the market in February 2020 due to unrelated 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 in treatment under an Expanded Access Program (NCT04457687) following the voluntary withdrawal of Belviq from the market.

In 2020, Eisai announced the initiation of a Phase 3 trial with lorcaserin in patients with Dravet syndrome (NCT04572243), enrolling 58 patients and with an initial target completion in late 2021 (*Eisai press release 2020* and NCT04572243). As of December of 2022 the trial is still recruiting. Eisai also received an Orphan Drug Designation by the FDA for the treatment of seizures in Dravet syndrome with lorcaserin in August 2020.

Epygenix is developing three drug candidates or the treatment of DEEs that also act via modulation of the serotonin signaling pathway: clemizole (EPX-100), lorcaserin (EPX-200) and trazodone (EPX-300). The three drug candidates obtained the Orphan Drug Designation by the FDA for the treatment of Dravet syndrome in 2017, and EPX-200 also received the Orphan Medicinal Product Designation in 2021 for Dravet syndrome (EMA).

In September 2020, Epygenix initiated a 24-patient Phase 2 study with clemizole/EPX-100 in Dravet syndrome (ARGUS trial) that was later expanded to recruit up to 100 participants ages 2 years and above (NCT04462770). Epygenix also

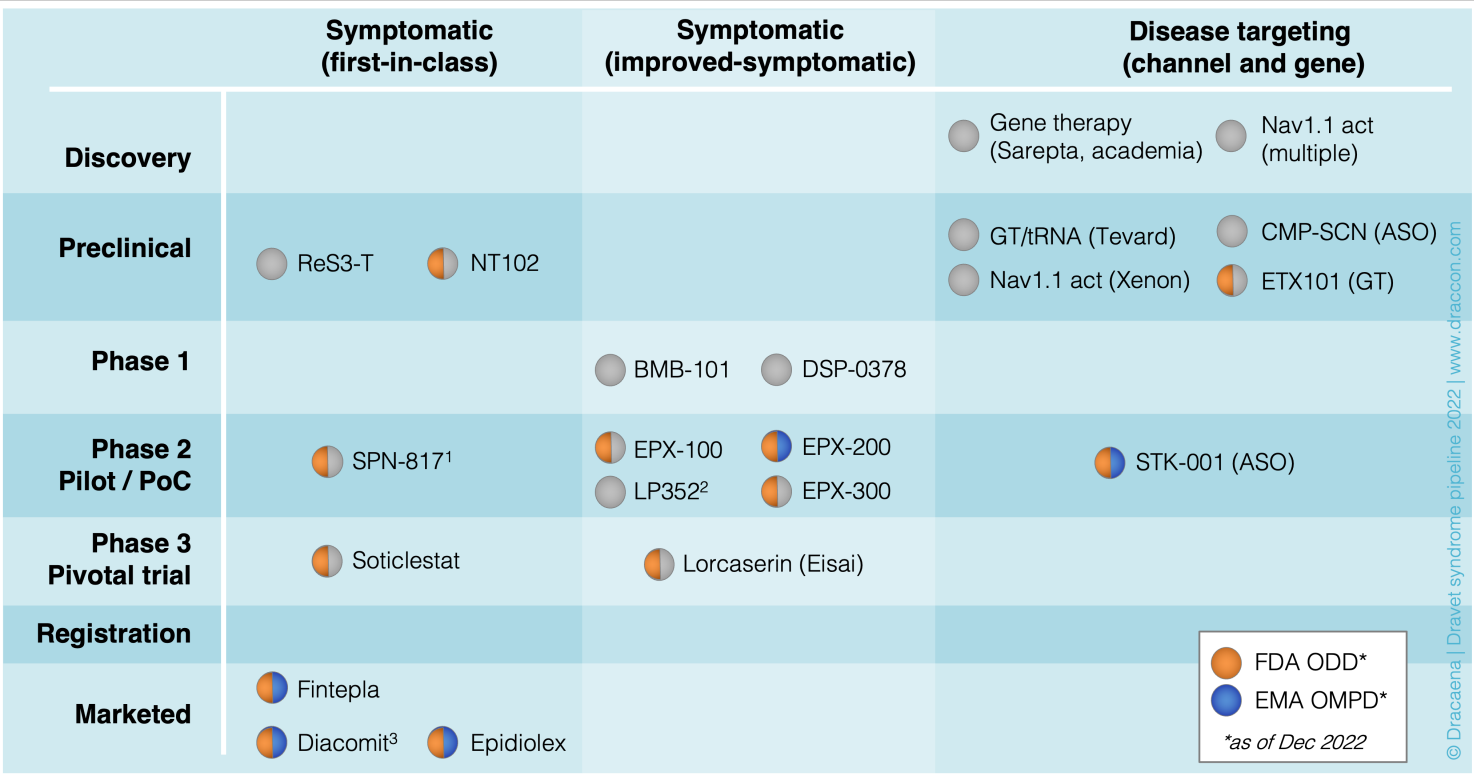

Figure 1 | Dravet syndrome pipeline overview and maturity state

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]Phase 2 for seizures in adults not for Dravet syndrome. [2]Phase 2 is basket study including Dravet syndrome. [3]After 10 years in the market, stiripentol no longer has the orphan drug status in Europe

indicated that EPX-200 has already been successfully tested in five Dravet syndrome patients at the University of Colorado Hospital as part of a small compassionate use trial (*Epygenix press release August 2021*).

