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 largely limited to the symptomatic management of epileptic seizures. Although there is no drug approved by the FDA for this indication and only one approved by the EMA, in the last 5 years Dravet syndrome has received significant attention from the pharmaceutical industry. As of June 2017, the Dravet syndrome pipeline comprises at least 13 drug candidates, of which 3 are in late-stage placebo-controlled Phase II or III trials. Two of the products in development are potentially disease-modifying treatments, and 8 different products have received orphan drug designations. This report reviews the state of the Dravet syndrome drug development pipeline and discusses current and future opportunities.

1. Dravet syndrome - Overview

Dravet syndrome is a neurological rare disease caused in most 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 rise to syndromes similar to Dravet (e.g. GABRG2, SCN1B).

Pharmacological management of Dravet syndrome focuses largely on the use anti-epileptic drugs (Chiron 2011). There is no drug approved for the treatment of Dravet syndrome by the FDA, and only one approved by the EMA as an add-on medication: Diacomit (stiripentol, marketed by Biocodex).

Most patients with Dravet syndrome are taking combinations of 3 or more anti-epileptic drugs, most notably valproate, clobazam, stiripentol, topiramate and levetiracetam. None of these drugs alone achieves complete seizure suppression in these patients and only a minority (less than 10%) of the patients becomes seizure-free (Aras et al., 2015).

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 2011; Guerrini 2012). Other
drugs such as vigabatrin are also reported to have unacceptable side effects (increase in myoclonic seizures) and are therefore contraindicated for this syndrome as well (Ceulemans 2011). This particularity of Dravet syndrome reduces the therapeutic options available and makes it particularly important to differentiate Dravet syndrome from related syndromes by performing genetic testing.

The recent growth in popularity of Dravet syndrome responds to multiple factors, including the increasing competition around classical (non-orphan) epilepsy indications, which are further discussed in section 6 in this report.

2. Population and market size

Incidence of Dravet syndrome caused by SCN1A mutations has been reported to be between 1 in 40,900 and 1 in 20,900 live births (Brunklaus 2012; Wu et al., 2015; Bayat et al 2015; Rosander and Hallbök 2015). The estimated number of patients in the US is of 7,000 to 20,000, with the same number for the EU5 (Germany, UK, Italy, Spain, France). Therefore the treatable population in the two large markets is estimated to range from 14,000 to 40,000 patients, although actual numbers are unknown.

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).

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

Clinical trial design for Dravet syndrome follows the usual standards for anti-epileptic medications. Importantly, all of the protocols for placebo-controlled trials in Dravet syndrome that have been published to date follow essentially the same protocol and monitor seizures as primary endpoints.

Table 1 offers a list of all double-blind, placebo-controlled trials for Dravet syndrome that have been announced to date. This list includes a clinical trial that was withdrawn prior to enrolment (clobazam, NCT02174094) but not open-label studies. All trials evaluate the experimental drug as an add-on treatment to baseline medication (usually 1-3 anti-epileptic drugs) in patients that have failed to control seizures after trying 2 or more anti-epileptic medications.

The two primary endpoints that have been used in double-blind, placebo-controlled clinical trial protocols for Dravet syndrome measure epilepsy outcomes.
The most common primary endpoint is the percentage of seizure reduction when comparing treatment period with baseline period (vs percentage reduction in the placebo group). Another primary endpoint that has been used is the percentage of responder patients, wherein a “responder” is a patient that experiences a reduction in seizure frequency greater than 50% during treatment. These endpoints are consistent with the standard clinical trial design for epilepsy trials.

The standard clinical trial protocol for Dravet syndrome recruits patients younger than 18 years old with a minimum of 4 to 6 convulsive seizures per month and compares the frequency of seizures during a baseline period with the frequency of seizures during the treatment period, which lasts about 3 months.

The appeal of this standard trial design is significant because it recruits a largely genetically uniform population, uses a very objective outcome (seizures), and has a relative short duration (12-16 weeks). This is one of the main reasons that has made Dravet syndrome such an attractive indication when compared to other neurological rare diseases that have more heterogeneous causes, less objective outcomes (e.g. behavioral outcomes) and require longer treatments in order to measure changes in those outcomes.

There are two preclinical models for Dravet syndrome that are considered to have translational validity: mouse models and zebrafish models (Table 2). Both preclinical models have established protocols for measuring seizure-related outcomes, which correspond to the seizure-related primary endpoints used in clinical trials.

There are 9 mouse models that have been developed for Dravet syndrome, all based on the removal (knock-out) or...
Table 2 - List of mouse and zebrafish models of Dravet syndrome that have been described.

