Dravet syndrome pipeline and opportunities review | July 2018

Dravet syndrome is a genetic neurological rare disease characterized by refractory epilepsy, intellectual disability, behavioral and movement disorders and a high mortality rate. The treatment approaches for this syndrome are currently limited to the symptomatic management of epileptic seizures. 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. In June 2018, Epidiolex (cannabidiol oral formulation) from GW Pharmaceuticals obtained marketing authorization by the FDA, becoming the first drug to be approved for the treatment of Dravet syndrome in the US market. As of July 2018, Epidiolex is followed by ZX008 from Zogenix, close to filing for marketing authorization, and at least 7 additional symptomatic treatments that include second-generation cannabidiol formulations and serotonergic drugs. There are also at least 5 programs in the late-preclinical or clinical stage that target the disease biology, including two antisense treatments. Overall the Dravet syndrome pipeline comprises 14 drug candidates, and 9 different products have received orphan drug designations. This report reviews the state of the Dravet syndrome drug development pipeline as of July 2018 and discusses current and future opportunities.

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Dravet syndrome pipeline and opportunities review is a publication by Dracaena Report, a division of Dracaena Consulting

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1. Dravet syndrome - Overview

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. Patients with Dravet syndrome fail to produce sufficient levels of functional Nav1.1 sodium channel, preventing inhibitory neurons from firing properly. As a consequence, there is an imbalance between brain excitation and inhibition that results in refractory epilepsy, intellectual disability, and 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 review we will only cover those products currently 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.

Pharmacological management of Dravet syndrome focuses largely on the use antiepileptic drugs (Chiron 2011). Importantly, sodium channel blockers, which are often a first-line medication for the treatment of epileptic seizures, 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. None of these drugs alone achieves complete seizure suppression in these patients and only a minority (about 10%) of the patients are seizure-free (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 (ZX008). Most of these compounds would have the potential to treat other forms of epilepsy.

Importantly, there are also new programs in the Dravet syndrome pipeline that have been developed specifically to treat this syndrome and that aim to restore the abnormal channel function or expression levels. As the competition increases, the pipeline is likely to shift towards less symptomatic treatments and more disease-targeting therapeutics.

2. Population and market size

Incidence of Dravet syndrome caused by SCN1A mutations has been reported to be around 1 in 20,000 live births (Brunklaus 2012; Wu et al., 2015; Bayat et al 2015; Rosander and Hallböök 2015).

Underdiagnosis or misdiagnosis are common problems in rare diseases, which reduces actual market size. A recent 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.

Analysts have estimated peak sales of a drug to treat Dravet syndrome of $195M to $350M assuming 50% market share (Edison Investment Research 2016 Outlook on GW Pharmaceuticals and LifeSci Capital Equity Research 2015 on Zogenix, respectively). These estimates of market share and sales will be refined within the next 12 months once Epidiolex is launched in the different markets and drug pricing and market penetration data become known.

Importantly, most companies developing products for Dravet syndrome are also evaluating their treatments in related orphan epilepsy syndromes or have disclosed their intentions to do so, thereby increasing the overall market size and potential future sales for their products.

3. Therapeutics development: clinical and preclinical protocols

The current clinical trial design for Dravet syndrome follows the usual protocol standards for antiepileptic medications. Importantly, all of the protocols for placebo-controlled trials in Dravet syndrome that have been published follow essentially the same protocol that only consider seizures as primary outcomes. A review of these protocols is included in the Dravet syndrome pipeline and opportunities review - June 2017 publication available at http://www.draccon.com/dravet-pipeline/

For a review on the preclinical models and protocols the reader is also referred to the 2017 review. Importantly, there is a mouse model of Dravet syndrome carrying a patient mutation that is available to for-profit companies without any license through the Jackson Laboratory mouse repository (strain number 026133) and that will be soon available through the Epilepsy Therapy Screening Program of the NINDS (http://www.nind.nih.gov/ETSP). The addition of a mouse model of a genetic rare epilepsy at the ETSP underscores the shift of attention in the epilepsy field from broad epilepsy indications towards orphan genetic indications.