Longboard Pharmaceuticals is also developing a follow-on to fenfluramine for the treatment of rare epilepsies. Their lead molecule, LP352, is currently in a randomized placebo-controlled Phase 1/2 trial in adults and adolescents with DEEs including patients with Dravet syndrome (NCT05364021, PACIFIC). Study completion is expected in H2 2023. LP352 is a 5-HT2c receptor agonist with selectivity over 5-HT2a or 5-HT2b (*Longboard website*), making its receptor profile more similar to lorcaserin than to fenfluramine.

Bright Mind Biosciences has also initiated dosing in Phase 1 clinical trials with their proprietary 5-HT2c agonist BMB-101 (*Company press release August 2022*). BMB-101 has preclinical data for activity in seizure models and the company aims to progress it towards clinical trials in Dravet syndrome (*Company press release August 2022*).

As a class, all of these programs are trying to establish themselves as best-in-class compared to fenfluramine, largely on the expectation of an improved safety profile. That said, the documented safety of fenfluramine in patients with Dravet syndrome and LGS, both during clinical trials and after approval, has been no different than the safety of other epilepsy medications. The black-box warning and Risk Evaluation and Mitigation Strategy

(REMS) program for Fintepla/fenfluramine are inherited from its initial indication use and market withdrawal for obesity. It therefore remains to be seen if any of these new 5-HT2c drugs can document better safety in patients with Dravet syndrome or document absence of 5-HT2b engagement at therapeutic doses, and whether regulators will apply a "class" black-box warning to them or not after eventual approval.

4.2.2. Second-generation GABAergic programs

The approval of Diacomit/stiripentol for Dravet syndrome also encouraged the development of additional programs with a GABA-related mechanism of action.

In 2019, NeuroCycle announced the award of a $0.5M grant from the NINDS to evaluate its advanced α2/α3 selective $GABA_A$ PAMs in mouse models of Dravet Syndrome (*NeuroCycle press release*). The lead compound NCT10004 was then undergoing IND-enabling studies, intended for the treatment of Dravet syndrome. The company was acquired by Engrail Therapeutics in 2021 and the new company only lists Focal Onset Seizures as an indication within epilepsy in their website (*Engrail pipeline on-line*).

The company Sumitomo Pharma is developing DSP-0378, a novel $GABA_A$ PAM, for Dravet syndrome and LGS (*company website*). The program has started Phase 1 trials in Japan.

4.2.3. Second-generation cannabinoid programs

Following the development and approval of Epidiolex for Dravet syndrome, other companies advanced cannabidiol-based products also for the treatment of Dravet syndrome, although those programs all appear discontinued.

INSYS Therapeutics was developing a liquid formulation of synthetic cannabidiol for the treatment of epilepsy and had announced a Phase 3 trial in children and young adults with Dravet syndrome, but this planned trial was later withdrawn (NCT02318563). INSYS then filed for bankruptcy in June 2019 and the program was eventually acquired by Benuvia Therapeutics but not developed for Dravet syndrome.

INSYS had obtained an Orphan Drug Designation for the treatment of Dravet syndrome with its synthetic cannabidiol oral solution in 2014 (FDA).

Zynerba Pharmaceuticals is developing a transdermal gel formulation of synthetic cannabidiol for a number of indications including developmental and epileptic encephalopathies (ZYN002). Although the company had an open-label Phase 2 basket trial in children and adolescents with DEEs including Dravet syndrome (ACTRN12618000516280), the product is currently in development for other disorders and not being considered for Dravet syndrome (*company website*).

It therefore seems likely that Epidiolex/Epidyolex will remain the only cannabidiol formulation to be specifically developed and approved for the treatment of Dravet syndrome. We have therefore removed these other cannabidiol programs as well as the GABAergic drug candidate from NeuroCycle/Engrail from the Dravet syndrome pipeline figure and from the table of companies with active programs (Figure 1 and Table 1).

