EDISON

GW Pharmaceuticals

2016 outlook

2016: A transformative year

Pharma & biotech

With four Phase III trials of Epidiolex (cannabidiol or CBD) in various forms of pediatric epilepsy, two for Dravet syndrome and two for Lennox-Gastaut syndrome (LGS) expected to provide top-line readouts in 2016 (with three in H116), investors are understandably laser-focused on these programmes. Based on an analysis of the previous results of other molecules in Dravet and LGS, as well as data from the expanded access programme, we are confident that the trials are sufficiently powered to demonstrate a statistically significant benefit for those patients taking Epidiolex.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
09/14	30.0	(18.3)	(6.4)	0.0	N/A	N/A
09/15	28.5	(55.8)	(17.6)	0.0	N/A	N/A
09/16e	8.8	(80.7)	(25.4)	0.0	N/A	N/A
09/17e	11.4	(79.2)	(23.9)	0.0	N/A	N/A

Note: *PBT and EPS are normalized, excluding amortization of acquired intangibles, exceptional items and share-based payments.

First up, Dravet

Dravet syndrome is a rare form of epilepsy, characterized by severe, intractable seizures that begin in infancy. Data from a 120-patient trial should be available in March. Expanded access programme data indicate a 63% median reduction in total seizures at week 12, which bodes well for the pivotal study, as historically there has been little/no placebo response observed in these highly refractory patients. Results from a second Dravet trial are expected in H216.

LGS data coming in Q216

Data from two Phase III trials (with 171 and 225 patients, respectively) in LGS are coming in the second quarter. In the latest expanded access programme data, Epidiolex reduced atonic/drop seizure frequency by a median of 71.1%. Previous data suggest a placebo response rate in LGS of around 10% which, combined with the size of the trials, indicates sufficient power to demonstrate a difference.

TSC extends the Epidiolex franchise further

Data from the expanded access programme with Epidiolex in the US have shown highly encouraging efficacy across a wide range of childhood epilepsies (including Dravet and LGS). Recent data indicate a tangible benefit for patients suffering TSC-related epilepsy, another hard-to-treat condition with few treatment options. GW plans to start a Phase III study in Q116. We estimate peak sales at $255m.

Valuation: £1.35bn (517p/share) ahead of catalysts

Our valuation is now £1.35bn or 517p/share (vs £1.21bn, 510p/share) after increasing the probability of success for Epidiolex in Dravet and LGS to 70% from 50%, for schizophrenia to 25% from 20% and adding TSC and IV GWP42003 for NHIE into our model. This was mitigated by the removal of estimates for Sativex for cancer pain and GWP42003 for ulcerative colitis due to the failure of the programmes.

25 February 2016

Price	**256.25p**
Market cap	**£673m**
	$1.51/£
Net cash (£m) at 31 December 2015	219
Shares in issue	262.6m
Free float	88%
Code	GWP
Primary exchange	LSE
Secondary exchange	NASDAQ

Share price performance

%	1m	3m	12m
Abs	(20.8)	(44.5)	(41.3)
Rel (local)	(20.4)	(40.8)	(31.9)
52-week high/low		696.0p	237.5p

Business description

GW Pharmaceuticals is a UK-based specialty pharma company focused on cannabinoids. Sativex is marketed in various European countries for multiple sclerosis spasticity. Lead pipeline candidate is Epidiolex for refractory childhood epilepsy, now undergoing Phase III studies.

Next events

First Dravet syndrome Phase III data	Q116
First LGS Phase III data	Q216
Second LGS Phase III data	Q216
Second Dravet syndrome Phase III data	H216

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Investment summary

Company description: Cannabinoid medicines specialist

Founded in 1998, GW Pharmaceuticals is a UK-based biopharmaceutical company that discovers, develops and commercializes proprietary cannabinoid (cannabis-derived) medicines for a broad range of diseases. GW's cannabinoid platform generated the world's first plant-derived cannabinoid therapeutic, Sativex, for the treatment of spasticity due to multiple sclerosis (MS), sold by multiple global partners. GW is also developing a broad pipeline of cannabinoid medicines targeting diabetes and central nervous system (CNS) disorders including epilepsy, schizophrenia, autism and neonatal hypoxic-ischemic encephalopathy (NHIE). The company currently has four Phase III trials ongoing in Dravet syndrome and LGS, particularly severe forms of epilepsy. GW listed on AIM in 2001 and on the NASDAQ exchange in 2013.

Valuation: £1.35bn or 517p per share, ahead of 2016 catalysts

Our DCF-based valuation is now £1.35bn or 517p/share (vs £1.21bn, 510p/share) after increasing the probability of success for Epidiolex in Dravet and LGS to 70% from 50% following positive data, increasing its probability of success in schizophrenia to 25% from 20% after proof-of-concept data and adding TSC and IV GWP42003 for NHIE into our model. This was mitigated by the removal of estimates for Sativex for cancer pain and GWP42003 for ulcerative colitis due to the failure of those programmes and a higher share count. We also note that our valuation represents fair value for the stock today, ahead of Phase III results with Epidiolex. For illustration, increasing the probability of success to 90% on positive outcomes from these trials would raise our overall valuation to approximately £1.73bn or 663p/share. Epidiolex also holds wider potential in other refractory forms of childhood epilepsy, which we do not currently capture in our model.