4. Dravet syndrome pipeline review – individual programs

The following sections review the state of the Dravet syndrome drug development pipeline as of July 2018, focusing on the developments during the last 12 months. 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 of the compounds in development.

Compounds are considered to be at the *Pilot* stage where the clinical study involves a reduced number of patients and is open-label, and at the *Proof-of-Concept* (PoC) stage when the trial is a small double-blind placebo-controlled trial. Only programs where a candidate has been named are listed as Preclinical programs.

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 only drug currently approved outside of the US 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).

After a 10-year period of market exclusivity following its initial approval, Diacomit is no longer an orphan medicine in Europe.

Company	Compound	Stage July 2018	ODD FDA/EMA
Biocodex	Diacomit (stiripentol)	Market (ex-US)	2008/2001
Biscayne Neurotherapeutics	BIS-001 (huperzine A)	Phase I	2017/-
Epygenix Therapeutics	EPX-100 (clemizole)	Preclinical	2017/-
	EPX-200 (lorcaserin)	Pilot (open label)	2017/-
	EPX-300 (trazodone)	Pilot (open label)	2017/-
GW Pharmaceuticals	Epidiolex (cannabidiol)	Approved (US)	2013/2014
OPKO Health	OPK88001 (CUR-1916)	Preclinical	2017/2017
Ovid Therapeutics / Takeda	OV935 (TAK-935)	PoC (placebo)	2017/-
PTC Therapeutics	Translarna (ataluren)	PoC (placebo)	-/-
Sage Therapeutics	SAGE-324	Preclinical	-/-
Stoke Therapeutics	SCN1A ASO	Preclinical	-/-
Xenon Pharmaceuticals	XEN901 (Nav1.6 inh)	Preclinical	-/-
Zogenix	ZX008 (fenfluramine)	Pivotal (Phase III)	2013/2014
Zynerba	ZYN002 (cannabidiol)	Pilot open label	-/-

Table 1 | **List of companies with compounds in development for Dravet syndrome or that could be developed for Dravet syndrome (see main text). ODD: Orphan Drug Designation year.**

Diacomit 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. While not approved by the FDA, Diacomit received the FDA orphan drug designation for treating seizures in Dravet syndrome in 2008.

4.1.2. Epidiolex (cannabidiol): GW Pharmaceuticals

Epidiolex is a liquid formulation of plant-derived cannabidiol, a non-psychoactive component of the cannabis plant, in development by GW Pharmaceuticals. It received the marketing authorization by the FDA for the adjunctive treatment of seizures associated with Dravet and Lennox-Gastaut syndromes on June 25th, 2018, following a unanimous 13-0 recommendation by the Peripheral and Central Nervous System Drugs Advisory Committee. It is currently being reviewed for marketing authorization by the EMA and a decision is expected in Q1 2019. Epidiolex obtained orphan drug designations for the treatment of Dravet syndrome in 2013 (FDA) and 2014 (EMA).

Epidiolex is the first drug to be approved by the FDA for the treatment of Dravet syndrome. Following the NDA approval,

the DEA has 90 days to reschedule cannabidiol. US launch is expected in H2 2018.

The NDA 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. By July 2018, over 2,000 patients have been treated with Epidiolex. 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. Publication of the results of the second Phase 3 clinical trial in Dravet syndrome is expected in H2 2018. In the US, Epidiolex will be commercialized through the subsidiary Greenwich Biosciences.

4.1.3. ZX008 (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).

Zogenix completed and communicated top-line data of a first Phase 3 clinical trial with ZX008 in Dravet syndrome in Q3 2017 (NCT02682927). 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 ZX008 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, ZX008 obtained the FDA Breakthrough Therapy Designation in Q1 2018.