4.3. Disease-targeting treatments

4.2.1. STK-001– Stoke Therapeutics

Stoke Therapeutics is developing the first disease-modifying treatment for Dravet syndrome, named STK-001. It is an antisense oligonucleotide (ASO) therapy targeting SCN1A pre-mRNA maturation that up-regulates Nav1.1 protein expression in rodents, human cell lines and non-human primates *(Stoke website; Han et al 2020).* STK-001 is based on Stoke's TANGO technology (Targeted Augmentation of Nuclear Gene Output) to modulate pre-mRNA splicing and increase protein expression in diseases caused by haploinsufficiency. The program follows a similar approach to Spinraza and has obtained the Orphan Drug Designation for treating Dravet syndrome caused by SCN1A mutations by the FDA in 2018 and the Orphan Medicinal Product Designation by the EMA in 2022.

In 2019, Stoke had an IPO with their lead program, STK-001, still in preclinical studies. Details on Stoke's TANGO technology and the preclinical proof-of-concept for STK-001 have been published *(Lim et al., 2020; Han et al., 2020).* In mice missing one copy of SCN1A, a single intracerebroventricular dose of a lead ASO at postnatal day 2 or 14 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).*

STK-001 is currently being evaluated in two parallel Phase 1/2 trials in patients with Dravet syndrome: MONARCH in the US (NCT04442295), and ADMIRAL in the UK (ISRCTN99651026).

The MONARCH study is a two-part open-label trial that started with Single Ascending Dose (SAD) in patients and later progressed to Multiple Ascending Dose (MAD). It initially aimed to enroll up to 48 participants ages 2 to 18 all with confirmed loss-of-function mutations in SCN1A but has later been expanded to enroll more patients (*Monarch study website*). The MAD phase of the study includes three intrathecal administrations of STK-001 in doses up to 45mg via lumbar puncture (spinal tap). Higher doses remain under partial clinical hold by FDA. The trial primary endpoints are safety and tolerability, while the secondary endpoints are change in seizure frequency and other non-seizure scales. At the time of the latest company presentation, enrollment is ongoing and the current dose being administered is 30mg (*Stoke presentation "Interim Analysis of STK-001 for the Treatment of Dravet Syndrome" November 2022*).

The UK ADMIRAL study mirrors the MAD phase of the MONARCH study but with a maximum dose of 70mg (currently dosing 45mg as of the time of the latest company presentation). This trial is currently enrolling up to 60 children and adolescents. In both trials, the follow-up period is 6 months and trial participants are offered to roll-over into an open-label extension trial.

In December of 2022 Stoke announced topline data from a combined interim analysis of the Phase 1/2 MONARCH and ADMIRAL studies including single and multiple doses of STK-001 up to 45mg (*Company press release and American Epilepsy Society 2022 meeting presentations*). The combined analysis of all of the doses indicates that STK-001 is well-tolerated, with 15/55 patients

reporting treatment-emergent adverse events, mainly vomiting, headache and seizures (consistent with the route of administration). Stoke reported elevation in CSF protein in 18 /55 patients, without any clinical manifestation. Analysis of treatment efficacy at the highest dose (45mg), which had been administered to 6 patients at the time of data cutoff, showed reductions from baseline in convulsive seizure frequency in 5/6 patients and a 55% median reduction from baseline in convulsive seizure frequency from Day 29 after the first dose to three months after receiving the last dose. Lower doses also resulted in around 20 to 30% seizure reduction, although there is significant noise due to the small cohort sizes. Notably, half of the patients treated with STK-001 were already on fenfluramine. Stoke reported that "reductions in seizure frequency began after the first dose and continued with additional treatment, consistent with the anticipated mechanism of action of STK-001" (*company press release*).

An important difference between STK-001 and all previous treatments in clinical trials for Dravet syndrome is that STK-001 is an ASO designed to target the underlying cause of Dravet syndrome (haploinsufficiency in SCN1A/Nav1.1), while all of the previous treatments were acute anticonvulsant medications. This means that any efficacy observed with STK-001 must come from increasing Nav1.1 channel expression in inhibitory neurons, which will then enable these neurons to normalize their inhibitory firing and restore (or improve) network activity likely for the first time in the life of these patients. Therefore patient response to STK-001 is expected to be much slower than to anticonvulsant drugs, but it also has the potential to more profoundly impact the clinical presentation of Dravet syndrome.

In December of 2022 Stoke released early data from additional outcome measures indicating that STK-001 might also improve non-seizure outcomes (*Company press release and American Epilepsy Society 2022 meeting*). Stoke initiated in 2019 an observational study in Dravet syndrome patients ages 2 to 18 (BUTTERFLY study) to document the suitability of non-seizure clinical outcome measures and their baseline and natural history in Dravet syndrome patients. This observational study documented that patients with Dravet syndrome don't show any changes over a 12-month period in an assessment of pediatric executive function called the BRIEF-P (Behavior Rating Inventory of Executive Function–Preschool Version). Data from the extension study SWALLOWTAIL, that followed patients who received multiple 30mg doses of STK-001, indicate that treatment with STK-001 translates into improvements in different domains of executive function as well as on global executive function all measured using the BRIEF-P inventory, with a trend towards improvement after week 16 (n=8 patients) and an improvement after week 32 (n=5 patients) (*Company presentation and American Epilepsy Society 2022 meeting presentations*).