Sensitivities: Clinical, regulatory and commercial

GW Pharma is subject to the sensitivities common to most biopharmaceutical companies, such as potential clinical or regulatory failure or delay, commercialization risks (launch, uptake, pricing, reimbursement, competition) and reliance on partners. With investor focus on the four Phase III trials in Dravet syndrome and LGS, any hiccups in relation to these trials could have a significant impact on the valuation of the company (especially given they all revolve around the same product, which represents the bulk of GW's value). Based on a sensitivity analysis, it appears that investors are currently pricing in a ~30% chance of success for those trials, so there would be downside if they fail. However, given the size of the trials, the expanded access data and the historic placebo responses in other trials, we believe they are more likely to succeed than fail.

Financials: Fully funded to execute clinical/commercial plans

The company announced that it finished Q116 with £219.3m ($324.1m) in cash. GW-funded research and development was £21.9m for the quarter, up £0.5m sequentially, but up £13.2 compared to the fourth calendar quarter of 2014. We have increased our R&D expense due to larger trial sizes and removed Otsuka-related R&D fees and expenses from future estimates (although the NPV impact is zero on the Otsuka changes). GW also announced a slight delay in receiving the results of its second Dravet trial to H216 from mid-2016, although the NDA filing is still expected to occur in Q416. While this change is minor, we had originally expected all results to be released in H116, so we do not now expect Epidiolex to launch in 2017 and have removed those revenues from our model. We currently estimate profitability in 2018 with a total cash burn of around £160m from 2016-17, providing GW with ample cash flow to achieve its goals without the need for additional capital. However, this profitability is dependent on successful Epidiolex trials in Dravet and LGS, as well as approval.

A focus on intransigent CNS diseases

GW has developed a broad pipeline, which is focused on areas of continued unmet medical need despite a number of approved therapies. Epilepsy patients have quite a number of choices for treatment, but 36% have pharmacoresistant epilepsy[1] that cannot be controlled by even three or more drugs taken concurrently. GW is focused on some of the most difficult-to-treat subpopulations in Dravet and LGS. It has recently expanded this to Tuberous Sclerosis Complex (TSC), another subtype of epilepsy, and is expanding to other CNS areas such as schizophrenia, where it recently had proof-of-concept data, and NHIE, a severe issue for newborns that often leads to disease or lifelong brain damage.

Exhibit 1: GW Pharmaceuticals' pipeline and expected newsflow

Product	Indication	Cannabinoids (ratio)	Stage	Status and next steps
Epilepsy				
Epidiolex (GWP42003-P)	Dravet syndrome	CBD	Phase III	Part B (n=120) enrolment complete in efficacy phase of Phase II/III trial, headline data expected March 2016. Second Phase III trial (n=150) ongoing; data expected in H216. NDA in Q416 (data dependent).
Epidiolex (GWP42003-P)	Lennox-Gastaut syndrome	CBD	Phase III	2x Phase III studies (n=171 + n=225) now underway; data expected in Q216. NDA in Q416 (data dependent).
Epidiolex (GWP42003-P)	Tuberous Sclerosis Complex	CBD	Phase III-ready	Phase III study to start in Q116.
Epidiolex	Childhood epilepsy syndromes (DS + LGS + others)			Expanded access, physician-led, IND treatment programme 313 children treated at 16 US clinical sites; efficacy data presented so far from 261 patients treated for at least 12 weeks.
GWP42006	Adult epilepsy	CBDV	Phase II	Part A (n=66) ongoing, in adults with inadequately controlled focal seizures; transfer to Part B (n=130) in Q315; data from Part B expected Q416.
Other orphan diseases				
GWP42002/ GWP42003	Refractory glioma	THC/CBD (1:1)	Phase Ib/IIa	Phase Ib safety cohort complete; Phase IIa (n=20) efficacy cohort ongoing; results in mid-2016.
GWP42003 (IV)	Neonatal hypoxic ischemic encephalopathy (NHIE)	CBD	Preclinical	Phase I to start in healthy volunteers in H216 (FDA has granted orphan drug designation).
Non-orphan diseases*				
GWP42003	Schizophrenia	CBD	Phase IIa	Further analysis of proof-of-concept results and announcement of next steps.
GWP42004	Type 2 diabetes	THCV	Phase IIb	Q216: results from 200-pt dose-ranging Phase IIb study.
Sativex	Cerebral palsy in pediatric MS patients	THC/CBD (1:1)	US (Phase II)	Data expected H216.

Source: GW Pharmaceuticals, Edison Investment Research. Note: *GWP42003 (CBD/THC 20:1) for ulcerative colitis removed from the pipeline. THC = tetrahydrocannabinol; CBD = cannabidiol; THCV = tetrahydrocannabivarin; CBDV = cannabidivarin.

Epidiolex – breakthrough potential

The development of Epidiolex, a liquid formulation of highly purified CBD extract, has been a rapid and clear example of the inherent potential in GW's cannabinoid technology platform. This has resulted in the investment case advancing well beyond Sativex, for many years the only significant valuation driver for the stock. In 2014, GW received Orphan Drug and Fast Track designations from the FDA for Epidiolex in the treatment of Dravet, as well as Orphan Designation from the EMA in Europe. Also in 2014, GW received Orphan Drug designation from the FDA for Epidiolex to treat LGS. These designations, coupled with highly encouraging data from an expanded access programme in the US (313 children treated across 16 clinical sites), have led to the design of an extensive pivotal clinical study programme for Epidiolex in DS and LGS, with data expected from four Phase III trials in the next six months.