Zogenix announced top-line data from a second pivotal Phase 3 trial in July 2018. The second trial follows the European standard-of-care, so the experimental drug is evaluated as an add-on to stiripentol, and uses the same primary endpoint as the first study (reduction in mean monthly convulsive seizures when compared to placebo). Patients taking ZX008 achieved a 54.7% greater reduction in mean monthly convulsive seizures compared to placebo ($p<0.001$). Secondary endpoints and safety were also in line with the results from the first Pivotal trial. Zogenix expects to file NDA and MAA by the end of 2018.

4.1.4. OV935 (TAK-935): Ovid Therapeutics, Takeda

OV935 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 antiepileptic activity in multiple preclinical epilepsy and seizure models,(company presentations).

After completing four Phase 1 trials in healthy volunteers, Ovid and Takeda are currently completing a Phase 1b/2a basket trial with OV935 in adults with rare developmental and epileptic encephalopathies (NCT03166215). Top-line data is expected in H2 2018 and the companies have announced their intention to initiate a Phase 2 clinical trials in paediatric patients with Dravet syndrome by the end of 2018.

4.1.5. Second-generation serotonergic treatments: Epygenix Therapeutics

Epygenix Therapeutics is developing three previously-approved drugs for the treatment fo Dravet syndrome, all acting 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 for the treatment of Dravet syndrome in 2017 (FDA).

Lorcaserin (EPX-200) is currently marketed under the name of Belviq by Arena Pharmaceuticals for weight loss. A small open-label study showed that 4 out of 5 patients with Dravet syndrome experienced a reduction in seizures when EPX-200 was used as an-add on to their baseline medication (Griffin et al., 2017). The three compounds have the potential to be second-generation serotonin modulators for the treatment of Dravet syndrome after the first-in-class fenfluramine (ZX008). The small investigator-initiated trial is not designed to be a pivotal study and additional trials will be needed to support an application for marketing authorization.

4.1.6. Second-generation cannabidiol-based treatments

INSYS Therapeutics is 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). The indication is no longer listed in the company website although the drug is still being developed for other forms or epilepsy. INSYS 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). The product is currently in an open-label Phase 2 basket trial in children and adolescents with developmental and epileptic encephalopathies that includes Dravet syndrome patients (BELIEVE 1, ACTRN12618000516280). Top-line data is expected in 2019. ZYN002 has the potential to become a second-generation cannabidiol treatment that avoids the bioavailability and tolerability limitations associated with oral administration.

4.1.7. BIS-001 (huperzine): Biscayne Neurotherapeutics

BIS-001 is a proprietary formulation of a synthetic form of huperzine A, which was originally extracted from a traditional Chinese medicine. Huperzine A is a

brain-penetrant acetylcholinesterase inhibitor with preclinical efficacy in multiple epilepsy models and has the potential to be a first-in-class treatment for epilepsy indications (Wong et al., 2016). BIS-001 received an orphan drug designation for the treatment of Dravet syndrome in 2017 (FDA).

BIS-001 recently completed a Phase 1b safety and pharmacokinetic study in adults with a new extended release formulation. The extended release formulation met all endpoints including suitability for twice-a-day dosing, and Biscayne announced in Q2 2018 the initiation of a Phase 2b in adults with Focal Impaired Awareness seizures. The company has communicated their intention to initiate Phase 2 trials in Dravet syndrome at some point in the future.

4.1.8. SAGE-324: Sage Therapeutics

Sage Therapeutics is developing SAGE-324, a novel, orally-active next-generation GABA modulator, for the treatment of rare epilepsies and other indications. 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). SAGE-324 is currently in late preclinical development. Sage has communicated the potential initiation of a Phase 1 trial in 2018.

4.2. Disease-targeting treatments

4.2.1. Translarna (ataluren): PTC Therapeutics

Ataluren is a read-through medication developed by PTC Therapeutics that is approved in Europe for the treatment of Duchenne muscular dystrophy patients with nonsense mutations under the brand name of Translarna (EMA provisional approval 2014, renewed in 2016).