These early results are consistent with a disease-modifying therapy that targets the underlying biological cause of Dravet syndrome.

As Stoke continues to administer higher treatment doses to larger patient cohorts, and as patients remain on treatment for longer (which will be needed to measure some non-seizure outcomes), a more complete picture of the efficacy as well as the safety of STK-001 will become more clear.

4.2.2. 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 gene 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 the Orphan Drug Designation and Rare Pediatric Disease Designation by the FDA in 2022 for the treatment of Dravet Syndrome caused by SCN1A mutations.

The SCN1A gene had traditionally 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 up-regulate SCN1A expression specifically in GABAergic cells instead of delivering the SCN1A gene (AAV9-RE^{GABA}-eTF^{SCN1A}).

The preclinical efficacy of ETX101 in a mouse model of Dravet syndrome and safety and tolerability in non-human primates were published in 2022 *(Tanenhaus et al., 2022).* Administration of ETX101 to mice used a single bilateral intracerebroventricular (ICV) injection to postnatal day 1 mice, and resulted in efficacy in all three mouse endpoints (hyperthermia seizures, spontaneous seizures and mortality). Non-human primates received a single ICV injection. The intended administration route to patients is also ICV administration.

In preparation for an IND, details on the Phase1/2 clinical trial with ETX101 were posted in clinicaltrials.gov (ENDEAVOR, NCT05419492). Encoded had indicated in its website that it anticipated treating the first trial participant in 2022, but at the time of writing this report in December of 2022 the ENDEAVOR trial is not yet recruiting and trial protocol details might change as a result of the regulatory discussions by the time the study starts.

The current version of the ENDEAVOR study in clinicaltrials.gov contemplates recruiting 22 patients with Dravet syndrome caused by SCN1A loss-of-function mutations ages 6 to 36 months. A first cohort would receive a dose-escalation of ETX101 (part 1, with two doses), and part 2 is a randomized, double-blind, sham delayed-treatment control, dose-selection study. In part 2, participants would be randomized 1:1:1 to three groups corresponding to the two dose levels and a sham delayed-treatment control. The study will be blinded through the end of week 16. Primary outcome measures are safety, percent change in monthly countable seizure frequency between baseline and the period between weeks 5 and 16 of the treatment period, and proportion of participants free from episodes of prolonged seizures and/or status epilepticus at 52 weeks (1 year). Secondary outcome measures are proportion of participants with ≥ 90% reduction in monthly countable seizure frequency (baseline versus week 5-16) and absolute change in the raw score of the Bayley-III receptive language sub-domain.

The selection of these outcomes, such as freedom from status epilepticus and the specific subscale within the Bayley-III

scale, are informed by the ENVISION observational study (NCT04537832), run by Encoded to explore the feasibility of cognitive, motor and behavioral outcome measures in addition to other seizure-related outcomes in patients with Dravet syndrome ages 6 to 60 months.

Stoke has indicated that treatment response to STK-001 appears to be larger in the youngest group of patients. Therefore Encoded's decision to limit the initial trial with ETX101 to patients ages 6 to 36 months is likely the right strategy to increase treatment response and see changes sooner, prior to future trials that are likely to include a broader age range. That said, preclinical data from different academic groups using mouse models of Dravet syndrome indicate that the window of opportunity to produce improvements in individuals with Dravet syndrome might extend into adulthood *(Mora-Jimenez et al., 2021; Valassina et al., 2022).*

4.2.3. CMP-SCN – CAMP4

OPKO Health was developing an ASO called OPK88001 (CUR-1916), designed to displace an endogenous repressor of SCN1A gene transcription. This ASO uses different base modifications than the ASO from Stoke and also targets a different biological process. OPK88001 received the Orphan Drug Designation (FDA) and the Orphan Medicinal Product Designation (EMA) for the treatment of Dravet syndrome in 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 but no news about the program were subsequently published. In 2021 the company CAMP4 acquired global rights to OPKO's RNA-based technology and prioritized the former OPK88001 program, renamed CMP-SCN-001, to enter clinical development for Dravet syndrome (*company press release*). At the American Epilepsy Society meeting in December of 2022, CAMP4 presented non-human primate biodistribution data for CMP-SCN-001 following intrathecal administration, confirming increase in SCN1A mRNA and Nav1.1 protein levels. At the time of their series B raise in mid-2022, CAMP4 indicated a potential IND date for this program in mid-2023 (*company press release*).