[1] Kwan P, Brodie MJ. N Engl J Med. 2000;342:314-319.

The nightmare that is Dravet

Dravet is an extremely malignant form of childhood epilepsy that typically presents itself within the first year of life with prolonged febrile and afebrile, generalized clonic or hemiclonic epileptic seizures in otherwise normally developing children. The incidence of Dravet ranges from 1:20,000 to 1:40,000 births, which suggests an overall disease prevalence of 5,500 patients in the US and 6,700 European patients.[2] The primary genetic cause is a mutation of the SCN1A gene which, while helping to increase the rate of diagnosis, has not done much for the outcomes of these patients. 10-14% of Dravet patients end up dying, typically around the age of six or seven (see Exhibit 2).

Exhibit 2: Average age of onset of Dravet, as well as death

Table 1. Clinical manifestations and phenotype

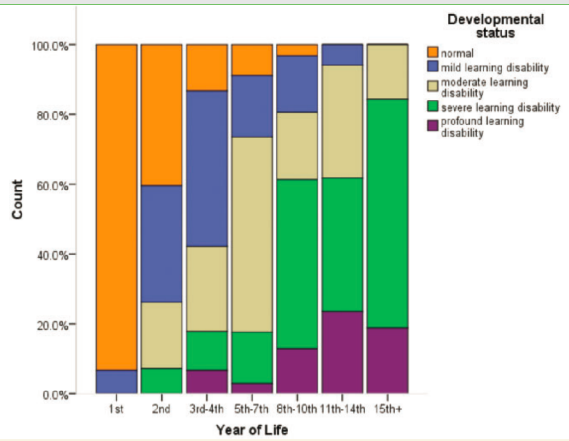
	Typical (N = 39)	Borderline (N = 20)	All cases (N = 59)	p-Value*
Gender (M/F)	17/22	9/11	26/33	3.99
Age at onset (mo.)	4.9 ± 1.7	5.5 ± 2.0	5.1 ± 1.8	2.04
Age at death (mo.)	80.7 ± 73.1	79.5 ± 70.5	80.4 ± 71.6	2.88
Cause of death	21/15/3	10/6/3	31/21/6	2.80
Sudden/status/drowning				
Seizure frequency	13/16/8	2/7/10	15/23/18	0.567
Daily/weekly/monthly				
Number of AED polytherapy (<4)/2–3	15/21	6/12	23/33	4.788
Mental retardation	18/14/6	4/9/7	22/23/13	0.980
Severe/moderate/mild				

M, male; F, female, mo., months; AEDs, antiepileptic drugs.
*The Bonferroni collection was added to p-values.

Source: Sakauchi et al. 2011 Epilepsia, 52(6):1144–1149, 2011

Besides the risk of death, by the time the children are teenagers they exhibit either severe or profound learning disabilities (see Exhibit 3). In one study of 31 typical and borderline Dravet patients (14 were typical Dravet, 17 were borderline) who were followed until adulthood, 22.6% could speak no words at all, 29% cold speak several words, 29% could make primitive conversation and 16.1% could make simple conversation and read to some extent. Only one (3.2%) with borderline Dravet could lead an independent life, although he developed psychosis.[3]

Exhibit 3: Developmental issues in Dravet patients



Source: Brunklaus A et al. Brain 2012: 135; 2329–2336

Epidiolex in Dravet patients

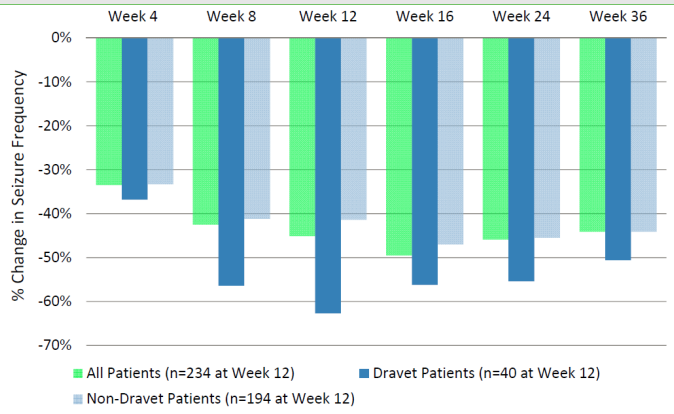
Thanks to data from the company's expanded access programme, which provided the drug to 313 patients at 16 different sites, including 40 with Dravet, we have evidence that the drug is efficacious in this subtype of epilepsy (see Exhibit 4). Patients were 12 years old on average and, importantly,

[2] Brunklaus A et al. Brain 2012: 135; 2329–2336.

[3] Akiyama M et al. 2010, Epilepsia, 51(6):1043–1052, 2010.

were already on three other anti-epilepsy drugs on average. At week 12, Dravet patients saw a median decrease of 63% in total seizures, with 13% being seizure free, a very impressive result in this high refractory population. In terms of safety, somnolence, diarrhea, fatigue and decreased appetite were the most common, but only 4% discontinued therapy due to an adverse event. Importantly, as the sample size for Dravet patients has increased from the original 23 patients reported back in April 2015, the data have remained consistent.