Nonsense mutations introduce a premature stop codon into a gene sequence that prevents the cell from producing a complete protein. Read-through medications 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 have nonsense mutations.

There is a Phase 2 double-blind placebo-controlled crossover clinical trial ongoing at New York University evaluating the safety and efficacy of ataluren for treating Dravet syndrome caused by nonsense mutations and the related CDKL5 deficiency syndrome caused by non-sense mutations (NCT02758626). An expected date for top-line data has not yet been announced.

The ongoing investigator-initiated trial is not designed to be a pivotal study and additional trials will be needed to support an eventual application for marketing authorization.

4.2.2. OPK88001 (CUR-1916): OPKO Health

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4.2.2. OPK88001 (CUR-1916): OPKO Health

OPK88001 (CUR-1916) 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 has obtained the orphan drug designation for the treatment of Dravet syndrome from both the FDA 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 elevated gene transcription in the brain of a non-human primate (Hsiao et al., 2016).

OPKO recently communicated the expected initiation of clinical trials with OPK88001 in patients with Dravet syndrome (Phase 2a) within 2018. Details about the clinical trial protocol have not yet been made public.

4.2.3. SCN1A antisense treatment: Stoke Therapeutics

Stoke Therapeutics recently announced an antisense oligonucleotide (ASO) targeting SCN1A in development for the treatment of Dravet syndrome. The SCN1A ASO facilitates the processing of pre-mRNA into mature functional mRNA, increasing mRNA and Nav1.1 protein levels in mice (ASGT 2918).

This program is similar to the OPK88001 program by OPKO, both using an antisense approach to target naturally-occurring mechanisms that regulate SCN1A expression in an attempt to upregulate the target. However, while OPKO is targeting gene transcription, Stoke has developed the TANGO technology (Targeted Augmentation of Nuclear Gene Output) to target splicing.

Stoke has announced that the program is moving into formal preclinical development.

4.2.4. XEN901: Xenon Pharmaceuticals

Xenon Pharmaceuticals is developing a highly selective Nav1.6 sodium channel blocker for the treatment of epilepsy (XEN901). Xenon recently announced interim Phase 1 data of XEN901 in healthy volunteers showing a favorable PK profile, and expects a regulatory filing by year-end to initiate a Phase 2 trial in adult patients with focal seizures. The company has indicated plans to advance XEN901 for the treatment of rare epilepsies but no specific timelines have been communicated.

4.2.5. Some additional disease-targeting approaches

There are additional promising programs in early discovery stages for Dravet syndrome that aim to target activity of the sodium channels or expression levels of the SCN1A gene. These programs might or might not ultimately progress into the clinical phase for Dravet syndrome.

Lundbeck has an early program looking for Nav1.1 activators to treat a number of neurological conditions including Alzheimer, epilepsy and presumably Dravet syndrome (Jensen et al., 2014;

Frederiksen et al., 2017). Lundbeck has shown efficacy of the Nav1.1 activator AA4327 in a mouse model of induced seizures but has not published results in a mouse model of Dravet syndrome (Frederiksen et al., 2017). Recently, the Gladstone Institute of Neurological Disease and Evotec have presented results from their own search for Nav1.1 activators for the treatment of Dravet syndrome and Alzheimer´s disease. The project is also at early stages of drug discovery (Nanion webinar, on-line). Depending on their ability to identify drug-like Nav1.1 activators, early preclinical proof-of-concept in mice with Dravet syndrome could be available within 12-18 months.

A more advanced sodium channel modulator, PRAX-330 (GS-458967, GS967), is in development by Praxis Precision Medicine for the treatment of epilepsy. PRAX-330 reduces persistent sodium current as opposed to peak current inhibition (Belardinelli et al., 2013). PRAX-330 has shown preclinical efficacy in a mouse model of Dravet syndrome where it increased survival and reduced seizure frequency (Anderson et al., 2017).