4.2.4. mRNA modulation – Tevard Biosciences

In 2020, Tevard Biosciences announced that it was developing and applying two novel tRNA-based gene therapy platforms for the treatment of Dravet syndrome and other rare diseases caused by genetic haploinsufficiency and/or nonsense mutations that are not amenable to traditional approaches with gene therapy (*company website*). About 20% of patients with Dravet syndrome are estimated to have nonsense mutations. As of 2022, Tevard is exploring the use of its novel Suppressor tRNA, Enhancer tRNA, and mRNA Amplifier platforms in neurological disorders, heart disease, and muscular dystrophies; and the company has

partnered with Zogenix to develop therapies for Dravet syndrome and other genetic epilepsies (*company press release August 2022*). Tevard is using AAV vectors to deliver genes for their mRNA-targeting therapeutics into cells. The programs are at preclinical stage.

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 several medical conferences including the American Epilepsy Society meeting in December of 2022. 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 approach to treating haploinsufficiency in Dravet syndrome, complementing read-tough approaches, ASOs and viral-based gene therapies.

At the latest scientific meeting, Xenon showed efficacy with compounds from two chemical series in slices from SCN1A+/- mice (increasing firing of GABAergic interneurons) and also *in vivo* efficacy in seizure and motor outcomes (*American Epilepsy Society meeting 2022 presentation*). The motor readout is particularly interesting because it indicates that Nav1.1 activators might have the potential to also treat non-seizure related symptoms in patients with Dravet syndrome and provide a novel small molecule potentially disease-modifying therapy for these patients. The program is at preclinical stage.

4.4. 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 their mechanism of action, or are still at early discovery stages. These are therefore potential therapeutics that might join the Dravet syndrome pipeline.

4.4.1. Other gene therapy – Sarepta/ StradeBio and academic programs

In late 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 2019*). There are no more news on this program after the initial announcement, although as of Q1 2022 the program remained listed in the company website. 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 size challenges of the SCN1A gene.

There are several academic programs at early discovery or preclinical stages that aim to develop gene therapy and gene editing approaches for Dravet syndrome. Because of the early stage of these programs and lack of company sponsor, they may or may not ultimately progress into the clinical phase. A group from the San Raffaele Scientific Institute in Italy is developing a dCas9 approach to increase SCN1A expression levels *(Colasante et al., 2020),* and a group from University of Navarra in Spain is

working on an adenovirus-based gene therapy carrying the SCN1A gene *(Mora-Jimenez et al., 2021).* The group of Dr Rajvinder Karda recently published a very good overview of all genetic therapeutics in development for Dravet syndrome *(Chilcott et al., 2022).*

4.4.2. Other sodium channel modulators – Lundbeck and academic programs

In addition to the program from Xenon, there are other groups seeking 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 tool Nav1.1 activators in mouse models of induced seizures *(Frederiksen et al., 2017)* and zebrafish model of Dravet syndrome *(Weuring et al., 2020).* At the American Epilepsy Society meeting in December of 2022 the company presented an expanded characterization of their main compound, showing that it did not have efficacy in the hyperthermia model in SCN1A +/- mice. The Gladstone Institute of Neurological Disease also has a 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).*

PRAX-330 (GS967) is a small molecule sodium channel modulator that was in development by the company Praxis Precision Medicine for the treatment of epilepsy. PRAX-330 reduced persistent sodium currents as opposed to peak current inhibition *(Belardinelli et al., 2013),* and has shown preclinical efficacy in a mouse model of Dravet syndrome where it increased survival and reduced seizure frequency *(Anderson et al., 2017).* Praxis has not released additional information about this molecule, plans for clinical development or target indications yet. Praxis has another program called PRAX-562 that could be the same or a similar molecule, which also reduces persistent sodium currents, about to start clinical trials in patients with SCN2A and SCN8A Gain-of-Function mutations (*corporate presentation November 2022*).

4.4.3. Other potential programs

Ataluren (brand name Translarna) is a read-through medication developed by PTC Therapeutics that is approved in Europe for the treatment of patients with Duchenne muscular dystrophy caused by nonsense mutations (EMA provisional approval since 2014, renewed in 2016). An investigator-initiated study evaluated the safety and efficacy of ataluren for treating Dravet syndrome caused by nonsense mutations (NCT02758626). The study failed to show efficacy in Dravet syndrome *(Devinsky et al., 2021)* and the drug is currently presumably discontinued for development in this indication.

Sage Therapeutics is developing SAGE-324, a novel, orally-active next-generation GABA modulator, for the treatment of essential tremor, epilepsies and Parkinson's disease (*company website*). A tool compound with related activity, SAGE-516, was used to obtain proof-of-concept for the treatment of Dravet syndrome in a mouse model of the

disease *(Hawkins et al., 2017).* In 2022, Sage was granted a patent for the use of a series of compounds in epilepsy indications including Dravet syndrome (US11396525B2). SAGE-324 is in Phase 2 trials for essential tremor and the company has not announced specific clinical trials plans in Dravet syndrome.

There is also a patent application from F. Hoffmann-La Roche for the use ASOs to modulate expression of the protein tau indicated for the treatment of several neurodegenerative diseases and also Dravet syndrome (WO2020007892A1).