Exhibit 4: Median % change in total seizures in Epidiolex expanded access programme

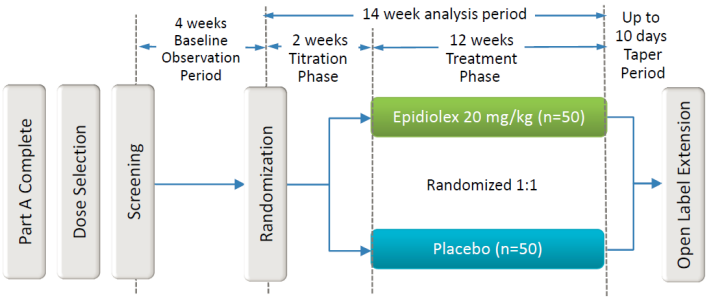


Source: American Epilepsy Society 2015

Will the two Phase III trials in Dravet be successful?

There is an ancient Chinese saying that "he who lives by the crystal ball ends up eating broken glass". This is often especially true for drug trials, as it seems a thousand things need to go right for a successful trial, while it only takes one thing to go wrong for the trial to be doomed. The design of the first Phase III trial is pretty straightforward (see Exhibit 5), with a four-week baseline observation period to understand the seizure rate in the patients before therapy. This is followed by a two-week titration phase up to 20mg/kg of Epidiolex or placebo, with each arm having 60 people (120 total).

Exhibit 5: Original design of first Dravet Phase III trial (sample size now 120 total)



Source: GW Pharmaceuticals

This design is relatively similar to the expanded access study, which produced exceptional results in Dravet patients, but with one difference, which is that dosing was not a flat 20mg/kg. However, the average dose was 19mg/kg in the Dravet patients and there was no clear increase in response rate for those dosed above 20mg/kg. In the second Phase III, which will test two doses of Epidiolex (10mg/kg and 20mg/kg) versus placebo in around 150 patients, the design is almost identical except for the inclusion of the lower 10mg/kg dose.

The percentage change from baseline in convulsive seizure frequency during the treatment period (0-14 weeks) compared to placebo is the primary endpoint of the trial, so it is important to understand what sort of placebo effect we can expect. There is very limited data from previous placebo controlled trials in Dravet patients. In a 41-patient trial comparing stiripentol to placebo in patients currently on valproate and clobazam, placebo patients actually saw a 7% increase in

seizures and only one patient (5%) was deemed a responder, which was defined as a 50% reduction in the frequency of clonic seizures. In a smaller 21-patient trial with stiripentol, the placebo response rate was a 12.7% decrease in seizures with, again, only one responder (9%). While these trials are small, given that Dravet is such an incredibly difficult subtype of epilepsy to treat, any placebo effect will likely be minimal, if not non-existent. According to the company, the trial has higher than 90% power to detect a 30% difference between the treatment arm and placebo. That means that even if the expanded access programme was overstating efficacy by 20-30% at week 12 (assuming little/no placebo efficacy), the trial would likely still be successful.

As an illustration of how the powering/statistics may work out, it is helpful to look at the clobazam trial in LGS patients (see Exhibit 6) since the individual treatment arms and placebo arm are roughly the same size as the arms in both the GW Dravet trials (although the clobazam trial was larger as a whole due to more dosage arms), and the trial design was generally similar. In the low-dose arm with 53 patients, clobazam demonstrated a 29.1% placebo-adjusted reduction in seizure rate, which was good enough to achieve a p-value of p=0.012-0.017, depending on the statistical tests. Higher placebo-adjusted reductions in seizure rates quickly added additional zeros to the p-value, signifying a highly statistically significant result. We expect data from the first Phase III in Dravet in March and the second in H216.

Exhibit 6: Clobazam LGS trial results

Parameter	Placebo (n=57)	Low dose (n=53)	Medium dose (n=58)	High dose (n=49)
Least squares mean % reduction in seizure rate	12.1	41.2	49.4	68.3
Least squares mean difference in seizure rate from placebo	N/A	29.1	37.3	56.1
p-value (ANCOVA model)		p=0.012	p=0.0015	p<0.0001
p-value (Wilcoxon rank-sum test)		p=0.017	p=0.0002	p<0.0001

Source: FDA

With an NDA filing expected in Q416, we expect a launch in early 2018, allowing for the FDA review, as well as DEA rescheduling (which by law should take 90 days). As patients and physicians are comfortable using a combination of drugs to treat these disorders, we would expect the addition of Epidiolex, with its novel mechanism of action, to be widely adopted (assuming the data support its use). In our model we assume 50% penetration in the US and 25% penetration in the EU. We project worldwide peak sales of around $200m in Dravet patients.

LGS: Another unmet need in pediatric epilepsy

LGS, like Dravet, is another rare form of epilepsy, although it typically starts later in life, at between two and eight years of age vs six months for Dravet. As with Dravet, outcomes are extremely poor for these patients, with 90% becoming mentally handicapped with a progressive reduction in IQ. The mortality rate is high, although the exact percentage varies based on the study and ranges between 3% and 25%.[4] Incidence estimates for LGS vary, but it accounts for approximately 2-5% of all childhood epilepsies. This suggests 16,000 patients with LGS in the US and 24,000 in Europe.