PRAX-330 is currently completing a Phase 1 trial in healthy volunteers (ACTRN12617001512314). Details about the next clinical trials have not yet been made public.

Last, a promising disease-targeting approach for treating Dravet syndrome is viral-mediated gene therapy. With a coding sequence of 6 kb, the SCN1A gene is too large to fit into adeno-associated virus (AAV), so at least four different alternative approaches are currently ongoing. A research group at the University College London is leading a project to explore the development of lentiviral vectors to increase the levels of SCN1A in Dravet syndrome. The same group has recently shown proof-of-feasibility data in mice for using two AAVs each carrying half of the SCN1A gene that result in functional channel formation once co-expressed (ASGCT 2018 meeting). Also, the international consortium CureDravet was one of the eleven rare disease collaborations recently funded by the European E-rare program and will explore the use of two additional large-capacity vectors, human and canine adenovirus, to deliver SCN1A to neurons in Dravet syndrome. Based on the stage of these programs, early preclinical proof-of-concept for using gene therapy in mice with Dravet syndrome could be available within 12 months.

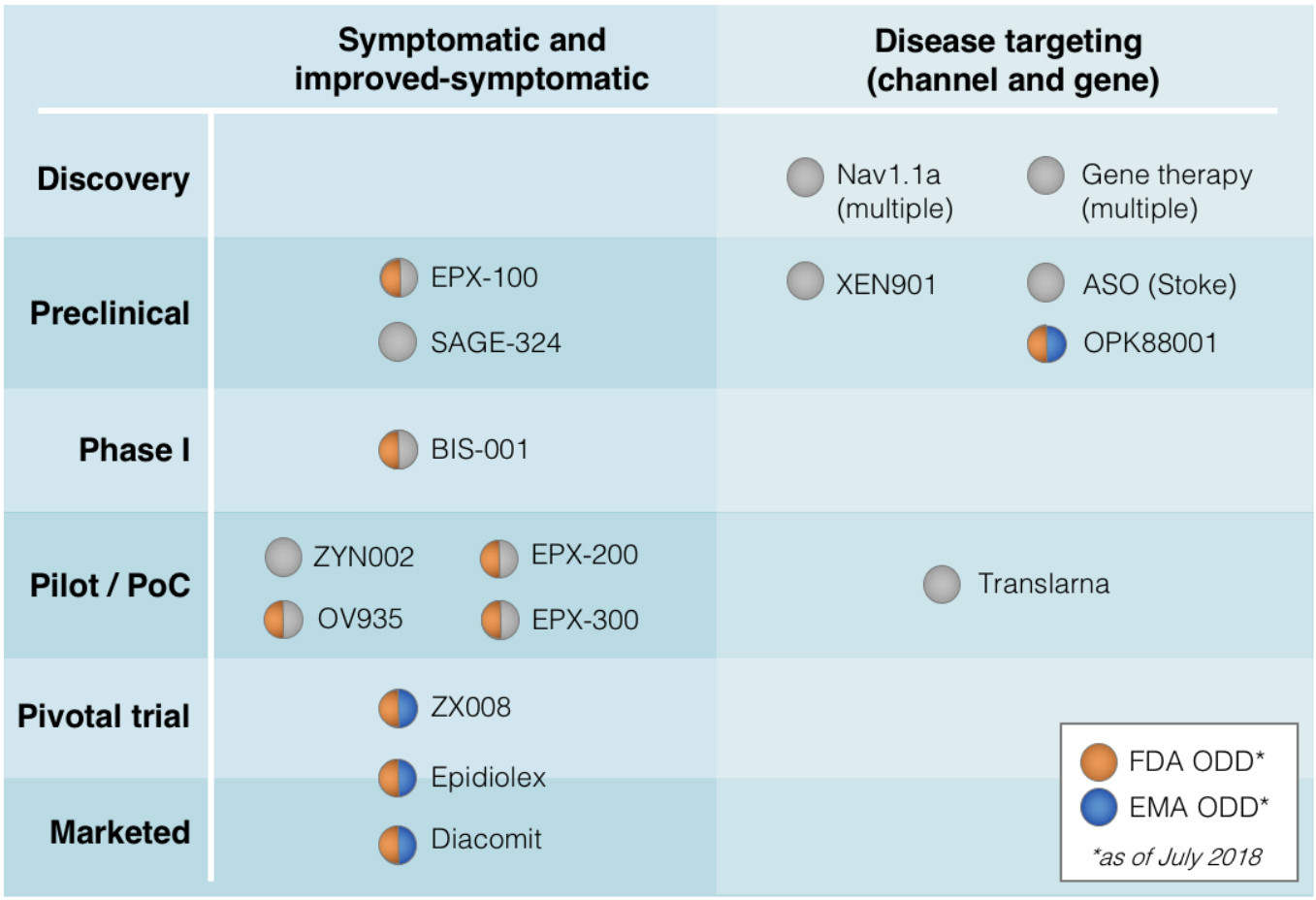

Figure 1 | **Dravet syndrome pipeline overview and maturity state**

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

Figure 1 summarizes the current state of the Dravet syndrome drug development pipeline as of July 2018. There are in total 13 named candidates (14 if we count Epidiolex in Europe), ranging from preclinical to Phase 3 clinical trial stages, and two approved medications (Epidiolex in the US, Diacomit outside of the US). Additional earlier discovery programs, searching directly for Nav1.1 channel activators and gene-replacement approaches, have also been highlighted.

The more advanced programs in development are Epidiolex (cannabidiol) from GW Pharmaceuticals, and ZX008 (fenfluramine) from Zogenix. Epidiolex obtained marketing authorization by the FDA in June of 2018, and is awaiting the decision of the EMA, currently expected around Q1 2019. Zogenix expects to file for marketing authorization of ZX008 in both markets by the end of 2018, with potential approvals by the FDA in H1 2019 and by EMA in late 2019 / early 2020.