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

5.1. From treating symptoms to treating the cause of the disease

Figure 1 summarizes the current state of the Dravet syndrome drug development pipeline as of December of 2022. There are in total 16 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 directly for Nav1.1 channel activators and gene-replacement approaches, have also been highlighted.

Following the 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 seeking 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 categories becomes apparent:

(1) First generation of symptomatic therapeutics. These are first-in-class small molecule drugs that have either already demonstrated clinical efficacy for treating seizures in Dravet syndrome, or have a compelling preclinical data package that supports the use of the mechanism for treating seizures in Dravet syndrome. Although some of these mechanisms might also have efficacy in treating other symptoms of Dravet syndrome, for the purpose of this review we will refer to all therapies that do not target SCN1A or Nav1.1 (and that are often regular anticonvulsant drugs) as *symptomatic*.

In addition to the already-approved Diacomit (GABA modulator), Epidiolex (cannabidiol) and Fintepla (fenfluramine), the first-generation of symptomatic therapeutics includes an enzyme inhibitor with potential for anti-neuroinflammation (Soticlestat) and an acetylcholinesterase inhibitor (SPN-817), although the latter has not been confirmed to still be under consideration for development for Dravet syndrome.

(2) The clinical target validation obtained by Diacomit, Epidiolex and Fintepla opened the pipeline door for a second

generation of aspiring best-in-class symptomatic treatments. This category is currently dominated by multiple fenfluramine follow-ons: lorcaserin by Eisai and Epygenix, two additional repurposed candidates by Epygenix, and molecules from Longboard and Bright Minds Biosciences. Sumitomo Pharma is 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 group of programs in development pursuing different therapeutic modalities all with potential to directly address the genetic defects that cause Dravet syndrome. Among these approaches are facilitators of read-through to rescue nonsense mutations, treatments to increase expression of the functional SCN1A copy that all patients have, and drugs to increasing activity of the Nav1.1 ion channel. The most advanced programs are those by Stoke and Encoded. Collectively, these approaches represent a third generation of disease-targeted and potentially disease-modifying treatments, expected to translate into improvements across multiple disease domains.

Overall the Dravet syndrome pipeline is currently very diversified and highly competitive, with best-in-class follow-on strategies already in place. It is also a relatively mature pipeline, with a number of disease-modifying programs already in development including an ongoing Phase 2 trial from Stoke Therapeutics.

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 (above 80% of the cases) the Dravet syndrome clinical presentation results from mutations in the SCN1A gene. The remaining cases of Dravet syndrome are due to different (likely also 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 loss-of-function 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 patients with Dravet syndrome. On the other hand, these therapy modalities also have the potential to go beyond Dravet syndrome, and will be able to target additional indications, such as Alzheimer's disease or schizophrenia, both shown to be associated with reduced Nav1.1 protein levels or activity (Jensen et al., 2014).

The expansion to diseases indications 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 or the gene therapy from Encoded, which are likely better targeted to Dravet syndrome and other severe epilepsy presentations also caused by SCN1A mutations. For these severe clinical presentations, Nav1.1 activators, ASOs and gene therapy have the potential to impact multiple disease domains 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 and interpretation for Dravet syndrome

The transition from first-generation symptomatic treatments to disease-targeting and potentially disease-modifying treatments requires a change in clinical trial design.

The current design for clinical trials with small molecule anticonvulsant drugs in Dravet syndrome, 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 that 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 ASOs and gene therapies require a different trial design, including significantly longer trials with different clinical outcome measures. This is already seen in the ongoing STK-001 clinical trials and the proposed ETX101 Phase 1/2 clinical trial. Importantly, we cannot do a head-to-head comparison of the efficacy of treatments that target the cause of Dravet syndrome with the results in clinical trials with acute anticonvulsant treatments. Doing so would lead to unfavorable and medically incorrect assessments of the efficacy of the disease-targeting treatment, in favor of the acute symptomatic. An example would be to compare antibiotics to ibuprofen based on their ability to reduce fever 4 hours after administration to patients with bacterial pneumonia.

6. Challenges and opportunities

6.1. 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.

Some of the companies that are currently pursuing Dravet syndrome are developing drugs with anticonvulsant activity that are not new chemical entities or that were first identified long time ago. To help offset their weaker intellectual property position, these companies target orphan indications 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 approved drugs, Dravet syndrome is an ideal target. However, one of the requirements by the EMA to retain Orphan Medicinal Product status after approval is to demonstrate significant benefit of the treatment over existing approved medications. After the approval of Fintepla, it might be 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 a variety of epilepsy indications, the increased competition around Dravet syndrome might drive sponsors away from the syndrome and towards other orphan disorders with epilepsy that have fewer or no approved medications yet. Some examples are CDKL5 Deficiency Disorder, PCDH19 encephalopathy or SCN2A-related epilepsy disorders. These additional DEEs 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.