<table>
<thead>
<tr>
<th>Mouse model</th>
<th>Genetic modification</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scn1a&lt;sup&gt;tm1Wac&lt;/sup&gt;</td>
<td>Knock-out</td>
<td>Yu et al., 2006</td>
</tr>
<tr>
<td>Scn1a&lt;sup&gt;tm1.1Kzy&lt;/sup&gt;</td>
<td>Knock-in (R1407X)</td>
<td>Ogiwara et al., 2007</td>
</tr>
<tr>
<td>Scn1a&lt;sup&gt;tm1.1Aesc&lt;/sup&gt;</td>
<td>Knock-in (R1648H)</td>
<td>Martin et al., 2010</td>
</tr>
<tr>
<td>Scn1a&lt;sup&gt;tm2.1Wac&lt;/sup&gt;</td>
<td>Conditional knock-out</td>
<td>Chaeh et al., 2012</td>
</tr>
<tr>
<td>Scn1a&lt;sup&gt;tm2.1Kzy&lt;/sup&gt;</td>
<td>Conditional knock-out</td>
<td>Ogiwara et al., 2013</td>
</tr>
<tr>
<td>Scn1a&lt;sup&gt;tm2.1Aesc&lt;/sup&gt;</td>
<td>Conditional knock-out</td>
<td>Dutton et al., 2013</td>
</tr>
<tr>
<td>Scn1a&lt;sup&gt;tm1Kea&lt;/sup&gt;</td>
<td>Knock-out</td>
<td>Milier et al., 2014</td>
</tr>
<tr>
<td>Scn1a&lt;sup&gt;tm1.1Swl&lt;/sup&gt;</td>
<td>Knock-in (E1099X)</td>
<td>Tsai et al., 2015</td>
</tr>
<tr>
<td>Scn1a&lt;sup&gt;tm1.1Def&lt;/sup&gt;</td>
<td>Conditional knock-in (A1783V)</td>
<td>Mingorance et al., 2016</td>
</tr>
<tr>
<td>Zebrafish model</td>
<td>Genetic modification</td>
<td>Reference</td>
</tr>
<tr>
<td>Scn1a Didy / Scn1aLab</td>
<td>Knock-in</td>
<td>Baraban et al., 2013</td>
</tr>
<tr>
<td>Scn1a morpholino knock-down</td>
<td>Knock-down</td>
<td>Zhang et al., 2015</td>
</tr>
</tbody>
</table>

Most mutations in Dravet patients occur de novo, with over 1,000 different mutations described to date. As with patients, who often carry unique mutations, all of the different SCN1A mutant mice have been described to have similar phenotypes.

Two main seizure endpoints have been described for Dravet mouse models: spontaneous seizures and hyperthermia-induced seizures. Reverse translational validation of the hyperthermia model has been established for the only drug approved for treating Dravet syndrome (stiripentol, Cao et al., 2012) as well as for other approved anti-epileptic drugs commonly used in the clinic for the management of Dravet syndrome (Hawkins et al., 2017).

Zebrafish models of Dravet syndrome based on the reduction (knock-down) or mutation (knock-in) of the SCN1A gene ortholog in the fish have also proven to have translational value using seizure endpoints (Baraban et al., 2013, Zhang et al., 2015).

4. Pipeline review

Outside of the US, the only drug currently approved for the treatment of Dravet syndrome is Diacomit (stiripentol), marketed by Biocodex, which was approved to be used only in combination with valproate and clobazam (EMA/476469/2014). Diacomit enhances 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. There is currently no drug approved by the FDA for treating Dravet syndrome, although Diacomit did receive an orphan drug designation from the FDA in 2008.

The following sections review the state of the Dravet syndrome drug development pipeline as of June 2017. Compound names, mechanism of action if known, available clinical data (or mouse data if no clinical data is available), stage of development, date of orphan drug designation and planned trial initiation or IND/NDA filing are reported for each compound in development.

All information used in this publication has been compiled from publicly available sources including conference presentations, publications, company websites, press releases, and sponsor SEC filings. In the few exceptions where a company expressly requested to include in the report some non-public domain information this is identified as “personal communication”.

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**Table 3 - List of companies with compounds in development for Dravet syndrome.**