While the sample size from the expanded access data is more limited than with Dravet, it is still impressive and the median seizure reduction has been consistently high, with the most recent data point suggesting a 71.1% median reduction in atonic seizures (which is also the primary endpoint of the two LGS trials).

[4] Rijckevorsel, K. Neuropsychiatric Disease and Treatment 2008:4(6) 1001–1019.

Exhibit 7: Epidiolex efficacy in LGS in expanded access programme

	AAN (Apr 2015)	Lancet (Dec 2015)	AES (Dec 2015)
Patients with atonic seizures	n=11	n=14	n=14
Atonic seizures median reduction	55%	68.8%	71.1%
Atonic seizure free at week 12	not reported	21%	Not reported
Analysis	3rd Month	Monthly average	3rd Month

Source: GW Pharmaceuticals

The first Phase III trial results for LGS, which will have results in Q216, has a design similar to the Dravet trial with two arms, although there will be 171 patients (approximately 85 patients each). This increases the power of the trial significantly and allows for both a lower than expected treatment effect and a higher than expected placebo effect. Historically, however, LGS placebo response rates have not been much more than 10% across trials (see Exhibit 8), so the trial should be powered for statistical significance even with only a 20% placebo-adjusted difference.

Exhibit 8: Data from previous LGS trials

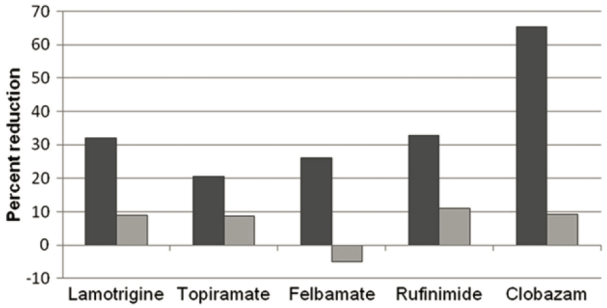


Figure 2. Median reduction in total seizure frequency with antiepileptic drugs approved for Lennox–Gastaut syndrome (dark gray columns) compared with placebo (light gray columns) [The Felbamate Study Group in Lennox–Gastaut Syndrome, 1993; Glauser *et al*. 2008; Jensen, 1994; Sachdeo *et al*. 1999; Ng *et al*. 2011].

Source: Purcarin G et al, Therapeutic Advances in Neurological Disorders 2014, Vol. 7(3) 169-176

The second trial is expected to have three arms of more than 70 patients each (placebo, 10mg/kg and 20mg/kg), but the powering should still be enough to detect a treatment effect. Note that in the lamotrigine trial in LGS patients (treatment arm had 78 patients, while 89 were in placebo), a 23% placebo-adjusted difference was able to achieve a p-value of 0.002.[5]

As with Dravet, combination therapy is very much the norm and Epidiolex has a novel mechanism of action compared to other therapies, so we expect that it will be widely used. In our model, we assume 50% penetration in the US and 25% penetration in the EU. We project worldwide peak sales of around $600m in LGS patients.

TSC epilepsy: Expansion of the Epidiolex franchise

TSC is a multisystem, autosomal dominant genetic disorder resulting from a mutation in one of two tumour suppressor genes, TSC1 (encoding hamartin) or TSC2 (tuberin). TSC is characterized by benign tumours, known as hamartomas, in various organs, most commonly the skin, brain, kidneys, heart and lungs. A hamartoma is composed of an overgrowth of mature cells and tissues, which normally occurs in the affected tissue. TSC affects both sexes and all ethnic groups, affecting as many as 25,000-40,000 individuals in the US and about one to two million individuals worldwide, with an estimated prevalence of one in 6,000 newborns (tuberous sclerosis fact sheet).

[5] Motte J et al, N Engl J Med 1997; 337:1807-1812.

The signs and symptoms of TSC vary depending on the organs involved. The most common symptom is epilepsy, which occurs in around 80-90% of patients and is a significant cause of morbidity and mortality.[6] Seizures of all types may occur, the most common being infantile spasms, partial motor seizures and generalized tonic-clonic seizures. Seizure onset occurs in the first year of life in almost two-thirds of patients, and within the first three years in around 80% of patients.[7] The seizures are often severe, and up to two-thirds of TSC patients are refractory to available medical and surgical therapies.[2] Developmental delays occur in around 50-60% of TSC patients, ranging from mild learning difficulties to severe mental retardation, and about one-third of children with TSC meet the criteria for autism spectrum disorder (tuberous sclerosis fact sheet). Behavioral problems are common and can be difficult to manage. The prevalence of cognitive impairment and neuropsychiatric and developmental disorders has also been found to be higher in those with refractory epilepsy.

Encouraging TSC data from the expanded access programme

Under an expanded access IND from the FDA, Epidiolex has been made available in licensed clinics as an adjunct treatment in children and young adults with drug-resistant epilepsy. GW presented updated data on the trial at the American Epilepsy Society's annual meeting, showing encouraging outcomes in 10 TSC patients treated with Epidiolex under this programme. Four of these TSC patients also had cognitive impairment. Six of the patients responded to adjunctive treatment with Epidiolex, with response defined as a 50% decrease in seizure frequency at 16 weeks of treatment compared to a four-week baseline period.