The data available on both programs are supportive of a favorable risk/benefit

profile and their likelihood of obtaining marketing authorization is high. Therefore, it is likely that by late 2019 both Epidiolex and ZX008 will be approved in the two larger markets, with Epidiolex having a 9 to12-month lead time advantage over Zogenix's product.

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), the first-generation approaches for the symptomatic treatment of Dravet syndrome include a cannabidiol formulation (Epidiolex), a serotonergic drug (ZX008), an indirect negative modulator of NMDA receptors (OV935) and an acetylcholinesterase inhibitor (BIS-001).

(2) The proof of clinical efficacy obtained by Epidiolex and ZX008 for the cannabidiol and serotonergic classes opened the door to a second generation of aspiring best-in-class symptomatic treatments. This class currently includes a synthetic transdermal formulation of cannabidiol by Zynerba, formerly included a synthetic oral formulation by INSYS Therapeutics which is no longer pursuing this indication, as well as three repurposed candidates with serotonergic activity being developed by Epygenix.

(3) There is also a growing class of therapeutic approaches in development with the potential ability to directly treat the genetic defect that causes Dravet syndrome, either by facilitating read-through in the case of nonsense mutations, or by increasing expression of the functional SCN1A copy that all patients have, or by increasing activity of the ion channel. These therapeutics represent a third generation of treatments that specifically target the disease biology and are potentially disease-modifying, and from which improvements across multiple disease domains 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-modifying programs already in development.

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 compounds with potential 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 has only one 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. If both Epidiolex and ZX008 get approved, in 2 years from now it will 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 epilepsies with no approved or few advanced drug candidates, such as CDKL5 deficiency disorder or epilepsy associated with mutations in SCN2A. As more patients get diagnosed with these syndromes, they 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.