<table>
<thead>
<tr>
<th>Company</th>
<th>Compound</th>
<th>Stage June 2017</th>
<th>ODD FDA/EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biscayne Neurotherapeutics</td>
<td>BIS-001 (huperzine A)</td>
<td>Phase I</td>
<td>2017/-</td>
</tr>
<tr>
<td>Epygenix Therapeutics</td>
<td>EPX-100</td>
<td>Preclinical</td>
<td>2017/-</td>
</tr>
<tr>
<td>Epygenix Therapeutics</td>
<td>EPX-200</td>
<td>Phase II</td>
<td>2017/-</td>
</tr>
<tr>
<td>Epygenix Therapeutics</td>
<td>EPX-300</td>
<td>Preclinical</td>
<td>-/-</td>
</tr>
<tr>
<td>GW Pharmaceuticals</td>
<td>Epidiolex (cannabidiol)</td>
<td>Phase III</td>
<td>2013/2014</td>
</tr>
<tr>
<td>INSYS Therapeutics</td>
<td>Cannabidiol</td>
<td>Phase I</td>
<td>2014/-</td>
</tr>
<tr>
<td>OPKO Health</td>
<td>OPK88001 (CUR-1916)</td>
<td>Preclinical</td>
<td>-/2017</td>
</tr>
<tr>
<td>Ovid Therapeutics</td>
<td>OV935 (TAK-935)</td>
<td>Phase I</td>
<td>-/</td>
</tr>
<tr>
<td>PTC Therapeutics</td>
<td>Translarna (ataluren)</td>
<td>Phase II</td>
<td>-/</td>
</tr>
<tr>
<td>Sage Therapeutics</td>
<td>SAGE-324</td>
<td>Preclinical</td>
<td>-/</td>
</tr>
<tr>
<td>Takeda</td>
<td>OV935 (TAK-935)</td>
<td>Phase I</td>
<td>-/</td>
</tr>
<tr>
<td>Xenon Pharmaceuticals</td>
<td>Nav1.6 inhibitor</td>
<td>Preclinical</td>
<td>-/</td>
</tr>
<tr>
<td>Zogenix</td>
<td>ZX008 (fenfluramine)</td>
<td>Phase III</td>
<td>2013/2014</td>
</tr>
</tbody>
</table>
4.1. Epidiolex (cannabidiol) – GW Pharmaceuticals

Epidiolex is a liquid formulation of pharmaceutical grade plant-derived cannabidiol, which is a non-psychoactive component of the cannabis plant. It is currently in Phase 3 clinical trials for the treatment of Dravet syndrome and additional related syndromes, and obtained orphan drug designations for the treatment of Dravet syndrome in 2013 (FDA) and 2014 (EMA).

Following a successful expanded access programme (Devinsky et al., 2016), GW Pharma launched two large Phase 3 pivotal trials for evaluating Epidiolex for the treatment of seizures in Dravet syndrome. The first of these trials is completed and the second is currently ongoing as of June 2017.

The results of the first clinical trial with 120 patients were positive and have been recently published in the New England Journal of Medicine (Devinsky et al., 2017; NCT02091375). The average reduction of seizure frequency while taking Epidiolex was 39% (primary endpoint), and the percentage of patients who had at least a 50% reduction in convulsive seizure frequency and are considered “responders” was 43% (secondary endpoint). Beyond seizures, 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 results where in line with those from Phase 3 trials in Lennox-Gastaut syndrome and support that Epidiolex provides clinically meaningful reductions in seizure frequency together with an acceptable safety and tolerability profile.

As of June 2017, over 1,200 patients with multiple rare epilepsies have been treated with Epidiolex through expanded access programs and open-label extensions. NDA submission is planned for mid-2017 with a potential launch in 2018, and EU regulatory submission for 2H 2017. In the US, Epidiolex will be commercialized through the GW Pharma subsidiary Greenwich Biosciences.

4.2. ZX008 (fenfluramine) – Zogenix

Fenfluramine is a serotonin receptor agonist developed by Zogenix currently in Phase 3 clinical trials for the treatment of Dravet syndrome. New research by the company has identified Sigma-1 receptor positive allosteric modulation as a likely additional mechanism of action (Martin et al., 2017). Fenfluramine obtained orphan drug designations for the treatment of Dravet syndrome in 2013 (FDA) and 2014 (EMA).

Fenfluramine was previously in the market for adult weight-loss used in combination with phentermine. It was withdrawn from the market in 1997 after it was discovered that some adult obese patients treated with high doses of the combined pill developed valvular heart disease or pulmonary hypertension. Interestingly, low-dose fenfluramine was also shown to have remarkable efficacy for treating Dravet syndrome in an ongoing 27-year observational study in Belgium (Ceulemans et al., 2012; Schoonjans et al., 2017; de Witte and Lagae, 2017), with more than half of the patients remaining seizure-free at the time of study (Ceulemans et al., 2012).

A further prospective open-label study of a new cohort of patients was recently published in which patients showed a median reduction of 75% in frequency of
major motor seizures (Schoonjans et al., 2017). No clinically meaningful clinical or echocardiographic signs of cardiac valve disease have been noted with long-term treatment in these studies (Ceulemans et al, 2012, Schoonjans et al. 2017). These data enabled the clinical development of a low-dose formulation of fenfluramine (ZX008) for the treatment of Dravet syndrome and additional related epilepsy syndromes.

The preclinical validation of fenfluramine for Dravet syndrome is much more recent than the clinical proof-of-concept. Fenfluramine was first shown to have high efficacy in treating seizures in a zebrafish model of Dravet syndrome (Zhang et al., 2015). The zebrafish model was also used to determine that the efficacy of fenfluramine was partly mediated by its serotonergic activity (Sourbron et al., 2016 and 2017). These results have later been independently replicated (Griffin et al., 2017).

Phase 3 pivotal trials for ZX008 in Dravet syndrome are currently ongoing. The first top-line data is expected in 2H 2017, with top-line data from the second trial following up on late 2017/early 2018. Zogenix expects to file an NDA in 2018.