The same competition challenge is true for disease-modifying therapeutics. With STK-001 in clinical trials and ETX101 about to start clinical trials, going after other haploinsufficiency disorders with younger development pipelines such as SYNGAP1, STXBP1 or SCN2A Loss-of-Function might appear an easier option, at least from a competition standpoint.

6.2. Change in the standard of care

The recent approvals of three drugs for treating seizures in Dravet syndrome have changed the standard of care for the disease. The availability of these drugs, the high efficacy of Fintepla/fenfluramine, and the better awareness by clinicians for how to treat Dravet syndrome, have improved the treatment standards for patients and reduced their seizure count.

Before Epidiolex and Fintepla, about half of the patients with Dravet syndrome in Europe already did not meet the usual criteria for trial inclusion of 4 countable convulsive seizures a month *(Aras et al., 2015).* With the arrival an adoption of these new medications, in particular Fintepla, this fraction is likely much smaller currently, 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.

Stoke recently reported that half of their patients from the MONARCH and ADMIRAL clinical trials are already taking fenfluramine, which means that these patients are having on average about 60-70% less seizures per month at the start of the trial than an equivalent population of patients prior to 2020. This is an example of the *"better than the Beatles" problem* of the Eroom's law, where new efficacious drugs might only have modest benefit when added on top of previously approved medications. Yet that is exactly how clinical trials work for epilepsy: as add-on to the standard of care. Potential efforts to go to ex-US and ex-EU countries to try to improve trial recruitment might be in conflict with ensuring that trials are run as add-on to the standard of care.

It seems likely that seizure reduction will remain as a primary endpoint in clinical trials for Dravet syndrome, even for trials with new disease-modifying treatments. 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. Therefore, the main challenge of a post-Fintepla standard of care will be for other symptomatic anticonvulsant medications in development (first-in-class and improved-symptomatic in Figure 1), as these are likely to be still assessed using the current short clinical trial design.

6.3. Trial feasibility and trial design

For companies developing symptomatic drugs for the treatment of seizures in Dravet syndrome, an important 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 and who meet the recruitment criteria. In addition to the change in standard of care discussed in section 6.2, there is also notable trial fatigue among patient families, and some are waiting for an opportunity to enroll in the disease-modifying treatment trials and less interested in symptomatic trials. Opening eligibility to patients over 18 years of age would be a way to make recruitment easier, since previous clinical trials have capped enrollment at that age. Increased disease awareness following three drug approvals is also likely to lead to increased diagnosis and therefore a larger patient community that might become available for 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 seizures in patients with Dravet syndrome. This differentiation will be important to demonstrate significant benefit in Europe, maintaining orphan status, and to secure a better pricing position. 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 are becoming needed for clinical trials in Dravet syndrome are the development and validation of non-seizure endpoints, as well as potentially 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 and Encoded have been designed to inform on outcome measures and potential non-seizure endpoints. The way these studies are being designed and run makes them exceptionally valuable not only for the respective companies but for the entire Dravet syndrome field, helping transition trials in Dravet syndrome from epilepsy trials to neurodevelopmental disorder trials.

The value of these observational studies has already been shown by Stoke, who documented stable executive function over 12 months in patients with Dravet syndrome ages 2-18 using the BRIEF-P scale, and then showed changes in the same scale in shorter time frames in patients treated with multiple doses of STK-001. It is likely that additional companies will not need to run similar observational studies of their own and instead will follow the clinical trial design agreed by regulators and Stoke, and potentially Encoded, in particular if these initial trials are successful.

6.4. Project specific challenges: Biodistribution and biomarkers

The companies developing advanced therapeutics for Dravet syndrome face the important additional challenge to reach the target cells in the target brain regions. Some of this challenge is technological (like limited biodistribution

of some viral vectors) and some is scientific (for example knowing which cells require more 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. A more complete list and discussion of these challenges is included in the Pipeline 2019 review.

On the scientific front, it is not yet clear if restoring wild-type functional levels of Nav1.1 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 involves all regions of the brain. 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 will also limit the burden to patients, improving trial recruitment and retention and quality of life.

Another challenge is the lack of target engagement biomarkers for SCN1A mRNA and Nav1.1 protein levels. 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 SCN1A or Nav1.1 expression in the brain to confirm target exposure and magnitude of change in expression levels. Short of a direct measurement of Nav1.1 protein levels, some of the network image signatures of Dravet syndrome such as changes in gamma-wave oscillations might be used as a surrogate for network normalization. It would be recommendable to include these potential biomarkers in the trial design. Such measures might add support when interpreting that disease improvements are due to normalization of GABAergic network activity, and might potentially enable obtaining accelerated approval (FDA) or conditional marketing authorization (EMA) for the programs.