Beyond epilepsy alone, Dravet syndrome will continue to be the preferred orphan indication for therapeutics designed to address SCN1A or Nav1.1-related disorders, regardless of the number of anticonvulsant medications approved for treating it. Some of these programs might be ultimately interested in addressing larger markets such as Alzheimer's disease or schizophrenia that have been shown to be associated with reduced Nav1.1 protein levels or activity (Jensen et al., 2014). Other programs might have been specifically developed for treating Dravet syndrome, such as the antisense oligonucleotides from OPKO and Stoke Therapeutics. By targeting the cause of the disease, all of these programs have the potential to impact multiple disease domains. Seeing more of these programs in the Dravet syndrome pipeline and less symptomatic antiepileptic drugs in development will indicate a more mature pipeline.

	Therapeutic advances needed	Innovative trial protocols and tools needed
1	Availability of multiple treatments for seizures in Dravet syndrome.	Clinical trials that include **adult patients**. (More diagnosed adults than children, Auvin et al., 2018). **Improve diagnostic** to increase number of patients identified and treated (all ages).
2	Availability of treatments for the non-seizure aspects of the disease.	New validated **non-seizure-related endpoints** to support efficacy in other disease domains. **Longer** clinical trial protocols adapted to the new clinical outcomes.
3	Availability of disease-targeting and disease-modifying treatments.	New validated non-seizure-related **endpoints** and **longer** clinical trial protocols. **Biomarkers** of increased channel activity and/or expression levels.

Figure 2 | **Needs in drug development for Dravet syndrome**

6. Remaining unmet medical need and pipeline requirements

In Patients with Dravet syndrome face a number of intellectual, motor and developmental challenges beyond their epilepsy. We know from animal studies that these aspects of the disease are all consequences of the ion channel dysfunction caused by the gene mutation, and are therefore not expected to be addressed by anticonvulsant medications. Nevertheless, epilepsy remains a major contributor to patient and caregiver burden, being directly responsible for the early mortality observed in 15-20% of patients with this syndrome. As the programs that currently populate the Dravet syndrome pipeline reach marketing authorization, the Dravet syndrome drug market is likely to go through three different stages, each one addressing a different medical need.

Figure 2 summarizes these stages of successful pipeline development as well as some of the changes in clinical trial design that are likely to be needed.

(1) In a first stage, we are likely to see multiple drugs approved for the treatment of seizures associated with Dravet syndrome. Epilepsy in Dravet syndrome is notably drug-resistant, with only about 10% of patients being currently seizure-free (Aras et al., 2015; Lagae et al., 2018). The existing standard-of-care uses combinations of antiepileptic drugs that are unique to each patient due to heterogeneous response to each drug. Poly-pharmacology is likely to remain as the standard-of-care in Dravet syndrome, with the upcoming new medications providing specialists with a better pharmacological armamentarium that can be better optimized to each patient.

There are two current challenges to the optimal development and market access of drug candidates against seizures in Dravet syndrome. The first one is clinical trial recruitment. Current and past clinical trial protocols have included only patients from 2 to 18 years old. Because these trials target the same sub-group of patients and are taking place at the same time or soon after a previous trial, the identification of patients of this age that are not already enrolled in another clinical trial (double-blind phase or open-label extension) is increasingly difficult. A recent study estimated that even with a higher rate of underdiagnosis (or misdiagnosis) of Dravet syndrome in adults, a majority of the currently diagnosed patients are adults (Auvin et al., 2018). Unlike the pediatric population, the adult population has not been enrolled in clinical trials and represents an untapped population for enrolment.

There is no substantiated reason for restricting clinical trials to 18 years old and younger in Dravet syndrome, in particular when parallel trials with the same drug candidates in other epilepsy syndromes such as Lennox-Gastaut have included patients of up to 35 or even 55 years in age (NCT03355209, NCT02224690). Other than a reduction in the frequency of status epilepticus, adult patients with Dravet syndrome continue to have epilepsy and their rate of seizure freedom is the same than at younger ages (Lagae et al., 2018). Also, almost all (11 of 12) patients in the initial series of 12 patients with Dravet syndrome treated with fenfluramine in Belgium were 13 years old or older at the time or reporting (6 were adults; Ceulemans et al., 2012). Therefore, the efficacy data that set the basis for the pediatric Phase III trials with ZX008 in Dravet syndrome came actually from an adolescent and adult cohort study. Including adult patients in clinical trials with Dravet syndrome will facilitate clinical trial recruitment and reduce an important current challenge to drug development in Dravet syndrome.