4.3 Translarna (ataluren) – PTC Therapeutics

Ataluren is a translational read-through drug 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).

Nonsense mutations are those that introduce a premature stop codon into a gene sequence that prevents the cell from producing a complete protein. Translational read-through medications enable the cell to move past this defect and complete a functional protein. In many genetic diseases a percentage of the patients carry nonsense mutations and are therefore potential candidates for treatment with Translarna.

There is a Phase 2 double-blind, placebo-controlled crossover clinical trial currently ongoing at New York University evaluating the safety and efficacy of ataluren for treating Dravet syndrome caused by nonsense mutations and CDKL5 deficiency syndrome caused by nonsense mutations (NCT02758626). There is no preclinical data on the use of ataluren in SCN1A nonsense mutations.

Although not initially intended for the treatment of Dravet syndrome, if proven effective to promote read-through of SCN1A nonsense mutations in patients and increase channel expression, Translarna might have the potential to treat some of the non-seizure aspects of Dravet syndrome, such as cognitive problems, behavioral abnormalities and motor problems in the subset of patients that carry those mutations.

PTC does not have an orphan drug designation for the treatment of Dravet syndrome with ataluren yet. The ongoing investigator-initiated trial is not designed to be a pivotal trial and additional studies will be needed to support an application for marketing authorization.

4.4 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 medicinal plant. Huperzine A is a brain-penetrant acetylcholinesterase inhibitor with preclinical efficacy in multiple epilepsy models that involves the muscarinic system to increase GABA-ergic tone (Wong et al., 2016). BIS-001 received an orphan drug designation for the treatment of Dravet syndrome earlier this year (2017, FDA).

A recent publication described the preclinical validation for the treatment of epilepsy and Dravet syndrome with huperzine A (Wong et al., 2016). In this study, huperzine A had acute and subchronic efficacy in a mouse model of Dravet syndrome as well as broad-spectrum anticonvulsant activity in a variety of seizure models (Wong et al., 2016).

BIS-001 has completed a Phase 1a safety and pharmacokinetic study in adults and has now initiated a Phase 1b in healthy adults in Australia with a new extended-release formulation. Biscayne expects to initiate a Phase 2b in 2018 also in adults with partial epilepsy. The company has communicated their intention to initiate Phase 2 trials in Dravet syndrome at some point in the future once all necessary regulatory studies for pediatric trials are completed.

**4.5 OPK88001 (CUR-1916) – OPKO Health**

OPK88001, also known as 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 obtained the orphan drug designation for the treatment of Dravet syndrome earlier this year (2017, EMA).

The efficacy data available to date is only preclinical. In a mouse model of Dravet syndrome, intrathecal administration of the murine version of OPK88001 was shown to increase expression of Nav1.1 by 30% and significantly reduce seizures (Hsiao et al., 2016). The human-specific version of the oligonucleotide, which needs to be slightly different due to genetic sequence differences, was also shown to elevate SCN1A transcription in the brain of a non-human primate (Hsiao et al., 2016).

Due to the disease-targeting mechanism of OPK88001, it might have the potential to treat some of the non-seizure aspects of the Dravet syndrome that include behavioral abnormalities, cognitive problems and motor problems. Unlike Translarna, which would benefit only a subset of the patients, OPK88001 is designed to correct protein expression in all patients with Dravet syndrome. As such, it is the best example of a second generation of treatments for Dravet syndrome that will target the disease biology, differentiating themselves from the first generation of anti-convulsant symptomatic treatments.

OPKO plans to file an IND and initiate clinical trials later this year (2H 2017). Details about the clinical trial protocol have not yet been made public.

**4.6 OV935 (TAK-935) – Ovid Therapeutics and Takeda**

In early 2017 Ovid Therapeutics and Takeda announced a partnership to co-develop and commercialize OV935 for the treatment of rare epilepsy syndromes including Dravet syndrome. OV935 is a
highly selective inhibitor of the enzyme cholesterol 24 hydroxylase (CH24H). CH24H is predominantly expressed in the brain, where it plays a central role in cholesterol homeostasis (Russell et al., 2009). Recent literature suggests that modulation of CH24H activity may have an impact on the over-activation of neurotransmitter pathways that have been implicated in a number of neurological disorders such as epilepsy (Paul et al., 2013). If approved, OV935 has the potential to become a first-in-class inhibitor of CH24H.

Ovid has disclosed that OV935 has shown anti-epileptic activity in multiple preclinical epilepsy and seizure models, including hyperthermia-induced seizures in a mouse model of Dravet syndrome.

OV935 has already completed Phase 1 trials in healthy volunteers and plans to initiate Phase 1b/2a trials in 2017 in a number of rare epilepsy syndromes, including Dravet syndrome. OV935 does not have an orphan drug designation for the treatment of Dravet syndrome yet.