Importantly, patient 9, who suffered from five separate seizure types, was on three concomitant antiepilepsy drugs and had a total of seven in the past, became seizure free after two months of treatment and has remained seizure free for 10 months. Diarrhea was the only side effect attributed directly to CBD. Drowsiness and irritability were due to drug-drug interactions in five patients, which were alleviated with antiepileptic drug dose adjustments while maintaining seizure control.

On the basis of these results, GW will start a Phase III trial in TSC in Q116. Once data are available for a larger number of TSC patients, we will see whether the seizure response and cognitive and behavioral effects are repeated. If the results suggest wider cognitive/behavioral benefits, this could provide the basis for an expanded use of Epidiolex beyond epilepsy.

Proof of concept of CBD in schizophrenia

In September, GW Pharma announced positive proof-of-concept data from a Phase IIa study of CBD in 88 patients suffering from schizophrenia who had failed at least one previous therapy. There was no primary endpoint, just a series of exploratory endpoints. CBD showed a statistically significant impact in the PANSS positive subscale, CGI-S and CGI-I, while showing trends in both cognition and the PANSS negative subscale (see Exhibit 9). The two most recent FDA approvals of schizophrenia medications (Vraylar and Aristada) both had PANSS total score as the primary endpoint, with CGI-S being the secondary endpoint in one and CGI-I being the secondary endpoint in the other. Given that CBD has demonstrated statistically significant results in some very key endpoints, we have increased our probability of success for the programme from 20% to 25%. We await further clarity on the complete dataset from the clinical trial, as well as the plan for the programme, before increasing the probability of success further.

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6 Krueger DA, et al. Everolimus Treatment of Refractory Epilepsy in Tuberous Sclerosis Complex. Ann Neurol. 74:679-687 (2013).

7 Chu-Shore CJ, et al. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 51(7):1236-1241 (2010).

Exhibit 9: Phase IIa data of CBD in schizophrenia	
Endpoint	**p-value**
Positive and Negative Syndrome Scale (PANSS) positive subscale	0.018
Clinical Global Impression of Severity (CGI-S)	0.04
Clinical Global Impression of Improvement (CGI-I)	0.02
Cognition	0.07
Positive and Negative Syndrome Scale (PANSS) negative subscale	N/A (trends in favor of CBD)
Source: GW Pharmaceuticals	

NHIE: An unmet medical need among neonates

NHIE is a condition that results from an interruption of blood flow and oxygen delivery to the brain due to a variety of reasons including placental insufficiency, cord compression or foetal hemorrhage (see Exhibit 10). According to Medscape, incidence is currently estimated at 2.5 per 1,000 live births, so as there are four million live births per year in the US; according to the CDC, there are around 10,000 cases of NHIE per year. Without treatment, 23-27% with moderate to severe NHIE die before leaving the hospital, with the overall death rate at 30-38% at the 18- to 22-month time point.[8,9] Those that survive often have cerebral palsy (36%), epilepsy (16%), hearing (10%) and visual impairment (13%).[10]

Exhibit 10: Causes of NHIE		
Maternal	**Uteroplacental**	**Foetal**
Cardiac arrest	Placental abruption	Fetomaternal hemorrhage
Asphyxiation	Cord prolapse	Twin to twin transfusion
Severe anaphylaxis	Uterine rupture	Severe isoimmune hemolytic disease
Status epilepticus	Hyperstimulation with oxytocic agents	Cardiac arrhythmia
Hypovolemic shock		
Source: University of Chicago Medical Center		

GW Pharma is developing an IV formulation of GWP42003, where CBD is the primary cannabinoid but also contains other cannabinoid and non-cannabinoid components, for use in neonates. There are no clinical data yet, as the company first needs to conduct a juvenile toxicology study followed by a ~100 newborn proof-of-concept study. The preclinical data seen so far have been quite remarkable, with brain activity and necrotic cell counts close to normal in newborn piglets.[11] CBD appears to be anti-inflammatory and modulates cerebral hemodynamic impairment and brain metabolic derangement, while also preventing the appearance of brain edema and seizures.

There are high costs associated with these infants, so if GW can demonstrate a large enough benefit it would be able to receive a premium price for its product. For the purposes of our valuation, we are currently assuming a price of $50,000 per treatment (which will last at least 72 hours and may last as long as a week) and a ~40% peak penetration, which results in ~$450m in worldwide peak sales.

Sativex: On the market for MS spasticity in 28 countries

Sativex is an oromucosal spray consisting of a formulated extract of the cannabis sativa plant, which contains the principal cannabinoids delta-9-tetrahydrocannabinol (THC) and CBD. Multiple sclerosis (MS) affects approximately 1.3 million people worldwide, of which up to 80% suffer from spasticity, a symptom of MS characterized by muscle stiffness and uncontrollable spasms. There is no cure for spasticity and Sativex provides an alternative for patients who fail to respond to conventional oral therapies (Baclofen/Zanaflex).