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

Despite the previous list of challenges, Dravet syndrome remains an excellent indication for many new approaches and modalities.

The disease is caused by a genetic haploinsufficiency, so it represents a good indication for treatments that boost expression from the non-mutated gene copy or that target the existing ion channels to increase their activity. We also 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 to 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 Dravet syndrome 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 for diseases where preclinical models fail to recapitulate patient phenotypes. Last, the patient community around 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 needs still include (1) poor seizure control for most 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

Since 2014, Dravet syndrome has gained significant attention from the biotech and pharma industry, and the pipeline has grown from only one drug approved (stiripentol, ex-US) to nearly 20 programs in development 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. Other reasons for this popularity are that Dravet syndrome is an ideal (almost) mono-genetic disease for genetic treatments.

The Dravet syndrome pipeline shows signs of maturity, with a third generation of treatments designed to target the biological cause of the disease entering clinical trials following the first and second generations of symptomatic treatments. The year 2022 has been a

key year, with the publication of positive interim clinical trial results from the first treatment designed to correct SCN1A haploinsufficiency (STK-001).

An attractive business and commercial model has emerged for the development of anticonvulsant medications for Dravet syndrome in combination with one or two additional rare epilepsy syndromes. This "Dravet syndrome plus" model has led to two multi-billion acquisitions: GW Pharma by Jazz Pharma, and of Zogenix by UCB Pharma. Adopting the same "Dravet syndrome plus" model, Takeda has recently ended co-development of soticlestat and taken sole ownership of the program for Dravet syndrome and LGS. A similar model starts emerging for the genetic approaches, with companies selecting Dravet syndrome as their first target indication with haploinsufficiency, quickly followed by programs for other similar DEEs (see Stoke and Tevard).

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

Overall there are many opportunities for new therapy development for Dravet syndrome, with a pipeline of disease-modifying programs that mirrors the sequence of treatment modalities first seen for Spinal Muscular Atrophy: first an ASO as the initial modality, then a one-time viral gene therapy, later followed by small molecules that target the disease biology.

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.

Chilcott E, Díaz JA, Bertram C, Berti M, Karda R. Genetic therapeutic advancements for Dravet Syndrome. Epilepsy Behav. 2022 Jul;132:108741.

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.

Devinsky O, King L, Bluvstein J, Friedman D. Ataluren for drug-resistant epilepsy in nonsense variant-mediated Dravet syndrome and CDKL5 deficiency disorder. Ann Clin Transl Neurol. 2021 Mar;8(3):639-644.

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.

Hawkins NA, Jurado M, Thaxton TT, Duarte SE, Barse L, Tatsukawa T, Yamakawa K, Nishi T, Kondo S, Miyamoto M, Abrahams BS, During MJ, Kearney JA. Soticlestat, a novel cholesterol 24-hydroxylase inhibitor, reduces seizures and premature death in Dravet syndrome mice. Epilepsia. 2021 Nov;62(11):2845-2857.

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

Hahn CD, Jiang Y, Villanueva V, Zolnowska M, Arkilo D, Hsiao S, Asgharnejad M, Dlugos D. A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of soticlestat as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox-Gastaut syndrome (ELEKTRA). Epilepsia. 2022 Oct;63(10):2671-2683.

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

Mora-Jimenez L, Valencia M, Sanchez-Carpintero R, Tønnesen J, Fadila S, Rubinstein M, Gonzalez-Aparicio M, Bunuales M, Fernandez-Pierola E, Nicolas MJ, Puerta E, Miguelez C, Minguez PG, Lumbreras S, Gonzalez-Aseguinolaza G, Ricobaraza A, Hernandez-Alcoceba R. Transfer of *SCN1A* to the brain of adolescent mouse model of Dravet syndrome improves epileptic, motor, and behavioral manifestations. Mol Ther Nucleic Acids. 2021 Aug 19;25:585-602.

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

Tanenhaus A, Stowe T, Young A, McLaughlin J, Aeran R, Lin IW, Li J, Hosur R, Chen M, Leedy J, Chou T, Pillay S, Vila MC, Kearney JA, Moorhead M, Belle A, Tagliatela S. Cell-Selective Adeno-Associated Virus-Mediated *SCN1A* Gene Regulation Therapy Rescues Mortality and Seizure Phenotypes in a Dravet Syndrome Mouse Model and Is Well Tolerated in Nonhuman Primates. Hum Gene Ther. 2022 Jun;33(11-12):579-597. doi: 10.1089/hum.2022.037.

Valassina N, Brusco S, Salamone A, Serra L, Luoni M, Giannelli S, Bido S, Massimino L, Ungaro F, Mazzara PG, D'Adamo P, Lignani G, Broccoli V, Colasante G. Scn1a gene reactivation after symptom onset rescues pathological phenotypes in a mouse model of Dravet syndrome. Nat Commun. 2022 Jan 10;13(1):161.

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.

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