**4.7 EPX-100, EPX-200 and EPX-300 – Epygenix Therapeutics**

Epygenix Therapeutics Inc. is a company recently created to develop three assets licensed from UCSF for the treatment of Dravet syndrome and related epilepsy syndromes. Epygenix has not publicly disclosed the active pharmaceutical ingredient for these programs and has requested that third-party sources not be used to identify the compounds in this review (personal communication).

EPX-100 is a first-generation anti-histaminic drug that is not currently marketed. The ability of EPX-100 to treat seizures in Dravet syndrome was discovered in a zebrafish model (Baraban et al., 2013). This activity was shown to be independent of H1 receptor inhibition (Baraban et al., 2013), and to involve instead serotonergic modulation (Griffin et al., 2017). There is no data available for EPX-100 efficacy in a mouse model of Dravet syndrome or in patients yet. Epygenix expects to file an IND in 2018 (personal communication).

EPX-200 is a 5-HT-2c agonist marketed for the treatment of obesity. The ability of EPX-200 to treat seizures in Dravet syndrome was first discovered in zebrafish by two separate groups (Sourbron et al., 2016 and 2017; Griffin et al., 2017). A recent publication described a small observational study with EPX-200 in 5 patients with Dravet syndrome who experienced a varied reduction of seizures (Griffin et al., 2017). Epygenix has not yet made public the estimated timelines for IND filing and clinical trial initiation for EPX-200.

EPX-300 is a serotonergic FDA-approved antidepressant, anti-anxiety and sleep-inducing insomnia drug. Epygenix has disclosed that EPX-300 has preclinical epilepsy efficacy in a zebrafish model of Dravet syndrome, and expects to file an IND in 2017 (personal communication).

**4.8 Cannabidiol – INSYS Therapeutics**

Similarly to GW Pharmaceuticals, INSYS Therapeutics is developing a liquid formulation of cannabidiol for the treatment of epilepsy. Unlike the plant-derived cannabidiol being developed by
GW Pharma, INSYS has opted for a proprietary formulation containing a synthetic form of the compound. INSYS obtained an orphan drug designation for the treatment of Dravet syndrome with its synthetic cannabidiol in 2014 (FDA).

INSYS recently completed a Phase 1 safety and pharmacokinetic study in refractory epilepsy. There is an open Phase 3 trial not yet recruiting in Dravet syndrome (NCT02318563), with an anticipated study start date of August 31 2017.

4.9 Nav1.6 inhibitor – Xenon Pharmaceuticals

Xenon Pharmaceuticals has disclosed that they are developing a preclinical drug candidate for rare epilepsy syndromes including the potential treatment of Dravet syndrome. The compound is a highly selective Nav1.6 sodium channel blocker. Excessive Nav1.6 channel activity has been associated with a syndrome caused by gain-of-function mutations in the SCN8A gene (encoding Nav1.6) and also with Dravet syndrome where the balance between Nav1.1 and Nav1.6 is disrupted by the absence of a second functional copy of the SCN1A gene. The candidate compound does not yet have an orphan drug designation for the treatment of Dravet syndrome.

Xenon expects to file an IND or IND equivalent with this candidate by the end of 2017, followed by a Phase 1 trial in healthy volunteers.

4.10 SAGE-324 – Sage Therapeutics

Sage Therapeutics is developing SAGE-324, a novel, orally-active next-generation GABA modulator, for the treatment of epilepsies including Dravet syndrome (personal communication). SAGE-324 does not yet have an orphan drug designation for the treatment of Dravet syndrome and is currently advancing through IND-enabling studies to allow for a potential submission of an IND.

4.11 Discontinued programs

Two companies had disclosed their intention to perform clinical trials in Dravet syndrome but later withdrew from the indication.

After the positive results of Diacomit (stiripentol) in combination with Frisium/Onfi (clobazam) in Dravet syndrome, Lundbeck, the marketing authorization holder for clobazam, performed pharmacokinetic/pharmacodynamic modelling and determined that 50% of the response observed with stiripentol was due to clobazam increase (Lee et al., 2015). In Q1 2015, Lundbeck announced the initiation of a clinical trial with clobazam in Dravet syndrome (NCT02174094). In Q3 2015 Lundbeck announced the discontinuation of the clinical study, and clobazam continues to be one of the most used drugs for treating Dravet syndrome despite lack of specific approval for this indication (Aras et al., 2015).

The second advanced program that withdrew the Dravet syndrome indication before initiating clinical trials is SAGE-217 from Sage Therapeutics. During the preclinical stages, Sage had announced the intention to develop SAGE-217 clinically for the treatment of some rare epilepsies including Dravet syndrome. They also reported preclinical efficacy in multiple epilepsy models including Dravet syndrome. In mid-2016...
Sage announced it was no longer pursuing these epilepsy syndromes with SAGE-217. Instead, Sage is positioning an earlier-stage differentiated compound, SAGE-324, for development in the treatment of epilepsies including Dravet syndrome. SAGE-217 is currently in Phase 2 clinical trials for postpartum depression, essential tremor, Parkinson’s disease and major depressive disorder.