8 Gluckman et al., Lancet 2005; 365, 663-670.

9 Shankaran et al., Pediatrics, 2008; 122(4):e791-8.

10 Azzopardi et al., NEJM 2014;371:140-149.

11 Lafuente et al., 2011, Pediatric Research 70:272-277.

Sativex is approved as a treatment for MS spasticity in 28 countries (outside the US). The product is licensed to a number of partners across global territories, including Almirall (EU ex-UK/Mexico), Otsuka (US), Bayer (UK/Canada), Novartis (Australia/New Zealand/Asia/Middle East/Africa) and Ipsen (Latin America ex-Mexico). GW receives upfront fees, milestones and royalties from these collaborations. In-market 10ml vial sales volumes grew 22% in FY15 and GW recorded £4.2m in Sativex commercial-related revenues in FY15, down £0.2m from the previous year. While it is a small product providing minimal value to GW currently, it did serve as proof of concept for cannabinoids as a medicinal product.

Valuation

Our DCF valuation has increased to £1.35bn or 517p/share (vs £1.21bn, 510p/share) by increasing the probability of success for Epidiolex in Dravet and Lennox-Gastaut syndromes to 70% from 50% following the positive expanded access data presentation in April and the update in December, increasing its probability of success in schizophrenia to 25% from 20% after positive proof-of-concept data and by adding TSC and IV GWP42003 for NHIE into our model (Exhibit 11). We estimate that the TSC programme could reach the market in 2018 and achieve peak global sales of $255m. For IV GWP42003 in NHIE, projected market launch is 2021, with peak sales of $448m.

Exhibit 11: GW pipeline valuation assumptions

Product	Indication	Status	Probability of success (%)	Launch year (CY)	Peak sales ($m)	Peak market share (%)
Epidiolex	Dravet syndrome	Phase III	70%	2018	195	50%
Epidiolex	Lennox-Gastaut	Phase III	70%	2018	601	50%
Epidiolex	TSC	Phase III ready	30%	2018	255	50%
IV GWP42003	NHIE	Phase I ready	10%	2021	448	40%
GWP42004	Type 2 diabetes	Phase IIb	30%	2020	1,024	10%
GWP42002:GWP42003	Recurrent GBM	Phase Ib/IIa	30%	2020	246	30%
GWP42003	Schizophrenia	Phase IIa	25%	2022	1,001	10%
GWP42006 (CBDV)	Adult epilepsy	Phase IIa-ready	25%	2023	677	10%

Source: Edison Investment Research

We have also rebased our model to 2016, and adjusted our revenue estimates for Sativex. We include cash at end December of 2015 of approximately £219m.

Offsetting the increase is the removal of estimates for Sativex for cancer pain and GWP42003 for ulcerative colitis due to trial failures. We have also pushed back our timeline for a launch in Dravet and Lennox-Gastaut from 2017 to 2018 as the company expects to file in Q416 and will also have to wait for the Drug Enforcement Agency (DEA) to reschedule the drug.

As a reminder, GW has the most extensive portfolio of cannabinoid-based therapeutics in the industry. It is at the forefront of developing cannabinoid-based medicines that hold potential across a wide spectrum of therapeutic areas. We note that the company announced that it is currently targeting autism spectrum disorders, Duchenne Muscular Dystrophy, oncology and cachexia in its preclinical research, although we do not ascribe any tangible value to those programmes yet.

Financials

The company announced that it finished Q116 with £219.3m ($324.1m) in cash. GW-funded research and development was £21.9m for the quarter, up £0.5m sequentially, but up £13.2 compared to the fourth calendar quarter of 2014. While we do expect R&D expenses to moderate as the four Phase III programmes conclude, we have increased our R&D expense assumptions somewhat to take into account the continued high spending rate. We have also removed all Otsuka-related R&D fees and expenses (~£7.5m from each line), although this has no NPV impact

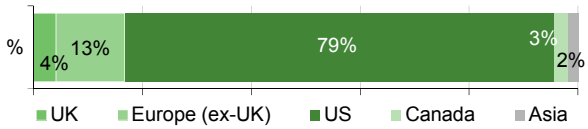
as every dollar of Otsuka-related revenues was matched by a dollar of Otsuka-related expenses. GW also announced a slight delay in receiving the results of its second Dravet trial to H216 from mid-2016. The NDA filing is still expected to occur in Q416 and the company will request a pre-NDA meeting with the FDA as soon as the first trial results are released. While this change is minor, we had originally expected all results to be released in H116, so we do not now expect Epidiolex to launch in 2017 (although it was likely only to be on the market for three months or so in our previous expectation) and have removed those revenues from our model. We currently estimate profitability in 2018 with a total cash burn of around £160m from 2016-17, providing GW with ample cash flow to achieve its goals without the need for additional capital.