Another challenge for the upcoming medications that treat epilepsy in Dravet syndrome is that the number of patients diagnosed with Dravet syndrome represents only a fraction of the actual number of patients that have the disease (Auvin et al., 2018), reducing the market size. Because of the refractory nature of Dravet syndrome, families and physicians are eager to access new therapeutic options. Therefore, the potential upcoming approval of Epidiolex and/or ZX008 is likely to have a positive impact on improving the diagnosis rate by encouraging physicians to identify potential cases of Dravet syndrome among their patient cohorts that would now be candidate for the new medications. As a consequence, the market for Dravet syndrome medications is likely to experience appreciable growth within the next several years.

(2) The need for product differentiation as well as the unmet medical need will lead to the development of treatments with efficacy for the non-seizure aspects of Dravet syndrome. Some of these are already present in the development pipeline, with OV935 and BIS-001 being good examples of candidates that based on their mechanism of action are expected to provide a broad therapeutic benefit beyond epilepsy to patients with Dravet syndrome.

All current clinical trials in Dravet syndrome use essentially classical epilepsy trial protocols. The need to

establish efficacy beyond (or instead of) seizure control in Dravet syndrome means that clinical trial protocols will need to be modified to support this differentiation.

Two important developments that will be needed are the development of non-seizure-related endpoints that could track 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.

(3) The developing of disease-targeting and disease-modifying therapies for the treatment of Dravet syndrome is already ongoing utilizing multiple approaches. Clinical trials using these candidates will face some of the same challenges as clinical trials using compounds against the non-seizure aspects of Dravet syndrome, including the need for non-seizure-related endpoints and trials of longer duration. In addition to these changes, clinical trials aiming to increase expression of Nav1.1 will need to incorporate some biomarker of increased channel expression or activity to establish proof-of-mechanism and to potentially act as surrogate endpoints. The apparent lack of SCN1A expression in peripheral tissues makes this challenge more complicated, and there is no currently available PET ligand for Nav1.1.

Companies and academic centers operating in this space might want to consider pre-competitive efforts to develop such ligand, which would be of use across therapeutic modalities (antisense therapies, gene therapy or small molecules).

Overall, the drug development pipeline for Dravet syndrome is very rich but it is important to remember that only Diacomit (stiripentol) and Epidiolex (cannabidiol) are currently approved for the treatment of the disease, and of these, only Diacomit is already on the market. In the meantime, the burden of Dravet syndrome is significant, and the unmet medical need includes (1) poor seizure control for 90% of the patients, (2) 15-20% rate of early mortality, (3) no medications to treat the non-seizure features of the syndrome, and (4) a large number of patients not receiving the standard of care because of not having a correct diagnosis.

7. Summary

Dravet syndrome is an orphan epilepsy disorder with multiple non-seizure comorbidities and high unmet medical need. In the last 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 at least 14 development programs, including a second, recently-approved drug. Some of this popularity is due to an increasing movement in epilepsy and other large disease areas away from highly competitive large disease indications and towards smaller, less-competitive, orphan indications.

The current Dravet syndrome pipeline shows signs of maturity, with a third generation of disease-targeting and potentially disease-modifying treatments differentiating themselves from the first and second generation of symptomatic treatments. As the competition around Dravet syndrome increases, the pipeline is likely to include less symptomatic treatments and more disease-targeting therapeutics.

UPDATE JULY 24, 2018: in a previous edition of this pipeline review, PRAX-330 from Praxis Precision Medicines was included in Table 1 and Figure 1. It has now been removed from these two figures following the request of the company.

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