4.12 Other discovery and preclinical programs

There are additional programs in preclinical development for Dravet syndrome that target either the activity of the Nav1.1 channel or the expression levels of the SCN1A gene, and that might or might not ultimately progress into the clinical phase. Lundbeck has an early program looking for Nav1.1 activators to treat a number of neurological conditions including epilepsy (Jensen et al., 2014; Crestey et al., 2015; Frederiksen et al., 2017). Northwestern University researchers recently published the preclinical validation of an atypical sodium channel blocker called GS967 in a mouse model of Dravet syndrome (Anderson et al., 2017). Lastly, there are also at least two groups in Spain and the UK with preclinical stage programs trying to develop gene therapy vectors to deliver a supplemental copy of SCN1A to patient brains.

5. The clinical perspective: remaining unmet medical need

With at least 13 drug candidates in different stages of development, it would be easy to dismiss Dravet syndrome as a rare disease that is well-served. This is, however, not the case (see also Box 1, measuring the unmet need).

A recent publication established the mortality of Dravet syndrome at about 15% within a 10 year period (Cooper et al., 2016). Of these, 10% correspond to Sudden Unexpected Death in Epilepsy (SUDEP) and the remaining 5% to seizure-related complications such as status epilepticus and accidents due to seizures. Because of these risks, it is of utmost importance to try to achieve complete seizure control. However, less than 10% of the patients with Dravet syndrome achieve seizure freedom despite having more than 20 anti-epileptic drugs on the market, underscoring the severe refractory nature of the syndrome and the need to develop new effective medications.

Although they are rarely seizure-free, a majority of patients with Dravet syndrome achieve some degree of seizure reduction with combinations of anti-epileptic medications and in some cases with ketogenic diet (Aras et al., 2015). A critical challenge for the pharmacological management of this syndrome is that not all patients respond equally well to the same drug or drug combination. This heterogeneous response is likely to also apply to most of the current drug candidates in development, and it would therefore be unreasonable to expect a new drug to have significant efficacy in a majority of patients with Dravet syndrome. Instead, it is likely that newly approved drugs will have improved efficacy, and will provide specialists with a better pharmacological armamentarium to try to increase the number of patients that achieve seizure freedom.

Besides seizures, Dravet syndrome patients present a collection of cognitive, behavioral and motor problems that pose a significant burden to their families’ quality of life. However, unlike
other complex neurodevelopmental disorders such as Rett syndrome, Dravet syndrome is usually classified as a type of epilepsy, and all of the drugs currently in clinical development for Dravet syndrome are evaluated by their ability to reduce seizure frequency in these patients. This is partly due to the life-threatening nature of seizures in this population, but also because seizures are a robust and relatively simple endpoint in clinical trials. In fact, no cognitive, behavioral or motor function scale (or combined score) has been validated for Dravet syndrome, and suitable clinical trial endpoints are not readily available for these outcomes. Therefore there is an urgent need to characterize these non-seizure features of Dravet syndrome in a way that will support the development of scales for measuring patient improvement and clinical trial endpoints.

Last, incidence studies indicate a larger prevalence of Dravet syndrome than what can be documented, in particularly in adults. Failing to diagnose Dravet syndrome, or misdiagnosing it as another syndrome, has important implications for disease management. In a study, parents reported that before their children received the diagnosis of Dravet syndrome, around a third of them had been treated with sodium channel blockers, a usual anti-epileptic drug category that is contraindicated for Dravet syndrome and can exacerbate seizures (Aras et al., 2015). There is therefore a need to perform earlier genetic testing of SCN1A mutations that could identify Dravet syndrome before patients are exposed to these drugs. Also, because of the refractory nature of Dravet and related syndromes, families and physicians are eager to access new therapeutic options. Therefore the potential approval of Epidiolex and/or ZX008 in the next two years is likely to have a positive impact on improving current 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.

In summary, the burden of Dravet syndrome is significant, and the unmet
medical need for this disease includes (1) poor seizure control for 90% of the patients, (2) 15% mortality within 10 years, (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 due to the lack of a correct diagnosis.

6. The drug development perspective: evolving business case

In the last 5 years, Dravet syndrome has gained significant attention from the pharmaceutical industry and the pipeline has gone from only one drug approved (ex-US) to at least 13 development programs. The syndrome was first described in 1978, and until 2012 only stiripentol had been developed, with a particularly lean clinical package based on two small pivotal clinical trials with 41 and 24 highly homogenous patients. Compared to that, the clinical package of the most likely second approval for Dravet syndrome, Epidiolex, includes two pivotal trials with over 300 Dravet syndrome patients and more than 1,200 patients in total on the treatment.

In this report we analyze the reasons why Dravet syndrome became so popular and offer some possible scenarios for how the business case for pursuing Dravet syndrome might evolve in the future.