Exhibit 12: Financial summary

£000s	2013	2014	2015	2016e	2017e
Year end 30 September	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	27,295	30,045	28,540	8,805	11,430
Cost of sales	(1,276)	(2,060)	(2,618)	(2,582)	(4,631)
Gross profit	26,019	27,985	25,922	6,222	6,800
R&D Expenses	(32,697)	(43,475)	(76,785)	(74,991)	(72,491)
SG&A Expenses	(3,555)	(7,337)	(12,569)	(13,826)	(15,208)
EBITDA	(8,865)	(17,003)	(54,569)	(79,908)	(78,188)
Operating profit (before goodwill and except.)	(9,854)	(18,401)	(55,967)	(81,306)	(79,586)
Intangible amortisation	0	0	0	0	0
Exceptionals	0	0	0	0	0
Share-based payment	(616)	(1,238)	(1,263)	(1,288)	(1,314)
Operating profit	(10,470)	(19,639)	(57,230)	(82,594)	(80,899)
Net Interest	114	69	169	587	380
Profit before tax (norm)	(9,740)	(18,332)	(55,798)	(80,719)	(79,205)
Profit before tax (as reported)	(10,356)	(19,570)	(57,061)	(82,007)	(80,519)
Tax	5,807	4,911	12,498	13,048	13,048
Profit after tax (as reported)	(4,549)	(14,659)	(44,563)	(68,959)	(67,471)
Average number of shares outstanding (m)	151.5	210.4	246.4	266.4	277.1
EPS - normalised (p)	(2.6)	(6.4)	(17.6)	(25.4)	(23.9)
EPS - as reported (p)	(3.0)	(7.0)	(18.1)	(25.9)	(24.4)
Dividend per share (p)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed assets	11,581	17,126	34,606	46,541	58,743
Intangible assets	5,210	5,210	5,455	5,455	5,455
Tangible assets	5,476	11,639	28,733	40,668	52,870
Deferred tax asset	895	277	418	418	418
Current assets	47,363	176,376	255,142	173,272	95,060
Stocks	4,661	4,777	4,756	5,264	7,877
Debtors	1,733	1,857	2,873	3,304	3,800
Cash	38,069	164,491	234,872	152,063	70,743
Other	2,900	5,251	12,641	12,641	12,641
Current liabilities	(12,721)	(17,329)	(27,768)	(28,666)	(29,658)
Creditors	(9,540)	(12,502)	(24,499)	(25,724)	(27,010)
Short-term borrowings	0	0	0	0	0
Deferred revenue & advance payments	(3,181)	(4,827)	(3,269)	(2,942)	(2,648)
Long-term liabilities	(10,821)	(17,589)	(16,710)	(14,540)	(12,661)
Long-term borrowings	0	0	0	0	0
Deferred revenue	(8,916)	(7,881)	(6,725)	(6,053)	(5,447)
Other long-term liabilities	(1,905)	(9,708)	(9,985)	(8,487)	(7,214)
Net assets	35,402	158,584	245,270	176,608	111,483
CASH FLOW					
Operating cash flow	(10,300)	(15,807)	(51,887)	(80,762)	(81,149)
Net interest	167	145	162	587	380
Tax	2,832	3,181	5,145	10,700	13,048
Capex	(2,243)	(7,254)	(17,915)	(13,333)	(13,600)
Expenditure on intangibles	0	0	(114)	0	0
Acquisitions/disposals	0	14	2	0	0
Financing	18,100	136,606	128,748	0	0
Dividends	0	0	0	0	0
Other	178	9,537	6,239	0	0
Net cash flow	8,734	126,422	70,381	(82,809)	(81,321)
Opening net debt/(cash)	(29,335)	(38,069)	(164,491)	(234,872)	(152,063)
HP finance leases initiated	0	0	0	0	0
Other	(0)	0	0	0	0
Closing net debt/(cash)	(38,069)	(164,491)	(234,872)	(152,063)	(70,742)

Source: Edison Investment Research, company reports

EDISON

Contact details	Revenue by geography
1 Cavendish Place London W1G 0QF United Kingdom +44 (0)20 7291 0555 www.gwpharma.com	

Management team

Chairman: Dr Geoffrey Guy

Dr Guy was a founder of GW and has served as chairman since 1998. He has over 30 years' experience in medical research and drug development. He founded Ethical Holdings (now Amarin) in 1985 and Phytopharm in 1989. He holds a BSc in pharmacology (University of London), a medical degree (MBBS) from St Bartholomew's Hospital and a diploma in pharmaceutical medicine (Royal College of Physicians).

CEO: Justin Gover

Mr Gover has been CEO since 1999. He has over 17 years' experience in the pharmaceutical industry. As CEO, he is responsible for directing operations and leads equity financings and business development activities. Before GW, he was head of corporate affairs at Ethical Holdings (1995-97), where he was responsible for strategic corporate activities. He holds an MBA from INSEAD and a BSc (hons) from Bristol University.

R&D director: Dr Stephen Wright

Dr Wright has been R&D director since 2004. He has over 20 years' experience in drug development. Before GW, he was SVP of clinical research and development at Ipsen. He has direct US drug development experience, first as medical director of Immunosciences, then as venture head of neuroscience at Abbott. He is a fellow of the Royal College of Physicians and Faculty of Pharmaceutical Medicine and visiting professor at the University of Reading. He holds an MD and MA (University of Cambridge) and a medical degree (MBBS) from the Royal London Hospital.

CFO: Adam George

Mr George has been CFO since 2012. He also serves as company secretary. Before his current role, he served as financial controller from 2007 and was finance director (2004-07) and group financial controller (2001-04) of Believe It Group (now 4Com). He holds a BSc in biology (Bristol University) and is a qualified chartered accountant.

Principal shareholders	(%)
Prudential PLC	15.16%
Capital Research and Management Company	11.99%
FMR, LLC	10.00%
Oppenheimer Funds	5.51%
Prudential PLC	5.20%
Janus Capital Management	3.83%
Bank of New York	3.74%
Bank of America	3.26%

Companies named in this report

Almirall (ALM.MC), Otsuka (3570.TO), Bayer (BAYN.DE), Novartis (NVS) and Ipsen (IPN.FP).

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