6.1. How Dravet syndrome became popular

It is important to note that the first wave of compounds developed or currently in development for the treatment of Dravet syndrome all followed an opportunistic strategy. These are drugs that had not been initially developed to specifically treat Dravet syndrome, but for which there was some early data or rationale to believe they might have symptomatic efficacy in the syndrome. Because these drugs are not specific for Dravet syndrome, the sponsors could have selected many other neurological diseases as target indications, yet they chose to pursue Dravet syndrome as their only target or one of their target indications.

There are multiple reasons that made Dravet syndrome particularly attractive:

(1) The epilepsy market is a multi-billion, highly profitable market that is also highly competitive. With over 20 different molecules approved and many generic drugs, it is becoming very difficult to show differentiation and secure sufficient market penetration. As a result, many of the most recent anti-epileptic drugs in development are choosing to target the epilepsy syndromes, which are orphan indications where the competition is lower and the possibilities to secure larger market share, facilitated by orphan market exclusivity, are higher. Also, clinical programs for rare diseases involve less patients than for non-orphan indications and are likely to be shorter and therefore cheaper.

(2) Dravet syndrome is rare, but not too rare. Although its prevalence is uncertain, the most recent incidence studies converge on a number of around 1 in 20,000 live births. This means that the potential treatable population for a new drug is counted in the several thousands, a very attractive population size for an orphan disease.

(3) Dravet syndrome is largely monogenic, which reduces patient variability as compared to other refractory epilepsy syndromes with multi-
factorial causes, such as Infantile Spasms and Lennox-Gastaut Syndrome.

(4) The clinical trial protocol for Dravet syndrome uses a very objective outcome (seizures), and has a relative short duration (12-16 weeks). This clinical protocol is particularly attractive when compared to other neurological rare diseases that have more heterogeneous causes, less objective outcomes, or that require longer treatments in order to measure changes in these outcomes.

(5) There are strong international patient organizations that raised the profile of Dravet syndrome, made it easier to diagnose more patients and facilitated the work of pharmaceutical companies. The importance of strong patient organizations is particularly critical in rare diseases, where patients, specialists and resources are limited and disperse.

Therefore, the initial business case that has attracted so many companies to Dravet syndrome is as a preferred alternative to classical (non-orphan) epilepsy, where increased competition drove sponsors towards smaller, less crowded epilepsy indications.

Perhaps the exception to this has been fenfluramine, which was discovered to have significant efficacy in a group of patients with self-induced seizures back in 1985, even before many of these patients were discovered to have Dravet syndrome (reviewed in Schoonjans et al., 2015). Fenfluramine was considered as a potential treatment for these patients because of the compulsive nature of self-induced epilepsy and the potential benefit of using serotonergic drugs, although it soon became clear that fenfluramine had direct anticonvulsant efficacy as well. Ever since then, the Belgian groups have treated epilepsy patients with fenfluramine and have pursued its development for Dravet syndrome.

6.2. The Dravet syndrome pipeline today

Figure 1 summarizes the current state of the Dravet syndrome drug development pipeline as of June 2017. There are in total 13 named candidates, ranging from preclinical to Phase 3 trial stages, and one approved medication. Two earlier-stage discovery programs, searching for Nav1.1 channel activators and gene-replacement approaches, have also been highlighted.

The more advanced programs in the Dravet syndrome pipeline are Epidiolex (cannabidiol) from GW Pharmaceuticals, and ZX008 (fenfluramine) from Zogenix. Both programs are close to NDA filing, with expected filing dates in 2017 and 2018, respectively. Similarly, both programs have sufficient clinical proof-of-concept data available to believe that their likelihood of obtaining regulatory approval is high, provided that the safety profile of the pivotal trials is favorable. Therefore it is likely that by 2019 the number of approved drugs for the treatment of Dravet syndrome will grow from one to three.

Behind these front-runners of the Dravet syndrome pipeline there are multiple compounds with various mechanisms of action. Some of these programs are also pursuing a best-in-class strategy, including a nonplant-derived cannabidiol formulation by INSYS Therapeutics and three repurposing candidates with serotonergic activity being developed by Epygenix.
From a high-level perspective, a division of the drugs in the Dravet syndrome pipeline into three large categories becomes apparent:

1. After the discovery of fenfluramine as a promising drug for Dravet syndrome, serotonergic agents have emerged as a class for the treatment of Dravet syndrome, and there are currently four programs, including ZX008 (fenfluramine) itself, at different stages of development.

2. Another class comprises those agents with the ability to directly treat the genetic defect that causes Dravet syndrome, either by facilitating translational read-through in the case of nonsense mutations (Translarna) or by increasing expression of the functional SCN1A copy that all patients have (OPKO antisense program and earlier gene therapy approaches). Compounds in this category represent a second generation of treatments that, unlike first generation drugs, have a potential to be disease-modifying and from which improvements across multiple disease symptoms are expected.

3. The remaining programs can be grouped into a third symptomatic non-serotonergic class, where some opportunistic programs (such as the two cannabidiol programs, OV935, BIS-001 and others) compete with programs that could treat the disease symptoms in a more targeted way, such as the Nav1.6

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**Figure 1 - Dravet syndrome pipeline 2017.**

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*as of June 2017

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**DRAVET SYNDROME PIPELINE 2017**
inhibitor candidate developed by Xenon Pharmaceuticals or the very early-stage Nav1.1 activators from Lundbeck.

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-specific programs and disease-modifying programs already in development. Overall, it is a very active area of clinical development that has emerged within a very short timeframe.

6.3. The evolving business case

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.

One of the main reasons why several companies are currently pursuing Dravet syndrome, as opposed to non-orphan epilepsy, is because they are developing compounds with anticonvulsant activity that are not new chemical entities. To offset their weaker intellectual property position, these companies target orphan forms of epilepsy in order to secure market protection through orphan drug status. As a relatively common rare disease that is largely monogenic and that has no FDA-approved drug, Dravet syndrome is an ideal target. However, one of the requirements by the EMA to keep orphan drug status after approval is to demonstrate significant benefit over existing approved medications. If both Epidiolex and ZX008 get approved, in just 2 years 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 advanced drug candidates.

Some potential indications that might come to replace the current attractive position of Dravet syndrome are other refractory epilepsy syndromes that have been described more recently, and that do not yet have advanced therapeutic programs. This group of epilepsy syndromes includes diseases such as CDKL5 deficiency syndrome, SCN2A encephalopathy and PCDH19 epilepsy. 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 to thereby enjoy market exclusivity.

We envision that a debate will soon emerge between patients, companies and regulators about the best way to develop drugs for the many genetic syndromes where epilepsy is part of the phenotype and for which there are few patients described – often less than 100. If a drug candidate specifically targets the gene or protein that causes one of these syndromes, then it makes sense to seek a syndrome-focused clinical program and specific approval. But for the more common compounds, which simply have broad symptomatic efficacy, it would make more sense to group many of these ultra-rare syndromes under a broader indication, such as genetic refractory epilepsy syndromes, or epilepsy encephalopathies, and use basket trials with patients from multiple syndromes as pivotal trials for such approval. While this approach would
mainly benefit patients – which would get more drugs evaluated in their ultra-rare epilepsies and get reimbursed after approval – the main deciding factor for drug sponsors will be if regulators will accept this new broad indication as an orphan indication or not. As discussed previously in this report, for a large number of compounds currently in development, orphan exclusivity is not just a bonus, but also a necessary condition to achieve an acceptable return on investment.

Outside of just epilepsy, Dravet syndrome will continue to be an attractive indication for compounds that combine both anticonvulsant and cognitive-enhancing properties. This is the case for some of the compounds in development (such as BIS-001) that have a mechanism of action that will potentially support differentiation from the current drugs in advanced clinical stages on the basis of efficacy in some of the non-seizure aspects of Dravet syndrome. In order to support these claims of significant benefit, the design of clinical trials for Dravet syndrome will need to change to include non-seizure endpoints. Attempting to support significant benefit solely on the basis of superior seizure reduction or seizure freedom using the classical protocol will get much harder as new drugs using the same protocol get approved. Therefore it is likely that we will see an evolution in the activity profile of compounds in development for Dravet syndrome, from purely anticonvulsant to compounds with broader efficacy activity, and also an evolution in the clinical trial protocols, from only using seizure outcomes as primary endpoints to including non-seizure endpoints or even combined endpoints.

Lastly, Dravet syndrome will continue to be the preferred target 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, which have also 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 oligonucleotide from OPKO health (Hsiao et al., 2016). By targeting the cause of the disease, all these programs have the potential to impact multiple syndrome domains and will therefore also benefit from the development of new endpoints for clinical trials in Dravet syndrome. Seeing more of these programs in the Dravet syndrome pipeline and less symptomatic anti-epileptic drugs in development will indicate a more mature pipeline.
7. Summary

Dravet syndrome is an orphan epilepsy disorder with multiple non-seizure comorbidities and high unmet medical need. In the last 5 years, Dravet syndrome has gained significant attention from the pharmaceutical industry, and the pipeline has grown from only one drug approved (ex-US) to at least 13 development programs. Some of this popularity is due to an increasing move away from highly competitive, large indications and towards orphan indications – a trend particularly strong in epilepsy. Dravet syndrome has also gained popularity as an attractive indication for serotonergic agents, with 4 different serotonergic programs currently in the pipeline. Overall the Dravet syndrome pipeline has started showing signs of maturity, with the arrival of a second generation of treatments that seek to target the disease biology, thereby differentiating themselves from the first generation of symptomatic anticonvulsant treatments. As the competition increases, the pipeline is likely to shift towards less symptomatic treatments and more disease-targeting therapeutics.
REFERENCES


